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(54) Title: TREATMENT OF MEDICATION OVERUSE HEADACHE USING ANTI-CGRP OR ANTI-CGRP-R ANTIBODIES

Figure 1A - Heavy Chain Protein Sequence

Sequence Name	FR1	CDR1	FR2	CDR2
Ab1	QSLEESGGRLVTPGTPLTLTCTVSGLDLS	SYYMQ	WVRQAPGKGLEWIG	VIGINDNTYYASWAKG
Ab2	EVQLVESGGGLVQPGGSLRLSCAVSGLDLS	SYYMQ	WVRQAPGKGLEWVG	VIGINDNTYYASWAKG
Ab3	EVQLVESGGGLVQPGGSLRLSCAVSGLDLS	SYYMQ	WVRQAPGKGLEWVG	VIGINDNTYYASWAKG
Ab4	QSLEESGGRLVTPGTPLTLTCSVSGIDLS	GYYMN	WVRQAPGKGLEWIG	VIGINGATYYASWAKG
Ab5	EVQLVESGGGLVQPGGSLRLSCAVSGIDLS	GYYMN	WVRQAPGKGLEWVG	VIGINGATYYASWAKG
Ab6	EVQLVESGGGLVQPGGSLRLSCAVSGIDLS	GYYMN	WVRQAPGKGLEWVG	VIGINGATYYASWAKG
Ab7	QEQLKESGGRLVTPGTSLTLTCTVSGIDLS	NHYMQ	WVRQAPGKGLEWIG	VVGINGRTYYASWAKG
Ab8	EVQLVESGGGLVQPGGSLRLSCAVSGIDLS	NHYMQ	WVRQAPGKGLEWVG	VVGINGRTYYASWAKG
Ab9	QSLEESGGRLVTPGTPLTLTCTVSGIGLS	SYYMQ	WVRQSPGRGLEWIG	VIGSDGKTYYATWAKG
Ab10	EVQLVESGGGLVQPGGSLRLSCAVSGIGLS	SYYMQ	WVRQAPGKGLEWVG	VIGSDGKTYYATWAKG
Ab11	QSLEESGGRLVTPGGSLTLTCTVSGIDVT	NYYMQ	WVRQAPGKGLEWIG	VIGVNGKRYYASWAKG
Ab12	EVQLVESGGGLVQPGGSLRLSCAVSGIDVT	NYYMQ	WVRQAPGKGLEWVG	VIGVNGKRYYASWAKG
Ab13	QSVEESGGGLVQPEGSLTLTCTASGFDFS	SNAMW	WVRQAPGKGLEWIG	CIYNGDGSTYYASWVNG
Ab14	EVQLVESGGGLVQPGGSLRLSCAVSGIGLS	SYYMQ	WVRQAPGKGLEWVG	VIGSDGKTYYATWAKG

(57) Abstract: Methods for treatment or prevention of medication overuse headache are provided. Exemplary methods comprise administration of an anti-CGRP antagonist antibody to a patient in need thereof.

[Continued on next page]

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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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— *with international search report (Art. 21(3))*

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— *with sequence listing part of description (Rule 5.2(a))*

TREATMENT OF MEDICATION OVERUSE HEADACHE USING ANTI-CGRP OR ANTI-CGRP-R ANTIBODIES

RELATED APPLICATIONS

[0001] The instant application claims priority to U.S. Provisional Application No. 62/840,967 filed April 30, 2019 (Attorney Docket No. 1143257.008800); U.S. Provisional Application No. 62/841,585 filed May 1, 2019 (Attorney Docket No. 1143257.008801); and U.S. Provisional Application No. 62/872,983 filed July 11, 2019 (Attorney Docket No. 1143257.008802), all of which applications are incorporated by reference in their entireties herein.

SEQUENCE LISTING DISCLOSURE

[0002] The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on December 11, 2019, is named "1143257o008803.txt" and is 357,503 bytes in size.

BACKGROUND

[0003] Field

[0004] This invention pertains to antibodies and fragments thereof (including Fab fragments) that specifically bind to human Calcitonin Gene Related Peptide (hereinafter "CGRP") or antibodies and fragments thereof (including Fab fragments) having that specifically bind to human Calcitonin Gene Related Peptide Receptor (hereinafter "CGRP-R"), and methods of preventing or treating diseases and disorders associated with CGRP, such as medication overuse headache, by administering said antibodies or fragments thereof.

[0005] Description of Related Art

[0006] Calcitonin Gene Related Peptide (CGRP) is produced as a multifunctional neuropeptide of 37 amino acids in length. Two forms of CGRP, the CGRP-alpha and CGRP-beta forms, exist in humans and have similar activities. CGRP-alpha and CGRP-beta differ by three amino acids in humans, and are derived from different genes. CGRP is released from numerous tissues such as trigeminal nerves, which when activated release neuropeptides within the meninges, mediating neurogenic inflammation that is characterized by vasodilation, vessel leakage, and mast-cell degradation. Durham, P.L., *New Eng. J. Med.*, 350 (11):1073-75 (2004). Biological effects of CGRP are mediated via the CGRP receptor (CGRP-R), which consists of a seven-transmembrane component, in conjunction with receptor-associated membrane protein (RAMP). CGRP-R further requires the activity of the receptor component protein (RCP), which is essential for an efficient

coupling to adenylate cyclase through G proteins and the production of cAMP. Doods, H., *Curr. Op. Invest. Drugs*, 2(9):1261-68 (2001).

[0007] Migraines are neurovascular disorder affecting approximately 10% of the adult population in the U.S., and are typically accompanied by intense headaches. CGRP is believed to play a prominent role in the development of migraines. In fact several companies, i.e., Amgen, Eli Lilly, Teva and Alder Biopharmaceuticals (recently acquired by Lundbeck A/S) have developed anti-CGRP and anti-CGRP-R antibodies for use in treating or preventing migraine headaches. The present assignee has previously filed patent applications related to anti-CGRP antibodies and uses thereof including published PCT Application WO/2012/162243 filed May 21, 2012 entitled "ANTI-CGRP COMPOSITIONS AND USE THEREOF", published PCT Application WO/2012/162257 filed May 21, 2012, entitled "USE OF ANTI-CGRP ANTIBODIES AND ANTIBODY FRAGMENTS TO PREVENT OR INHIBIT PHOTOPHOBIA OR LIGHT AVERSION IN SUBJECTS IN NEED THEREOF, ESPECIALLY MIGRAINE SUFFERERS" published PCT Application WO/2012/162253, filed May 21, 2012, entitled "USE OF ANTI-CGRP OR ANTI-CGRP-R ANTIBODIES OR ANTIBODY FRAGMENTS TO TREAT OR PREVENT CHRONIC AND ACUTE FORMS OF DIARRHEA" and published PCT Application WO/2015/003122, filed July 3, 2014, entitled "REGULATION OF GLUCOSE METABOLISM USING ANTI-CGRP ANTIBODIES" all of which applications are incorporated by reference in their entirety.

BRIEF SUMMARY

[0008] The present disclosure provides methods of treating or preventing medication overuse headache, e.g., associated with the overuse of anti-migraine drugs and/or associated with triptan and/or ergot and/or analgesic overuse, comprising administering to a patient in need an effective amount of at least one anti-CGRP antibody or antibody fragment or an anti-CGRP-R antibody or antibody fragment or one or more formulations comprising said antibody or antibody fragment as disclosed herein. Said anti-CGRP antibody or antibody fragment optionally comprises any one of Ab1-Ab14 or a Fab fragment thereof, such as Ab6 or a Fab fragment thereof, e.g., having the light chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively and the heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208; or having the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively. Said anti-CGRP antibody may comprise the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202. Said anti-CGRP antibody may comprise the variable light chain polypeptide encoded by SEQ ID NO: 232 and the variable heavy chain polypeptide encoded by SEQ ID NO: 212. Said anti-CGRP antibody may comprise the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of

SEQ ID NO: 201 or SEQ ID NO: 566. Said anti-CGRP antibody may comprise the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567. Said anti-CGRP antibody may comprise the antibody expression product isolated from recombinant cells which express nucleic acid sequences encoding the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202, which polypeptides optionally are respectively linked to human light and heavy constant region polypeptides, e.g., human IgG1, IgG2, IgG3 or IgG4 constant regions, which constant regions optionally may be modified to alter glycosylation or proteolysis, wherein said recombinant cells optionally comprise yeast or mammalian cells, e.g., *Pichia pastoris* or CHO cells. Said anti-CGRP antibody may comprise the antibody expression product isolated from recombinant cells which express nucleic acid sequences encoding the light chain of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566, wherein said recombinant cells optionally comprise yeast or mammalian cells, e.g., *Pichia pastoris* or CHO cells, wherein the constant regions thereof optionally may be modified to alter glycosylation or proteolysis or other effector functions. Any of the aforementioned anti-CGRP antibodies or antibody fragments, preferably Ab6, may be optionally comprised in a formulation as disclosed herein, e.g., comprising histidine (L-histidine), sorbitol, polysorbate 80, such as, per 1 mL volume, about 100 mg anti-CGRP antibody, about 3.1 mg L-Histidine, about 40.5 mg Sorbitol, and about 0.15 mg Polysorbate 80, having a pH of about 5.8. The administered dosage of said antibody may be between about 100 mg and about 300 mg, such as about 100 mg, about 300 mg, 100 mg, or 300 mg. The dosage may be administered by different means, e.g., intravenously, e.g., in a saline solution such as 0.9% sodium chloride in a suitable volume, such as 100 mL.

[0009] Said medication overuse headache may be determined based on meeting the following criteria: (a) headache occurring on 15 or more days/month in a patient with a pre-existing headache disorder; and (b) overuse for more than 3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache.

[0010] Said overuse may comprise use of an ergot alkoid (e.g., ergotamine) on 10 or more days/month, use of a triptan on 10 or more days/month, use of one or more non-opioid analgesics (such as paracetamol (acetaminophen), acetylsalicylic acid (aspirin), another NSAID, or another non-opioid analgesic) on 15 or more days/month, use of one or more combination-analgesics (as further described below) on 10 or more days/month, use of one or more opioids on 10 or more days/month, or use of a combination of two or more drug classes (as further described below) on 10 or more days/month.

[0011] In the methods herein, said triptan may include, without limitation thereto, any one of or any combination of triptans such as sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan, among others.

[0012] Said medication overuse headache may comprise ergotamine-overuse headache, triptan-overuse headache, non-opioid analgesic-overuse headache, opioid-overuse headache, combination-analgesic-overuse headache, medication-overuse headache attributed to multiple drug classes not individually overused, medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes, or medication-overuse headache attributed to other medication.

[0013] Said non-opioid analgesic-overuse headache may comprise paracetamol (acetaminophen)-overuse headache, non-steroidal anti-inflammatory drug (NSAID)-overuse headache such as acetylsalicylic acid (aspirin)-overuse headache or ibuprofen-overuse headache, or another non-opioid analgesic-overuse headache.

[0014] Said ergotamine-overuse headache may comprise headache occurring on 15 or more days/month in a patient with a pre-existing primary headache and developing as a consequence of regular use of an ergot alkaloid such as ergotamine on 10 or more days/month for more than 3 months.

[0015] In the methods herein, said ergot alkaloid may comprise ergotamine, nicergoline, methysergide, or dihydroergotamine.

[0016] Said triptan-overuse headache may comprise headache occurring on 15 or more days/month in a patient with a pre-existing primary headache and developing as a consequence of regular use of one or more triptans on 10 or more days/month for more than 3 months.

[0017] Said non-opioid analgesic-overuse headache may comprise headache occurring on 15 or more days/month in a patient with a pre-existing primary headache and developing as a consequence of regular use of one or more non-opioid analgesics (such as paracetamol (acetaminophen), acetylsalicylic acid (aspirin), ibuprofen, another NSAID, or another non-opioid analgesic) on 15 or more days/month for more than 3 months.

[0018] In the methods herein, said NSAID may comprise any NSAID or combination thereof, including without limitation thereto, ibuprofen, naproxen, or indomethacin.

[0019] Said combination-analgesic-overuse headache may comprise headache occurring on 15 or more days/month developing as a consequence of regular use of one or more combination-analgesics on 10 or more days/month for more than 3 months. In the context of medication overuse headache, the term combination-analgesic refers to formulations combining drugs of two or more classes, each with analgesic effects (for example, paracetamol and codeine) or analgesics in combination with agents acting as adjuvants (for example, caffeine). Commonly overused combination-analgesics combine non-opioid analgesics with at least one opioid, barbiturate such as butalbital and/or caffeine. In exemplary embodiments, the combination-analgesic overuse-headache is due to the combination of acetaminophen, aspirin, and caffeine, e.g., EXCEDRIN ® or EXCEDRIN MIGRAINE ®. Other known combination analgesics comprise an analgesic in combination with at least one non-analgesic, e.g., with a vasoconstrictor drug such as pseudoephedrine for sinus-related preparations, antihistamine drug used to treat allergy sufferers, etc.

[0020] Said opioid-overuse headache may comprise headache occurring on 15 or more days/month in a patient with a pre-existing primary headache and developing as a consequence of regular use of one or more opioids 10 or more days/month for more than 3 months.

[0021] Said medication-overuse headache attributed to multiple drug classes not individually overused may comprise headache occurring on 15 or more days/month in a patient with a pre-existing primary headache and developing as a result of regular intake of any combination of ergotamine, triptans, non-opioid analgesics and/or opioids on a total of at least 10 days/month for more than 3 months without overuse of any single drug or drug class alone.

[0022] In the methods herein, said opioid may be any one or any combination of opioid drugs, including without limitation thereto, oxycodone, tramadol, butorphanol, morphine, codeine, hydrocodone, thebaine, oripavine, mixed opium alkaloids such as papaveretum, diacetylmorphine, nicomorphine, dipropanoylmorphine, diacetyldihydromorphine, acetylpropionylmorphine, desomorphine, methyldesorphine, dibenzoylmorphine, ethylmorphine, heterocodeine, buprenorphine, etorphine, hydromorphone, oxymorphone, fentanyl, alphamethylfentanyl, alfentanil, sufentanil, remifentanil, carfentanyl, ohmefentanyl, pethidine (meperidine), ketobemidone, MPPP, allylprodine, prodine, PEPAP, promedol, diphenylpropylamine, propoxyphene, dextropropoxyphene, dextromoramide, bezitramide, piritramide, among others.

[0023] Said medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes may comprise headache occurring on 15 or more days/month in a patient with a pre-existing primary headache and developing as a result of regular intake of any combination of ergotamine, triptans, non-opioid analgesics and/or opioids on at least 10 days/month for more than 3 months, wherein the identity, quantity and/or pattern of use or overuse of these classes of drug is not reliably established.

[0024] Said medication-overuse headache attributed to other medication may comprise headache occurring on 15 or more days/month in a patient with a pre-existing primary headache and developing as a result of regular intake of one or more medications other than those described above, taken for acute or symptomatic treatment of headache, on at least 10 days/month for more than 3 months.

[0025] The amount and duration of medication use may be determined utilizing known methods, such as the usage reported by the patient or a relative, a diary, medical records, drug purchase history, prescription fulfilment, biomarkers of medication use, incidence of medication toxicity, incidence of medication overdose, and/or other indicators of a patient's medication use.

[0026] The present disclosure provides methods of treating or preventing probable medication overuse headache, comprising administering to a patient in need an effective amount of an anti-CGRP antibody or anti-CGRP antibody fragment or one or more formulations comprising said anti-CGRP antibody or anti-CGRP antibody fragment as disclosed herein. Said anti-CGRP antibody optionally comprises any one of Ab1-Ab14, such as Ab6, e.g., having the light chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively and

the heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208; or having the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively. Said anti-CGRP antibody may comprise the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202. Said anti-CGRP antibody may comprise the variable light chain polypeptide encoded by SEQ ID NO: 232 and the variable heavy chain polypeptide encoded by SEQ ID NO: 212. Said anti-CGRP antibody may comprise the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566. Said anti-CGRP antibody may comprise the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567. Said anti-CGRP antibody may comprise the antibody expression product isolated from recombinant cells which express nucleic acid sequences encoding the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202, which polypeptides optionally are respectively linked to human light and heavy constant region polypeptides, e.g., human IgG1, IgG2, IgG3 or IgG4 constant regions, which constant regions optionally may be modified to alter glycosylation or proteolysis, wherein said recombinant cells optionally comprise yeast or mammalian cells, e.g., *Pichia pastoris* or CHO cells. Said anti-CGRP antibody may comprise the antibody expression product isolated from recombinant cells which express nucleic acid sequences encoding the light chain of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566, wherein said recombinant cells optionally comprise yeast or mammalian cells, e.g., *Pichia pastoris* or CHO cells, wherein the constant regions thereof optionally may be modified to alter glycosylation or proteolysis or other effector functions. Any of the aforementioned anti-CGRP antibodies or antibody fragments, preferably Ab6, may be optionally comprised in a formulation as disclosed herein, e.g., comprising histidine (L-histidine), sorbitol, polysorbate 80, such as, per 1 mL volume, about 100 mg anti-CGRP antibody, about 3.1 mg L-Histidine, about 40.5 mg Sorbitol, and about 0.15 mg Polysorbate 80, having a pH of about 5.8. The administered dosage of said antibody may be between about 100 mg and about 300 mg, such as about 100 mg, about 300 mg, 100 mg, or 300 mg. The dosage may be administered by different means, e.g., intravenously, e.g., in a saline solution such as 0.9% sodium chloride in a suitable volume, such as 100 mL. Probable medication overuse headache refers to criteria (a) and (b) not being entirely fulfilled, e.g., having at least 80% or at least 90% of the specified number of headache days and/or medication use days per month, and/or over a shorter time period such as at least 2 months, optionally in the absence of another ICHD-3 diagnosis.

[0027] Said medication-overuse headache (such as ergotamine-overuse headache, triptan-overuse headache, non-opioid analgesic-overuse headache, opioid-overuse headache, combination-analgesic-overuse headache, medication-overuse headache attributed to multiple drug classes not individually

overused, medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes, or medication-overuse headache attributed to other medication) may be diagnosed according to the third edition of the International Classification of Headache Disorders (ICHD-3). *See* Headache Classification Committee of the International Headache Society (IHS), The International Classification of Headache Disorders, 3rd edition, Cephalalgia. 2018 Jan;38(1):1-211, which is hereby incorporated by reference in its entirety.

[0028] Herein, the criterion that a headache occurs "as a consequence of" over use of a medication or medications refers to the apparent association between the medication(s) overuse and the headache, e.g., that the medication(s) overuse and headache are present at the above-specified frequency such that causation may be presumed.

[0029] In some exemplary embodiments the dosage of said anti-CGRP antibody may be 100 mg.

[0030] In other exemplary embodiments the dosage of said anti-CGRP antibody may be 300 mg.

[0031] The method may further comprise intravenously administering 100 mg of said anti-CGRP antibody every 12 weeks.

[0032] The method may further comprise intravenously administering 300 mg of said anti-CGRP antibody every 12 weeks.

[0033] Said patient may be a chronic migraine patient or episodic migraine patient at risk of developing medication overuse headache. Said patient may use acute headache medication on at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 day(s) per month. Said patient may use acute headache medication on at least 10 days per month. Optionally said acute medication use is determined over a baseline period of at least 28 days. Said acute medication use may be reported by the patient, a caregiver, or based on records. Said acute medication may comprise use of ergot alkaloids, triptans, non-opioid analgesics, acetaminophen, aspirin, NSAIDs, non-opioid analgesics, combination-analgesics, or opioids.

[0034] Prior to said administration, the patient may exhibit between about 15 and about 30 migraine days per month, such as between about 16 and about 28 migraine days per month, such as between about 17 and about 26 migraine days per month, such as about 16 migraine days per month.

[0035] Prior to said administration, the patient may exhibit between about 15 and about 27 headache days per month, such as between about 17 and about 24 headache days per month, such as about 20 or about 21 headache days per month.

[0036] Said patient may have been diagnosed with migraine at least 10 years prior to said administration, such as at least 15 years prior to said administration, such as at least 18 or at least 19 years prior to said administration.

[0037] Said patient may have been diagnosed with chronic migraine at least 5 years prior to said administration, such as at least 8 years prior to said administration, such as at least 11 or at least 12 years prior to said administration.

[0038] Said patient may have a reduction in the number of migraine days by at least 50% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0039] Said patient may have a reduction in the number of migraine days by at least 75% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0040] Said patient may have a reduction in the number of migraine days by 100% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0041] Said patient may have a reduction in the number of migraine days by at least 50% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0042] Said patient may have a reduction in the number of migraine days by at least 75% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0043] Said patient may have a reduction in the number of migraine days by 100% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0044] The method may further comprise administering, e.g., intravenously, a second dose of said anti-CGRP antibody to said patient about 12 weeks or about 3 months after said administration.

[0045] Said administration may comprise about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, or about 300 mg of said anti-CGRP antibody.

[0046] Said anti-CGRP antibody may be aglycosylated or if glycosylated only may contain only mannose residues.

[0047] Said anti-CGRP antibody may consist of the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566. Said anti-CGRP antibody may consist of the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

[0048] In some embodiments, said anti-human CGRP antibody or antibody fragment comprises the variable light chain of SEQ ID NO: 222 and/or the variable heavy chain of SEQ ID NO: 202. In some embodiments, said anti-human CGRP antibody or antibody fragment comprises the variable light chain encoded by SEQ ID NO: 232 and/or the variable heavy chain encoded by SEQ ID NO: 212.

[0049] In some embodiments, said anti-human CGRP antibody or antibody fragment comprises the light chain of SEQ ID NO: 221 and/or the heavy chain of SEQ ID NO: 201 or SEQ ID NO: 566. In some embodiments, said anti-human CGRP antibody or antibody fragment comprises the light

chain encoded by SEQ ID NO: 231 and/or the heavy chain encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

[0050] In some embodiments, said anti-CGRP antibody may comprise the antibody expression product isolated from recombinant cells which express nucleic acid sequences encoding the VL polypeptide of SEQ ID NO: 222 and the VH polypeptide of SEQ ID NO: 202, which polypeptides optionally are respectively linked to human light and heavy constant region polypeptides, e.g., human IgG1, IgG2, IgG3 or IgG4 constant regions, which constant regions optionally may be modified to alter glycosylation or proteolysis, wherein said recombinant cells optionally comprise yeast or mammalian cells, e.g., *Pichia pastoris* or CHO cells.

[0051] In some embodiments, said anti-CGRP antibody may comprise the antibody expression product isolated from recombinant cells which express nucleic acid sequences encoding the light chain of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566, wherein said recombinant cells optionally comprise yeast or mammalian cells, e.g., *Pichia pastoris* or CHO cells, wherein the constant regions thereof optionally may be modified to alter glycosylation or proteolysis or other effector functions.

[0052] Inn some embodiments any of the aforementioned anti-CGRP antibodies or antibody fragments may be comprised in a formulation as disclosed herein, e.g., comprising histidine (L-histidine), sorbitol, polysorbate 80, such as, per 1 mL volume, about 100 mg anti-CGRP antibody, about 3.1 mg L-Histidine, about 40.5 mg Sorbitol, and about 0.15 mg Polysorbate 80, having a pH of about 5.8. The antibody or fragment may be administered by different means, e.g., intravenously, e.g., in a saline solution such as 0.9% sodium chloride in a suitable volume, such as 100 mL.

[0053] In some embodiments, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, or about 300 mg of said anti-CGRP antibody or antibody fragment is administered, e.g., intravenously.

[0054] In other embodiments, about 100 mg of said anti-CGRP antibody or antibody fragment is administered.

[0055] In other embodiments, about 300 mg of said anti-CGRP antibody or antibody fragment is administered, e.g., intravenously.

[0056] In exemplary embodiments, the anti-human CGRP antibody or antibody fragment is administered, e.g., intravenously at a frequency which is at most every 3 months or every 12 weeks, wherein the antibody dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 3 months or every 12 weeks. The phrase "the antibody dosage is administered in a single formulation or divided into different formulations" refers to the administration of the recited amount of antibody within a relatively short period of time, e.g., within a period of several hours, e.g., 1 to 8 hours, about one day, within about two days, or within about one week, which may be by the same or different routes (e.g., i.v., i.m., and/or s.c.), sites of administration. The term "different formulations" in this context refers

to antibody dosages that are administered at different times and/or at different sites and/or different routes, irrespective of whether the dosages are the same or different with respect to the chemical composition of the pharmaceutical formulation in with each dosage is administered; for example, the concentration, excipients, carriers, pH, and the like may be the same or different between the different administered dosages.

[0057] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 8 weeks or every 2 months.

[0058] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 12 weeks or every 3 months.

[0059] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 16 weeks or every 4 months.

[0060] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 20 weeks or every 5 months.

[0061] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 24 weeks or every 6 months.

[0062] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 28 weeks or every 7 months.

[0063] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 32 weeks or every 8 months.

[0064] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 36 weeks or every 9 months.

[0065] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 40 weeks or every 8 months.

[0066] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 44 weeks or every 9 months.

[0067] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 48 weeks or every 10 months.

[0068] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 52 weeks or every 11 months.

[0069] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 56 weeks or every 12 months.

[0070] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 15-18 months.

[0071] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 18-21 months.

[0072] In other exemplary embodiments, the anti-human CGRP antibody dosage or antibody fragment used in the afore-mentioned methods is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 2 years.

[0073] In other exemplary embodiments, the anti-human CGRP antibody used in the afore-mentioned methods is administered systemically.

[0074] In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment used in the afore-mentioned methods is administered by a mode of administration is selected from intravenous, intramuscular, intravenous, intrathecal, intracranial, topical, intranasal, and oral. In a preferred embodiment, the anti-human CGRP antibody or antibody fragment used in the afore-mentioned methods is administered intravenously.

[0075] In other exemplary embodiments, the anti-human CGRP antibody used in the afore-mentioned methods has an *in vivo* half-life of at least 10 days.

[0076] In other exemplary embodiments, the anti-human CGRP antibody has an *in vivo* half-life of at least 15 days.

[0077] In other exemplary embodiments, the anti-human CGRP antibody used in the afore-mentioned methods has an *in vivo* half-life of at least 20 days.

[0078] In other exemplary embodiments, the anti-human CGRP antibody used in the afore-mentioned methods has an *in vivo* half-life of at least 20-30 days.

[0079] In other exemplary embodiments, the anti-human CGRP antibody is administered at a dosage of between about 100 mg and about 300 mg has an *in vivo* half-life of ± 20% of at least about (284 ± 44 hours).

[0080] In other exemplary embodiments, the anti-human CGRP antibody used in the afore-mentioned methods binds to human α- and β-CGRP.

[0081] In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in the inhibition of vasodilation induced by topically applied capsaicin at least 30 days after antibody administration.

[0082] In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in the inhibition of vasodilation induced by topically applied capsaicin at least 60 days after antibody administration.

[0083] In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in inhibition of vasodilation induced by topically applied capsaicin at least 90 days after antibody administration.

[0084] In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in the inhibition of vasodilation induced by topically applied capsaicin at least 120 days after antibody administration.

[0085] In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in the inhibition of vasodilation induced by topically applied capsaicin at least 150 days after antibody administration.

[0086] In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in the inhibition of vasodilation induced by topically applied capsaicin at least 180 days after antibody administration.

[0087] In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in the inhibition of vasodilation induced by topically applied capsaicin more than 180 days after antibody administration.

[0088] In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in sustained pharmacodynamic (PK) activity, within 5% of the maximal response (Imax) (as compared to lower antibody doses).

[0089] In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in sustained pharmacodynamic (PK) activity which is maintained for at least 2-3 months after antibody administration, wherein PK analysis of the anti-human CGRP antibody is derived from plasma concentrations.

[0090] In other exemplary embodiments, the administered anti-human CGRP antibody dosage is between about 100 mg and about 300 mg or more which is administered no more frequently than every 2 months.

[0091] The present invention is additionally directed to the use of specific antibodies and fragments thereof having binding specificity for CGRP, in particular antibodies having desired epitopic specificity, high affinity or avidity and/or functional properties. A preferred embodiment of the invention is directed to usage of chimeric or humanized antibodies and fragments thereof

(including Fab fragments) capable of binding to CGRP and/or inhibiting the biological activities mediated by the binding of CGRP to the CGRP receptor ("CGRP-R") e.g., wherein such antibodies optionally are derived from recombinant cells engineered to express same, optionally yeast or mammalian cells, further optionally *Pichia pastoris* and CHO cells.

[0092] In another preferred embodiment of the invention, full length antibodies and Fab fragments thereof are contemplated that inhibit the CGRP-alpha-, CGRP-beta-, and rat CGRP-driven production of cAMP. In a further preferred embodiment of the invention, full length and Fab fragments thereof are contemplated that reduce vasodilation in a recipient following administration.

[0093] The invention also contemplates usage of conjugates of anti-CGRP antibodies and binding fragments thereof conjugated to one or more functional or detectable moieties. The invention also contemplates usage of chimeric or humanized anti-CGRP or anti-CGRP/CGRP-R complex antibodies and binding fragments thereof. In one embodiment, binding fragments include, but are not limited to, Fab, Fab', $F(ab')_2$, Fv, scFv fragments, SMIPs (small molecule immunopharmaceuticals), camelbodies, nanobodies, and IgNAR.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

[0094] **FIGs. 1A-1F** provide the polypeptide sequences of the full-length heavy chain for antibodies Ab1-Ab14 with their framework regions (FR), complementarity determining regions (CDRs), and constant region sequences delimited.

[0095] **FIGs. 2A-2D** provide the polypeptide sequences of the full-length light chain for antibodies Ab1-Ab14 with their framework regions (FR), complementarity determining regions (CDRs), and constant region sequences delimited.

[0096] **FIGs. 3A-3P** provide exemplary polynucleotide sequences encoding the full-length heavy chain for antibodies Ab1-Ab14 with their framework regions (FR), complementarity determining regions (CDRs), and constant region coding sequences delimited.

[0097] **FIGs. 4A-4I** provide exemplary polynucleotide sequences encoding the full-length light chain for antibodies Ab1-Ab14 with their framework regions (FR), complementarity determining regions (CDRs), and constant region coding sequences delimited.

[0098] **FIG. 5** provides the polypeptide sequence coordinates within the full-length heavy chain polypeptide sequences of antibodies Ab1-Ab14 of sequence features including the variable region and complementarity determining regions (CDRs), and the SEQ ID NO of each individual feature.

[0099] **FIG. 6** provides the polypeptide sequence coordinates within the full-length heavy chain polypeptide sequences of antibodies Ab1-Ab14 of sequence features including the framework regions (FRs) and constant region, and the SEQ ID NO of each individual feature.

[0100] **FIG. 7** provides the polypeptide sequence coordinates within the full-length light chain polypeptide sequences of antibodies Ab1-Ab14 of sequence features including the variable region and complementarity determining regions (CDRs), and the SEQ ID NO of each individual feature.

[0101] **FIG. 8** provides the polypeptide sequence coordinates within the full-length light chain polypeptide sequences of antibodies Ab1-Ab14 of sequence features including the framework regions (FRs) and constant region, and the SEQ ID NO of each individual feature.

[0102] **FIG. 9** provides the polynucleotide sequence coordinates within the exemplary polynucleotide sequences encoding the full-length heavy chain polypeptide sequences of antibodies Ab1-Ab14 of sequence features including the variable region and complementarity determining regions (CDRs), and the SEQ ID NO of each individual feature.

[0103] **FIG. 10** provides the polynucleotide sequence coordinates within the exemplary polynucleotide sequences encoding the full-length heavy chain polypeptide sequences of antibodies Ab1-Ab14 of sequence features including the framework regions (FRs) and constant region, and the SEQ ID NO of each individual feature.

[0104] **FIG. 11** provides the polynucleotide sequence coordinates within the exemplary polynucleotide sequences encoding the full-length light chain polypeptide sequences of antibodies Ab1-Ab14 of sequence features including the variable region and complementarity determining regions (CDRs), and the SEQ ID NO of each individual feature.

[0105] **FIG. 12** provides the polynucleotide sequence coordinates within the exemplary polynucleotide sequences encoding the full-length light chain polypeptide sequences of antibodies Ab1-Ab14 of sequence features including the framework regions (FRs) and constant region, and the SEQ ID NO of each individual feature.

[0106] **FIG. 13** shows the number of subjects in a human clinical trial described in Example 2 who were either treated with Ab6 (treatment group) or placebo groups who showed a 50, 75 or 100% reduction in migraines at each monitoring point throughout the period. The right bar in each group corresponds to patients receiving 1000 mg Ab6 and the left bar in each group corresponds to matched placebo controls. In each response rate group the patients receiving Ab6 had a significantly greater response rate than placebo-treated controls, with p values of 0.0155, 0.0034, and 0.0006 in each respective group as indicated. The administered antibody was produced in *P. pastoris* and consisted of the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201.

[0107] **FIG. 14** shows the median (± QR) % change from baseline in the number of migraine days per month in the placebo and Ab6 –treated group over the 12 weeks post-treatment. (p=0.0078). The upper (red) line and lower (blue) line show results for placebo-treated controls and patients administered 1000 mg Ab6, respectively.

[0108] **FIG. 15** shows the median (± QR) % change from baseline in the number of migraine episodes per month in the placebo and Ab6 –treated group over the 12 weeks post-treatment. The upper (red) line and lower (blue) line show results for placebo-treated controls and patients administered 1000 mg Ab6, respectively.

[0109] **FIG. 16** shows the median (± QR) % change from baseline in the number of migraine hours per month in the placebo and Ab6 –treated group over the 12 weeks post-treatment. The upper

(red) line and lower (blue) line show results for placebo-treated controls and patients administered 1000 mg Ab6, respectively.

[0110] **FIG. 17** summarizes the screening of patients, allocation into the treatment and control groups, and loss of patients through follow-up.

[0111] **FIG. 18** compares the HIT-6 responder analysis for the Ab6-treated and placebo groups at baseline, week 4 after treatment, week 8 after treatment and week 12 after treatment.

[0112] **FIG. 19** shows the percentage of patients for whom the HIT-6 analysis indicated that the effect of headaches was only "some" or "little/none" at baseline and after Ab6 administration. At baseline most patients had either "substantial" or "severe" impact from migraines. At each subsequent time point, a significantly greater percentage of patients administered 1000 mg Ab6 had only "some" or "little/none" HIT-6 impact (left bar in each group, colored blue) as compared to placebo controls (right bar in each group, colored red).

[0113] **FIG. 20** contains the pharmacokinetic (PK) profile for Ab6 administered intravenously at a single dosage of 1000 mg.

[0114] **FIG. 21** contains plasma-free pharmacokinetic (PK) parameters N (number of patients), mean, and standard deviation (SD) for a single 1000 mg intravenous dosage of Ab6. The parameters shown in the table and the units are C_{max} (μg/mL), $AUC_{0-\infty}$ (mg*hr/mL), half-life (days), V_z (L) and C_L (mL/hr).

[0115] **FIG. 22** shows the change (mean +- SEM) change from baseline in migraine days per month for Ab6 (1000 mg i.v.) versus placebo as a single dose for the study described in Example 2.

[0116] **FIG. 23** shows the average migraine days (+/- SD) over time for the full analysis population for the study described in Example 2. Normalization was applied to visit intervals where eDiaries were completed for 21-27 days by multiplying the observed frequency by the inverse of the completion rate.

[0117] **FIG. 24** shows the distribution of migraine days actual and change for the Ab6 treatment group during weeks 1-4 for the study described in Example 2.

[0118] **FIG. 25** shows the distribution of migraine days actual and change for the placebo group during weeks 1-4 for the study described in Example 2.

[0119] **FIG. 26** shows the distribution of migraine days actual and change for the Ab6 treatment group during weeks 5-8 for the study described in Example 2.

[0120] **FIG. 27** shows the distribution of migraine days actual and change for the placebo group during weeks 5-8 for the study described in Example 2.

[0121] **FIG. 28** shows the distribution of migraine days actual and change for the Ab6 treatment group during weeks 9-12 for the study described in Example 2.

[0122] **FIG. 29** shows the distribution of migraine days actual and change for the placebo group during weeks 9-12 for the study described in Example 2.

[0123] **FIG. 30** shows the 50% responder rate for the Ab6 and placebo treatment groups for the study described in Example 2. Subjects with ≥ 50% reduction in migraine frequency were considered to be a 50% responder. Normalization was applied to visit intervals where eDiary was completed for 21-27 days by multiplying the observed frequency by the inverse of the completion rate.

[0124] **FIG. 31** shows the 75% responder rate for the Ab6 and placebo treatment groups for the study described in Example 2. Subjects with ≥ 75% reduction in migraine frequency were considered to be a 75% responder. Normalization was applied as described with **FIG. 30**.

[0125] **FIG. 32** shows the 100% responder rate for the Ab6 and placebo treatment group for the study described in Example 2. Subjects with 100% reduction in migraine frequency were considered to be a 100% responder. Normalization was applied as described with **FIG. 30**.

[0126] **FIG. 33** shows the mean migraine severity over time for the full analysis population for the study described in Example 2. On the scale used, a mean migraine score of 3 represents "moderate pain."

[0127] **FIG. 34** summarizes the change from baseline in measured attributes for the placebo and treatment groups in the study described in Example 2.

[0128] **FIG. 35** shows the percentages of patients with migraine in the 300 mg, 100 mg, and placebo treatment groups at days 1, 7, 14, 21, and 28 in the clinical trial described in Example 3. The uppermost line shows results for placebo, the lowest line shows results for the 300 mg dosage, and the middle line shows results for the 100 mg dosage.

[0129] **FIG. 36** show the percentage of patients in the 300 mg and 100 mg treatment groups achieving a 50% reduction in migraine days in month 1, over months 1-3 (after the 1st infusion), and over months 4-5 (after the 2nd infusion) in the clinical trial described in Example 3. In each graph, the data bars, from left to right, show results for the 100 mg, 300 mg, and placebo groups. Statistical significance is as shown. ++ indicates a statistically significant difference from placebo; + indicates a statistically significant difference from placebo (unadjusted); and § indicates a statistically significant difference from placebo (post hoc).

[0130] **FIG. 37** show the percentage of patients in the 300 mg and 100 mg treatment groups achieving a 75% reduction in migraine days in month 1, over months 1-3 (after the 1st infusion), and over months 4-5 (after the 2nd infusion) in the clinical trial described in Example 3. Data order and statistical significance labels are as indicated with **FIG. 36**.

[0131] **FIG. 38** show the percentage of patients in the 300 mg and 100 mg treatment groups achieving a 100% reduction in migraine days in month 1, over months 1-3 (after the 1st infusion), and over months 4-5 (after the 2nd infusion) in the clinical trial described in Example 3. Data order and statistical significance labels are as indicated with **FIG. 36**.

[0132] **FIG. 39** summarizes the characteristics of patients in each treatment group in the clinical trial described in Example 3. * According to the American Academy of Neurology/American

Headache Society guidelines for migraine preventative treatment (medications identified by clinical review of coded medical data); SD, standard deviation; BMI, body mass index.

[0133] **FIG. 40**. Difference from placebo in change from baseline in mean migraine days (MMD) over months 1-3 by baseline subgroup for a human clinical trial of chronic migraine patients. In the graph, the data point refers to the mean value and the line shows the 95% confidence interval (CI) of the change from placebo for the 100 mg (upper line) or 300 mg (lower line) treatment group, for each subgroup as labeled at the far left.

[0134] **FIG. 41**. Difference from placebo in change from baseline in mean migraine days (MMD) over months 1-3 by baseline subgroup for a human clinical trial of episodic migraine patients. The graph is labeled as in **FIG. 40**.

[0135] **FIG. 42**. Change from baseline in mean migraine days (MMDs) across 2 dose intervals in chronic migraine patients with at least 1 day of acute medication use per month at baseline. Triangle: placebo (n=366). Circle: 100 mg Ab6 per dose (n=356). Square: 300 mg Ab6 per dose (n=350).

[0136] **FIG. 43**. Mean days with acute medication use in chronic migraine patients with at least one day per month of acute medication use at baseline. Triangle: placebo (n=366). Circle: 100 mg Ab6 per dose (n=356). Square: 300 mg Ab6 per dose (n=350).

[0137] **FIG. 44**. Change from baseline in acute medication use by subgroups of chronic migraine patients with differing baseline days of acute medication use. Solid lines: patients with 10 or more days of acute medication use per month at baseline. Dashed lines: patients with at least 1 and less than 10 days of acute medication use per month at baseline. Triangle: placebo. Circle: 100 mg Ab6 per dose. Square: 300 mg Ab6 per dose.

[0138] **FIG. 45**. Summary of Acute Medication Days by Subgroups of Chronic Migraine Patients with Baseline Acute Medication Use.

[0139] **FIG. 46**. Change from baseline in mean migraine days (MMDs) across 2 dose intervals in episodic migraine patients with at least 1 day of acute medication use per month at baseline. Triangle: placebo (n=222). Circle: 100 mg Ab6 per dose (n=221). Square: 300 mg Ab6 per dose (n=222).

[0140] **FIG. 47**. Mean days with acute medication use in episodic migraine patients with at least one day per month of acute medication use at baseline. Triangle: placebo (n=222). Circle: 100 mg Ab6 per dose (n=221). Square: 300 mg Ab6 per dose (n=222).

[0141] **FIG. 48**. Change from baseline in acute medication use by subgroups of episodic migraine patients with differing baseline days of acute medication use. Solid lines: patients with 10 or more days of acute medication use per month at baseline. Dashed lines: patients with at least 1 and less than 10 days of acute medication use per month at baseline. Triangle: placebo. Circle: 100 mg Ab6 per dose. Square: 300 mg Ab6 per dose.

[0142] **FIG. 49**. Summary of Acute Medication Days by Subgroups of Episodic Migraine Patients with Baseline Acute Medication Use.

DETAILED DESCRIPTION

[0143] Use of anti-CGRP antibodies for treatment of medication overuse headache is described herein.

[0144] Definitions

[0145] It is to be understood that this invention is not limited to the particular methodology, protocols, cell lines, animal species or genera, and reagents described, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims. As used herein the singular forms "a", "and", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a cell" includes a plurality of such cells and reference to "the protein" includes reference to one or more proteins and equivalents thereof known to those skilled in the art, and so forth. All technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention belongs unless clearly indicated otherwise.

[0146] As used herein, the term "medication overuse headache" refers to a headache that meets the criteria for that condition specified in ICHD-3 (Headache Classification Committee of the International Headache Society (IHS), The International Classification of Headache Disorders, 3rd edition, Cephalalgia. 2018 Jan;38(1):1-211). The term includes subtypes of medication overuse headache, as defined in the ICHD-3, such as triptan-overuse headache, non-opioid analgesic overuse headache, opioid overuse headache, etc.

[0147] As used herein, the term "chronic migraine" refers to a condition wherein a patient exhibits, on average, at least 15 migraine and/or headache days per month. The term “episodic migraine” refers to a condition wherein the patient exhibits, on average, less than 15 headache and/or migraine days per month.

[0148] As used herein, the term "diagnosed with chronic migraine" refers to a patient meeting the clinical criteria for chronic migraine, whether or not a formal diagnosis of that patient was performed.

[0149] As used herein, the term "intravenously administering" refers to a mode of administration wherein a substance, e.g., an antibody, is introduced directly into the circulation of that patient, most typically into the venous circulation. The substance may be introduced in a carrier fluid, such as an aqueous solution, e.g., normal saline. The substance may be administered in a single formulation or in multiple formulations, as long as the administration is completed over a short period of time (e.g., within 1 day, preferably within 12 hours, more preferably within 6 hours, and most preferably within 1-2 hours).

[0150] As used herein, the term "the baseline number of migraine days" refers to the number of migraine days exhibited by a patient in a specified time period, e.g., prior to treatment. For example, the baseline number of migraine days may be determined over a period of one month, or longer, e.g., by recording each day whether or not a migraine occurred.

[0151] As used herein, the term "migraine days per month" refers to the number of days per month on which a patient has a migraine, i.e., at any time during that day, the patient has symptoms that meet the clinical definition of migraine. The number of migraine days per month may be determined by recording each day whether or not a migraine occurred.

[0152] As used herein, the term "headache days per month" refers to the number of days per month on which a patient has a headache, i.e., at any time during that day, the patient has symptoms that meet the clinical definition of a headache. The number of headache days per month may be determined by recording each day whether or not a headache occurred.

[0153] *Calcitonin Gene Related Peptide* (*CGRP*): As used herein, CGRP encompasses not only the following *Homo sapiens* CGRP-alpha and *Homo sapiens* CGRP-beta amino acid sequences available from American Peptides (Sunnyvale CA) and Bachem (Torrance, CA):

[0154] CGRP-alpha: ACDTATCVTHRLAGLLSRSGGVVKNNFVPTNVGSKAF-NH_2 (SEQ ID NO: 561), wherein the terminal phenylalanine is amidated;

[0155] CGRP-beta: ACNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF-NH_2 (SEQ ID NO: 562), wherein the terminal phenylalanine is amidated; but also any membrane-bound forms of these CGRP amino acid sequences, as well as mutants (mutiens), splice variants, isoforms, orthologs, homologues and variants of this sequence.

[0156] *Expression Vector*: These DNA vectors contain elements that facilitate manipulation for the expression of a foreign protein within the target host cell, e.g., a yeast or mammalian cell such as *Pichia pastoris* or CHO cells. Conveniently, manipulation of sequences and production of DNA for transformation is first performed in a bacterial host, *e.g. E. coli,* and usually vectors will include sequences to facilitate such manipulations, including a bacterial origin of replication and appropriate bacterial selection marker. Selection markers encode proteins necessary for the survival or growth of transformed host cells grown in a selective culture medium. Host cells not transformed with the vector containing the selection gene will not survive in the culture medium. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media. Exemplary vectors and methods for transformation of yeast are described, for example, in Burke, D., Dawson, D., & Stearns, T. (2000). Methods in yeast genetics: a Cold Spring Harbor Laboratory course manual. Plainview, N.Y.: Cold Spring Harbor Laboratory Press.

[0157] Expression vectors for use in yeast or mammalian cells will generally further include yeast or mammalian specific sequences, including a selectable auxotrophic or drug marker for

identifying transformed yeast strains or transformed mammalian cells. A drug marker may further be used to amplify copy number of the vector in the host cell.

[0158] The polypeptide coding sequence of interest is operably linked to transcriptional and translational regulatory sequences that provide for expression of the polypeptide in host cells, e.g., *Pichia pastoris* or CHO cells. These vector components may include, but are not limited to, one or more of the following: an enhancer element, a promoter, and a transcription termination sequence. Sequences for the secretion of the polypeptide may also be included, e.g. a signal sequence, and the like. A yeast or mammalian origin of replication is optional, as expression vectors are often integrated into the host cell genome. In one embodiment of the invention, the polypeptide of interest is operably linked, or fused, to sequences providing for optimized secretion of the polypeptide from yeast diploid cells.

[0159] Nucleic acids are "operably linked" when placed into a functional relationship with another nucleic acid sequence. For example, DNA for a signal sequence is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading frame. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites or alternatively via a PCR/recombination method familiar to those skilled in the art (Gateway^{R} Technology; Invitrogen, Carlsbad California). If such sites do not exist, the synthetic oligonucleotide adapters or linkers are used in accordance with conventional practice.

[0160] Promoters are untranslated sequences located upstream (5') to the start codon of a structural gene (generally within about 100 to 1000 bp) that control the transcription and translation of particular nucleic acid sequences to which they are operably linked. Such promoters fall into several classes: inducible, constitutive, and repressible promoters (that increase levels of transcription in response to absence of a repressor). Inducible promoters may initiate increased levels of transcription from DNA under their control in response to some change in culture conditions, *e.g.*, the presence or absence of a nutrient or a change in temperature.

[0161] The promoter fragment may also serve as the site for homologous recombination and integration of the expression vector into the same site in the host genome; alternatively a selectable marker is used as the site for homologous recombination. Examples of suitable promoters from *Pichia* include the AOX1 and promoter (Cregg *et al.* (1989) Mol. Cell. Biol. **9**:1316-1323); ICL1 promoter (Menendez *et al.* (2003) Yeast **20**(13):1097-108); glyceraldehyde-3-phosphate dehydrogenase promoter (GAP) (Waterham *et al.* (1997) Gene **186**(1):37-44); and FLD1 promoter (Shen *et al.* (1998) Gene **216**(1):93-102). The *GAP* promoter is a strong constitutive promoter and the AOX and FLD1 promoters are inducible.

[0162] Other yeast promoters include ADH1, alcohol dehydrogenase II, GAL4, PHO3, PHO5, Pyk, and chimeric promoters derived therefrom. Additionally, non-yeast promoters may be used in the invention such as mammalian, insect, plant, reptile, amphibian, viral, and avian promoters. Most typically the promoter will comprise a mammalian promoter (potentially endogenous to the expressed genes) or will comprise a yeast or viral promoter that provides for efficient transcription in yeast systems.

[0163] Examples of mammalian promoters include cytomegalovirus (CMV) derived promoters, chicken 3-actin (CBM) derived promoters, adenomatous polyposis coli (APC) derived promoters, leucine-rich repeat containing G protein-coupled receptor 5 (LGR5) promoters, CAG promoter, Beta actin promoter, elongation factor-1 (EF1) promoter, early growth response 1 (EGR-1) promoter, eukaryotic initiation factor 4A (EIF4A1) promoter, simian virus 40 (SV40) early promoter, mouse mammary tumor virus (MMTV), human immunodeficiency virus (HIV) long terminal repeat (LTR) promoter, MoMuLV promoter, an avian leukemia virus promoter, an Epstein-Barr virus immediate early promoter, a Rous sarcoma virus promoter, as well as human gene promoters such as, but not limited to, the actin promoter, the myosin promoter, the hemoglobin promoter, and the creatine kinase promoter, among others. Combinations of two or more of the foregoing promoters may also be used. Further, inducible promoters may be used. The use of an inducible promoter provides a molecular switch capable of turning on expression of the polynucleotide sequence which it is operatively linked when such expression is desired, or turning off the expression when expression is not desired. Examples of inducible promoters include, but are not limited to a metallothionine promoter, a glucocorticoid promoter, a progesterone promoter, and a tetracycline promoter.

[0164] The polypeptides of interest may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, *e.g.* a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the polypeptide coding sequence that is inserted into the vector. The heterologous signal sequence selected preferably is one that is recognized and processed through one of the standard pathways available within the host cell. The *S. cerevisiae* alpha factor pre-pro signal has proven effective in the secretion of a variety of recombinant proteins from *P. pastoris*. Other yeast signal sequences include the alpha mating factor signal sequence, the invertase signal sequence, and signal sequences derived from other secreted yeast polypeptides. Additionally, these signal peptide sequences may be engineered to provide for enhanced secretion in diploid yeast expression systems. Secretion signals for use in mammalian as well as yeast cells include mammalian signal sequences, which may be heterologous to the protein being secreted, or may be a native sequence for the protein being secreted. Signal sequences include pre-peptide sequences, and in some instances may include propeptide sequences. Many such signal sequences are known in the art, including the signal sequences found on immunoglobulin chains, *e.g.*, K28 preprotoxin sequence, PHA-E, FACE, human MCP-1, human serum albumin signal sequences,

human Ig heavy chain, human Ig light chain, and the like. For example, see Hashimoto *et. al.* Protein Eng 11(2) 75 (1998); and Kobayashi *et. al.* Therapeutic Apheresis 2(4) 257 (1998).

[0165] Transcription may be increased by inserting a transcriptional activator sequence into the vector. These activators are cis-acting elements of DNA, usually about from 10 to 300 bp, which act on a promoter to increase its transcription. Transcriptional enhancers are relatively orientation and position independent, having been found 5' and 3' to the transcription unit, within an intron, as well as within the coding sequence itself. The enhancer may be spliced into the expression vector at a position 5' or 3' to the coding sequence, but is preferably located at a site 5' from the promoter.

[0166] Expression vectors used in eukaryotic host cells may also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from 3' to the translation termination codon, in untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA.

[0167] Construction of suitable vectors containing one or more of the above-listed components employs standard ligation techniques or PCR/recombination methods. Isolated plasmids or DNA fragments are cleaved, tailored, and re-ligated in the form desired to generate the plasmids required or via recombination methods. For analysis to confirm correct sequences in plasmids constructed, the ligation mixtures are used to transform host cells, and successful transformants selected by antibiotic resistance (e.g. ampicillin or Zeocin) where appropriate. Plasmids from the transformants are prepared, analyzed by restriction endonuclease digestion and/or sequenced.

[0168] As an alternative to restriction and ligation of fragments, recombination methods based on att sites and recombination enzymes may be used to insert DNA sequences into a vector. Such methods are described, for example, by Landy (1989) *Ann.Rev.Biochem. 58*:913-949; and are known to those of skill in the art. Such methods utilize intermolecular DNA recombination that is mediated by a mixture of lambda and *E. coli* –encoded recombination proteins. Recombination occurs between specific attachment (*att*) sites on the interacting DNA molecules. For a description of att sites see Weisberg and Landy (1983) Site-Specific Recombination in Phage Lambda, in *Lambda II*, Weisberg, ed.(Cold Spring Harbor, NY:Cold Spring Harbor Press), pp. 211-250. The DNA segments flanking the recombination sites are switched, such that after recombination, the *att* sites are hybrid sequences comprised of sequences donated by each parental vector. The recombination can occur between DNAs of any topology.

[0169] *Att* sites may be introduced into a sequence of interest by ligating the sequence of interest into an appropriate vector; generating a PCR product containing *att* B sites through the use of specific primers; generating a cDNA library cloned into an appropriate vector containing att sites; and the like.

[0170] *Folding*, as used herein, refers to the three-dimensional structure of polypeptides and proteins, where interactions between amino acid residues act to stabilize the structure. Proper folding

is typically the arrangement of a polypeptide that results in optimal biological activity, and in the case of antibodies can conveniently be monitored by assays for activity, *e.g.* antigen binding.

[0171] The expression host may be further modified by the introduction of sequences encoding one or more enzymes that enhance folding and disulfide bond formation, *i.e.* foldases, chaperonins, *etc.* Such sequences may be constitutively or inducibly expressed in the yeast host cell, using vectors, markers, *etc.* as known in the art. Preferably the sequences, including transcriptional regulatory elements sufficient for the desired pattern of expression, are stably integrated in the yeast genome through a targeted methodology.

[0172] For example, the eukaryotic PDI is not only an efficient catalyst of protein cysteine oxidation and disulfide bond isomerization, but also exhibits chaperone activity. Co-expression of PDI can facilitate the production of active proteins having multiple disulfide bonds. Also of interest is the expression of BIP (immunoglobulin heavy chain binding protein); cyclophilin; and the like. In one embodiment of the invention, each of the haploid parental strains expresses a distinct folding enzyme, *e.g.* one strain may express BIP, and the other strain may express PDI or combinations thereof.

[0173] The terms "*desired protein*" or "*desired antibody*" are used interchangeably and refer generally to a parent antibody specific to a target, i.e., CGRP or a chimeric or humanized antibody or a binding portion thereof derived therefrom as described herein. The term "antibody" is intended to include any polypeptide chain-containing molecular structure with a specific shape that fits to and recognizes an epitope, where one or more non-covalent binding interactions stabilize the complex between the molecular structure and the epitope. The archetypal antibody molecule is the immunoglobulin, and all types of immunoglobulins, IgG, IgM, IgA, IgE, IgD, etc., from all sources, e.g. human, rodent, rabbit, cow, sheep, pig, dog, other mammals, chicken, other avians, etc., are considered to be "antibodies." A preferred source for producing antibodies useful as starting material according to the invention is rabbits. Numerous antibody coding sequences have been described; and others may be raised by methods well-known in the art. Examples thereof include chimeric antibodies, human antibodies and other non-human mammalian antibodies, humanized antibodies, single chain antibodies (such as scFvs), camelbodies, nanobodies, IgNAR (single-chain antibodies derived from sharks), small-modular immunopharmaceuticals (SMIPs), and antibody fragments such as Fabs, Fab', $F(ab')_2$ and the like. See Streltsov VA, et al., Structure of a shark IgNAR antibody variable domain and modeling of an early-developmental isotype, Protein Sci. 2005 Nov;14(11):2901-9. Epub 2005 Sep 30; Greenberg AS, et al., A new antigen receptor gene family that undergoes rearrangement and extensive somatic diversification in sharks, Nature. 1995 Mar 9;374(6518):168-73; Nuttall SD, et al., Isolation of the new antigen receptor from wobbegong sharks, and use as a scaffold for the display of protein loop libraries, Mol Immunol. 2001 Aug;38(4):313-26; Hamers-Casterman C, et al., Naturally occurring antibodies devoid of light chains, Nature. 1993 Jun 3;363(6428):446-8; Gill

DS, et al., Biopharmaceutical drug discovery using novel protein scaffolds, Curr Opin Biotechnol. 2006 Dec; 17(6):653-8. Epub 2006 Oct 19.

[0174] For example, antibodies or antigen binding fragments may be produced by genetic engineering. In this technique, as with other methods, antibody-producing cells are sensitized to the desired antigen or immunogen. The messenger RNA isolated from antibody producing cells is used as a template to make cDNA using PCR amplification. A library of vectors, each containing one heavy chain gene and one light chain gene retaining the initial antigen specificity, is produced by insertion of appropriate sections of the amplified immunoglobulin cDNA into the expression vectors. A combinatorial library is constructed by combining the heavy chain gene library with the light chain gene library. This results in a library of clones which co-express a heavy and light chain (resembling the Fab fragment or antigen binding fragment of an antibody molecule). The vectors that carry these genes are co-transfected into a host cell. When antibody gene synthesis is induced in the transfected host, the heavy and light chain proteins self-assemble to produce active antibodies that can be detected by screening with the antigen or immunogen.

[0175] Antibody coding sequences of interest include those encoded by native sequences, as well as nucleic acids that, by virtue of the degeneracy of the genetic code, are not identical in sequence to the disclosed nucleic acids, and variants thereof. Variant polypeptides can include amino acid (aa) substitutions, additions or deletions. The amino acid substitutions can be conservative amino acid substitutions or substitutions to eliminate non-essential amino acids, such as to alter a glycosylation site, or to minimize misfolding by substitution or deletion of one or more cysteine residues that are not necessary for function. Variants can be designed so as to retain or have enhanced biological activity of a particular region of the protein (*e.g.*, a functional domain, catalytic amino acid residues, *etc*). Variants also include fragments of the polypeptides disclosed herein, particularly biologically active fragments and/or fragments corresponding to functional domains. Techniques for in vitro mutagenesis of cloned genes are known. Also included in the subject invention are polypeptides that have been modified using ordinary molecular biological techniques so as to improve their resistance to proteolytic degradation or to optimize solubility properties or to render them more suitable as a therapeutic agent.

[0176] Chimeric antibodies may be made by recombinant means by combining the variable light and heavy chain regions (V_L and V_H), obtained from antibody producing cells of one species with the constant light and heavy chain regions from another. Typically chimeric antibodies utilize rodent or rabbit variable regions and human constant regions, in order to produce an antibody with predominantly human domains. The production of such chimeric antibodies is well known in the art, and may be achieved by standard means (as described, e.g., in U.S. Patent No. 5,624,659, incorporated herein by reference in its entirety). It is further contemplated that the human constant regions of chimeric antibodies of the invention may be selected from IgG1, IgG2, IgG3, and IgG4 constant regions.

[0177] Humanized antibodies are engineered to contain even more human-like immunoglobulin domains, and incorporate only the complementarity-determining regions of the animal-derived antibody. This is accomplished by carefully examining the sequence of the hyper-variable loops of the variable regions of the monoclonal antibody, and fitting them to the structure of the human antibody chains. Although facially complex, the process is straightforward in practice. See, e.g., U.S. Patent No. 6,187,287, incorporated fully herein by reference.

[0178] In addition to entire immunoglobulins (or their recombinant counterparts), immunoglobulin fragments comprising the epitope binding site (e.g., Fab', $F(ab')_2$, or other fragments) may be synthesized. "Fragment," or minimal immunoglobulins may be designed utilizing recombinant immunoglobulin techniques. For instance "Fv" immunoglobulins for use in the present invention may be produced by synthesizing a fused variable light chain region and a variable heavy chain region. Combinations of antibodies are also of interest, *e.g.* diabodies, which comprise two distinct Fv specificities. In another embodiment of the invention, SMIPs (small molecule immunopharmaceuticals), camelbodies, nanobodies, and IgNAR are encompassed by immunoglobulin fragments.

[0179] Immunoglobulins and fragments thereof may be modified post-translationally, *e.g.* to add effector moieties such as chemical linkers, detectable moieties, such as fluorescent dyes, enzymes, toxins, substrates, bioluminescent materials, radioactive materials, chemiluminescent moieties and the like, or specific binding moieties, such as streptavidin, avidin, or biotin, and the like may be utilized in the methods and compositions of the present invention. Examples of additional effector molecules are provided *infra.*

[0180] A polynucleotide sequence "corresponds" to a polypeptide sequence if translation of the polynucleotide sequence in accordance with the genetic code yields the polypeptide sequence (i.e., the polynucleotide sequence "encodes" the polypeptide sequence), one polynucleotide sequence "corresponds" to another polynucleotide sequence if the two sequences encode the same polypeptide sequence.

[0181] A "heterologous" region or domain of a DNA construct is an identifiable segment of DNA within a larger DNA molecule that is not found in association with the larger molecule in nature. Thus, when the heterologous region encodes a mammalian gene, the gene will usually be flanked by DNA that does not flank the mammalian genomic DNA in the genome of the source organism. Another example of a heterologous region is a construct where the coding sequence itself is not found in nature (e.g., a cDNA where the genomic coding sequence contains introns, or synthetic sequences having codons different than the native gene). Allelic variations or naturally-occurring mutational events do not give rise to a heterologous region of DNA as defined herein.

[0182] A "coding sequence" is an in-frame sequence of codons that (in view of the genetic code) correspond to or encode a protein or peptide sequence. Two coding sequences correspond to each other if the sequences or their complementary sequences encode the same amino acid sequences. A

coding sequence in association with appropriate regulatory sequences may be transcribed and translated into a polypeptide. A polyadenylation signal and transcription termination sequence will usually be located 3' to the coding sequence. A "promoter sequence" is a DNA regulatory region capable of binding RNA polymerase in a cell and initiating transcription of a downstream (3' direction) coding sequence. Promoter sequences typically contain additional sites for binding of regulatory molecules (e.g., transcription factors) which affect the transcription of the coding sequence. A coding sequence is "under the control" of the promoter sequence or "operatively linked" to the promoter when RNA polymerase binds the promoter sequence in a cell and transcribes the coding sequence into mRNA, which is then in turn translated into the protein encoded by the coding sequence.

[0183] Vectors are used to introduce a foreign substance, such as DNA, RNA or protein, into an organism or host cell. Typical vectors include recombinant viruses (for polynucleotides) and liposomes (for polypeptides). A "DNA vector" is a replicon, such as plasmid, phage or cosmid, to which another polynucleotide segment may be attached so as to bring about the replication of the attached segment. An "expression vector" is a DNA vector which contains regulatory sequences which will direct polypeptide synthesis by an appropriate host cell. This usually means a promoter to bind RNA polymerase and initiate transcription of mRNA, as well as ribosome binding sites and initiation signals to direct translation of the mRNA into a polypeptide(s). Incorporation of a polynucleotide sequence into an expression vector at the proper site and in correct reading frame, followed by transformation of an appropriate host cell by the vector, enables the production of a polypeptide encoded by said polynucleotide sequence.

[0184] "Amplification" of polynucleotide sequences is the *in vitro* production of multiple copies of a particular nucleic acid sequence. The amplified sequence is usually in the form of DNA. A variety of techniques for carrying out such amplification are described in a review article by Van Brunt (1990, Bio/Technol., 8(4):291-294). Polymerase chain reaction or PCR is a prototype of nucleic acid amplification, and use of PCR herein should be considered exemplary of other suitable amplification techniques.

[0185] The general structure of antibodies in vertebrates now is well understood (Edelman, G. M., Ann. N.Y. Acad. Sci., 190: 5 (1971)). Antibodies consist of two identical light polypeptide chains of molecular weight approximately 23,000 daltons (the "light chain"), and two identical heavy chains of molecular weight 53,000-70,000 (the "heavy chain"). The four chains are joined by disulfide bonds in a "Y" configuration wherein the light chains bracket the heavy chains starting at the mouth of the "Y" configuration. The "branch" portion of the "Y" configuration is designated the F_{ab} region; the stem portion of the "Y" configuration is designated the F_C region. The amino acid sequence orientation runs from the N-terminal end at the top of the "Y" configuration to the C-terminal end at the bottom of each chain. The N-terminal end possesses the variable region having specificity for the

antigen that elicited it, and is approximately 100 amino acids in length, there being slight variations between light and heavy chain and from antibody to antibody.

[0186] The variable region is linked in each chain to a constant region that extends the remaining length of the chain and that within a particular class of antibody does not vary with the specificity of the antibody (i.e., the antigen eliciting it). There are five known major classes of constant regions that determine the class of the immunoglobulin molecule (IgG, IgM, IgA, IgD, and IgE corresponding to γ, μ, α, δ, and ε (gamma, mu, alpha, delta, or epsilon) heavy chain constant regions). The constant region or class determines subsequent effector function of the antibody, including activation of complement (Kabat, E. A., Structural Concepts in Immunology and Immunochemistry, 2nd Ed., p. 413-436, Holt, Rinehart, Winston (1976)), and other cellular responses (Andrews, D. W., *et al.*, Clinical Immunobiology, pp 1-18, W. B. Sanders (1980); Kohl, S., *et al.*, Immunology, 48: 187 (1983)); while the variable region determines the antigen with which it will react. Light chains are classified as either κ (kappa) or λ (lambda). Each heavy chain class can be prepared with either kappa or lambda light chain. The light and heavy chains are covalently bonded to each other, and the "tail" portions of the two heavy chains are bonded to each other by covalent disulfide linkages when the immunoglobulins are generated either by hybridomas or by B cells.

[0187] The expression "variable region" or "VR" refers to the domains within each pair of light and heavy chains in an antibody that are involved directly in binding the antibody to the antigen. Each heavy chain has at one end a variable domain (V_H) followed by a number of constant domains. Each light chain has a variable domain (V_L) at one end and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain.

[0188] The expressions "complementarity determining region," "hypervariable region," or "CDR" refer to one or more of the hyper-variable or complementarity determining regions (CDRs) found in the variable regions of light or heavy chains of an antibody (*See* Kabat, E. A. *et al.*, Sequences of Proteins of Immunological Interest, National Institutes of Health, Bethesda, Md., (1987)). These expressions include the hypervariable regions as defined by Kabat *et al.* ("Sequences of Proteins of Immunological Interest," Kabat E., *et al.*, US Dept. of Health and Human Services, 1983) or the hypervariable loops in 3-dimensional structures of antibodies (Chothia and Lesk, *J Mol. Biol.* 196 901-917 (1987)). The CDRs in each chain are held in close proximity by framework regions and, with the CDRs from the other chain, contribute to the formation of the antigen binding site. Within the CDRs there are select amino acids that have been described as the selectivity determining regions (SDRs) which represent the critical contact residues used by the CDR in the antibody-antigen interaction (Kashmiri, S., Methods, 36:25-34 (2005)). In the present invention when specific antibody amino acid or nucleic acid residues are referenced by number this generally refers to its position within a specified amino acid or nucleic acid sequence (i.e., particular sequence identifier) and/or in accordance with Kabat *et al* numbering.

[0189] The expressions "framework region" or "FR" refer to one or more of the framework regions within the variable regions of the light and heavy chains of an antibody (*See* Kabat, E. A. *et al.*, Sequences of Proteins of Immunological Interest, National Institutes of Health, Bethesda, Md., (1987)). These expressions include those amino acid sequence regions interposed between the CDRs within the variable regions of the light and heavy chains of an antibody.

[0190] "Cmax" refers to the maximum (or peak) concentration that an antibody or other compound achieves in tested area (e.g., in the serum or another compartment such as cerebrospinal fluid) after the drug has been administered. For example, serum Cmax may be measured from serum, e.g., prepared by collecting a blood sample, allowing it to clot and separating solid components by centrifugation or other means to yield serum (blood containing neither blood cells nor clotting factors), and then detecting the concentration of the analyte in the serum by ELISA or other means known in the art.

[0191] "AUC" refers to the area under the concentration-time curve which is expressed in units of mg/mL * hr (or equivalently mg*hr/ml) unless otherwise specified. "AUC_{0-t}" refers to the area under the concentration-time curve from time=0 to last quantifiable concentration. "AUC_{0-inf}" refers to the area under the concentration-time curve from time=0 extrapolated to infinity.

[0192] "I_{max}" refers to the maximal pharmacodynamic response elicited by an anti-CGRP antibody dosage, preferably a dosage of 350 mg or more, more typically at least 750 or 1000 mg, as compared to the response elicited by a lower anti-CGRP antibody doses, e.g., wherein such response may be detected by the inhibition of vasodilation after topical application of capsaicin.

[0193] Anti-CGRP Antibodies and Binding Fragments Thereof Having Binding Specificity for CGRP

[0194] The invention specifically includes the use of specific anti-CGRP antibodies and antibody fragments referred to herein as Ab1-Ab14 which comprise or consist of the CDR, VL, VH, CL, CH polypeptides sequences identified in **FIGs. 1A-12**. The polypeptides comprised in an especially preferred anti-CGRP antibody, Ab6 is further described below.

[0195] Antibody Ab6

[0196] In a preferred exemplary embodiment, the invention includes humanized antibodies having binding specificity to CGRP and possessing a variable light chain sequence comprising the sequence set forth below:

QVLTQSPSSLSASVGDRVTINCQASQSVYHNTYLAWYQQKPGKVPKQLIYDASTLASGVPSR FSGSGSGTDFTLTISSLQPEDVATYYCLGSYDCTNGDCFVFGGGTKVEIKR (SEQ ID NO: 222).

[0197] The invention also includes humanized antibodies having binding specificity to CGRP and possessing a light chain sequence comprising the sequence set forth below:

QVLTQSPSSLSASVGDRVTINCQASQSVYHNTYLAWYQQKPGKVPKQLIYDASTLASGVPSR FSGSGSGTDFTLTISSLQPEDVATYYCLGSYDCTNGDCFVFGGGTKVEIKRTVAAPSVFIFPPS

DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 221).

[0198] The invention further includes humanized antibodies having binding specificity to CGRP and possessing a variable heavy chain sequence comprising the sequence set forth below: EVQLVESGGGLVQPGGSLRLSCAVSGIDLSGYYMNWVRQAPGKGLEWVGVIGINGATYYAS WAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCARGDIWGQGTLVTVSS (SEQ ID NO: 202).

[0199] The invention also includes humanized antibodies having binding specificity to CGRP and possessing a heavy chain sequence comprising the sequence set forth below: EVQLVESGGGLVQPGGSLRLSCAVSGIDLSGYYMNWVRQAPGKGLEWVGVIGINGATYYAS WAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCARGDIWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK (SEQ ID NO: 201).

[0200] Alternatively, the heavy chain of Ab6 may lack the C-terminal lysine of SEQ ID NO: 201, i.e., a heavy chain sequence comprising the sequence set forth below: EVQLVESGGGLVQPGGSLRLSCAVSGIDLSGYYMNWVRQAPGKGLEWVGVIGINGATYYAS WAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCARGDIWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPG (SEQ ID NO: 566).

[0201] The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 222 or the light chain sequence of SEQ ID NO: 221, and/or one or more of the polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 202 or the heavy chain sequence of SEQ ID NO: 201 or SEQ ID NO: 566, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of,

combinations of one or more of the CDRs, the variable heavy and variable light chain sequences, and the heavy and light chain sequences set forth above, including all of them.

[0202] The invention also contemplates fragments of the antibody having binding specificity to CGRP. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 222 or SEQ ID NO: 221. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 202 or SEQ ID NO: 201 or SEQ ID NO: 566.

[0203] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 222 or the light chain sequence of SEQ ID NO: 221.

[0204] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 202 or the heavy chain sequence of SEQ ID NO: 201 or SEQ ID NO: 566.

[0205] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 222; the variable heavy chain region of SEQ ID NO: 202; the complementarity-determining regions (SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228) of the variable light chain region of SEQ ID NO: 222; and the complementarity-determining regions (SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208) of the variable heavy chain region of SEQ ID NO: 202.

[0206] In a particularly preferred embodiment of the invention, the humanized anti- CGRP antibody is Ab6, comprising, or alternatively consisting of, SEQ ID NO: 221 and SEQ ID NO: 201 or SEQ ID NO: 566, and having at least one of the biological activities set forth herein.

[0207] In a further particularly preferred embodiment of the invention, antibody fragments comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab6, the Fab fragment includes the variable light chain sequence of SEQ ID NO: 222 and the variable heavy chain sequence of SEQ ID NO: 202. This embodiment of the invention further contemplates additions, deletions, and variants of SEQ ID NO: 222 and/or SEQ ID NO: 202 in said Fab while retaining binding specificity for CGRP.

[0208] In another particularly preferred embodiment of the invention, said anti-CGRP antibody may comprise the antibody expression product isolated from recombinant cells which express nucleic acid sequences encoding the variable light chain polypeptide of SEQ ID NO: 222 and the variable

heavy chain polypeptide of SEQ ID NO: 202, which polypeptides optionally are respectively linked to human light and heavy constant region polypeptides, e.g., human IgG1, IgG2, IgG3 or IgG4 constant regions, which constant regions optionally may be modified to alter glycosylation or proteolysis, wherein said recombinant cells optionally comprise yeast or mammalian cells, e.g., *Pichia pastoris* or CHO cells.

[0209] In another particularly preferred embodiment of the invention, said anti-CGRP antibody may comprise the antibody expression product isolated from recombinant cells which express nucleic acid sequences encoding the light chain of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566, wherein said recombinant cells optionally comprise yeast or mammalian cells, e.g., *Pichia pastoris* or CHO cells, wherein the constant regions thereof optionally may be modified to alter glycosylation or proteolysis or other effector functions.

[0210] In another particularly preferred embodiment of the invention, any of the aforementioned anti-CGRP antibodies or antibody fragments may be optionally comprised in a formulation as disclosed herein, e.g., comprising histidine (L-histidine), sorbitol, polysorbate 80, such as, per 1 mL volume, about 100 mg anti-CGRP antibody, about 3.1 mg L-Histidine, about 40.5 mg Sorbitol, and about 0.15 mg Polysorbate 80, having a pH of about 5.8.

[0211] In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab6. In another embodiment of the invention, anti-CGRP antibodies such as Ab6 or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid *Pichia*) and other yeast strains. Suitable *Pichia* species include, but are not limited to, *Pichia pastoris*.

[0212] In another embodiment, antibody fragments may be present in one or more of the following non-limiting forms: Fab, Fab', $F(ab')_2$, Fv and single chain Fv antibody forms. In a preferred embodiment, the anti-CGRP antibodies described herein further comprises the kappa constant light chain sequence comprising the sequence set forth below:

[0213] TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESV TEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 563).

[0214] In another preferred embodiment, the anti-CGRP antibodies described herein further comprises the gamma-1 constant heavy chain polypeptide sequence comprising the sequence set forth below or the same sequence lacking the carboxy terminal lysine residue (SEQ ID NO: 564 and SEQ ID NO: 565, respectively):

[0215] ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY ASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEM

TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 564).

[0216] ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY ASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEM TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 565).

[0217] For clarity, any antibody disclosed herein is intended to include any variant of the disclosed constant region variant sequences, e.g., Ab6 may comprise the constant region of SEQ ID NO: 564 containing the C-terminal lysine or may comprise the constant region of SEQ ID NO: 565 lacking the C-terminal lysine. Thus, every disclosure herein of the heavy chain of SEQ ID NO: 201 also includes a variant lacking the C-terminal lysine residue thereof, *i.e.*, having the heavy chain variable region sequence of Ab6 (SEQ ID NO: 202) and the constant region sequence of SEQ ID NO: 565. For example, the sequence encoding an antibody comprising a C-terminal lysine in the heavy chain may, when expressed in cell lines such as CHO cells, produce an antibody lacking said C-terminal lysine due to proteolysis, or a mixture of heavy chains containing or lacking said C-terminal lysine.

[0218] In another embodiment, the invention contemplates use of an isolated anti-CGRP antibody comprising a V_H polypeptide sequence selected from: SEQ ID NO: 2, SEQ ID NO: 42, SEQ ID NO: 82, SEQ ID NO: 122, SEQ ID NO: 162, SEQ ID NO: 202, SEQ ID NO: 242, SEQ ID NO: 282, SEQ ID NO: 322, SEQ ID NO: 362, SEQ ID NO: 402, SEQ ID NO: 442, SEQ ID NO: 482, or SEQ ID NO: 522, or a variant thereof; and further comprising a V_L polypeptide sequence selected from: SEQ ID NO: 22, SEQ ID NO: 62, SEQ ID NO: 102, SEQ ID NO: 142, SEQ ID NO: 182, SEQ ID NO: 222, SEQ ID NO: 262, SEQ ID NO: 302, SEQ ID NO: 342, SEQ ID NO: 382, SEQ ID NO: 422, SEQ ID NO: 462, SEQ ID NO: 502, or SEQ ID NO: 542, or a variant thereof, wherein one or more of the framework residues (FR residues) in said V_H or V_L polypeptide has been substituted with another amino acid residue resulting in an anti-CGRP antibody that specifically binds CGRP. The invention contemplates humanized and chimeric forms of these antibodies. The chimeric antibodies may include an Fc derived from IgG1, IgG2, IgG3, or IgG4 constant regions.

[0219] In one embodiment of the invention, the antibodies or V_H or V_L polypeptides originate or are selected from one or more rabbit B cell populations prior to initiation of the humanization process referenced herein.

[0220] In another embodiment of the invention, the anti-CGRP antibodies and fragments thereof do not have binding specificity for CGRP-R. In a further embodiment of the invention, the anti-CGRP antibodies and fragments thereof inhibit the association of CGRP with CGRP-R. In another embodiment of the invention, the anti-CGRP antibodies and fragments thereof inhibit the association

of CGRP with CGRP-R and/or additional proteins and/or multimers thereof, and/or antagonizes the biological effects thereof.

[0221] As stated herein, antibodies and fragments thereof may be modified post-translationally to add effector moieties such as chemical linkers, detectable moieties such as for example fluorescent dyes, enzymes, substrates, bioluminescent materials, radioactive materials, and chemiluminescent moieties, or functional moieties such as for example streptavidin, avidin, biotin, a cytotoxin, a cytotoxic agent, and radioactive materials.

[0222] Antibodies or fragments thereof may also be chemically modified to provide additional advantages such as increased solubility, stability and circulating time (*in vivo* half-life) of the polypeptide, or decreased immunogenicity (See U.S. Pat. No. 4,179,337). The chemical moieties for derivatization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The antibodies and fragments thereof may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

[0223] The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa. Branched polyethylene glycols are described, for example, in U.S. Pat. No. 5,643,575; Morpurgo et al., Appl. Biochem. Biotechnol. 56:59-72 (1996); Vorobjev et al., Nucleosides Nucleotides 18:2745-2750 (1999); and Caliceti et al., Bioconjug. Chem. 10:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

[0224] There are a number of attachment methods available to those skilled in the art, See e.g., EP 0 401 384, herein incorporated by reference (coupling PEG to G-CSF), See also Malik et al., Exp. Hematol. 20:1028-1035 (1992) (reporting pegylation of GM-CSF using tresyl chloride). For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as, a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include

lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

[0225] As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to polypeptides via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or cysteine) or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof).

[0226] Alternatively, antibodies or fragments thereof may have increased *in vivo* half-lives via fusion with albumin (including but not limited to recombinant human serum albumin or fragments or variants thereof (See, e.g., U.S. Pat. No. 5,876,969, issued Mar. 2, 1999, EP Patent 0 413 622, and U.S. Pat. No. 5,766,883, issued Jun. 16, 1998, herein incorporated by reference in their entirety)) or other circulating blood proteins such as transferrin or ferritin. In a preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with the mature form of human serum albumin (i.e., amino acids 1-585 of human serum albumin as shown in FIGS. 1 and 2 of EP Patent 0 322 094) which is herein incorporated by reference in its entirety. Polynucleotides encoding fusion proteins of the invention are also encompassed by the invention.

[0227] Regarding detectable moieties, further exemplary enzymes include, but are not limited to, horseradish peroxidase, acetylcholinesterase, alkaline phosphatase, beta-galactosidase and luciferase. Further exemplary fluorescent materials include, but are not limited to, rhodamine, fluorescein, fluorescein isothiocyanate, umbelliferone, dichlorotriazinylamine, phycoerythrin and dansyl chloride. Further exemplary chemiluminescent moieties include, but are not limited to, luminol. Further exemplary bioluminescent materials include, but are not limited to, luciferin and aequorin. Further exemplary radioactive materials include, but are not limited to, Iodine 125 (^{125}I), Carbon 14 (^{14}C), Sulfur 35 (^{35}S), Tritium (^{3}H) and Phosphorus 32 (^{32}P).

[0228] Regarding functional moieties, exemplary cytotoxic agents include, but are not limited to, methotrexate, aminopterin, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine; alkylating agents such as mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU), mitomycin C, lomustine (CCNU), 1-methylnitrosourea, cyclothosphamide, mechlorethamine, busulfan, dibromomannitol, streptozotocin, mitomycin C, cis-dichlorodiamine platinum (II) (DDP) cisplatin and carboplatin (paraplatin); anthracyclines include daunorubicin (formerly daunomycin), doxorubicin (adriamycin), detorubicin, carminomycin, idarubicin, epirubicin, mitoxantrone and bisantrene; antibiotics include dactinomycin (actinomycin D), bleomycin, calicheamicin,

mithramycin, and anthramycin (AMC); and antimytotic agents such as the vinca alkaloids, vincristine and vinblastine. Other cytotoxic agents include paclitaxel (taxol), ricin, pseudomonas exotoxin, gemcitabine, cytochalasin B, gramicidin D, ethidium bromide, emetine, etoposide, tenoposide, colchicin, dihydroxy anthracin dione, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, puromycin, procarbazine, hydroxyurea, asparaginase, corticosteroids, mytotane (O,P'-(DDD)), interferons, and mixtures of these cytotoxic agents.

[0229] Further cytotoxic agents include, but are not limited to, chemotherapeutic agents such as carboplatin, cisplatin, paclitaxel, gemcitabine, calicheamicin, doxorubicin, 5-fluorouracil, mitomycin C, actinomycin D, cyclophosphamide, vincristine and bleomycin. Toxic enzymes from plants and bacteria such as ricin, diphtheria toxin and Pseudomonas toxin may be conjugated to the humanized or chimeric antibodies, or binding fragments thereof, to generate cell-type-specific-killing reagents (Youle, et al., Proc. Nat'l Acad. Sci. USA 77:5483 (1980); Gilliland, et al., Proc. Nat'l Acad. Sci. USA 77:4539 (1980); Krolick, et al., Proc. Nat'l Acad. Sci. USA 77:5419 (1980)).

[0230] Other cytotoxic agents include cytotoxic ribonucleases as described by Goldenberg in U.S. Pat. No. 6,653,104. Embodiments of the invention also relate to radioimmunoconjugates where a radionuclide that emits alpha or beta particles is stably coupled to the antibody, or binding fragments thereof, with or without the use of a complex-forming agent. Such radionuclides include beta-emitters such as Phosphorus-32 (^{32}P), Scandium-47 (^{47}Sc), Copper-67 (^{67}Cu), Gallium-67 (^{67}Ga), Yttrium-88 (^{88}Y), Yttrium-90 (^{90}Y), Iodine-125 (^{125}I), Iodine-131 (^{131}I), Samarium-153 (^{153}Sm), Lutetium-177 (^{177}Lu), Rhenium-186 (^{186}Re) or Rhenium-188 (^{188}Re), and alpha-emitters such as Astatine-211 (^{211}At), Lead-212 (^{212}Pb), Bismuth-212 (^{212}Bi) or -213 (^{213}Bi) or Actinium-225 (^{225}Ac).

[0231] Methods are known in the art for conjugating an antibody or binding fragment thereof to a detectable moiety and the like, such as for example those methods described by Hunter et al, Nature 144:945 (1962); David et al, Biochemistry 13:1014 (1974); Pain et al, J. Immunol. Meth. 40:219 (1981); and Nygren, J., Histochem. and Cytochem. 30:407 (1982).

[0232] Embodiments described herein further include variants and equivalents that are substantially homologous to the antibodies, antibody fragments, diabodies, SMIPs, camelbodies, nanobodies, IgNAR, polypeptides, variable regions and CDRs set forth herein. These may contain, e.g., conservative substitution mutations, (i.e., the substitution of one or more amino acids by similar amino acids). For example, conservative substitution refers to the substitution of an amino acid with another within the same general class, e.g., one acidic amino acid with another acidic amino acid, one basic amino acid with another basic amino acid, or one neutral amino acid by another neutral amino acid. What is intended by a conservative amino acid substitution is well known in the art.

[0233] In another embodiment, the invention contemplates polypeptide sequences having at least 90% or greater sequence homology to any one or more of the polypeptide sequences of antibody fragments, variable regions and CDRs set forth herein. More preferably, the invention contemplates polypeptide sequences having at least 95% or greater sequence homology, even more preferably at

least 98% or greater sequence homology, and still more preferably at least 99% or greater sequence homology to any one or more of the polypeptide sequences of antibody fragments, variable regions and CDRs set forth herein. Methods for determining homology between nucleic acid and amino acid sequences are well known to those of ordinary skill in the art.

[0234] In another embodiment, the invention further contemplates the above-recited polypeptide homologs of the antibody fragments, variable regions and CDRs set forth herein further having anti-CGRP activity. Non-limiting examples of anti-CGRP activity are set forth herein.

[0235] The present invention also contemplates anti-CGRP antibodies comprising any of the polypeptide or polynucleotide sequences described herein substituted for any of the other polynucleotide sequences described herein. For example, without limitation thereto, the present invention contemplates antibodies comprising the combination of any of the variable light chain and variable heavy chain sequences described herein, and further contemplates antibodies resulting from substitution of any of the CDR sequences described herein for any of the other CDR sequences described herein.

[0236] Additional Exemplary Embodiments of the Invention

[0237] In another embodiment, the invention contemplates treatment methods using one or more anti-human CGRP antibodies or antibody fragments thereof which specifically bind to the same overlapping linear or conformational epitope(s) and/or competes for binding to the same overlapping linear or conformational epitope(s) on an intact human CGRP polypeptide or fragment thereof as an anti-human CGRP antibody selected from Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, or Ab14. In a preferred embodiment, the anti-human CGRP antibody or fragment thereof specifically binds to the same overlapping linear or conformational epitope(s) and/or competes for binding to the same overlapping linear or conformational epitope(s) on an intact human CGRP polypeptide or a fragment thereof as Ab3, Ab6, Ab13, or Ab14.

[0238] A preferred embodiment of the invention is directed to treatment methods using chimeric or humanized antibodies and fragments thereof (including Fab fragments) having binding specificity for CGRP and inhibiting biological activities mediated by the binding of CGRP to the CGRP receptor. In a particularly preferred embodiment of the invention, the chimeric or humanized anti-CGRP antibodies are selected from Ab3, Ab6, Ab13, or Ab14.

[0239] In another embodiment of the invention, the anti-human CGRP antibody used in the described treatment methods is an antibody which specifically binds to the same overlapping linear or conformational epitopes on an intact CGRP polypeptide or fragment thereof that is (are) specifically bound by Ab3, Ab6, Ab13, or Ab14 as ascertained by epitopic mapping using overlapping linear peptide fragments which span the full length of the native human CGRP polypeptide.

[0240] The invention is also directed to treatment methods using an anti-CGRP antibody that binds with the same CGRP epitope and/or competes with an anti-CGRP antibody for binding to CGRP as an antibody or antibody fragment disclosed herein, including but not limited to an anti-

CGRP antibody selected from Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, or Ab14.

[0241] In another embodiment, the invention is also directed to treatment methods using an isolated anti-CGRP antibody or antibody fragment comprising one or more of the CDRs contained in the V_H polypeptide sequences selected from: 3, 13, 23, 33, 43, 53, 63, 73, 83, 93, 103, 113, 123, or 133, or a variant thereof, and/or one or more of the CDRs contained in the V_L polypeptide sequences selected from: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, or 131, or a variant thereof.

[0242] In one embodiment of the invention, the anti-human CGRP antibody discussed in the two prior paragraphs comprises at least 2 complementarity determining regions (CDRs) in each the variable light and the variable heavy regions which are identical to those contained in an anti-human CGRP antibody selected from Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, or Ab14.

[0243] In a preferred embodiment, the anti-human CGRP antibody used in the described treatment methods comprises at least 2 complementarity determining regions (CDRs) in each the variable light and the variable heavy regions which are identical to those contained in Ab3 or Ab6. In another embodiment, all of the CDRs of the anti-human CGRP antibody discussed above are identical to the CDRs contained in an anti-human CGRP antibody selected from Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, or Ab14. In a preferred embodiment of the invention, all of the CDRs of the anti-human CGRP antibody discussed above are identical to the CDRs contained in an anti-human CGRP antibody selected from Ab3 or Ab6.

[0244] The invention further contemplates treatment methods wherein the one or more anti-human CGRP antibodies discussed above are aglycosylated or if glycosylated are only mannosylated; that contain an Fc region that has been modified to alter effector function, half-life, proteolysis, and/or glycosylation; are human, humanized, single chain or chimeric; and are a humanized antibody derived from a rabbit (parent) anti-human CGRP antibody. An exemplary mutation which impairs glycosylation comprises the mutation of the Asn residue at position 297 of an IgG heavy chain constant region such as IgG1 to another amino acid, such as Ala as described in U.S. Pat. No. 5,624,821, which is incorporated by reference in its entirety.

[0245] The invention further contemplates one or more anti-human CGRP antibodies wherein the framework regions (FRs) in the variable light region and the variable heavy regions of said antibody respectively are human FRs which are unmodified or which have been modified by the substitution of one or more human FR residues in the variable light or heavy chain region with the corresponding FR residues of the parent rabbit antibody, and wherein said human FRs have been derived from human variable heavy and light chain antibody sequences which have been selected from a library of human germline antibody sequences based on their high level of homology to the corresponding rabbit variable heavy or light chain regions relative to other human germline antibody sequences contained in the library.

[0246] The invention also contemplates a method of treating or preventing medication overuse headache, e.g., associated with the overuse of anti-migraine drugs and/or associated with triptan and/or ergot and/or analgesic overuse, comprising administering to a patient exhibiting medication overuse headache or at risk of developing medication overuse headache a therapeutically effective amount of at least one anti-human CGRP antibody or fragment described herein. The invention also contemplates that the treatment method may involve the administration of two or more anti-CGRP antibodies or fragments thereof and disclosed herein. If more than one antibody is administered to the patient, the multiple antibodies may be administered simultaneously or concurrently, or may be staggered in their administration. The anti-CGRP activity of the anti-CGRP antibodies of the present invention, and fragments thereof having binding specificity to CGRP, may also be described by their strength of binding or their affinity for CGRP. In one embodiment of the invention, the anti-CGRP antibodies of the present invention, and fragments thereof having binding specificity to CGRP, bind to CGRP with a dissociation constant (K_D) of less than or equal to $5x10^{-7}$ M, 10^{-7} M, $5x10^{-8}$ M, 10^{-8} M, $5x10^{-9}$ M, 10^{-9} M, $5x10^{-10}$ M, 10^{-10} M, $5x10^{-11}$ M, 10^{-11} M, $5x10^{-12}$ M, 10^{-12} M, $5x10^{-13}$ M, or 10^{-13} M. Preferably, the anti-CGRP antibodies and fragments thereof bind CGRP with a dissociation constant of less than or equal to 10^{-11} M, $5x10^{-12}$ M, or 10^{-12} M. In another embodiment of the invention, the anti-CGRP antibodies of the present invention, and fragments thereof having binding specificity to CGRP, bind to a linear or conformational CGRP epitope.

[0247] In another embodiment of the invention, the anti-CGRP activity of the anti-CGRP antibodies of the present invention, and fragments thereof having binding specificity to CGRP, bind to CGRP with an off-rate of less than or equal to 10^{-4} S^{-1}, $5x10^{-5}$ S^{-1}, 10^{-5} S^{-1}, $5x10^{-6}$ S^{-1}, 10^{-6} S^{-1}, $5x10^{-7}$ S^{-1}, or 10^{-7} S^{-1}.

[0248] In a further embodiment of the invention, the anti-CGRP activity of the anti-CGRP antibodies of the present invention, and fragments thereof having binding specificity to CGRP, exhibit anti-CGRP activity by preventing, ameliorating or reducing the symptoms of, or alternatively treating, diseases and disorders associated with CGRP. Non-limiting examples of diseases and disorders associated with CGRP are set forth herein and include headache and migraine disorders.

[0249] Polynucleotides Encoding Anti-CGRP Antibody Polypeptides

[0250] As aforementioned the invention specifically includes the use of specific anti-CGRP antibodies and antibody fragments referred to herein as Ab1-Ab14 which comprise or consist of the CDR, VL, VH, CL, and CH polypeptides having the sequences identified in **FIGs. 1A-12**. The nucleic acid sequences encoding the foregoing VL, VH, CL, and CH polypeptides comprised in Ab1-Ab14 are also comprised in **FIGs. 1A-12**. The nucleic acid sequences which encode the CDR, VL, VH, CL, and CH polypeptides of an especially preferred anti-CGRP antibody, Ab6, are further described below.

[0251] Antibody Ab6

[0252] The invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to CGRP. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 222:

[0253] CAAGTGCTGacccagtctccatcctccctgtctgcatctgtaggagacagagtcaccatcAATtgcCAGGCCA GTCAGAGTGTTTATCATAACACCTACCTGGCCtggtatcagcagaaaccagggaaagttcctaagCAActgatcta tGATGCATCCACTCTGGCATCTggggtcccatctcgtttcagtggcagtggatctgggacagatttcactctcaccatcagcagc ctgcagcctgaagatgttgcaacttattactgtCTGGGCAGTTATGATTGTACTAATGGTGATTGTTTTGTTttcg gcggaggaaccaaggtggaaatcaaacgt (SEQ ID NO: 232).

[0254] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 221:

[0255] CAAGTGCTGacccagtctccatcctccctgtctgcatctgtaggagacagagtcaccatcAATtgcCAGGCCA GTCAGAGTGTTTATCATAACACCTACCTGGCCtggtatcagcagaaaccagggaaagttcctaagCAActgatcta tGATGCATCCACTCTGGCATCTggggtcccatctcgtttcagtggcagtggatctgggacagatttcactctcaccatcagcagc ctgcagcctgaagatgttgcaacttattactgtCTGGGCAGTTATGATTGTACTAATGGTGATTGTTTTGTTttcg gcggaggaaccaaggtggaaatcaaacgtACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGAT GAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGA GAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAG TGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGA GCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTG AGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 231).

[0256] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 202:

[0257] gaggtgcagctTgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcaGTCtctggaAT CGACCTCagtGGCTACTACATGAACtgggtccgtcaggctccagggaaggggctggagtgggtcGGAGTCATTGG TATTAATGGTGCCACATACTACGCGAGCTGGGCGAAAGGCcgattcaccatctccagagacaattccaagA CCACGGTGtatcttcaaatgaacagcctgagagctgaggacactgctgtgtatTTCtgtGCTAGAGGGGACATCtggggcc aagggaccctcgtcaccgtcTCGAGC (SEQ ID NO: 212).

[0258] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain polypeptide sequence of SEQ ID NO: 201:

[0259] gaggtgcagctTgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcaGTCtctggaAT CGACCTCagtGGCTACTACATGAACtgggtccgtcaggctccagggaaggggctggagtgggtcGGAGTCATTGG TATTAATGGTGCCACATACTACGCGAGCTGGGCGAAAGGCcgattcaccatctccagagacaattccaagA CCACGGTGtatcttcaaatgaacagcctgagagctgaggacactgctgtgtatTTCtgtGCTAGAGGGGACATCtggggcc

aagggaccctcgtcaccgtcTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCAcCCTCC
TCCaAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCC
GAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCC
GGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAG
CAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGG
TGGACGCGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCA
GCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACC
CTCATGaTCTCCCgGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGAC
CCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
GCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGC
ACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCA
GCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTA
CACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG
TCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAG
AACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGC
AAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGAT
GCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATG
A (SEQ ID NO: 211).

[0260] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain polypeptide sequence of SEQ ID NO: 566:

gaggtgcagctTgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcaGTCtctggaATCGACCTCa
gtGGCTACTACATGAACtgggtccgtcaggctccagggaaggggctggagtgggtcGGAGTCATTGGTATTAAT
GGTGCCACATACTACGCGAGCTGGGCGAAAGGCcgattcaccatctccagagacaattccaagACCACGGT
GtatcttcaaatgaacagcctgagagctgaggacactgctgtgtatTTCtgtGCTAGAGGGGACATCtggggccaagggaccctc
gtcaccgtcTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCAcCCTCCTCCaAGA
GCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCG
GTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTC
CTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTG
GGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACGC
GAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTG
AACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGa
TCTCCCgGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGG
TCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGG
GAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGA
CTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCA
TCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTG

CCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGG CTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACT ACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCA CCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAG GCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTTGA (SEQ ID NO: 567).

[0261] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 222 or the light chain sequence of SEQ ID NO: 221.

[0262] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 202 or the heavy chain sequence of SEQ ID NO: 201 or SEQ ID NO: 566.

[0263] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 232 encoding the light chain variable sequence of SEQ ID NO: 222; the polynucleotide SEQ ID NO: 231 encoding the light chain sequence of SEQ ID NO: 221; the polynucleotide SEQ ID NO: 212 encoding the heavy chain variable sequence of SEQ ID NO: 202; the polynucleotide SEQ ID NO: 211 encoding the heavy chain sequence of SEQ ID NO: 201; the polynucleotide SEQ ID NO: 567 encoding the heavy chain sequence of SEQ ID NO: 566; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238) of the light chain variable sequence of SEQ ID NO: 222 or the light chain sequence of SEQ ID NO: 221; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218) of the heavy chain variable sequence of SEQ ID NO: 202 or the heavy chain sequence of SEQ ID NO: 201 or SEQ ID NO: 566.

[0264] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab6, the polynucleotides encoding the full length Ab6 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 231

encoding the light chain sequence of SEQ ID NO: 221 and the polynucleotide SEQ ID NO: 211 encoding the heavy chain sequence of SEQ ID NO: 201 or the polynucleotide SEQ ID NO: 567 encoding the heavy chain sequence of SEQ ID NO: 566.

[0265] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab6 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-CGRP antibodies such as Ab6 or Fab fragments thereof may be produced via expression of Ab6 polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0266] In one embodiment, the invention is directed to an isolated polynucleotide comprising a polynucleotide encoding an anti-CGRP V_H antibody amino acid sequence selected from SEQ ID NO: 2, SEQ ID NO: 42, SEQ ID NO: 82, SEQ ID NO: 122, SEQ ID NO: 162, SEQ ID NO: 202, SEQ ID NO: 242, SEQ ID NO: 282, SEQ ID NO: 322, SEQ ID NO: 362, SEQ ID NO: 402, SEQ ID NO: 442, SEQ ID NO: 482, or SEQ ID NO: 522 or encoding a variant thereof wherein at least one framework residue (FR residue) has been substituted with an amino acid present at the corresponding position in a rabbit anti-CGRP antibody V_H polypeptide or a conservative amino acid substitution.

[0267] In another embodiment, the invention is directed to an isolated polynucleotide comprising the polynucleotide sequence encoding an anti-CGRP V_L antibody amino acid sequence of SEQ ID NO: 22, SEQ ID NO: 62, SEQ ID NO: 102, SEQ ID NO: 142, SEQ ID NO: 182, SEQ ID NO: 222, SEQ ID NO: 262, SEQ ID NO: 302, SEQ ID NO: 342, SEQ ID NO: 382, SEQ ID NO: 422, SEQ ID NO: 462, SEQ ID NO: 502, or SEQ ID NO: 542, or encoding a variant thereof wherein at least one framework residue (FR residue) has been substituted with an amino acid present at the corresponding position in a rabbit anti-CGRP antibody V_L polypeptide or a conservative amino acid substitution.

[0268] In yet another embodiment, the invention is directed to one or more heterologous polynucleotides comprising a sequence encoding the polypeptides contained in SEQ ID NO: 22 and SEQ ID NO: 2; SEQ ID NO: 62 and SEQ ID NO: 42; SEQ ID NO: 102 and SEQ ID NO: 82; SEQ ID NO: 142 and SEQ ID NO: 122; SEQ ID NO: 182 and SEQ ID NO: 162; SEQ ID NO: 222 and SEQ ID NO: 202; SEQ ID NO: 262 and SEQ ID NO: 242; SEQ ID NO: 302 and SEQ ID NO: 282; SEQ ID NO: 342 and SEQ ID NO: 322; SEQ ID NO: 382 and SEQ ID NO: 362; SEQ ID NO: 422 and SEQ ID NO: 402; SEQ ID NO: 462 and SEQ ID NO: 442; SEQ ID NO: 502 and SEQ ID NO: 482; or SEQ ID NO: 542 and SEQ ID NO: 522.

[0269] In another embodiment, the invention is directed to an isolated polynucleotide that expresses a polypeptide containing at least one CDR polypeptide derived from an anti-CGRP

antibody wherein said expressed polypeptide alone specifically binds CGRP or specifically binds CGRP when expressed in association with another polynucleotide sequence that expresses a polypeptide containing at least one CDR polypeptide derived from an anti-CGRP antibody wherein said at least one CDR is selected from those contained in the V_L or V_H polypeptides of SEQ ID NO: 22, SEQ ID NO: 2, SEQ ID NO: 62, SEQ ID NO: 42, SEQ ID NO: 102, SEQ ID NO: 82, SEQ ID NO: 142, SEQ ID NO: 122, SEQ ID NO: 182, SEQ ID NO: 162, SEQ ID NO: 222, SEQ ID NO: 202, SEQ ID NO: 262, SEQ ID NO: 242, SEQ ID NO: 302, SEQ ID NO: 282, SEQ ID NO: 342, SEQ ID NO: 322, SEQ ID NO: 382, SEQ ID NO: 362, SEQ ID NO: 422, SEQ ID NO: 402, SEQ ID NO: 462, SEQ ID NO: 442, SEQ ID NO: 502, SEQ ID NO: 482, SEQ ID NO: 542, or SEQ ID NO: 522.

[0270] Host cells and vectors comprising said polynucleotides are also contemplated.

[0271] The invention further contemplates vectors comprising the polynucleotide sequences encoding the variable heavy and light chain polypeptide sequences, as well as the individual complementarity-determining regions (CDRs, or hypervariable regions), as set forth herein, as well as host cells comprising said vector sequences. In one embodiment of the invention, the host cell is a yeast cell. In another embodiment of the invention, the yeast host cell belongs to the genus Pichia.

[0272] Methods of Producing Antibodies and Fragments thereof

[0273] In another embodiment, the present invention contemplates methods for producing anti-CGRP antibodies and fragments thereof. Methods for producing antibodies and fragments thereof secreted from polyploidal, preferably diploid or tetraploid strains of mating competent yeast are taught, for example, in U.S. patent application publication no. US 2009/0022659 to Olson et al., and in U.S. patent no. 7,935,340 to Garcia-Martinez et al., the disclosures of each of which are herein incorporated by reference in their entireties. Methods for producing antibodies and fragments thereof in mammalian cells, e.g., CHO cells are further well known in the art.

[0274] Other methods of producing antibodies are also well known to those of ordinary skill in the art. For example, methods of producing chimeric antibodies are now well known in the art (See, for example, U.S. Patent No. 4,816,567 to Cabilly et al.; Morrison et al., P.N.A.S. USA, 81:8651-55 (1984); Neuberger, M.S. et al., Nature, 314:268-270 (1985); Boulianne, G.L. et al., Nature, 312:643-46 (1984), the disclosures of each of which are herein incorporated by reference in their entireties).

[0275] Likewise, other methods of producing humanized antibodies are now well known in the art (See, for example, U.S. Patent Nos. 5,530,101, 5,585,089, 5,693,762, and 6,180,370 to Queen et al; U.S. Patent Nos. 5,225,539 and 6,548,640 to Winter; U.S. Patent Nos. 6,054,297, 6,407,213 and 6,639,055 to Carter et al; U.S. Patent No. 6,632,927 to Adair; Jones, P.T. et al, Nature, 321:522-525 (1986); Reichmann, L., et al, Nature, 332:323-327 (1988); Verhoeyen, M, et al, Science, 239:1534-36 (1988), the disclosures of each of which are herein incorporated by reference in their entireties).

[0276] The term "opioid analgesic" herein refers to all drugs, natural or synthetic, with morphine-like actions. The synthetic and semi-synthetic opioid analgesics are derivatives of five chemical classes of compound: phenanthrenes; phenylheptylamines; phenylpiperidines; morphinans;

and benzomorphans, all of which are within the scope of the term. Exemplary opioid analgesics include codeine, dihydrocodeine, diacetylmorphine, hydrocodone, hydromorphone, levorphanol, oxymorphone, alfentanil, buprenorphine, butorphanol, fentanyl, sufentanyl, meperidine, methadone, nalbuphine, propoxyphene and pentazocine or pharmaceutically acceptable salts thereof.

[0277] The term "NSAID" refers to a non-steroidal anti-inflammatory compound. NSAIDs are categorized by virtue of their ability to inhibit cyclooxygenase. Cyclooxygenase 1 and cyclooxygenase 2 are two major isoforms of cyclooxygenase and most standard NSAIDs are mixed inhibitors of the two isoforms. Most standard NSAIDs fall within one of the following five structural categories: (1) propionic acid derivatives, such as ibuprofen, naproxen, naprosyn, diclofenac, and ketoprofen; (2) acetic acid derivatives, such as tolmetin and slindac; (3) fenamic acid derivatives, such as mefenamic acid and meclofenamic acid; (4) biphenylcarboxylic acid derivatives, such as diflunisal and flufenisal; and (5) oxicams, such as piroxim, sudoxicam, and isoxicam. Another class of NSAID has been described which selectively inhibit cyclooxygenase 2. Cox-2 inhibitors have been described, e.g., in U.S. Pat. Nos. 5,616,601; 5,604,260; 5,593,994; 5,550,142; 5,536,752; 5,521,213; 5,475,995; 5,639,780; 5,604,253; 5,552,422; 5,510,368; 5,436,265; 5,409,944; and 5,130,311, all of which are hereby incorporated by reference. Certain exemplary COX-2 inhibitors include celecoxib (SC-58635), DUP-697, flosulide (CGP-28238), meloxicam, 6-methoxy-2 naphthylacetic acid (6-MNA), rofecoxib, MK-966, nabumetone (prodrug for 6-MNA), nimesulide, NS-398, SC-5766, SC-58215, T-614; or combinations thereof.

[0278] In some embodiments, aspirin and/or acetaminophen may be taken in conjunction with the subject CGRP antibody or fragment. Aspirin is another type of non-steroidal anti-inflammatory compound.

[0279] The subject to which the pharmaceutical formulation is administered can be, e.g., any human or non-human animal that is in need of such treatment, prevention and/or amelioration, or who would otherwise benefit from the inhibition or attenuation of medication overuse headache. For example, the subject can be an individual that is diagnosed with, or who is deemed to be at risk of being afflicted by medication overuse headache. The present invention further includes the use of any of the pharmaceutical formulations disclosed herein in the manufacture of a medicament for the treatment, prevention and/or amelioration of medication overuse headache.

[0280] Administration

[0281] In one embodiment of the invention, the anti-CGRP antibodies described herein, or CGRP binding fragments thereof, as well as combinations of said antibodies or antibody fragments, are administered to a subject at a concentration of between about 0.1 and 100.0 mg/kg of body weight of recipient subject. In a preferred embodiment of the invention, the anti-CGRP antibodies described herein, or CGRP binding fragments thereof, as well as combinations of said antibodies or antibody fragments, are administered to a subject at a concentration of about 0.4 mg/kg of body weight of recipient subject and/or at a dosage of 100 or 300 mg. In a preferred embodiment of the invention, the

anti-CGRP antibodies described herein, or CGRP binding fragments thereof, as well as combinations of said antibodies or antibody fragments, are administered to a recipient subject with a frequency of once every twenty-six weeks or six months or less, such as once every sixteen weeks or four months or less, once every eight weeks or two months or less, once every four weeks or monthly or less, once every two weeks or bimonthly or less, once every week or less, or once daily or less. In general the administration of sequential doses may vary by plus or minus a few days from the aforementioned schedule, e.g., administration every 3 months or every 12 weeks includes administration of a dose varying from the schedule day by plus or minus 1, 2, 3, 4, 5, 5, or 7 days.

[0282] Fab fragments may be administered every two weeks or less, every week or less, once daily or less, multiple times per day, and/or every few hours. In one embodiment of the invention, a patient receives Fab fragments of 0.1 mg/kg to 40 mg/kg per day given in divided doses of 1 to 6 times a day, or in a sustained release form, effective to obtain desired results.

[0283] It is to be understood that the concentration of the antibody or Fab administered to a given patient may be greater or lower than the exemplary administration concentrations set forth above.

[0284] A person of skill in the art would be able to determine an effective dosage and frequency of administration through routine experimentation, for example guided by the disclosure herein and the teachings in Goodman, L. S., Gilman, A., Brunton, L. L., Lazo, J. S., & Parker, K. L. (2006). Goodman & Gilman's the pharmacological basis of therapeutics. New York: McGraw-Hill; Howland, R. D., Mycek, M. J., Harvey, R. A., Champe, P. C., & Mycek, M. J. (2006). Pharmacology. Lippincott's illustrated reviews. Philadelphia: Lippincott Williams & Wilkins; and Golan, D. E. (2008). Principles of pharmacology: the pathophysiologic basis of drug therapy. Philadelphia, Pa., [etc.]: Lippincott Williams & Wilkins.

[0285] In another embodiment of the invention, the anti-CGRP antibodies described herein, or CGRP binding fragments thereof, as well as combinations of said antibodies or antibody fragments, are administered to a subject in a pharmaceutical formulation.

[0286] A "pharmaceutical composition" refers to a chemical or biological composition suitable for administration to a mammal. Such compositions may be specifically formulated for administration via one or more of a number of routes, including but not limited to buccal, epicutaneous, epidural, inhalation, intraarterial, intracardial, intracerebroventricular, intradermal, intramuscular, intranasal, intraocular, intraperitoneal, intraspinal, intrathecal, intravenous, oral, parenteral, rectally via an enema or suppository, subcutaneous, subdermal, sublingual, transdermal, and transmucosal, preferably intravenous. In addition, administration can occur by means of injection, powder, liquid, gel, drops, or other means of administration.

[0287] A "pharmaceutical excipient" or a "pharmaceutically acceptable excipient" is a carrier, usually a liquid, in which an active therapeutic agent is formulated. In one embodiment of the invention, the active therapeutic agent is a humanized antibody described herein, or one or more fragments thereof. The excipient generally does not provide any pharmacological activity to the

formulation, though it may provide chemical and/or biological stability, and release characteristics. Exemplary formulations can be found, for example, in Remington's Pharmaceutical Sciences, 19th Ed., Grennaro, A., Ed., 1995 which is incorporated by reference.

[0288] As used herein "pharmaceutically acceptable carrier" or "excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents that are physiologically compatible. In one embodiment, the carrier is suitable for parenteral administration. Alternatively, the carrier can be suitable for intravenous, intraperitoneal, intramuscular, or sublingual administration. Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions of the invention is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[0289] Pharmaceutical compositions typically must be sterile and stable under the conditions of manufacture and storage. The invention contemplates that the pharmaceutical composition is present in lyophilized form. The composition can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. The invention further contemplates the inclusion of a stabilizer in the pharmaceutical composition. The proper fluidity can be maintained, for example, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants.

[0290] In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, monostearate salts and gelatin. Moreover, the alkaline polypeptide can be formulated in a time release formulation, for example in a composition which includes a slow release polymer. The active compounds can be prepared with carriers that will protect the compound against rapid release, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, polylactic acid and polylactic, polyglycolic copolymers (PLG). Many methods for the preparation of such formulations are known to those skilled in the art.

[0291] An exemplary composition comprises, consists essentially of, or consists of an anti-CGRP antibody or fragment thereof (e.g., Ab6), an excipient such as histidine, an isotonic agent such as sorbitol, and a surfactant such as polysorbate 80 in an aqueous solution. For example, the

composition may comprise, consist essentially of, or consist of histidine (L-histidine), sorbitol, polysorbate 80, such as, per 1 mL volume, about 100 mg anti-CGRP antibody (e.g., Ab6), about 3.1 mg L-Histidine, about 40.5 mg Sorbitol, and about 0.15 mg Polysorbate 80, having a pH of about 5.8, or approximately that constitution, e.g., within 10% of those values, within 5% of those values, within 1% of those values, within 0.5% of those values, or within 0.1% of those values, and water. For example, the pH value may be within 10% of 5.8, i.e., between 5.22 and 6.38. The Ab6 antibody may comprise or consist of the variable light and heavy chain polypeptides of SEQ ID NO: 222 and SEQ ID NO: 202 respectively, or the light and heavy chain polypeptides of SEQ ID NO: 221 and SEQ ID NO: 201 respectively, or the light and heavy chain polypeptides of SEQ ID NO: 221 and SEQ ID NO: 566 respectively. The composition may be in the form of an aqueous solution, or a concentrate (e.g., lyophilized) which when reconstituted, e.g., by addition of water, yields the aforementioned constitution. An exemplary composition consists of, per mL, 100 mg of the light and heavy chain polypeptides of SEQ ID NO: 221 and SEQ ID NO: 201 respectively, about 3.1 mg L-Histidine, about 40.5 mg Sorbitol, and about 0.15 mg Polysorbate 80, and water Q.S, or approximately that constitution, e.g., within 10% of those quantities, within 5% of those quantities, within 1% of those quantities, within 0.5% of those quantities, or within 0.1% of those quantities. Another exemplary composition consists of, per mL, 100 mg of the light and heavy chain polypeptides of SEQ ID NO: 221 and SEQ ID NO: 566 respectively, about 3.1 mg L-Histidine, about 40.5 mg Sorbitol, and about 0.15 mg Polysorbate 80, and water Q.S, or approximately that constitution, e.g., within 10% of those quantities, within 5% of those quantities, within 1% of those quantities, within 0.5% of those quantities, or within 0.1% of those quantities. The composition may be suitable for intravenous or subcutaneous administration, preferably intravenous administration. For example, the composition may be suitable for mixing with an intravenous solution (such as 0.9% sodium chloride) at an amount of between about 100 mg and about 300 mg antibody added to 100 mL of intravenous solution. Preferably the composition may be shelf-stable for at least 1, 3, 6, 12, 18, or 24 months, e.g., showing formation of aggregates of no more than 5% or no more than 10% of the antibody or fragment after storage at room temperature or when refrigerated at 4°C for the specified duration, or in an accelerated aging test that simulates storage for that duration.

[0292] For each of the recited embodiments, the compounds can be administered by a variety of dosage forms. Any biologically-acceptable dosage form known to persons of ordinary skill in the art, and combinations thereof, are contemplated. Examples of such dosage forms include, without limitation, reconstitutable powders, elixirs, liquids, solutions, suspensions, emulsions, powders, granules, particles, microparticles, dispersible granules, cachets, inhalants, aerosol inhalants, patches, particle inhalants, implants, depot implants, injectables (including subcutaneous, intramuscular, intravenous, and intradermal, preferably intravenous), infusions, and combinations thereof.

[0293] The above description of various illustrated embodiments of the invention is not intended to be exhaustive or to limit the invention to the precise form disclosed. While specific embodiments

of, and examples for, the invention are described herein for illustrative purposes, various equivalent modifications are possible within the scope of the invention, as those skilled in the relevant art will recognize. The teachings provided herein of the invention can be applied to other purposes, other than the examples described above.

[0294] These and other changes can be made to the invention in light of the above detailed description. In general, in the following claims, the terms used should not be construed to limit the invention to the specific embodiments disclosed in the specification and the claims. Accordingly, the invention is not limited by the disclosure, but instead the scope of the invention is to be determined entirely by the following claims.

[0295] The invention may be practiced in ways other than those particularly described in the foregoing description and examples. Numerous modifications and variations of the invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

[0296] Certain CGRP antibody polynucleotides and polypeptides are disclosed in the sequence listing accompanying this patent application filing, and the disclosure of said sequence listing is herein incorporated by reference in its entirety.

[0297] The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is herein incorporated by reference in their entireties.

[0298] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the subject invention, and are not intended to limit the scope of what is regarded as the invention. Efforts have been made to ensure accuracy with respect to the numbers used (e.g. amounts, temperature, concentrations, etc.) but some experimental errors and deviations should be allowed for. Unless otherwise indicated, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees centigrade; and pressure is at or near atmospheric.

[0299] ADDITIONAL EXEMPLARY EMBODIMENTS

[0300] Additional exemplary embodiments of the invention are provided as follows:

[0301] S1. Use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for the manufacture of an agent for treating or preventing medication overuse headache.

[0302] S2. Use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for the manufacture of an agent for treating or preventing probable medication overuse headache.

[0303] S3. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises any one of Ab1-Ab14 or a fragment thereof.

[0304] S4. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises Ab6 or a fragment thereof.

[0305] S5. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain complementarity-determining region (CDR) 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively.

[0306] S6. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively.

[0307] S7. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively.

[0308] S8. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively.

[0309] S9. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively.

[0310] S10. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively.

[0311] S11. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing

embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide of SEQ ID NO: 222.

[0312] S12. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide encoded by SEQ ID NO: 232.

[0313] S13. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable heavy chain polypeptide of SEQ ID NO: 202.

[0314] S14. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

[0315] S15. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202.

[0316] S16. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide encoded by SEQ ID NO: 232 and the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

[0317] S17. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221.

[0318] S18. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide encoded by SEQ ID NO: 231.

[0319] S19. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

[0320] S20. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing

embodiments, wherein said anti-CGRP antibody comprises the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

[0321] S21. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

[0322] S22. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

[0323] S23. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is expressed in or obtained by expression in *Pichia pastoris*.

[0324] S24. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is expressed in or obtained by expression in CHO cells.

[0325] S25. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein the administered amount of said anti-CGRP antibody is between about 100 mg and about 300 mg, or is about 100 mg, or is about 300 mg.

[0326] S26. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein the administered amount of said anti-CGRP antibody is 100 mg.

[0327] S27. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, further comprising intravenously administering 100 mg of said anti-CGRP antibody every 12 weeks.

[0328] S28. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S1-S26, further comprising intravenously administering 300 mg of said anti-CGRP antibody every 12 weeks.

[0329] S29. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said patient is a chronic migraine patient or episodic migraine or cluster headache patient at risk of developing medication overuse headache.

[0330] S30. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of embodiment S29, wherein said patient uses acute headache medication on at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 day(s) per month, wherein optionally said acute medication use is determined over a baseline period of at least 28 days.

[0331] S31. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of embodiment S29, wherein said patient uses acute headache medication on at least 10 days per month, wherein optionally said acute medication use is determined over a baseline period of at least 28 days.

[0332] S32. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S30-S31, wherein said acute medication comprises use of ergot alkaloids, triptans, non-opioid analgesics, acetaminophen, aspirin, NSAIDs, non-opioid analgesics, combination-analgesics, or opioids.

[0333] S33. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said medication overuse headache comprises (a) headache occurring on 15 or more days/month in said patient, wherein said patient has a pre-existing headache disorder; and (b) overuse by said patient for more than 3 months of one or more drugs taken for acute and/or symptomatic treatment of headache.

[0334] S34. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments wherein, prior to said administration, the patient exhibits between about 15 and about 22 migraine days per month.

[0335] S35. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments wherein, prior to said administration, the patient exhibits between about 15 and about 27 headache days per month.

[0336] S36. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments wherein, prior to said administration, the patient exhibits between about 17 and about 24 headache days per month.

[0337] S37. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments wherein, prior to said administration, the patient exhibits between about 15 and about 19 migraine days per month, or about 20 or about 21 headache days per month, or about 16 migraine days per month.

[0338] S38. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing

embodiments wherein said patient was diagnosed with migraine at least 10 years prior to said administration.

[0339] S39. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments wherein said patient was diagnosed with migraine at least 15 years prior to said administration.

[0340] S40. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments wherein said patient was diagnosed with migraine at least 18 or at least 19 years prior to said administration.

[0341] S41. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by at least 50% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0342] S42. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by at least 75% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0343] S43. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by 100% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0344] S44. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by at least 50% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0345] S45. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by at least 75% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0346] S46. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing

embodiments, wherein said patient has a reduction in the number of migraine days by 100% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0347] S47. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, further comprising administering a second dose of said anti-CGRP antibody to said patient about 12 weeks or about 3 months after said administration.

[0348] S48. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said administration comprises administering about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, or about 300 mg of said anti-CGRP antibody.

[0349] S49. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said anti-CGRP antibody or antibody fragment is aglycosylated or if glycosylated only contains only mannose residues.

[0350] S50. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said anti-CGRP antibody consists of the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

[0351] S51. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said anti-CGRP antibody consists of the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

[0352] S52. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said medication overuse headache comprises (a) headache occurring on 15 or more days/month in said patient, wherein said patient has a pre-existing headache disorder; and (b) overuse by said patient for more than 3 months of one or more drugs taken for acute and/or symptomatic treatment of headache.

[0353] S53. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said medication overuse comprises use of ergotamine on 10 or more days/month, use of a triptan on 10 or more days/month, use of one or more non-opioid analgesics (such as paracetamol (acetaminophen), acetylsalicylic acid (aspirin), another NSAID, or another non-opioid analgesic) on 15 or more days/month, use of one or more combination-analgesics (as further described below) on 10 or more days/month, use of one or more opioids on 10 or more days/month, or

use of a combination of two or more drug classes (as further described below) on 10 or more days/month, wherein said triptan use optionally comprises use of one or more of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan, and/or wherein said opioid use optionally comprises use of one or more of oxycodone, tramadol, butorphanol, morphine, codeine, and hydrocodone.

[0354] S54. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said medication overuse headache comprises ergotamine-overuse headache, triptan-overuse headache, non-opioid analgesic-overuse headache, opioid-overuse headache, combination-analgesic-overuse headache, medication-overuse headache attributed to multiple drug classes not individually overused, medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes, or medication-overuse headache attributed to other medication, wherein said triptan use optionally comprises use of one or more of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan, and/or wherein said opioid use optionally comprises use of one or more of oxycodone, tramadol, butorphanol, morphine, codeine, and hydrocodone.

[0355] S55. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said non-opioid analgesic-overuse headache comprises paracetamol (acetaminophen)-overuse headache, non-steroidal anti-inflammatory drug (NSAID)-overuse headache such as acetylsalicylic acid (aspirin)-overuse headache, or other non-opioid analgesic-overuse headache.

[0356] S56. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said ergotamine-overuse headache comprises headache occurring on 15 or more days/month and use of ergotamine on 10 or more days/month for more than 3 month.

[0357] S57. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said triptan-overuse headache comprises headache occurring on 15 or more days/month and use of one or more triptans on 10 or more days/month for more than 3 months, wherein said triptan use optionally comprises use of one or more of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan.

[0358] S58. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said non-opioid analgesic-overuse headache comprises headache occurring on 15 or more days/month and use of one or more non-opioid analgesics (such as paracetamol

(acetaminophen), acetylsalicylic acid (aspirin), another NSAID, or another non-opioid analgesic) on 15 or more days/month for more than 3 months.

[0359] S59. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said combination-analgesic-overuse headache comprises headache occurring on 15 or more days/month and use of one or more combination-analgesics on 10 or more days/month for more than 3 months, wherein said combination-analgesic comprises drugs of two or more classes, each with analgesic effects (for example, paracetamol and codeine) or acting as adjuvants (for example, caffeine), optionally wherein said combination-analgesics combine non-opioid analgesic includes use of at least one opioid (such as tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof), barbiturate such as butalbital and/or caffeine.

[0360] S60. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said opioid-overuse headache comprises headache occurring on 15 or more days/month and use of one or more opioids (such as oxycodone, tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof) on 10 or more days/month for more than 3 months.

[0361] S61. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said medication-overuse headache attributed to multiple drug classes not individually overused comprises headache occurring on 15 or more days/month and use of any combination of ergotamine, triptans (such as sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, frovatriptan, or any combination thereof), non-opioid analgesics and/or opioids (such as oxycodone, tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof) on a total of at least 10 days/month for more than 3 months.

[0362] S62. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes comprises headache occurring on 15 or more days/month and use of any combination of ergotamine, triptans (such as sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, frovatriptan, or any combination thereof), non-opioid analgesics and/or opioids (such as oxycodone, tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof) on at least 10 days/month for more than 3 months, wherein the identity, quantity and/or pattern of use or overuse of these classes of drug is not reliably established.

[0363] S63. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said medication-overuse headache attributed to other medication comprises

headache occurring on 15 or more days/month and use of one or more medications other than those described above, taken for acute or symptomatic treatment of headache, on at least 10 days/month for more than 3 months.

[0364] S64. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said patient had a pre-existing primary headache prior to developing said medication overuse headache.

[0365] S65. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein headache days and/or medication use days are determined by reporting by the patient or a relative, a diary, medical records, drug purchase history, prescription fulfilment, biomarkers of medication use, incidence of medication toxicity, incidence of medication overdose, and/or other indicators of a patient's medication use.

[0366] S66. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said medication-overuse headache is diagnosed according to the third edition of the International Classification of Headache Disorders, wherein said medication–overuse headache optionally comprises ergotamine-overuse headache, triptan-overuse headache, non-opioid analgesic-overuse headache, opioid-overuse headache, combination-analgesic-overuse headache, medication-overuse headache attributed to multiple drug classes not individually overused, medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes, or medication-overuse headache attributed to other medication.

[0367] S67. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of the foregoing embodiments, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is comprised in a formulation comprising or consisting of histidine (L-histidine), sorbitol, polysorbate 80, and water.

[0368] S68. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of embodiment S67, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within 10% of said values, and having a pH of 5.8 or within +/-10% of said value.

[0369] S69. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of embodiment S67, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 5% of said values, and/or having a pH of 5.8 or within +/-5% of said value.

[0370] S70. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of embodiment S67, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 1% of said values, and/or having a pH of 5.8 or within 1% of said value.

[0371] S71. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of embodiment S67, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 0.5% of said values, and/or having a pH of 5.8 or within 0.5% of said value.

[0372] S72. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of embodiment S67, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 0.1% of said values, and/or having a pH of 5.8 or within 0.1% of said value.

[0373] S73. A pharmaceutical composition comprising or consisting of an anti-CGRP antibody or anti-CGRP antibody fragment in a formulation comprising or consisting of histidine (L-histidine), sorbitol, polysorbate 80, and water.

[0374] S74. The pharmaceutical composition of embodiment S73, wherein said formulation comprises or consist of, per 1 mL volume, 100 mg of an anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within 10% of said values, and having a pH of 5.8 or within +/- 10% of said value, in an aqueous solution.

[0375] S75. The pharmaceutical composition of embodiment S73, wherein said formulation comprises or consist of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 5% of said values, and/or having a pH of 5.8 or within 5% of said value, in an aqueous solution.

[0376] S76. The pharmaceutical composition of embodiment S73, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 1% of said values, and/or having a pH of 5.8 or within 1% of said value.

[0377] S77. The pharmaceutical composition of embodiment S73, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 0.5% of said values, and/or having a pH of 5.8 or within 0.5% of said value.

[0378] S78. The pharmaceutical composition of embodiment S73, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 0.1% of said values, and/or having a pH of 5.8 or within 0.1% of said value.

[0379] S79. The pharmaceutical composition of any one of embodiments S73-S79, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively.

[0380] S80. The pharmaceutical composition of any one of embodiments S73-S79, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively.

[0381] S81. The pharmaceutical composition of any one of embodiments S73-S79, wherein said anti-CGRP antibody comprises the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202.

[0382] S82. The pharmaceutical composition of any one of embodiments S73-S79, wherein said anti-CGRP antibody comprises the variable light chain polypeptide encoded by SEQ ID NO: 232 and the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

[0383] S83. The pharmaceutical composition of any one of embodiments S73-S79, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

[0384] S84. The pharmaceutical composition of any one of embodiments S73-S79, wherein said anti-CGRP antibody comprises the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

[0385] S85. The pharmaceutical composition of any one of embodiments S73-S84, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is expressed in or obtained by expression in *Pichia pastoris*.

[0386] S86. The pharmaceutical composition of any one of embodiments S73-S84, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is expressed or obtained by expression in in CHO cells.

[0387] S87. Use of at least one anti-CGRP antibody or anti-CGRP antibody fragment and/or use of at least one anti-CGRP-R antibody or anti-CGRP-R antibody fragment for the manufacture of an agent for treating or preventing migraine, further comprising the use of at least one further medication taken for acute and/or symptomatic treatment of headache selected from the group

comprising ergot alkaloids, triptans, non-opioid analgesics, acetaminophen, aspirin, NSAIDs, non-opioid analgesics, combination-analgesics, or opioids.

[0388] S88. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of embodiment S87, wherein the combined administration of (i) and (ii) reduces the symptoms, severity and/or episodes of medication overuse headache in the patient.

[0389] S89. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of embodiment S87 or S88, wherein said medication taken for acute and/or symptomatic treatment of headache comprises an ergot alkaloid.

[0390] S90. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of embodiment S89, wherein said ergot alkaloid is selected from ergotamine, nicergoline, methysergide, dihydroergotamine and combinations of the foregoing.

[0391] S91. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of embodiment S87 or S88, wherein said medication taken for acute and/or symptomatic treatment of headache comprises a triptan.

[0392] S92. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of embodiment S91, wherein said triptan is selected from sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, frovatriptan, and combinations of the foregoing.

[0393] S93. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of embodiment S87 or S88, wherein said medication taken for acute and/or symptomatic treatment of headache comprises a non-opioid analgesic.

[0394] S94. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of embodiment S93, wherein said non-opioid analgesic comprises paracetamol (acetaminophen), or aspirin.

[0395] S95. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of embodiment S87 or S88, wherein said medication taken for acute and/or symptomatic treatment of headache comprises an NSAID.

[0396] S96. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of embodiment S95, wherein said NSAID is selected from salicylates, propinic acid derivatives, enolic acid derivatives, anthralic acid derivatives (fenamates), selective COX-2 inhibitors (coxinbs), sulfonanilides, and combinations of the foregoing.

[0397] S97. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of embodiment S95, wherein said NSAID

is selected from Salicylates such as Aspirin (acetylsalicylic acid), Diflunisal (Dolobid), Salicylic acid and its salts, and Salsalate (Disalcid); Propionic acid derivatives such as Ibuprofen, Dexibuprofen, Naproxen, Fenoprofen, Ketoprofen, Dexketoprofen, Flurbiprofen, Oxaprozin, and Loxoprofen; Acetic acid derivatives such as Indomethacin, Tolmetin, Sulindac, Etodolac, Ketorolac, Diclofenac, Aceclofenac, and Nabumetone, Enolic acid (oxicam) derivatives such as Piroxicam, Meloxicam, Tenoxicam, Droxicam, Lornoxicam, Isoxicam, and Phenylbutazone (Bute); Anthranilic acid derivatives (fenamates) such as Mefenamic acid, Meclofenamic acid, Flufenamic acid, and Tolfenamic acid; Selective COX-2 inhibitors (coxibs) such as Celecoxib, Rofecoxib, Valdecoxib, Parecoxib, Lumiracoxib, Etoricoxib, and Firocoxib; Sulfonanilides such as Nimesulide; Clonixin, Licofelone, H-harpagide or Devil's Claw and combinations of the foregoing.

[0398] S98. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of embodiment S87 or S88, wherein said medication taken for acute and/or symptomatic treatment of headache comprises a non-opioid analgesic.

[0399] S99. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of embodiment S87 or S88, wherein said medication taken for acute and/or symptomatic treatment of headache comprises a combination-analgesic.

[0400] S100. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of embodiment S99, wherein said combination-analgesics comprises the combination of a non-opioid analgesic with at least one opioid or barbiturate such as butalbital and/or caffeine or comprises the combination of acetaminophen, aspirin, and caffeine, e.g., EXCEDRIN ® or EXCEDRIN MIGRAINE ® or comprises a combination analgesic comprising an analgesic in combination with at least one non-analgesic, e.g., a vasoconstrictor drug such as pseudoephedrine, or an antihistamine drug.

[0401] S101. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of embodiment S87 or S88, wherein said medication taken for acute and/or symptomatic treatment of headache comprises an opioid.

[0402] S102. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of embodiment S101, wherein said opioid is selected from oxycodone, tramadol, butorphanol, morphine, codeine, hydrocodone, thebaine, oripavine, mixed opium alkaloids such as papaveretum, diacetylmorphine, nicomorphine, dipropanoylmorphine, diacetyldihydromorphine, acetylpropionylmorphine, desomorphine, methyldesorphine, dibenzoylmorphine, ethylmorphine, heterocodeine, buprenorphine, etorphine, hydromorphone, oxymorphone, fentanyl, alphamethylfentanyl, alfentanil, sufentanil, remifentanil, carfentanyl, ohmefentanyl, pethidine (meperidine), ketobemidone, MPPP, allylprodine, prodine,

PEPAP, promedol, diphenylpropylamine, propoxyphene, dextropropoxyphene, dextromoramide, bezitramide, piritramide, and combinations of the foregoing.

[0403] S103. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S102, wherein said anti-CGRP antibody comprises any one of Ab1-Ab14 or a fragment thereof.

[0404] S104. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S103, wherein said anti-CGRP antibody comprises Ab6 or a fragment thereof.

[0405] S105. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S104, wherein said anti-CGRP antibody comprises the light chain complementarity-determining region (CDR) 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively.

[0406] S106. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S105, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively.

[0407] S107. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S106, wherein said anti-CGRP antibody comprises the heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively.

[0408] S108. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S107, wherein said anti-CGRP antibody comprises the heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively.

[0409] S109. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S108, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively.

[0410] S110. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S109, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively.

[0411] S111. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S110, wherein said anti-CGRP antibody comprises the variable light chain polypeptide of SEQ ID NO: 222.

[0412] S112. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S111, wherein said anti-CGRP antibody comprises the variable light chain polypeptide encoded by SEQ ID NO: 232.

[0413] S113. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S112, wherein said anti-CGRP antibody comprises the variable heavy chain polypeptide of SEQ ID NO: 202.

[0414] S114. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S113, wherein said anti-CGRP antibody comprises the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

[0415] S115. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S114, wherein said anti-CGRP antibody comprises the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202.

[0416] S116. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S115, wherein said anti-CGRP antibody comprises the variable light chain polypeptide encoded by SEQ ID NO: 232 and the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

[0417] S117. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S116, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221.

[0418] S118. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S117, wherein said anti-CGRP antibody comprises the light chain polypeptide encoded by SEQ ID NO: 231.

[0419] S119. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S118, wherein said anti-CGRP antibody comprises the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

[0420] S120. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S119, wherein said anti-CGRP antibody comprises the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

[0421] S121. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S120, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

[0422] S122. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S121, wherein said anti-CGRP antibody comprises the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

[0423] S123. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S122, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is expressed in or obtained by expression in *Pichia pastoris*.

[0424] S124. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S123, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is expressed in or obtained by expression in CHO cells.

[0425] S125. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S124, wherein the administered amount of said anti-CGRP antibody is between about 100 mg and about 300 mg, or is about 100 mg, or is about 300 mg.

[0426] S126. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S125, wherein the administered amount of said anti-CGRP antibody is 100 mg.

[0427] S127. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S126, further comprising intravenously administering 100 mg of said anti-CGRP antibody every 12 weeks.

[0428] S128. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S127, further comprising intravenously administering 300 mg of said anti-CGRP antibody every 12 weeks.

[0429] S129. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S128, wherein said patient is a chronic migraine patient or episodic migraine or cluster headache patient at risk of developing medication overuse headache.

[0430] S130. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S129, wherein said patient uses acute headache medication on at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 day(s)

per month, wherein optionally said acute medication use is determined over a baseline period of at least 28 days.

[0431] S131. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S130, wherein said patient uses acute headache medication on at least 10 days per month, wherein optionally said acute medication use is determined over a baseline period of at least 28 days.

[0432] S132. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S131, wherein said medication overuse headache comprises (a) headache occurring on 15 or more days/month in said patient, wherein said patient has a pre-existing headache disorder; and (b) overuse by said patient for more than 3 months of one or more drugs taken for acute and/or symptomatic treatment of headache.

[0433] S133. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any of embodiments S87-S132, wherein, prior to said administration, the patient exhibits between about 15 and about 22 migraine days per month.

[0434] S134. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any of embodiments S87-S133, wherein, prior to said administration, the patient exhibits between about 15 and about 27 headache days per month.

[0435] S135. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any of embodiments S87-S134, wherein, prior to said administration, the patient exhibits between about 17 and about 24 headache days per month.

[0436] S136. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any of embodiments S87-S135, wherein, prior to said administration, the patient exhibits between about 15 and about 19 migraine days per month, or about 20 or about 21 headache days per month, or about 16 migraine days per month.

[0437] S137. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any of embodiments S87-S136, wherein said patient was diagnosed with migraine at least 10 years prior to said administration.

[0438] S138. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any of embodiments S87-S137, wherein said patient was diagnosed with migraine at least 15 years prior to said administration.

[0439] S139. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any of embodiments S87-S138,

wherein said patient was diagnosed with migraine at least 18 or at least 19 years prior to said administration.

[0440] S140. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any of embodiments S87-S139, wherein said patient has a reduction in the number of migraine days by at least 50% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0441] S141. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any of embodiments S87-S140, wherein said patient has a reduction in the number of migraine days by at least 75% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0442] S142. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any of embodiments S87-S141, wherein said patient has a reduction in the number of migraine days by 100% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0443] S143. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any of embodiments S87-S142, wherein said patient has a reduction in the number of migraine days by at least 50% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0444] S144. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any of embodiments S87-S143, wherein said patient has a reduction in the number of migraine days by at least 75% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0445] S145. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any of embodiments S87-S144, wherein said patient has a reduction in the number of migraine days by 100% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0446] S146. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S145, further comprising administering a second dose of said anti-CGRP antibody to said patient about 12 weeks or about 3 months after said administration.

[0447] S147. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S146, wherein said administration comprises administering about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, or about 300 mg of said anti-CGRP antibody.

[0448] S148. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S147, wherein said anti-CGRP antibody or antibody fragment is aglycosylated or if glycosylated only contains only mannose residues.

[0449] S149. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S148, wherein said anti-CGRP antibody consists of the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

[0450] S150. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S149, wherein said anti-CGRP antibody consists of the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

[0451] S151. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S150, wherein said medication overuse headache comprises (a) headache occurring on 15 or more days/month in said patient, wherein said patient has a pre-existing headache disorder; and (b) overuse by said patient for more than 3 months of one or more drugs.

[0452] S152. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S151, wherein said medication overuse comprises use of ergotamine on 10 or more days/month, use of a triptan on 10 or more days/month, use of one or more non-opioid analgesics (such as paracetamol (acetaminophen), acetylsalicylic acid (aspirin), another NSAID, or another non-opioid analgesic) on 15 or more days/month, use of one or more combination-analgesics (as further described below) on 10 or more days/month, use of one or more opioids on 10 or more days/month, or use of a combination of two or more drug classes (as further described below) on 10 or more days/month, wherein said triptan use optionally comprises use of one or more of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan, and/or wherein said opioid use optionally comprises use of one or more of oxycodone, tramadol, butorphanol, morphine, codeine, and hydrocodone.

[0453] S153. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S152, wherein said medication overuse headache comprises ergotamine-overuse headache, triptan-overuse

headache, non-opioid analgesic-overuse headache, opioid-overuse headache, combination-analgesic-overuse headache, medication-overuse headache attributed to multiple drug classes not individually overused, medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes, or medication-overuse headache attributed to other medication, wherein said triptan use optionally comprises use of one or more of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan, and/or wherein said opioid use optionally comprises use of one or more of oxycodone, tramadol, butorphanol, morphine, codeine, and hydrocodone.

[0454] S154. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S153, wherein said non-opioid analgesic-overuse headache comprises paracetamol (acetaminophen)-overuse headache, non-steroidal anti-inflammatory drug (NSAID)-overuse headache such as acetylsalicylic acid (aspirin)-overuse headache, or other non-opioid analgesic-overuse headache.

[0455] S155. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S154, wherein said ergotamine-overuse headache comprises headache occurring on 15 or more days/month and use of ergotamine on 10 or more days/month for more than 3 month.

[0456] S156. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S155, wherein said triptan-overuse headache comprises headache occurring on 15 or more days/month and use of one or more triptans on 10 or more days/month for more than 3 months, wherein said triptan use optionally comprises use of one or more of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan.

[0457] S157. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S156, wherein said non-opioid analgesic-overuse headache comprises headache occurring on 15 or more days/month and use of one or more non-opioid analgesics (such as paracetamol (acetaminophen), acetylsalicylic acid (aspirin), another NSAID, or another non-opioid analgesic) on 15 or more days/month for more than 3 months.

[0458] S158. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S157, wherein said combination-analgesic-overuse headache comprises headache occurring on 15 or more days/month and use of one or more combination-analgesics on 10 or more days/month for more than 3 months, wherein said combination-analgesic comprises drugs of two or more classes, each with analgesic effects (for example, paracetamol and codeine) or acting as adjuvants (for example, caffeine), optionally wherein said combination-analgesics combine non-opioid analgesic includes at least one opioid (such as tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof), barbiturate such as butalbital and/or caffeine.

[0459] S159. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S158, wherein said opioid-overuse headache comprises headache occurring on 15 or more days/month and use of one or more opioids (such as oxycodone, tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof) on 10 or more days/month for more than 3 months.

[0460] S160. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S159, wherein said medication-overuse headache attributed to multiple drug classes not individually overused comprises headache occurring on 15 or more days/month and use of any combination of ergotamine, triptans (such as sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, frovatriptan, or any combination thereof), non-opioid analgesics and/or opioids (such as oxycodone, tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof) on a total of at least 10 days/month for more than 3 months.

[0461] S161. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S160, wherein said medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes comprises headache occurring on 15 or more days/month and use of any combination of ergotamine, triptans (such as sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, frovatriptan, or any combination thereof), non-opioid analgesics and/or opioids (such as oxycodone, tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof) on at least 10 days/month for more than 3 months, wherein the identity, quantity and/or pattern of use or overuse of these classes of drug is not reliably established.

[0462] S162. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S161, wherein said medication-overuse headache attributed to other medication comprises headache occurring on 15 or more days/month and use of one or more medications other than those described above, taken for acute or symptomatic treatment of headache, on at least 10 days/month for more than 3 months.

[0463] S163. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S162, wherein said patient had a pre-existing primary headache prior to developing said medication overuse headache.

[0464] S164. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S163, wherein headache days and/or medication use days are determined by reporting by the patient or a relative, a diary, medical records, drug purchase history, prescription fulfilment, biomarkers of

medication use, incidence of medication toxicity, incidence of medication overdose, and/or other indicators of a patient's medication use.

[0465] S165. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S164, wherein said medication-overuse headache is diagnosed according to the third edition of the International Classification of Headache Disorders, wherein said medication–overuse headache optionally comprises ergotamine-overuse headache, triptan-overuse headache, non-opioid analgesic-overuse headache, opioid-overuse headache, combination-analgesic-overuse headache, medication-overuse headache attributed to multiple drug classes not individually overused, medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes, or medication-overuse headache attributed to other medication.

[0466] S166. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of any one of embodiments S87-S165, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is comprised in a formulation comprising or consisting of histidine (L-histidine), sorbitol, polysorbate 80, and water.

[0467] S167. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of embodiment S166, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within 10% of said values, and having a pH of 5.8 or within +/-10% of said value.

[0468] S168. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of embodiment S166, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 5% of said values, and/or having a pH of 5.8 or within +/-5% of said value.

[0469] S169. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of embodiment S166, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 1% of said values, and/or having a pH of 5.8 or within 1% of said value.

[0470] S170. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of embodiment S166, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 0.5% of said values, and/or having a pH of 5.8 or within 0.5% of said value.

[0471] S171. The use of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment of embodiment S166, wherein said

formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 0.1% of said values, and/or having a pH of 5.8 or within 0.1% of said value.

[0472] FURTHER EXEMPLARY EMBODIMENTS

[0473] Further exemplary embodiments of the invention are provided as follows:

[0474] E1. At least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use in treating or preventing medication overuse headache.

[0475] E2. At least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use in treating or preventing probable medication overuse headache.

[0476] E3. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises any one of Ab1-Ab14 or a fragment thereof.

[0477] E4. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises Ab6 or a fragment thereof.

[0478] E5. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain complementarity-determining region (CDR) 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively.

[0479] E6. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively.

[0480] E7. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively.

[0481] E8. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively.

[0482] E9. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively.

[0483] E10. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively.

[0484] E11. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide of SEQ ID NO: 222.

[0485] E12. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide encoded by SEQ ID NO: 232.

[0486] E13. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable heavy chain polypeptide of SEQ ID NO: 202.

[0487] E14. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

[0488] E15. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202.

[0489] E16. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide encoded by SEQ ID NO: 232 and the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

[0490] E17. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221.

[0491] E18. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide encoded by SEQ ID NO: 231.

[0492] E19. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

[0493] E20. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

[0494] E21. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

[0495] E22. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

[0496] E23. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is expressed in or obtained by expression in *Pichia pastoris*.

[0497] E24. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is expressed in or obtained by expression in CHO cells.

[0498] E25. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein the administered amount of said anti-CGRP antibody is between about 100 mg and about 300 mg, or is about 100 mg, or is about 300 mg.

[0499] E26. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein the administered amount of said anti-CGRP antibody is 100 mg.

[0500] E27. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, further comprising intravenously administering 100 mg of said anti-CGRP antibody every 12 weeks.

[0501] E28. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E1-E26, further comprising intravenously administering 300 mg of said anti-CGRP antibody every 12 weeks.

[0502] E29. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said patient is a chronic migraine patient or episodic migraine or cluster headache patient at risk of developing medication overuse headache.

[0503] E30. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to embodiment E29, wherein said patient uses acute headache medication on at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 day(s) per month, wherein optionally said acute medication use is determined over a baseline period of at least 28 days.

[0504] E31. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to embodiment E29, wherein said patient uses acute headache medication on at least 10 days per month, wherein optionally said acute medication use is determined over a baseline period of at least 28 days.

[0505] E32. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E30-E31, wherein said acute medication comprises use of ergot alkaloids, triptans, non-opioid analgesics, acetaminophen, aspirin, NSAIDs, non-opioid analgesics, combination-analgesics, or opioids.

[0506] E33. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said medication overuse headache comprises (a) headache occurring on 15 or more days/month in said patient, wherein said patient has a pre-existing headache disorder; and (b) overuse by said patient for more than 3 months of one or more drugs taken for acute and/or symptomatic treatment of headache.

[0507] E34. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the

foregoing embodiments wherein, prior to said administration, the patient exhibits between about 15 and about 22 migraine days per month.

[0508] E35. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments wherein, prior to said administration, the patient exhibits between about 15 and about 27 headache days per month.

[0509] E36. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments wherein, prior to said administration, the patient exhibits between about 17 and about 24 headache days per month.

[0510] E37. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments wherein, prior to said administration, the patient exhibits between about 15 and about 19 migraine days per month, or about 20 or about 21 headache days per month, or about 16 migraine days per month.

[0511] E38. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments wherein said patient was diagnosed with migraine at least 10 years prior to said administration.

[0512] E39. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments wherein said patient was diagnosed with migraine at least 15 years prior to said administration.

[0513] E40. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments wherein said patient was diagnosed with migraine at least 18 or at least 19 years prior to said administration.

[0514] E41. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by at least 50% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0515] E42. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by at least 75% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0516] E43. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by 100% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0517] E44. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by at least 50% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0518] E45. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by at least 75% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0519] E46. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by 100% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0520] E47. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, further comprising administering a second dose of said anti-CGRP antibody to said patient about 12 weeks or about 3 months after said administration.

[0521] E48. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said administration comprises administering about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, or about 300 mg of said anti-CGRP antibody.

[0522] E49. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody or antibody fragment is aglycosylated or if glycosylated only contains only mannose residues.

[0523] E50. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody consists of the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

[0524] E51. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody consists of the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

[0525] E52. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said medication overuse headache comprises (a) headache occurring on 15 or more days/month in said patient, wherein said patient has a pre-existing headache disorder; and (b) overuse by said patient for more than 3 months of one or more drugs taken for acute and/or symptomatic treatment of headache.

[0526] E53. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said medication overuse comprises use of ergotamine on 10 or more days/month, use of a triptan on 10 or more days/month, use of one or more non-opioid analgesics (such as paracetamol (acetaminophen), acetylsalicylic acid (aspirin), another NSAID, or another non-opioid analgesic) on 15 or more days/month, use of one or more combination-analgesics (as further described below) on 10 or more days/month, use of one or more opioids on 10 or more days/month, or use of a combination of two or more drug classes (as further described below) on 10 or more days/month, wherein said triptan use optionally comprises use of one or more of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan, and/or wherein said opioid use optionally comprises use of one or more of oxycodone, tramadol, butorphanol, morphine, codeine, and hydrocodone.

[0527] E54. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said medication overuse headache comprises ergotamine-overuse headache, triptan-overuse headache, non-opioid analgesic-overuse headache, opioid-overuse headache, combination-analgesic-overuse headache, medication-overuse headache attributed to multiple drug classes not individually overused, medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes, or medication-overuse headache attributed to other medication, wherein said triptan use optionally comprises use of one or more of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan, and/or wherein said opioid use optionally comprises use of one or more of oxycodone, tramadol, butorphanol, morphine, codeine, and hydrocodone.

[0528] E55. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said non-opioid analgesic-overuse headache comprises paracetamol

(acetaminophen)-overuse headache, non-steroidal anti-inflammatory drug (NSAID)-overuse headache such as acetylsalicylic acid (aspirin)-overuse headache, or other non-opioid analgesic-overuse headache.

[0529] E56. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said ergotamine-overuse headache comprises headache occurring on 15 or more days/month and use of ergotamine on 10 or more days/month for more than 3 month.

[0530] E57. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said triptan-overuse headache comprises headache occurring on 15 or more days/month and use of one or more triptans on 10 or more days/month for more than 3 months, wherein said triptan use optionally comprises use of one or more of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan.

[0531] E58. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said non-opioid analgesic-overuse headache comprises headache occurring on 15 or more days/month and use of one or more non-opioid analgesics (such as paracetamol (acetaminophen), acetylsalicylic acid (aspirin), another NSAID, or another non-opioid analgesic) on 15 or more days/month for more than 3 months.

[0532] E59. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said combination-analgesic-overuse headache comprises headache occurring on 15 or more days/month and use of one or more combination-analgesics on 10 or more days/month for more than 3 months, wherein said combination-analgesic comprises drugs of two or more classes, each with analgesic effects (for example, paracetamol and codeine) or acting as adjuvants (for example, caffeine), optionally wherein said combination-analgesics combine non-opioid analgesic includes at least one opioid (such as tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof), barbiturate such as butalbital and/or caffeine.

[0533] E60. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said opioid-overuse headache comprises headache occurring on 15 or more days/month and use of one or more opioids (such as oxycodone, tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof) on 10 or more days/month for more than 3 months.

[0534] E61. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said medication-overuse headache attributed to multiple drug classes

not individually overused comprises headache occurring on 15 or more days/month and use of any combination of ergotamine, triptans (such as sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, frovatriptan, or any combination thereof), non-opioid analgesics and/or opioids (such as oxycodone, tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof) on a total of at least 10 days/month for more than 3 months.

[0535] E62. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes comprises headache occurring on 15 or more days/month and use of any combination of ergotamine, triptans (such as sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, frovatriptan, or any combination thereof), non-opioid analgesics and/or opioids (such as oxycodone, tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof) on at least 10 days/month for more than 3 months, wherein the identity, quantity and/or pattern of use or overuse of these classes of drug is not reliably established.

[0536] E63. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said medication-overuse headache attributed to other medication comprises headache occurring on 15 or more days/month and use of one or more medications other than those described above, taken for acute or symptomatic treatment of headache, on at least 10 days/month for more than 3 months.

[0537] E64. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said patient had a pre-existing primary headache prior to developing said medication overuse headache.

[0538] E65. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein headache days and/or medication use days are determined by reporting by the patient or a relative, a diary, medical records, drug purchase history, prescription fulfilment, biomarkers of medication use, incidence of medication toxicity, incidence of medication overdose, and/or other indicators of a patient's medication use.

[0539] E66. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said medication-overuse headache is diagnosed according to the third edition of the International Classification of Headache Disorders, wherein said medication–overuse headache optionally comprises ergotamine-overuse headache, triptan-overuse headache, non-opioid analgesic-overuse headache, opioid-overuse headache, combination-analgesic-overuse headache, medication-overuse headache attributed to multiple drug classes not individually overused,

medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes, or medication-overuse headache attributed to other medication.

[0540] E67. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is comprised in a formulation comprising or consisting of histidine (L-histidine), sorbitol, polysorbate 80, and water.

[0541] E68. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to embodiment E67, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within 10% of said values, and having a pH of 5.8 or within +/-10% of said value.

[0542] E69. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to embodiment E67, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 5% of said values, and/or having a pH of 5.8 or within +/-5% of said value.

[0543] E70. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to embodiment E67, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 1% of said values, and/or having a pH of 5.8 or within 1% of said value.

[0544] E71. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to embodiment E67, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 0.5% of said values, and/or having a pH of 5.8 or within 0.5% of said value.

[0545] E72. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to embodiment E67, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 0.1% of said values, and/or having a pH of 5.8 or within 0.1% of said value.

[0546] E73. A pharmaceutical composition comprising or consisting of an anti-CGRP antibody or anti-CGRP antibody fragment in a formulation comprising or consisting of histidine (L-histidine), sorbitol, polysorbate 80, and water.

[0547] E74. The pharmaceutical composition of embodiment E73, wherein said formulation comprises or consist of, per 1 mL volume, 100 mg of an anti-CGRP antibody, 3.1 mg L-

Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within 10% of said values, and having a pH of 5.8 or within +/- 10% of said value, in an aqueous solution.

[0548] E75. The pharmaceutical composition of embodiment E73, wherein said formulation comprises or consist of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 5% of said values, and/or having a pH of 5.8 or within 5% of said value, in an aqueous solution.

[0549] E76. The pharmaceutical composition of embodiment E73, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 1% of said values, and/or having a pH of 5.8 or within 1% of said value.

[0550] E77. The pharmaceutical composition of embodiment E73, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 0.5% of said values, and/or having a pH of 5.8 or within 0.5% of said value.

[0551] E78. The pharmaceutical composition of embodiment E73, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 0.1% of said values, and/or having a pH of 5.8 or within 0.1% of said value.

[0552] E79. The pharmaceutical composition of any one of embodiments E73-E79, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively.

[0553] E80. The pharmaceutical composition of any one of embodiments E73-E79, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively.

[0554] E81. The pharmaceutical composition of any one of embodiments E73-E79, wherein said anti-CGRP antibody comprises the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202.

[0555] E82. The pharmaceutical composition of any one of embodiments E73-E79, wherein said anti-CGRP antibody comprises the variable light chain polypeptide encoded by SEQ ID NO: 232 and the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

[0556] E83. The pharmaceutical composition of any one of embodiments E73-E79, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

[0557] E84. The pharmaceutical composition of any one of embodiments E73-E79, wherein said anti-CGRP antibody comprises the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

[0558] E85. The pharmaceutical composition of any one of embodiments E73-E84, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is expressed in or obtained by expression in *Pichia pastoris*.

[0559] E86. The pharmaceutical composition of any one of embodiments E73-E84, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is expressed or obtained by expression in in CHO cells.

[0560] E87. At least one anti-CGRP antibody or anti-CGRP antibody fragment and/or at least one anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use in treating or preventing migraine further comprising the use of at least one medication taken for acute and/or symptomatic treatment of headache selected from the group comprising ergot alkaloids, triptans, non-opioid analgesics, acetaminophen, aspirin, NSAIDs, non-opioid analgesics, combination-analgesics, or opioids for treating or preventing migraine.

[0561] E88. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to embodiment E87, wherein the combined administration of (i) and (ii) reduces the symptoms, severity and/or episodes of medication overuse headache in the patient.

[0562] E89. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to embodiment E87 or E88, wherein said medication taken for acute and/or symptomatic treatment of headache comprises an ergot alkaloid.

[0563] E90. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to embodiment E89, wherein said ergot alkaloid is selected from ergotamine, nicergoline, methysergide, dihydroergotamine and combinations of the foregoing.

[0564] E91. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to embodiment E87 or E88, wherein said medication taken for acute and/or symptomatic treatment of headache comprises a triptan.

[0565] E92. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to embodiment E91, wherein

said triptan is selected from sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, frovatriptan, and combinations of the foregoing.

[0566] E93. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to embodiment E87 or E88, wherein said medication taken for acute and/or symptomatic treatment of headache comprises a non-opioid analgesic.

[0567] E94. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to embodiment E93, wherein said non-opioid analgesic comprises paracetamol (acetaminophen), or aspirin.

[0568] E95. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to embodiment E87 or E88, wherein said medication taken for acute and/or symptomatic treatment of headache comprises an NSAID.

[0569] E96. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to embodiment E95, wherein said NSAID is selected from salicylates, propinic acid derivatives, enolic acid derivatives, anthralic acid derivatives (fenamates), selective COX-2 inhibitors (coxinbs), sulfonanilides, and combinations of the foregoing.

[0570] E97. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to embodiment E95, wherein said NSAID is selected from Salicylates such as Aspirin (acetylsalicylic acid), Diflunisal (Dolobid), Salicylic acid and its salts, and Salsalate (Disalcid); Propionic acid derivatives such as Ibuprofen, Dexibuprofen, Naproxen, Fenoprofen, Ketoprofen, Dexketoprofen, Flurbiprofen, Oxaprozin, and Loxoprofen; Acetic acid derivatives such as Indomethacin, Tolmetin, Sulindac, Etodolac, Ketorolac, Diclofenac, Aceclofenac, and Nabumetone, Enolic acid (oxicam) derivatives such as Piroxicam, Meloxicam, Tenoxicam, Droxicam, Lornoxicam, Isoxicam, and Phenylbutazone (Bute); Anthranilic acid derivatives (fenamates) such as Mefenamic acid, Meclofenamic acid, Flufenamic acid, and Tolfenamic acid; Selective COX-2 inhibitors (coxibs) such as Celecoxib, Rofecoxib, Valdecoxib, Parecoxib, Lumiracoxib, Etoricoxib, and Firocoxib; Sulfonanilides such as Nimesulide; Clonixin, Licofelone, H-harpagide or Devil's Claw and combinations of the foregoing.

[0571] E98. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to embodiment E87 or E88, wherein said medication taken for acute and/or symptomatic treatment of headache comprises a non-opioid analgesic.

[0572] E99. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to embodiment E87 or E88,

wherein said medication taken for acute and/or symptomatic treatment of headache comprises a combination-analgesic.

[0573] E100. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to embodiment E99, wherein said combination-analgesics comprises the combination of a non-opioid analgesic with at least one opioid or barbiturate such as butalbital and/or caffeine or comprises the combination of acetaminophen, aspirin, and caffeine, e.g., EXCEDRIN ® or EXCEDRIN MIGRAINE ® or comprises a combination analgesic comprising an analgesic in combination with at least one non-analgesic, e.g., a vasoconstrictor drug such as pseudoephedrine, or an antihistamine drug.

[0574] E101. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to embodiment E87 or E88, wherein said medication taken for acute and/or symptomatic treatment of headache comprises an opioid.

[0575] E102. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to embodiment E101, wherein said opioid is selected from oxycodone, tramadol, butorphanol, morphine, codeine, hydrocodone, thebaine, oripavine, mixed opium alkaloids such as papaveretum, diacetylmorphine, nicomorphine, dipropanoylmorphine, diacetyldihydromorphine, acetylpropionylmorphine, desomorphine, methyldesorphine, dibenzoylmorphine, ethylmorphine, heterocodeine, buprenorphine, etorphine, hydromorphone, oxymorphone, fentanyl, alphamethylfentanyl, alfentanil, sufentanil, remifentanil, carfentanyl, ohmefentanyl, pethidine (meperidine), ketobemidone, MPPP, allylprodine, prodine, PEPAP, promedol, diphenylpropylamine, propoxyphene, dextropropoxyphene, dextromoramide, bezitramide, piritramide, and combinations of the foregoing.

[0576] E103. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E102, wherein said anti-CGRP antibody comprises any one of Ab1-Ab14 or a fragment thereof.

[0577] E104. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E103, wherein said anti-CGRP antibody comprises Ab6 or a fragment thereof.

[0578] E105. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E104, wherein said anti-CGRP antibody comprises the light chain complementarity-determining region (CDR) 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively.

[0579] E106. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of

embodiments E87-E105, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively.

[0580] E107. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E106, wherein said anti-CGRP antibody comprises the heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively.

[0581] E108. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E107, wherein said anti-CGRP antibody comprises the heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively.

[0582] E109. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E108, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively.

[0583] E110. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E109, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively.

[0584] E111. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E110, wherein said anti-CGRP antibody comprises the variable light chain polypeptide of SEQ ID NO: 222.

[0585] E112. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E111, wherein said anti-CGRP antibody comprises the variable light chain polypeptide encoded by SEQ ID NO: 232.

[0586] E113. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E112, wherein said anti-CGRP antibody comprises the variable heavy chain polypeptide of SEQ ID NO: 202.

[0587] E114. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E113, wherein said anti-CGRP antibody comprises the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

[0588] E115. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E114, wherein said anti-CGRP antibody comprises the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202.

[0589] E116. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E115, wherein said anti-CGRP antibody comprises the variable light chain polypeptide encoded by SEQ ID NO: 232 and the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

[0590] E117. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E116, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221.

[0591] E118. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E117, wherein said anti-CGRP antibody comprises the light chain polypeptide encoded by SEQ ID NO: 231.

[0592] E119. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E118, wherein said anti-CGRP antibody comprises the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

[0593] E120. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E119, wherein said anti-CGRP antibody comprises the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

[0594] E121. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E120, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

[0595] E122. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E121, wherein said anti-CGRP antibody comprises the light chain polypeptide

encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

[0596] E123. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E122, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is expressed in or obtained by expression in Pichia pastoris.

[0597] E124. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E123, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is expressed in or obtained by expression in CHO cells.

[0598] E125. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E124, wherein the administered amount of said anti-CGRP antibody is between about 100 mg and about 300 mg, or is about 100 mg, or is about 300 mg.

[0599] E126. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E125, wherein the administered amount of said anti-CGRP antibody is 100 mg.

[0600] E127. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E126, further comprising intravenously administering 100 mg of said anti-CGRP antibody every 12 weeks.

[0601] E128. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E127, further comprising intravenously administering 300 mg of said anti-CGRP antibody every 12 weeks.

[0602] E129. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E128, wherein said patient is a chronic migraine patient or episodic migraine or cluster headache patient at risk of developing medication overuse headache.

[0603] E130. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E129, wherein said patient uses acute headache medication on at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 day(s) per month, wherein optionally said acute medication use is determined over a baseline period of at least 28 days.

[0604] E131. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E130, wherein said patient uses acute headache medication on at least 10 days per

month, wherein optionally said acute medication use is determined over a baseline period of at least 28 days.

[0605] E132. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E131, wherein said medication overuse headache comprises (a) headache occurring on 15 or more days/month in said patient, wherein said patient has a pre-existing headache disorder; and (b) overuse by said patient for more than 3 months of one or more drugs taken for acute and/or symptomatic treatment of headache.

[0606] E133. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any of embodiments E87-E132, wherein, prior to said administration, the patient exhibits between about 15 and about 22 migraine days per month.

[0607] E134. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any of embodiments E87-E133, wherein, prior to said administration, the patient exhibits between about 15 and about 27 headache days per month.

[0608] E135. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any of embodiments E87-E134, wherein, prior to said administration, the patient exhibits between about 17 and about 24 headache days per month.

[0609] E136. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any of embodiments E87-E135, wherein, prior to said administration, the patient exhibits between about 15 and about 19 migraine days per month, or about 20 or about 21 headache days per month, or about 16 migraine days per month.

[0610] E137. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any of embodiments E87-E136, wherein said patient was diagnosed with migraine at least 10 years prior to said administration.

[0611] E138. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any of embodiments E87-E137, wherein said patient was diagnosed with migraine at least 15 years prior to said administration.

[0612] E139. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any of embodiments E87-E138, wherein said patient was diagnosed with migraine at least 18 or at least 19 years prior to said administration.

[0613] E140. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any of embodiments E87-E139, wherein said patient has a reduction in the number of migraine days by at least 50% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0614] E141. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any of embodiments E87-E140, wherein said patient has a reduction in the number of migraine days by at least 75% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0615] E142. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any of embodiments E87-E141, wherein said patient has a reduction in the number of migraine days by 100% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0616] E143. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any of embodiments E87-E142, wherein said patient has a reduction in the number of migraine days by at least 50% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0617] E144. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any of embodiments E87-E143, wherein said patient has a reduction in the number of migraine days by at least 75% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0618] E145. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any of embodiments E87-E144, wherein said patient has a reduction in the number of migraine days by 100% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

[0619] E146. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E145, further comprising administering a second dose of said anti-CGRP antibody to said patient about 12 weeks or about 3 months after said administration.

[0620] E147. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E146, wherein said administration comprises administering about 100 mg, about

125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, or about 300 mg of said anti-CGRP antibody.

[0621] E148. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E147, wherein said anti-CGRP antibody or antibody fragment is aglycosylated or if glycosylated only contains only mannose residues.

[0622] E149. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E148, wherein said anti-CGRP antibody consists of the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

[0623] E150. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E149, wherein said anti-CGRP antibody consists of the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

[0624] E151. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E150, wherein said medication overuse headache comprises (a) headache occurring on 15 or more days/month in said patient, wherein said patient has a pre-existing headache disorder; and (b) overuse by said patient for more than 3 months of one or more drugs.

[0625] E152. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E151, wherein said medication overuse comprises use of ergotamine on 10 or more days/month, use of a triptan on 10 or more days/month, use of one or more non-opioid analgesics (such as paracetamol (acetaminophen), acetylsalicylic acid (aspirin), another NSAID, or another non-opioid analgesic) on 15 or more days/month, use of one or more combination-analgesics (as further described below) on 10 or more days/month, use of one or more opioids on 10 or more days/month, or use of a combination of two or more drug classes (as further described below) on 10 or more days/month, wherein said triptan use optionally comprises use of one or more of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan, and/or wherein said opioid use optionally comprises use of one or more of oxycodone, tramadol, butorphanol, morphine, codeine, and hydrocodone.

[0626] E153. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E152, wherein said medication overuse headache comprises ergotamine-overuse headache, triptan-overuse headache, non-opioid analgesic-overuse headache, opioid-overuse headache, combination-analgesic-overuse headache, medication-overuse headache attributed to

multiple drug classes not individually overused, medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes, or medication-overuse headache attributed to other medication, wherein said triptan use optionally comprises use of one or more of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan, and/or wherein said opioid use optionally comprises use of one or more of oxycodone, tramadol, butorphanol, morphine, codeine, and hydrocodone.

[0627] E154. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E153, wherein said non-opioid analgesic-overuse headache comprises paracetamol (acetaminophen)-overuse headache, non-steroidal anti-inflammatory drug (NSAID)-overuse headache such as acetylsalicylic acid (aspirin)-overuse headache, or other non-opioid analgesic-overuse headache.

[0628] E155. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E154, wherein said ergotamine-overuse headache comprises headache occurring on 15 or more days/month and use of ergotamine on 10 or more days/month for more than 3 month.

[0629] E156. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E155, wherein said triptan-overuse headache comprises headache occurring on 15 or more days/month and use of one or more triptans on 10 or more days/month for more than 3 months, wherein said triptan use optionally comprises use of one or more of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan.

[0630] E157. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E156, wherein said non-opioid analgesic-overuse headache comprises headache occurring on 15 or more days/month and use of one or more non-opioid analgesics (such as paracetamol (acetaminophen), acetylsalicylic acid (aspirin), another NSAID, or another non-opioid analgesic) on 15 or more days/month for more than 3 months.

[0631] E158. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E157, wherein said combination-analgesic-overuse headache comprises headache occurring on 15 or more days/month and use of one or more combination-analgesics on 10 or more days/month for more than 3 months, wherein said combination-analgesic comprises drugs of two or more classes, each with analgesic effects (for example, paracetamol and codeine) or acting as adjuvants (for example, caffeine), optionally wherein said combination-analgesics combine non-opioid analgesic includes at least one opioid (such as tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof), barbiturate such as butalbital and/or caffeine.

[0632] E159. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E158, wherein said opioid-overuse headache comprises headache occurring on 15 or more days/month and use of one or more opioids (such as oxycodone, tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof) on 10 or more days/month for more than 3 months.

[0633] E160. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E159, wherein said medication-overuse headache attributed to multiple drug classes not individually overused comprises headache occurring on 15 or more days/month and use of any combination of ergotamine, triptans (such as sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, frovatriptan, or any combination thereof), non-opioid analgesics and/or opioids (such as oxycodone, tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof) on a total of at least 10 days/month for more than 3 months.

[0634] E161. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E160, wherein said medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes comprises headache occurring on 15 or more days/month and use of any combination of ergotamine, triptans (such as sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, frovatriptan, or any combination thereof), non-opioid analgesics and/or opioids (such as oxycodone, tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof) on at least 10 days/month for more than 3 months, wherein the identity, quantity and/or pattern of use or overuse of these classes of drug is not reliably established.

[0635] E162. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E161, wherein said medication-overuse headache attributed to other medication comprises headache occurring on 15 or more days/month and use of one or more medications other than those described above, taken for acute or symptomatic treatment of headache, on at least 10 days/month for more than 3 months.

[0636] E163. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E162, wherein said patient had a pre-existing primary headache prior to developing said medication overuse headache.

[0637] E164. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E163, wherein headache days and/or medication use days are determined by reporting by the patient or a relative, a diary, medical records, drug purchase history, prescription

fulfilment, biomarkers of medication use, incidence of medication toxicity, incidence of medication overdose, and/or other indicators of a patient's medication use.

[0638] E165. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E164, wherein said medication-overuse headache is diagnosed according to the third edition of the International Classification of Headache Disorders, wherein said medication–overuse headache optionally comprises ergotamine-overuse headache, triptan-overuse headache, non-opioid analgesic-overuse headache, opioid-overuse headache, combination-analgesic-overuse headache, medication-overuse headache attributed to multiple drug classes not individually overused, medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes, or medication-overuse headache attributed to other medication.

[0639] E166. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to any one of embodiments E87-E165, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is comprised in a formulation comprising or consisting of histidine (L-histidine), sorbitol, polysorbate 80, and water.

[0640] E167. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to embodiment E166, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within 10% of said values, and having a pH of 5.8 or within +/-10% of said value.

[0641] E168. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to embodiment E166, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 5% of said values, and/or having a pH of 5.8 or within +/-5% of said value.

[0642] E169. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to embodiment E166, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 1% of said values, and/or having a pH of 5.8 or within 1% of said value.

[0643] E170. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to embodiment E166, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 0.5% of said values, and/or having a pH of 5.8 or within 0.5% of said value.

[0644] E171. The at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment for use according to embodiment E166, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 0.1% of said values, and/or having a pH of 5.8 or within 0.1% of said value.

EXAMPLES

[0645] The following examples are provided in order to illustrate the invention, but are not to be construed as limiting the scope of the claims in any way.

[0646] EXAMPLE 1

[0647] Preparation of Antibodies that Bind CGRP

[0648] The preparation of exemplary anti-CGRP antibodies Ab1-Ab14 having the sequences in **FIGs. 1A-12** is disclosed in commonly owned PCT Application WO/2012/162243, published on November 29, 2012, the contents of which are incorporated by reference herein. This application exemplifies synthesis of these antibodies in *Pichia pastoris* cells. The present Applicant further contemplates synthesis of anti-CGRP antibodies Ab1-Ab14, and Ab6 in particular in CHO cells.

[0649] EXAMPLE 2

[0650] Human Clinical Study Evaluating the Safety and Efficacy of an Anti-CGRP Antibody According to the Invention

[0651] CLINICAL TREATMENT PROTOCOL

[0652] The humanized anti-CGRP IgG1 antibody identified herein as Ab6 was assessed in human subjects for its ability to inhibit, alleviate or prevent the number of, duration, and/or the intensity of migraine episodes. The Ab6 antibody contains the V_L and light chain polypeptides respectively in SEQ ID NO: 222 and SEQ ID NO: 221, and contains the V_H and heavy chain polypeptides respectively in SEQ ID NO: 202 and SEQ ID NO: 201. This antibody comprises an IgG1 constant region that contains a mutation in the heavy chain constant region (replacement of asparagine residue at position 297 with an alanine residue which substantially eliminates glycosylation and lytic activity (*see* US Patent No. 5,624,821).

[0653] Specifically, the clinical efficacy of the Ab6 antibody was tested in a placebo controlled double-blind, randomized study. The individuals in the study were all selected based on specific criteria. Particularly all were diagnosed as migraine sufferers at $\leq$ 50 years of age (ICHD-II, 2004 Section 1), and further had a history of migraine $\geq$ 12 months with $\geq$ 5 and $\leq$ 14 migraine days in each 28 day period in the 3 months prior to screening.

[0654] Further, all of the individuals in the study used acute migraine medications $\leq$ 14 days per 28 day period and, within those days, $\leq$ 10 days of triptan use per 28 day period in the 3 months prior to screening and the 28 day period of completion of eDiary prior to randomization.

[0655] Table 1 summarizes the demographic characteristics of the study population.

Table 1: Baseline Demographics and Clinical Characteristics		
Characteristic	**Placebo iv (n=82)**	**Ab6 1000mg iv (n=81)**
Mean ±SD Age (years)	39.0 (9.6)	38.6 (10.8)
Mean ±SD Weight (kg)	75.4 (14.4)	75.0 (16.5)
Female Gender	66 (80%)	67 (83%)
Race:		
Caucasian	66 (80.5%)	66 (81.5%)
African American	9 (11.0%)	10 (12.4%)
Asian	3 (3.7%)	4 (5.0%)
Other	4 (4.8%)	1 (1.1%)
Baseline (per 28 days):		
Mean ±SD Migraine Days	8.8 (2.7)	8.4 (2.1)
Mean ±SD Migraine Episodes	6.7 (2.4)	6.0 (2.2)
Mean ±SD Headache Frequency	9.6 (2.8)	9.2 (2.6)
Mean ±SD Migraine Hours	72.2 (51.0)	80.1 (49.1)
Mean ±SD HIT-6 Score	64.5 (4.44)	63.8 (5.21)
Mean ±SD MSQ RFP Score	49.0 (17.9)	49.5 (21.2)
Mean ±SD MSQ RFR Score	61.9 (22.7)	63.9 (24.0)
Mean ±SD MSQ EF Score	59.5 (22.9)	59.8 (27.0)

[0656] Throughout the study all of the individuals were required to record their migraine status daily using an e-diary. In the e-diary the subjects in the study were required to record the number of migraine days/month, migraine episodes/month, migraine hours/month, migraine severity, and the use of any abortive medicine such as triptans.

[0657] In addition, the study participants were required to use the e-diary to record their migraine status in the 28 day period prior to treatment with antibody or placebo in order to establish a migraine day/hour/episode baseline per month. Also, this allowed the subjects in the study to become familiar with the use of the e-diary.

[0658] After the 28-day run-in the subjects in the study were broken into two groups, each including 80 subjects (**FIG. 17**). In the first group, i.e., the antibody treatment group, (n=80) each subject in the group was administered intravenously a single 1000 mg dose of Ab6. In the second group (n=80), i.e., the placebo group, each of the subjects was given an intravenous injection containing only the aqueous antibody carrier solution.

[0659] The individuals in the treated and placebo groups were assessed in the 24 weeks post-dose administration. Initially, a 12 week interim analysis was conducted. Subsequent to the 12 week interm analysis, a refined analysis was conducted. This refined analysis potentially included, for example, addition or removal of patient data in accord with the study protocol, e.g., updating data that had not been fully loaded from the e-diaries. This refinement resulted in slight changes but did not alter the overall conclusions.

[0660] The efficacy of the antibody versus the placebo was assessed in part based on the recorded data in the e-diary entries. For example, this analysis included a comparison of the number of recorded migraine days/month, migraine episodes/month, migraine hours/month in the subjects in the treated versus the placebo group. The percentage of responders in each group (i.e., the subjects with 50%, 75%, and 100% reduction in migraine days) in both groups was also compared.

[0661] In addition, the responses of the Ab6- and placebo-treated subjects in both groups to MSQ and HIT-6 questionnaires are to be evaluated and compared. MSQ is a frequently utilized disease-specific tool to assess the impact of migraine on health-related quality of life (HRQL). MSQ comprises a 16-item Migraine-Specific Quality-of-Life Questionnaire (Version 1.0), which was developed by Glaxo Wellcome Inc. MSQ is hypothesized to measure 3 parameters: (i) Role Function-Restrictive; (ii) Role Function-Preventive; and (iii) Emotional Function.

[0662] The HIT-6 or functional impact (also called the Headache Impact Test or HIT-6) similarly is a well known tool for assessing migraine intensity. This test uses six questions to capture the impact of headache and its treatment on an individual's functional health and well-being.

[0663] Also, the pharmacokinetic (PK) properties of the CGRP antibody and immunogenicity are to be assessed in the Ab6 antibody treated subjects.

[0664] CLINICAL RESULTS AND ANALYSIS

[0665] The results of this human clinical trial and analysis through week 12 in the treated subjects are summarized in the Table 2 below.

[0666] Table 2. Responder analysis for migraine days

Time period	% reduction migraine days	Placebo iv	Ab6 1000mg iv	P value
Week 1-4		n=80	n=75	

	50	40 (50.0)	58 (77.3)	p=0.0005
	75	19 (23.8)	39 (52.0)	p=0.0005
	100	4 (5.0)	21 (28.0)	p=0.0001
Week 5-8		n=80	n=78	
	50	43 (53.8)	59 (75.6)	p=0.0048
	75	28 (35.0)	35 (44.9)	p=0.2555
	100	12 (15.0)	21 (26.9)	p=0.0791
Week 9-12		n=77	n=72	
	50	51 (66.2)	54 (75.0)	p=0.2827
	75	24 (31.2)	38 (52.8)	p=0.0083
	100	13 (16.9)	29 (40.3)	p=0.0019

[0667] In addition, the results of the clinical study were compared based on the number of responders in the treatment and placebo groups. As shown in **FIG. 13** the number of subjects who showed a 50, 75 or 100% reduction in migraine days for each month of the interim period were compared in the treatment and placebo groups. As shown in the figure, 60% of the Ab6- treated group had at least 50 % reduction in headache days, 31% of the Ab6- treated group had at least 75 % reduction in headache days and 15 % of the Ab6 treated group had 100 % reduction in headache days.

[0668] By contrast, 33% of the placebo-treated group had at least 50 % reduction in headache days, 9% of the placebo-treated group had at least 75 % reduction in headache days, and 0 % (none) of the placebo- treated group had 100 % reduction in headache days.

[0669] These results clearly show that the reduction in the number of migraine days was much greater in the Ab6-treated group. But for the significant placebo effect, the difference in these numbers would have been more pronounced. (Elevated placebo effect is not surprising as the phenomenon is often very high for migraine and other neurological drugs).

[0670] In addition, the % change from baseline in the number of migraine days per month in the placebo and Ab6 –treated group was compared. As shown in **FIG. 14**, the median (± QR) % change from baseline in the number of migraine days per month in the placebo and Ab6 –treated group was compared for the 2 groups during the 12 weeks post-treatment. These results which are statistically significant (p=0.0078) clearly show the Ab6-treated group had a much greater reduction in the number of headache days per month compared to baseline than the placebo-treated group.

[0671] Also, the % change from baseline in the number of migraine episodes per month in the placebo and Ab6 –treated group was compared. As shown in **FIG. 15** the median (± QR) % change from baseline in the number of migraine episodes per month in the placebo and Ab6 –treated group was compared during the 12 weeks post-treatment. These results indicate that the Ab6-treated group had a significantly greater reduction in the number of migraine episodes per month compared to baseline than the placebo-treated group.

[0672] Further, the % change from baseline in the number of migraine hours per month in the placebo and Ab6-treated group was compared. As shown in **FIG. 16**, the median (± QR) % change from baseline in the number of migraine hours per month in the placebo and Ab6 –treated group was compared for the 2 groups during the 12 weeks post-treatment. These results clearly show the Ab6-treated group had a greater reduction in the number of migraine hours per month compared to baseline than the placebo-treated group.

[0673] In addition, the HIT-6 results were compared for both groups. As noted, this questionnaire finds well accepted usage in assessing the migraine status of individuals with frequent/chronic migraine. **FIG. 18** compares the HIT-6 responder analysis for the Ab6-treated and placebo groups at baseline, week 4 after treatment, week 8 after treatment and week 12 after treatment. The results at each time point reveal that the Ab6-treated group had a statistically significant improvement in the HIT-6 scores relative to the placebo group, i.e., 54.4% for the Ab6-treated compared to 30% for the placebo at week 4 (p=0.0023), 51.3% for the Ab6-treated compared to 38.0% for the placebo at week 8 (p=0.1094) and 61.1% for the Ab6-treated compared to 33.3% for the placebo at week 12 (p=0.0007). **FIG. 19** shows the percentage of patients having a HIG-6 score of some or little/none over time in the placebo and Ab6 treatment groups (statistical significance a shown).

[0674] In addition, **FIG. 20** contains the pharmacokinetic (PK) profile for Ab6 administered intravenously at a single dosage of 1000 mg in mg/mL over the 24 week period following Ab6 administration.

[0675] **FIG. 21** contains plasma-free pharmacokinetic (PK) parameters N (number of patients), mean, and standard deviation (SD) for a single 1000 mg intravenous dosage of Ab6. The parameters shown in the table and the units are C_{max} (μg/mL), $AUC_{0-\infty}$ (mg*hr/mL), half-life (days), V_z (L) and C_L (mL/hr).

[0676] Further analysis was conducted for patient data between 12-weeks and 24-weeks. The treatment group continued to exhibit decreased migraine days relative to the control group, however, the magnitude of the difference decreased over time. Additionally, the control group exhibited fewer migraine days per month than at baseline. This was thought to result at least in part from "diary fatigue" wherein patients potentially report no migraine on a day in which a migraine actually occurred, in order to avoid the time and effort of answering further queries about the migraine that would result from giving an affirmative answer to the question of whether they had a migraine on a given day.

[0677] Further analysis of the study results are shown in **FIGs. 22-33**. These result include analysis of the change (mean +/- SEM) from baseline in migraine days per month for Ab6 (1000 mg i.v.) versus placebo (**FIG. 22**), change in average migraine days (+/- SD) over time for the full analysis population (**FIG. 23**). Additionally, shown are the distribution of migraine days actual and change for the Ab6 treatment group during weeks 1-4 (**FIG. 24**), distribution of migraine days actual and change for the placebo group during weeks 1-4 (**FIG. 25**), distribution of migraine days actual and change for the Ab6 treatment group during weeks 5-8 (**FIG. 26**), distribution of migraine days actual and change for the placebo group during weeks 5-8 (**FIG. 27**), distribution of migraine days actual and change for the Ab6 treatment group during weeks 9-12 (**FIG. 28**), and distribution of migraine days actual and change for the placebo group during weeks 9-12 (**FIG. 29**).

[0678] Responder rate analysis was also performed (**FIGs. 30-32**). These figures respectively show the 50%, 75%, and 100% responder rate for the Ab6 and placebo treatment groups. Subjects with ≥ 50% reduction in migraine frequency were considered to be a 50% responder. Subjects with ≥ 75% reduction in migraine frequency were considered to be a 75% responder. Likewise, subjects with 100% reduction in migraine frequency were considered to be a 100% responder.

[0679] In **FIGs. 22 and 30-32**, normalization was applied to visit intervals where eDiaries were completed for 21-27 days by multiplying the observed frequency by the inverse of the completion rate.

[0680] Migraine severity was also analyzed. **FIG. 33** shows the mean migraine severity over time for the full analysis population. On the scale used, a mean migraine score of 3 represents "moderate pain."

[0681] **FIG. 34** summarizes the change from baseline in migraine days, migraine episodes, migraine hours, average migraine severity, headache frequency, and outcome measures including the HIT-6 score, MSQ (Migraine Specific Quality of Life Questionnaire) RFP (Role Function-Preventative), MSQ RFR (Role Function-Restrictive), and MSQ EF (Emotional Function).

[0682] EXAMPLE 3

[0683] Human Clinical Study Evaluating the Safety and Efficacy of an Anti-CGRP Antibody in Chronic Migraine Patients

[0684] This example describes a randomized, double-blind, placebo-controlled clinical trial evaluating the safety and efficacy of Ab6 for chronic migraine prevention. In the study, 1,072 patients were randomized to receive Ab6 (300 mg or 100 mg), or placebo administered by infusion once every 12 weeks. To be eligible for the trial, patients must have experienced at least 15 headache days per month, of which at least eight met criteria for migraine. Patients that participated in the trial had an average of 16.1 migraine days per month at baseline. Study endpoints included the mean change from baseline in monthly migraine days, reduction in migraine prevalence at day 1 and over days 1-28, and reduction of at least 50%, 75%, and 100% from baseline in mean monthly migraine days, change from baseline in mean monthly acute migraine-specific medication days, and reductions from baseline in patient-reported impact scores on the Headache Impact Test (HIT-6). The administered antibody, Ab6, is an anti-CGRP antibody consisting of the light chain polypeptide of SEQ ID NO: 221 and heavy chain polypeptide of SEQ ID NO: 201.

[0685] Patient characteristics are summarized in **FIG. 39**, with separate columns for patients receiving placebo, 100 mg of the antibody, or 300 mg of the antibody. Patients had a mean number of years from migraine diagnosis of between 17.0 and 19.0 years, a mean duration of suffering from chronic migraine of between 11.5 and 12.4 years, and between 44.3% and 45.2% of patients utilized at least one prophylactic medication. At baseline, in both antibody treatment groups the mean number of migraine days per month was 16.1, while for the placebo group, the mean number of migraine days per month was 16.2.

[0686] The reduction in a specified percentage (50%, 75%, or 100%) from baseline in mean monthly migraine days refers to the number or percentage of patients in a treatment group that exhibited the given percentage reduction in the number of migraine days per month. For example, a patient exhibiting 16 migraine days per month at baseline would be a 75% responder if the number of migraine days per month was decreased by at least 12 days per month over specified period.

[0687] The results are shown in **FIGs. 35-39**. **FIG. 35** shows the percentages of patients with migraine in the 300 mg, 100 mg, and placebo treatment groups at days 1, 7, 14, 21, and 28. The uppermost line shows results for placebo, the lowest line shows results for the 300 mg dosage, and the middle line shows results for the 100 mg dosage.

[0688] As shown in **FIG. 35**, at day 1 the percentage reduction in migraine prevalence was 52% for the 300 mg dosage, 50% at the 100 mg dosage, and 27% for placebo. The decrease was statistically significant compared to the placebo group for both the 100 mg and 300 mg treatment groups.

[0689] **FIGs. 36-38** show the percentage of patients in the 300 mg and 100 mg treatment groups achieving, respectively, 50%, 75%, and 100% reduction in migraine days in month 1, over months 1-3 (after the 1st infusion), and over months 4-5 (after the 2nd infusion). In each graph, the data bars, from left to right, show results for the 100 mg, 300 mg, and placebo groups. Statistical significance is as shown. ++ indicates a statistically significant difference from placebo; + indicates a statistically

significant difference from placebo (unadjusted); and § indicates a statistically significant difference from placebo (post hoc).

[0690] EXAMPLE 4

[0691] Baseline Subgroup Analysis for Human Clinical Studies Evaluating the Safety and Efficacy of an Anti-CGRP Antibody in Chronic or Episodic Migraine Patients

[0692] In the study of Chronic Migraine described in Example 3, at intake, each patient was assessed for potential medication overuse headache (MOH). MOH was present in 39.9% (139 patients) in the 100 mg treatment group, 42.0% (147 patients) in the 300 mg treatment group, and 39.6% (145 patients) in the placebo group. Assessment of the treatment outcomes in this patient subset indicated that treatment with the anti-CGRP antibody was efficacious for MOH (**FIG. 41**). Specifically, in the 100 mg treatment group, mean migraine days per month changed by -3.0 days (95% CI, -4.56 to -1.52 days) in the patients having MOH at baseline, compared to MOH patients receiving placebo. Similarly, in the 300 mg treatment group, mean migraine days per month changed by -3.2 days (95% CI, -4.66 to -1.78 days) in the patients having MOH at baseline, compared to MOH patients receiving placebo. By contrast, for patients without MOH at baseline, in the 100 mg treatment group, mean migraine days per month changed by -1.3 days (95% CI, -2.43 to -0.16 days), compared to patients without MOH at baseline receiving placebo. Likewise, for patients without MOH at baseline in the 300 mg treatment group, mean migraine days per month changed by -2.1 days (95% CI, -3.24 to -0.88 days), compared to patients without MOH at baseline receiving placebo. Efficacy for other subgroups was shown as well, including efficacy for patients with mean migraine day (MMD) frequency less than 17 days or greater than or equal to 17 days, patients with an age at diagnosis of less than or equal to 21 years or greater than 21 years, patients having a duration of migraine of less than or equal to 15 year or greater than 15 years, patients suffering from migraine with aura or migraine with no aura, patients with prior prophylactic medication use or no prior prophylactic medication use, patients with concomitant prophylactic medication use or no concomitant prophylactic medication use, ant patients with triptan use on greater than or equal to 33% of days, or less than 33% of days. In each case, efficacy for each subgroup was shown (**FIG. 41**).

[0693] In another human clinical trial of patients with episodic migraine, patients were randomized to receive Ab6 100 mg (n=221), 300 mg (n=222), or placebo (n=222) in a double blind, parallel study. After a 28 day screening period, patients were administered the drug or placebo intravenously every 3 months for 4 total infusions (**FIG. 40**). Efficacy was shown over months 1-3 for both the 100 mg and 300 mg treatment groups, with a mean change in migraine days of -3.9 for the 100 mg treatment group and -4.3 days for the 300 mg treatment group, compared to -3.2 days for the placebo group. Efficacy for subgroups of patients was also shown, including efficacy for patients with mean migraine day (MMD) frequency less than or equal to 9 days or greater than 9 days, patients with an age at diagnosis of less than or equal to 21 years or greater than 21 years, patients having a

duration of migraine of less than or equal to 15 year or greater than 15 years, and patients suffering from migraine with aura or migraine with no aura.

[0694] EXAMPLE 5

[0695] Effects of Ab6 treatment on medication use in chronic and episodic migraine patients

[0696] During the studies of chronic migraine patients described in Example 3 and episodic migraine patients described in Example 4, patients also recorded use of acute medication in a daily eDiary and were allowed to use acute medication at their own discretion. Acute medications for migraine included ergots, triptans, and analgesics (e.g., NSAIDS, opioids, and caffeine-containing combination analgesics).

[0697] For further analysis, patients were stratified by the number of days with acute medication use during the 28-day screening period (1-9 or ≥10 days; "baseline"). Acute medication days were calculated for individual types of acute medications and combined, meaning that if 2 or more types medications were used on the same calendar days, they were counted as separate medication use days. For example, if a patient took an opioid and a triptan on the same day, it counted as 2 days of acute medication use. These analyses included patients with at least 1 acute medication use day during the 28-day baseline screening period.

[0698] In both chronic migraine and episodic migraine patients who used acute medication during the 28-day baseline period, Ab6 treatment resulted in greater average reductions in monthly migraine days and acute medication days than placebo as early as Month 1 after dosing, with similar results across 2 dose intervals over 6 months.

[0699] Ab6 consistently demonstrated greater reductions in mean monthly migraine days over 6 months of treatment than placebo in chronic migraine patients taking ≥1 day of acute medication use during baseline (**FIG. 42**). Chronic migraine patients who had at least one day of acute medication use per month during baseline demonstrated greater decreases in acute medication use than placebo as early as month 1 after treatment and across the entire 6 month treatment period (**FIG. 43**). In the subgroup of chronic migraine patients who were taking 1–9 days of acute medication during baseline, the change from baseline in days of acute medication use was greater in the 300 mg Ab6 group than placebo across 6 months of treatment (**FIG. 44**). A clear decrease in medication days per month was observed for patients with at least 10 days of medication use per month at baseline for both Ab6 treatment group compared to placebo over the entire 6 month period. **FIG. 45** shows the changes in medication use days at Month 1 and Month 6 in the subgroups of chronic migraine patients with ≥1, 1–9, and ≥10 days of acute medication use at baseline. With the exception of Ab6 100 mg at month 6 in patients with 1–9 days/month of use at baseline, Ab6 demonstrated a greater treatment effect in reducing acute medication use than placebo.

[0700] Similarly, across 2 dose intervals over 6 months, episodic migraine patients with one or more days of acute medication use during baseline experienced greater reductions in mean monthly migraine days with Ab6 than Placebo (**FIG. 46**). Episodic migraine patients who had at least one day

of acute medication use per month during baseline demonstrated greater decreases in acute medication use than placebo as early as month 1 after treatment and across the entire 6 month treatment period (**FIG. 47**). In the subgroup of episodic migraine patients who were taking 1–9 days of acute medication during baseline, the change from baseline in days of acute medication use was greater with Ab6 than placebo across 6 months of treatment (**FIG. 48**). A similar pattern was observed in the subgroup of patients who were taking ≥10 days of acute medication during baseline, though smaller sample sizes may have contributed to the less consistent pattern over time. **FIG. 49** shows the changes in medication use days at Month 1 and Month 6 in the subgroups of episodic migraine patients with ≥1, 1–9, and ≥10 days of acute medication use at baseline. With the exception of Ab6 100 mg at Month 6 in patients with ≥10 days/month of use at baseline, the reduction in acute medication use was greater in the Ab6 treatment groups than placebo.

[0701] The results show that both episodic migraine and chronic migraine patients who were at risk for medication-overuse headache (≥10 days/month of acute medication use) demonstrated the greatest reductions in acute medication use, with Ab6 treatment generally resulting in larger decreases in medication use days than placebo.

[0702] The most frequently reported acute headache medications in > 10% of subjects included Thomapyrin N (44.5%) (a combination of paracetamol, aspirin, and caffeine), ibuprofen (40.6%), sumatriptan (33.6%), paracetamol (acetaminophen) (20.3%), and naproxen sodium (10.2%). The most frequently reported preventive headache medication in > 10% of subjects was topiramate (12.5%).

CLAIMS

What is claimed is:

1. A method of treating or preventing medication overuse headache, comprising administering to a patient in need an effective amount of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment.

2. A method of treating or preventing probable medication overuse headache, comprising administering to a patient in need an effective amount of at least one anti-CGRP antibody or anti-CGRP antibody fragment or anti-CGRP-R antibody or anti-CGRP-R antibody fragment.

3. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises any one of Ab1-Ab14 or a fragment thereof.

4. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises Ab6 or a fragment thereof.

5. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the light chain complementarity-determining region (CDR) 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively.

6. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively.

7. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively.

8. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively.

9. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively.

10. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ

ID NO: 236; and SEQ ID NO: 238, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively.

11. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the variable light chain polypeptide of SEQ ID NO: 222.

12. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the variable light chain polypeptide encoded by SEQ ID NO: 232.

13. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the variable heavy chain polypeptide of SEQ ID NO: 202.

14. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

15. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202.

16. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the variable light chain polypeptide encoded by SEQ ID NO: 232 and the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

17. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221.

18. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the light chain polypeptide encoded by SEQ ID NO: 231.

19. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

20. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

21. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

22. The method of any one of the foregoing claims, wherein said anti-CGRP antibody comprises the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

23. The method of any one of the foregoing claims, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is expressed in or obtained by expression in *Pichia pastoris*.

24. The method of any one of the foregoing claims, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is expressed in or obtained by expression in CHO cells.

25. The method of any one of the foregoing claims, wherein the administered amount of said anti-CGRP antibody is between about 100 mg and about 300 mg, or is about 100 mg, or is about 300 mg.

26. The method of any one of the foregoing claims, wherein the administered amount of said anti-CGRP antibody is 100 mg.

27. The method of any one of the foregoing claims, further comprising intravenously administering 100 mg of said anti-CGRP antibody every 12 weeks.

28. The method of any one of claims 1-26, further comprising intravenously administering 300 mg of said anti-CGRP antibody every 12 weeks.

29. The method of any one of the foregoing claims, wherein said patient is a chronic migraine patient or episodic migraine or cluster headache patient at risk of developing medication overuse headache.

30. The method of claim 29, wherein said patient uses acute headache medication on at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 day(s) per month, wherein optionally said acute medication use is determined over a baseline period of at least 28 days.

31. The method of claim 29, wherein said patient uses acute headache medication on at least 10 days per month, wherein optionally said acute medication use is determined over a baseline period of at least 28 days.

32. The method of any one of claims 30-31, wherein said acute medication comprises use of ergot alkaloids, triptans, non-opioid analgesics, acetaminophen, aspirin, NSAIDs, non-opioid analgesics, combination-analgesics, or opioids.

33. The method of any one of the foregoing claims, wherein said medication overuse headache comprises (a) headache occurring on 15 or more days/month in said patient, wherein said patient has a

pre-existing headache disorder; and (b) overuse by said patient for more than 3 months of one or more drugs taken for acute and/or symptomatic treatment of headache.

34. The method of any of the foregoing claims wherein, prior to said administration, the patient exhibits between about 15 and about 22 migraine days per month.

35. The method of any of the foregoing claims wherein, prior to said administration, the patient exhibits between about 15 and about 27 headache days per month.

36. The method of any of the foregoing claims wherein, prior to said administration, the patient exhibits between about 17 and about 24 headache days per month.

37. The method of any of the foregoing claims wherein, prior to said administration, the patient exhibits between about 15 and about 19 migraine days per month, or about 20 or about 21 headache days per month, or about 16 migraine days per month.

38. The method of any of the foregoing claims wherein said patient was diagnosed with migraine at least 10 years prior to said administration.

39. The method of any of the foregoing claims wherein said patient was diagnosed with migraine at least 15 years prior to said administration.

40. The method of any of the foregoing claims wherein said patient was diagnosed with migraine at least 18 or at least 19 years prior to said administration.

41. The method of any of the foregoing claims, wherein said patient has a reduction in the number of migraine days by at least 50% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

42. The method of any of the foregoing claims, wherein said patient has a reduction in the number of migraine days by at least 75% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

43. The method of any of the foregoing claims, wherein said patient has a reduction in the number of migraine days by 100% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

44. The method of any of the foregoing claims, wherein said patient has a reduction in the number of migraine days by at least 50% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

45. The method of any of the foregoing claims, wherein said patient has a reduction in the number of migraine days by at least 75% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

46. The method of any of the foregoing claims, wherein said patient has a reduction in the number of migraine days by 100% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

47. The method of any one of the foregoing claims, further comprising administering a second dose of said anti-CGRP antibody to said patient about 12 weeks or about 3 months after said administration.

48. The method of any one of the foregoing claims, wherein said administration comprises administering about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, or about 300 mg of said anti-CGRP antibody.

49. The method of any one of the foregoing claims, wherein said anti-CGRP antibody or antibody fragment is aglycosylated or if glycosylated only contains only mannose residues.

50. The method of any one of the foregoing claims, wherein said anti-CGRP antibody consists of the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

51. The method of any one of the foregoing claims, wherein said anti-CGRP antibody consists of the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

52. The method of any one of the foregoing claims, wherein said medication overuse headache comprises (a) headache occurring on 15 or more days/month in said patient, wherein said patient has a pre-existing headache disorder; and (b) overuse by said patient for more than 3 months of one or more drugs taken for acute and/or symptomatic treatment of headache.

53. The method of any one of the foregoing claims, wherein said medication overuse comprises use of ergotamine on 10 or more days/month, use of a triptan on 10 or more days/month, use of one or more non-opioid analgesics (such as paracetamol (acetaminophen), acetylsalicylic acid (aspirin), another NSAID, or another non-opioid analgesic) on 15 or more days/month, use of one or more combination-analgesics (as further described below) on 10 or more days/month, use of one or more opioids on 10 or more days/month, or use of a combination of two or more drug classes (as further described below) on 10 or more days/month, wherein said triptan use optionally comprises use of one or more of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan,

and/or wherein said opioid use optionally comprises use of one or more of oxycodone, tramadol, butorphanol, morphine, codeine, and hydrocodone.

54. The method of any one of the foregoing claims, wherein said medication overuse headache comprises ergotamine-overuse headache, triptan-overuse headache, non-opioid analgesic-overuse headache, opioid-overuse headache, combination-analgesic-overuse headache, medication-overuse headache attributed to multiple drug classes not individually overused, medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes, or medication-overuse headache attributed to other medication, wherein said triptan use optionally comprises use of one or more of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan, and/or wherein said opioid use optionally comprises use of one or more of oxycodone, tramadol, butorphanol, morphine, codeine, and hydrocodone.

55. The method of any one of the foregoing claims, wherein said non-opioid analgesic-overuse headache comprises paracetamol (acetaminophen)-overuse headache, non-steroidal anti-inflammatory drug (NSAID)-overuse headache such as acetylsalicylic acid (aspirin)-overuse headache, or other non-opioid analgesic-overuse headache.

56. The method of any one of the foregoing claims, wherein said ergotamine-overuse headache comprises headache occurring on 15 or more days/month and use of ergotamine on 10 or more days/month for more than 3 month.

57. The method of any one of the foregoing claims, wherein said triptan-overuse headache comprises headache occurring on 15 or more days/month and use of one or more triptans on 10 or more days/month for more than 3 months, wherein said triptan use optionally comprises use of one or more of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan.

58. The method of any one of the foregoing claims, wherein said non-opioid analgesic-overuse headache comprises headache occurring on 15 or more days/month and use of one or more non-opioid analgesics (such as paracetamol (acetaminophen), acetylsalicylic acid (aspirin), another NSAID, or another non-opioid analgesic) on 15 or more days/month for more than 3 months.

59. The method of any one of the foregoing claims, wherein said combination-analgesic-overuse headache comprises headache occurring on 15 or more days/month and use of one or more combination-analgesics on 10 or more days/month for more than 3 months, wherein said combination-analgesic comprises drugs of two or more classes, each with analgesic effects (for example, paracetamol and codeine) or acting as adjuvants (for example, caffeine), optionally wherein said combination-analgesics combine non-opioid analgesic includes at least one opioid (such as tramadol, butorphanol,

morphine, codeine, hydrocodone, or any combination thereof), barbiturate such as butalbital and/or caffeine.

60. The method of any one of the foregoing claims, wherein said opioid-overuse headache comprises headache occurring on 15 or more days/month and use of one or more opioids (such as oxycodone, tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof) on 10 or more days/month for more than 3 months.

61. The method of any one of the foregoing claims, wherein said medication-overuse headache attributed to multiple drug classes not individually overused comprises headache occurring on 15 or more days/month and use of any combination of ergotamine, triptans (such as sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, frovatriptan, or any combination thereof), non-opioid analgesics and/or opioids (such as oxycodone, tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof) on a total of at least 10 days/month for more than 3 months.

62. The method of any one of the foregoing claims, wherein said medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes comprises headache occurring on 15 or more days/month and use of any combination of ergotamine, triptans (such as sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, frovatriptan, or any combination thereof), non-opioid analgesics and/or opioids (such as oxycodone, tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof) on at least 10 days/month for more than 3 months, wherein the identity, quantity and/or pattern of use or overuse of these classes of drug is not reliably established.

63. The method of any one of the foregoing claims, wherein said medication-overuse headache attributed to other medication comprises headache occurring on 15 or more days/month and use of one or more medications other than those described above, taken for acute or symptomatic treatment of headache, on at least 10 days/month for more than 3 months.

64. The method of any one of the foregoing claims, wherein said patient had a pre-existing primary headache prior to developing said medication overuse headache.

65. The method of any one of the foregoing claims, wherein headache days and/or medication use days are determined by reporting by the patient or a relative, a diary, medical records, drug purchase history, prescription fulfilment, biomarkers of medication use, incidence of medication toxicity, incidence of medication overdose, and/or other indicators of a patient's medication use.

66. The method of any one of the foregoing claims, wherein said medication-overuse headache is diagnosed according to the third edition of the International Classification of Headache Disorders, wherein said medication–overuse headache optionally comprises ergotamine-overuse headache,

triptan-overuse headache, non-opioid analgesic-overuse headache, opioid-overuse headache, combination-analgesic-overuse headache, medication-overuse headache attributed to multiple drug classes not individually overused, medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes, or medication-overuse headache attributed to other medication.

67. The method of any one of the foregoing claims, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is comprised in a formulation comprising or consisting of histidine (L-histidine), sorbitol, polysorbate 80, and water.

68. The method of claim 67, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within 10% of said values, and having a pH of 5.8 or within +/-10% of said value.

69. The method of claim 67, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 5% of said values, and/or having a pH of 5.8 or within +/-5% of said value.

70. The method of claim 67, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 1% of said values, and/or having a pH of 5.8 or within 1% of said value.

71. The method of claim 67, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 0.5% of said values, and/or having a pH of 5.8 or within 0.5% of said value.

72. The method of claim 67, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 0.1% of said values, and/or having a pH of 5.8 or within 0.1% of said value.

73. A pharmaceutical composition comprising or consisting of an anti-CGRP antibody or anti-CGRP antibody fragment in a formulation comprising or consisting of histidine (L-histidine), sorbitol, polysorbate 80, and water.

74. The pharmaceutical composition of claim 73, wherein said formulation comprises or consist of, per 1 mL volume, 100 mg of an anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol,

and 0.15 mg Polysorbate 80, or having amounts of each constituent within 10% of said values, and having a pH of 5.8 or within +/- 10% of said value, in an aqueous solution.

75. The pharmaceutical composition of claim 73, wherein said formulation comprises or consist of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 5% of said values, and/or having a pH of 5.8 or within 5% of said value, in an aqueous solution.

76. The pharmaceutical composition of claim 73, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 1% of said values, and/or having a pH of 5.8 or within 1% of said value.

77. The pharmaceutical composition of claim 73, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 0.5% of said values, and/or having a pH of 5.8 or within 0.5% of said value.

78. The pharmaceutical composition of claim 73, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 0.1% of said values, and/or having a pH of 5.8 or within 0.1% of said value.

79. The pharmaceutical composition of any one of claims 73-79, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively.

80. The pharmaceutical composition of any one of claims 73-79, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively.

81. The pharmaceutical composition of any one of claims 73-79, wherein said anti-CGRP antibody comprises the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202.

82. The pharmaceutical composition of any one of claims 73-79, wherein said anti-CGRP antibody comprises the variable light chain polypeptide encoded by SEQ ID NO: 232 and the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

83. The pharmaceutical composition of any one of claims 73-79, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

84. The pharmaceutical composition of any one of claims 73-79, wherein said anti-CGRP antibody comprises the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

85. The pharmaceutical composition of any one of claims 73-84, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is expressed in or obtained by expression in *Pichia pastoris*.

86. The pharmaceutical composition of any one of claims 73-84, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is expressed or obtained by expression in in CHO cells.

87. A method of treating or preventing migraine comprising administering to a patient in need thereof an effective amount of:

(i) at least one anti-CGRP antibody or anti-CGRP antibody fragment and/or at least one anti-CGRP-R antibody or anti-CGRP-R antibody fragment and

(ii) at least one medication taken for acute and/or symptomatic treatment of headache selected from the group comprising ergot alkaloids, triptans, non-opioid analgesics, acetaminophen, aspirin, NSAIDs, non-opioid analgesics, combination-analgesics, or opioids.

88. The method of claim 87, wherein the combined administration of (i) and (ii) reduces the symptoms, severity and/or episodes of medication overuse headache in the patient.

89. The method of claim 87 or 88, wherein said medication taken for acute and/or symptomatic treatment of headache comprises an ergot alkaloid.

90. The method of claim 89, wherein said ergot alkaloid is selected from ergotamine, nicergoline, methysergide, dihydroergotamine and combinations of the foregoing.

91. The method of claim 87 or 88, wherein said medication taken for acute and/or symptomatic treatment of headache comprises a triptan.

92. The method of claim 91, wherein said triptan is selected from sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, frovatriptan, and combinations of the foregoing.

93. The method of claim 87 or 88, wherein said medication taken for acute and/or symptomatic treatment of headache comprises a non-opioid analgesic.

94. The method of claim 93, wherein said non-opioid analgesic comprises paracetamol (acetaminophen), or aspirin.

95. The method of claim 87 or 88, wherein said medication taken for acute and/or symptomatic treatment of headache comprises an NSAID.

96. The method of claim 95, wherein said NSAID is selected from salicylates, propinic acid derivatives, enolic acid derivatives, anthralic acid derivatives (fenamates), selective COX-2 inhibitors (coxinbs), sulfonanilides, and combinations of the foregoing.

97. The method of claim 95, wherein said NSAID is selected from Salicylates such as Aspirin (acetylsalicylic acid), Diflunisal (Dolobid), Salicylic acid and its salts, and Salsalate (Disalcid); Propionic acid derivatives such as Ibuprofen, Dexibuprofen, Naproxen, Fenoprofen, Ketoprofen, Dexketoprofen, Flurbiprofen, Oxaprozin, and Loxoprofen; Acetic acid derivatives such as Indomethacin, Tolmetin, Sulindac, Etodolac, Ketorolac, Diclofenac, Aceclofenac, and Nabumetone, Enolic acid (oxicam) derivatives such as Piroxicam, Meloxicam, Tenoxicam, Droxicam, Lornoxicam, Isoxicam, and Phenylbutazone (Bute); Anthranilic acid derivatives (fenamates) such as Mefenamic acid, Meclofenamic acid, Flufenamic acid, and Tolfenamic acid; Selective COX-2 inhibitors (coxibs) such as Celecoxib, Rofecoxib, Valdecoxib, Parecoxib, Lumiracoxib, Etoricoxib, and Firocoxib; Sulfonanilides such as Nimesulide; Clonixin, Licofelone, H-harpagide or Devil's Claw and combinations of the foregoing.

98. The method of claim 87 or 88, wherein said medication taken for acute and/or symptomatic treatment of headache comprises a non-opioid analgesic.

99. The method of claim 87 or 88, wherein said medication taken for acute and/or symptomatic treatment of headache comprises a combination-analgesic.

100. The method of claim 99, wherein said combination-analgesics comprises the combination of a non-opioid analgesic with at least one opioid or barbiturate such as butalbital and/or caffeine or comprises the combination of acetaminophen, aspirin, and caffeine, e.g., EXCEDRIN ® or EXCEDRIN MIGRAINE ® or comprises a combination analgesic comprising an analgesic in combination with at least one non-analgesic, e.g., a vasoconstrictor drug such as pseudoephedrine, or an antihistamine drug.

101. The method of claim 87 or 88, wherein said medication taken for acute and/or symptomatic treatment of headache comprises an opioid.

102. The method of claim 101, wherein said opioid is selected from oxycodone, tramadol, butorphanol, morphine, codeine, hydrocodone, thebaine, oripavine, mixed opium alkaloids such as papaveretum, diacetylmorphine, nicomorphine, dipropanoylmorphine, diacetyldihydromorphine, acetylpropionylmorphine, desomorphine, methyldesorphine, dibenzoylmorphine, ethylmorphine, heterocodeine, buprenorphine, etorphine, hydromorphone, oxymorphone, fentanyl, alphamethylfentanyl, alfentanil, sufentanil, remifentanil, carfentanyl, ohmefentanyl, pethidine (meperidine), ketobemidone, MPPP, allylprodine, prodine, PEPAP, promedol, diphenylpropylamine, propoxyphene, dextropropoxyphene, dextromoramide, bezitramide, piritramide, and combinations of the foregoing.

103. The method of any one of claims 87-102, wherein said anti-CGRP antibody comprises any one of Ab1-Ab14 or a fragment thereof.

104. The method of any one of claims 87-103, wherein said anti-CGRP antibody comprises Ab6 or a fragment thereof.

105. The method of any one of claims 87-104, wherein said anti-CGRP antibody comprises the light chain complementarity-determining region (CDR) 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively.

106. The method of any one of claims 87-105, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively.

107. The method of any one of claims 87-106, wherein said anti-CGRP antibody comprises the heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively.

108. The method of any one of claims 87-107, wherein said anti-CGRP antibody comprises the heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively.

109. The method of any one of claims 87-108, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively.

110. The method of any one of claims 87-109, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236;

and SEQ ID NO: 238, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively.

111. The method of any one of claims 87-110, wherein said anti-CGRP antibody comprises the variable light chain polypeptide of SEQ ID NO: 222.

112. The method of any one of claims 87-111, wherein said anti-CGRP antibody comprises the variable light chain polypeptide encoded by SEQ ID NO: 232.

113. The method of any one of claims 87-112, wherein said anti-CGRP antibody comprises the variable heavy chain polypeptide of SEQ ID NO: 202.

114. The method of any one of claims 87-113, wherein said anti-CGRP antibody comprises the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

115. The method of any one of claims 87-114, wherein said anti-CGRP antibody comprises the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202.

116. The method of any one of claims 87-115, wherein said anti-CGRP antibody comprises the variable light chain polypeptide encoded by SEQ ID NO: 232 and the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

117. The method of any one of claims 87-116, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221.

118. The method of any one of claims 87-117, wherein said anti-CGRP antibody comprises the light chain polypeptide encoded by SEQ ID NO: 231.

119. The method of any one of claims 87-118, wherein said anti-CGRP antibody comprises the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

120. The method of any one of claims 87-119, wherein said anti-CGRP antibody comprises the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

121. The method of any one of claims 87-120, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

122. The method of any one of claims 87-121, wherein said anti-CGRP antibody comprises the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

123. The method of any one of claims 87-122, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is expressed in or obtained by expression in Pichia pastoris.

124. The method of any one of claims 87-123, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is expressed in or obtained by expression in CHO cells.

125. The method of any one of claims 87-124, wherein the administered amount of said anti-CGRP antibody is between about 100 mg and about 300 mg, or is about 100 mg, or is about 300 mg.

126. The method of any one of claims 87-125, wherein the administered amount of said anti-CGRP antibody is 100 mg.

127. The method of any one of claims 87-126, further comprising intravenously administering 100 mg of said anti-CGRP antibody every 12 weeks.

128. The method of any one of claims 87-127, further comprising intravenously administering 300 mg of said anti-CGRP antibody every 12 weeks.

129. The method of any one of claims 87-128, wherein said patient is a chronic migraine patient or episodic migraine or cluster headache patient at risk of developing medication overuse headache.

130. The method of any one of claims 87-129, wherein said patient uses acute headache medication on at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 day(s) per month, wherein optionally said acute medication use is determined over a baseline period of at least 28 days.

131. The method of any one of claims 87-130, wherein said patient uses acute headache medication on at least 10 days per month, wherein optionally said acute medication use is determined over a baseline period of at least 28 days.

132. The method of any one of claims 87-131, wherein said medication overuse headache comprises (a) headache occurring on 15 or more days/month in said patient, wherein said patient has a pre-existing headache disorder; and (b) overuse by said patient for more than 3 months of one or more drugs taken for acute and/or symptomatic treatment of headache.

133. The method of any of claims 87-132, wherein, prior to said administration, the patient exhibits between about 15 and about 22 migraine days per month.

134. The method of any of claims 87-133, wherein, prior to said administration, the patient exhibits between about 15 and about 27 headache days per month.

135. The method of any of claims 87-134, wherein, prior to said administration, the patient exhibits between about 17 and about 24 headache days per month.

136. The method of any of claims 87-135, wherein, prior to said administration, the patient exhibits between about 15 and about 19 migraine days per month, or about 20 or about 21 headache days per month, or about 16 migraine days per month.

137. The method of any of claims 87-136, wherein said patient was diagnosed with migraine at least 10 years prior to said administration.

138. The method of any of claims 87-137, wherein said patient was diagnosed with migraine at least 15 years prior to said administration.

139. The method of any of claims 87-138, wherein said patient was diagnosed with migraine at least 18 or at least 19 years prior to said administration.

140. The method of any of claims 87-139, wherein said patient has a reduction in the number of migraine days by at least 50% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

141. The method of any of claims 87-140, wherein said patient has a reduction in the number of migraine days by at least 75% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

142. The method of any of claims 87-141, wherein said patient has a reduction in the number of migraine days by 100% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

143. The method of any of claims 87-142, wherein said patient has a reduction in the number of migraine days by at least 50% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

144. The method of any of claims 87-143, wherein said patient has a reduction in the number of migraine days by at least 75% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

145. The method of any of claims 87-144, wherein said patient has a reduction in the number of migraine days by 100% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

146. The method of any one of claims 87-145, further comprising administering a second dose of said anti-CGRP antibody to said patient about 12 weeks or about 3 months after said administration.

147. The method of any one of claims 87-146, wherein said administration comprises administering about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, or about 300 mg of said anti-CGRP antibody.

148. The method of any one of claims 87-147, wherein said anti-CGRP antibody or antibody fragment is aglycosylated or if glycosylated only contains only mannose residues.

149. The method of any one of claims 87-148, wherein said anti-CGRP antibody consists of the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

150. The method of any one of claims 87-149, wherein said anti-CGRP antibody consists of the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

151. The method of any one of claims 87-150, wherein said medication overuse headache comprises (a) headache occurring on 15 or more days/month in said patient, wherein said patient has a pre-existing headache disorder; and (b) overuse by said patient for more than 3 months of one or more drugs.

152. The method of any one of claims 87-151, wherein said medication overuse comprises use of ergotamine on 10 or more days/month, use of a triptan on 10 or more days/month, use of one or more non-opioid analgesics (such as paracetamol (acetaminophen), acetylsalicylic acid (aspirin), another NSAID, or another non-opioid analgesic) on 15 or more days/month, use of one or more combination-analgesics (as further described below) on 10 or more days/month, use of one or more opioids on 10 or more days/month, or use of a combination of two or more drug classes (as further described below) on 10 or more days/month, wherein said triptan use optionally comprises use of one or more of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan, and/or wherein said opioid use optionally comprises use of one or more of oxycodone, tramadol, butorphanol, morphine, codeine, and hydrocodone.

153. The method of any one of claims 87-152, wherein said medication overuse headache comprises ergotamine-overuse headache, triptan-overuse headache, non-opioid analgesic-overuse

headache, opioid-overuse headache, combination-analgesic-overuse headache, medication-overuse headache attributed to multiple drug classes not individually overused, medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes, or medication-overuse headache attributed to other medication, wherein said triptan use optionally comprises use of one or more of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan, and/or wherein said opioid use optionally comprises use of one or more of oxycodone, tramadol, butorphanol, morphine, codeine, and hydrocodone.

154. The method of any one of claims 87-153, wherein said non-opioid analgesic-overuse headache comprises paracetamol (acetaminophen)-overuse headache, non-steroidal anti-inflammatory drug (NSAID)-overuse headache such as acetylsalicylic acid (aspirin)-overuse headache, or other non-opioid analgesic-overuse headache.

155. The method of any one of claims 87-154, wherein said ergotamine-overuse headache comprises headache occurring on 15 or more days/month and use of ergotamine on 10 or more days/month for more than 3 month.

156. The method of any one of claims 87-155, wherein said triptan-overuse headache comprises headache occurring on 15 or more days/month and use of one or more triptans on 10 or more days/month for more than 3 months, wherein said triptan use optionally comprises use of one or more of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan.

157. The method of any one of claims 87-156, wherein said non-opioid analgesic-overuse headache comprises headache occurring on 15 or more days/month and use of one or more non-opioid analgesics (such as paracetamol (acetaminophen), acetylsalicylic acid (aspirin), another NSAID, or another non-opioid analgesic) on 15 or more days/month for more than 3 months.

158. The method of any one of claims 87-157, wherein said combination-analgesic-overuse headache comprises headache occurring on 15 or more days/month and use of one or more combination-analgesics on 10 or more days/month for more than 3 months, wherein said combination-analgesic comprises drugs of two or more classes, each with analgesic effects (for example, paracetamol and codeine) or acting as adjuvants (for example, caffeine), optionally wherein said combination-analgesics combine non-opioid analgesic includes at least one opioid (such as tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof), barbiturate such as butalbital and/or caffeine.

159. The method of any one of claims 87-158, wherein said opioid-overuse headache comprises headache occurring on 15 or more days/month and use of one or more opioids (such as oxycodone, tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof) on 10 or more days/month for more than 3 months.

160. The method of any one of claims 87-159, wherein said medication-overuse headache attributed to multiple drug classes not individually overused comprises headache occurring on 15 or more days/month and use of any combination of ergotamine, triptans (such as sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, frovatriptan, or any combination thereof), non-opioid analgesics and/or opioids (such as oxycodone, tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof) on a total of at least 10 days/month for more than 3 months.

161. The method of any one of claims 87-160, wherein said medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes comprises headache occurring on 15 or more days/month and use of any combination of ergotamine, triptans (such as sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, frovatriptan, or any combination thereof), non-opioid analgesics and/or opioids (such as oxycodone, tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof) on at least 10 days/month for more than 3 months, wherein the identity, quantity and/or pattern of use or overuse of these classes of drug is not reliably established.

162. The method of any one of claims 87-161, wherein said medication-overuse headache attributed to other medication comprises headache occurring on 15 or more days/month and use of one or more medications other than those described above, taken for acute or symptomatic treatment of headache, on at least 10 days/month for more than 3 months.

163. The method of any one of claims 87-162, wherein said patient had a pre-existing primary headache prior to developing said medication overuse headache.

164. The method of any one of claims 87-163, wherein headache days and/or medication use days are determined by reporting by the patient or a relative, a diary, medical records, drug purchase history, prescription fulfilment, biomarkers of medication use, incidence of medication toxicity, incidence of medication overdose, and/or other indicators of a patient's medication use.

165. The method of any one of claims 87-164, wherein said medication-overuse headache is diagnosed according to the third edition of the International Classification of Headache Disorders, wherein said medication–overuse headache optionally comprises ergotamine-overuse headache, triptan-overuse headache, non-opioid analgesic-overuse headache, opioid-overuse headache, combination-analgesic-overuse headache, medication-overuse headache attributed to multiple drug classes not individually overused, medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes, or medication-overuse headache attributed to other medication.

166. The method of any one of claims 87-165, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is comprised in a formulation comprising or consisting of histidine (L-histidine), sorbitol, polysorbate 80, and water.

167. The method of claim 166, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within 10% of said values, and having a pH of 5.8 or within +/-10% of said value.

168. The method of claim 166, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 5% of said values, and/or having a pH of 5.8 or within +/-5% of said value.

169. The method of claim 166, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 1% of said values, and/or having a pH of 5.8 or within 1% of said value.

170. The method of claim 166, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 0.5% of said values, and/or having a pH of 5.8 or within 0.5% of said value.

171. The method of claim 166, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/- 0.1% of said values, and/or having a pH of 5.8 or within 0.1% of said value.

Figure 1A - Heavy Chain Protein Sequence

Sequence Name	FR1	CDR1	FR2	CDR2
Ab1	QSLEESGGRLVTPGTPLTLTCTVSGLDLS	SYYMQ	WVRQAPGKGLEWIG	VIGINDNTYYASWAKG
Ab2	EVQLVESGGGLVQPGGSLRLSCAVSGLDLS	SYYMQ	WVRQAPGKGLEWVG	VIGINDNTYYASWAKG
Ab3	EVQLVESGGGLVQPGGSLRLSCAVSGLDLS	SYYMQ	WVRQAPGKGLEWVG	VIGINDNTYYASWAKG
Ab4	QSLEESGGRLVTPGTPLTLTCSVSGIDLS	GYYMN	WVRQAPGKGLEWIG	VIGINGATYYASWAKG
Ab5	EVQLVESGGGLVQPGGSLRLSCAVSGIDLS	GYYMN	WVRQAPGKGLEWVG	VIGINGATYYASWAKG
Ab6	EVQLVESGGGLVQPGGSLRLSCAVSGIDLS	GYYMN	WVRQAPGKGLEWVG	VIGINGATYYASWAKG
Ab7	QEQLKESGGRLVTPGTSLTLTCTVSGIDLS	NHYMQ	WVRQAPGKGLEWIG	VVGINGRTYYASWAKG
Ab8	EVQLVESGGGLVQPGGSLRLSCAVSGIDLS	NHYMQ	WVRQAPGKGLEWVG	VVGINGRTYYASWAKG
Ab9	QSLEESGGRLVTPGTPLTLTCTVSGIGLS	SYYMQ	WVRQSPGRGLEWIG	VIGSDGKTYYATWAKG
Ab10	EVQLVESGGGLVQPGGSLRLSCAVSGIGLS	SYYMQ	WVRQAPGKGLEWVG	VIGSDGKTYYATWAKG
Ab11	QSLEESGGRLVTPGGSLTLTCTVSGIDVT	NYYMQ	WVRQAPGKGLEWIG	VIGVNGKRYYASWAKG
Ab12	EVQLVESGGGLVQPGGSLRLSCAVSGIDVT	NYYMQ	WVRQAPGKGLEWVG	VIGVNGKRYYASWAKG
Ab13	QSVEESGGGLVQPEGSLTLTCTASGFDFS	SNAMW	WVRQAPGKGLEWIG	CIYNGDGSTYYASWVNG
Ab14	EVQLVESGGGLVQPGGSLRLSCAVSGIGLS	SYYMQ	WVRQAPGKGLEWVG	VIGSDGKTYYATWAKG

Figure 1B - Heavy Chain Protein Sequence

Sequence Name	FR3	CDR3	FR4
Ab1	RFTISRASSTTVDLKMTSLTTEDTATYFCAR	GDI	WGPGTLVTVSS
Ab2	RFTISRDNSKTTVYLQMNSLRAEDTAVYFCAR	GDI	WGQGTLVTVSS
Ab3	RFTISRDNSKTTVYLQMNSLRAEDTAVYFCAR	GDI	WGQGTLVTVSS
Ab4	RFTISKTSSTTVDLKMTSLTTEDTATYFCAR	GDI	WGPGTLVTVSS
Ab5	RFTISRDNSKTTVYLQMNSLRAEDTAVYFCAR	GDI	WGQGTLVTVSS
Ab6	RFTISRDNSKTTVYLQMNSLRAEDTAVYFCAR	GDI	WGQGTLVTVSS
Ab7	RFTISRTSSTTVDLKMTRLTTEDTATYFCAR	GDI	WGPGTLVTVSS
Ab8	RFTISRDNSKTTVYLQMNSLRAEDTAVYFCAR	GDI	WGQGTLVTVSS
Ab9	RFTISKTSSTTVDLRMASLTTEDTATYFCTR	GDI	WGPGTLVTVSS
Ab10	RFTISRDNSKTTVYLQMNSLRAEDTAVYFCTR	GDI	WGQGTLVTVSS
Ab11	RFTISKTSSTTVDLKMTSLTTEDTATYFCAR	GDI	WGPGTLVTVSS
Ab12	RFTISRDNSKTTVYLQMNSLRAEDTAVYFCAR	GDI	WGQGTLVTVSS
Ab13	RFSISKTSSTTVTLQLNSLTVADTATYYCAR	DLDL	WGPGTLVTVSS
Ab14	RFTISRDNSKTTVYLQMNSLRAEDTAVYFCTR	GDI	WGQGTLVTVSS

Figure 1C - Heavy Chain Protein Sequence

Sequence Name	Constant Region
Ab1	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
Ab2	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
Ab3	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
Ab4	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
Ab5	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
Ab6	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
Ab7	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
Ab8	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
Ab9	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
Ab10	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
Ab11	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
Ab12	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
Ab13	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
Ab14	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV

Figure 1D - Heavy Chain Protein Sequence

Sequence Name	Constant Region
Ab1	NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
Ab2	NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
Ab3	NHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
Ab4	NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
Ab5	NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
Ab6	NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
Ab7	NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
Ab8	NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
Ab9	NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
Ab10	NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
Ab11	NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
Ab12	NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
Ab13	NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
Ab14	NHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA

Figure 1E - Heavy Chain Protein Sequence

Sequence Name	Constant Region
Ab1	KTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF
Ab2	KTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF
Ab3	KTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF
Ab4	KTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF
Ab5	KTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF
Ab6	KTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF
Ab7	KTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF
Ab8	KTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF
Ab9	KTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF
Ab10	KTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF
Ab11	KTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF
Ab12	KTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF
Ab13	KTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF
Ab14	KTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF

Figure 1F - Heavy Chain Protein Sequence

Sequence Name	Constant Region
Ab1	YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1)
Ab2	YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 41)
Ab3	YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 81)
Ab4	YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 121)
Ab5	YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 161)
Ab6	YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 201)
Ab7	YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 241)
Ab8	YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 281)
Ab9	YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 321)
Ab10	YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 361)
Ab11	YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 401)
Ab12	YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 441)
Ab13	YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 481)
Ab14	YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 521)

Figure 2A - Light Chain Protein Sequence

Sequence Name	FR1	CDR1	FR2	CDR2
Ab1	QVLTQTASPVSAAVGSTVTINC	QASQSVYDNNYLA	WYQQKPGQPPKQLIY	STSTLAS
Ab2	QVLTQSPSSLSASVGDRVTINC	QASQSVYDNNYLA	WYQQKPGKVPKQLIY	STSTLAS
Ab3	QVLTQSPSSLSASVGDRVTINC	QASQSVYDNNYLA	WYQQKPGKVPKQLIY	STSTLAS
Ab4	QVLTQTPSPVSAAVGSTVTINC	QASQSVYHNTYLA	WYQQKPGQPPKQLIY	DASTLAS
Ab5	QVLTQSPSSLSASVGDRVTINC	QASQSVYHNTYLA	WYQQKPGKVPKQLIY	DASTLAS
Ab6	QVLTQSPSSLSASVGDRVTINC	QASQSVYHNTYLA	WYQQKPGKVPKQLIY	DASTLAS
Ab7	QVLTQTASPVSAAVGSTVTINC	QASQSVYNYNYLA	WYQQKPGQPPKQLIY	STSTLAS
Ab8	QVLTQSPSSLSASVGDRVTINC	QASQSVYNYNYLA	WYQQKPGKVPKQLIY	STSTLAS
Ab9	QVLTQTPSPVSAAVGSTVTINC	QASQNVYNNNYLA	WYQQKPGQPPKQLIY	STSTLAS
Ab10	QVLTQSPSSLSASVGDRVTINC	QASQNVYNNNYLA	WYQQKPGKVPKQLIY	STSTLAS
Ab11	QVLTQTASPVSPAVGSTVTINC	RASQSVYYNNYLA	WYQQKPGQPPKQLIY	STSTLAS
Ab12	QVLTQSPSSLSASVGDRVTINC	RASQSVYYNNYLA	WYQQKPGKVPKQLIY	STSTLAS
Ab13	AIVMTQTPSSKSVPVGDTVTINC	QASESLYNNNALA	WFQQKPGQPPKRLIY	DASKLAS
Ab14	QVLTQSPSSLSASVGDRVTINC	QASQNVYNNNYLA	WYQQKPGKVPKQLIY	STSTLAS

Figure 2B - Light Chain Protein Sequence

Sequence Name	FR3	CDR3	FR4
Ab1	GVSSRFKGSGSGTQFTLTISDLECADAATYYC	LGSYDCSSGDCFV	FGGGTEVVVKR
Ab2	GVPSRFSGSGSGTDFTLTISSLQPEDVATYYC	LGSYDCSSGDCFV	FGGGTKVEIKR
Ab3	GVPSRFSGSGSGTDFTLTISSLQPEDVATYYC	LGSYDCSSGDCFV	FGGGTKVEIKR
Ab4	GVPSRFSGSGSGTQFTLTISGVQCNDAAAYYC	LGSYDCTNGDCFV	FGGGTEVVVKR
Ab5	GVPSRFSGSGSGTDFTLTISSLQPEDVATYYC	LGSYDCTNGDCFV	FGGGTKVEIKR
Ab6	GVPSRFSGSGSGTDFTLTISSLQPEDVATYYC	LGSYDCTNGDCFV	FGGGTKVEIKR
Ab7	GVSSRFKGSGSGTQFTLTISDVQCDDAATYYC	LGSYDCSTGDCFV	FGGGTEVVVKR
Ab8	GVPSRFSGSGSGTDFTLTISSLQPEDVATYYC	LGSYDCSTGDCFV	FGGGTKVEIKR
Ab9	GVSSRFRGSGSGTQFTLTISDVQCDDAATYYC	LGSYDCSRGDCFV	FGGGTEVVVKR
Ab10	GVPSRFSGSGSGTDFTLTISSLQPEDVATYYC	LGSYDCSRGDCFV	FGGGTKVEIKR
Ab11	GVSSRFKGSGSGTQFTLTISDVQCDDAATYYC	LGSYDCSNGDCFV	FGGGTEVVVKR
Ab12	GVPSRFSGSGSGTDFTLTISSLQPEDVATYYC	LGSYDCSNGDCFV	FGGGTKVEIKR
Ab13	GVPSRFSGGGSGTQFTLTISGVQCDDAATYYC	GGYRSDSVDGVA	FAGGTEVVVKR
Ab14	GVPSRFSGSGSGTDFTLTISSLQPEDVATYYC	LGSYDCSRGDCFV	FGGGTKVEIKR

Figure 2C - Light Chain Protein Sequence

Sequence Name	Constant Region
Ab1	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA
Ab2	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA
Ab3	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA
Ab4	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA
Ab5	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA
Ab6	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA
Ab7	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA
Ab8	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA
Ab9	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA
Ab10	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA
Ab11	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA
Ab12	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA
Ab13	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA
Ab14	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA

Figure 2D - Light Chain Protein Sequence

Sequence Name	Constant Region
Ab1	CEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 21)
Ab2	CEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 61)
Ab3	CEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 101)
Ab4	CEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 141)
Ab5	CEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 181)
Ab6	CEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 221)
Ab7	CEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 261)
Ab8	CEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 301)
Ab9	CEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 341)
Ab10	CEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 381)
Ab11	CEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 421)
Ab12	CEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 461)
Ab13	CEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 501)
Ab14	CEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 541)

Figure 3A - Heavy Chain DNA Sequence

Sequence Name	FR1
Ab1	CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACAGTCTCTGGACTCGACCTCAGT
Ab2	GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGGACTCGACCTCAGT
Ab3	GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGGACTCGACCTCAGT
Ab4	CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGTTCCGTCTCTGGCATCGACCTCAGT
Ab5	GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGGAATCGACCTCAGT
Ab6	GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGGAATCGACCTCAGT
Ab7	CAGGAGCAGCTGAAGGAGTCCGGGGGGTCGCCTGGTCACGCCTGGGACATCCCTGACACTCACCTGCACCGTCTCTGGAATCGACCTCAGT
Ab8	GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGGAATCGACCTCAGT
Ab9	CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACAGTCTCTGGAATCGGCCTCAGT
Ab10	GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGGAATCGGCCTCAGT
Ab11	CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGAGGATCCCTGACACTCACCTGCACAGTCTCTGGAATCGACGTCACT
Ab12	GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGGAATCGACGTCACT
Ab13	CAGTCGGTGGAGGAGTCCGGGGGAGGCCTGGTCCAGCCTGAGGGATCCCTGACACTCACCTGCACAGCCTCTGGATTCGACTTCAGT
Ab14	GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGGAATCGGCCTCAGT

Figure 3B - Heavy Chain DNA Sequence

Sequence Name	CDR1	FR2
Ab1	AGCTACTACATGCAA	TGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGA
Ab2	AGCTACTACATGCAA	TGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGA
Ab3	AGCTACTACATGCAA	TGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGA
Ab4	GGCTACTACATGAAC	TGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGA
Ab5	GGCTACTACATGAAC	TGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGA
Ab6	GGCTACTACATGAAC	TGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGA
Ab7	AACCACTACATGCAA	TGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGA
Ab8	AACCACTACATGCAA	TGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGA
Ab9	AGCTACTACATGCAG	TGGGTCCGCCAGTCTCCAGGGAGGGGGCTGGAATGGATCGGA
Ab10	AGCTACTACATGCAA	TGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGA
Ab11	AACTACTATATGCAA	TGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGA
Ab12	AACTACTACATGCAA	TGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGA
Ab13	AGCAATGCAATGTGG	TGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGA
Ab14	AGCTACTACATGCAA	TGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGA

Figure 3C - Heavy Chain DNA Sequence

Sequence Name	CDR2
Ab1	GTCATTGGTATTAATGATAACACATACTACGCGAGCTGGGCGAAAGGC
Ab2	GTCATTGGTATCAATGATAACACATACTACGCGAGCTGGGCGAAAGGC
Ab3	GTCATTGGTATCAATGATAACACATACTACGCGAGCTGGGCGAAAGGC
Ab4	GTCATTGGTATTAATGGTGCCACATACTACGCGAGCTGGGCGAAAGGC
Ab5	GTCATTGGTATTAATGGTGCCACATACTACGCGAGCTGGGCGAAAGGC
Ab6	GTCATTGGTATTAATGGTGCCACATACTACGCGAGCTGGGCGAAAGGC
Ab7	GTCGTTGGTATTAATGGTCGCACATACTACGCGAGCTGGGCGAAAGGC
Ab8	GTCGTTGGTATCAATGGTCGCACATACTACGCGAGCTGGGCGAAAGGC
Ab9	GTCATTGGTAGTGATGGTAAGACATACTACGCGACCTGGGCGAAAGGC
Ab10	GTCATTGGTAGTGATGGTAAGACATACTACGCGACCTGGGCGAAAGGC
Ab11	GTCATTGGTGTGAATGGTAAGAGATACTACGCGAGCTGGGCGAAAGGC
Ab12	GTCATTGGTGTGAATGGTAAGAGATACTACGCGAGCTGGGCGAAAGGC
Ab13	TGCATTTACAATGGTGATGGCAGCACATACTACGCGAGCTGGGTGAATGGC
Ab14	GTCATTGGTAGTGATGGTAAGACATACTACGCGACCTGGGCGAAAGGC

Figure 3D - Heavy Chain DNA Sequence

Sequence Name	FR3
Ab1	CGATTCACCATCTCCAGAGCCTCGTCGACCACGGTGGATCTGAAAATGACCAGTCTGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGA
Ab2	CGATTCACCATCTCCAGAGACAATTCCAAGACCACGGTGTATCTTCAAATGAACAGCCTGAGAGCTGAGGACACTGCTGTGTATTTCTGTGCTAGA
Ab3	CGATTCACCATCTCCAGAGACAATTCCAAGACCACGGTGTATCTTCAAATGAACAGCCTGAGAGCTGAGGACACTGCTGTGTATTTCTGTGCTAGA
Ab4	CGATTCACCATCTCCAAAACCTCGTCGACCACGGTGGATCTGAAAATGACCAGTCTGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGA
Ab5	CGATTCACCATCTCCAGAGACAATTCCAAGACCACGGTGTATCTTCAAATGAACAGCCTGAGAGCTGAGGACACTGCTGTGTATTTCTGTGCTAGA
Ab6	CGATTCACCATCTCCAGAGACAATTCCAAGACCACGGTGTATCTTCAAATGAACAGCCTGAGAGCTGAGGACACTGCTGTGTATTTCTGTGCTAGA
Ab7	CGATTCACCATCTCCAGAACCTCGTCGACCACGGTGGATCTGAAAATGACCAGGCTGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGA
Ab8	CGATTCACCATCTCCAGAGACAATTCCAAGACCACGGTGTATCTTCAAATGAACAGCCTGAGAGCTGAGGACACTGCTGTGTATTTCTGTGCTAGA
Ab9	CGATTCACCATCTCCAAGACCTCGTCGACCACGGTGGATCTGAGAATGGCCAGTCTGACAACCGAGGACACGGCCACCTATTTCTGTGTACCAGA
Ab10	CGATTCACCATCTCCAGAGACAATTCCAAGACCACGGTGTATCTTCAAATGAACAGCCTGAGAGCTGAGGACACTGCTGTGTATTTCTGTGTACCAGA
Ab11	CGATTCACCATCTCCAAAACCTCGTCGACCACGGTGGATCTGAAAATGACCAGTCTGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGA
Ab12	CGATTCACCATCTCCAGAGACAATTCCAAGACCACGGTGTATCTTCAAATGAACAGCCTGAGAGCTGAGGACACTGCTGTGTATTTCTGTGCCAGA
Ab13	CGATTCTCCATCTCCAAAACCTCGTCGACCACGGTGACTCTGCAACTGAATAGTCTGACAGTCGCGGACACGGCCACGTATTATTGTGCGAGA
Ab14	CGATTCACCATCTCCAGAGACAATTCCAAGACCACGGTGTATCTTCAAATGAACAGCCTGAGAGCTGAGGACACTGCTGTGTATTTCTGTACCAGA

Figure 3E - Heavy Chain DNA Sequence

Sequence Name	CDR3	FR4	Constant Region
Ab1	GGGGACATC	TGGGGCCCAGGCACCCTCGTCACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCC
Ab2	GGGGACATC	TGGGGCCAAGGGACCCTCGTCACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCC
Ab3	GGGGACATC	TGGGGCCAAGGGACCCTCGTCACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCC
Ab4	GGGGACATC	TGGGGCCCGGGCACCCTCGTCACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCC
Ab5	GGGGACATC	TGGGGCCAAGGGACCCTCGTCACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCC
Ab6	GGGGACATC	TGGGGCCAAGGGACCCTCGTCACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCC
Ab7	GGGGACATC	TGGGGCCCAGGCACCCTGGTCACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCC
Ab8	GGGGACATC	TGGGGCCAAGGGACCCTCGTCACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCC
Ab9	GGGGACATC	TGGGGCCCGGGGACCCTCGTCACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCC
Ab10	GGGGACATC	TGGGGCCAAGGGACCCTCGTCACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCC
Ab11	GGCGACATC	TGGGGCCCGGGGACCCTCGTCACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCC
Ab12	GGGGACATC	TGGGGCCAAGGGACCCTCGTCACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCC
Ab13	GATCTTGACTTG	TGGGGCCCGGGCACCCTCGTCACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCC
Ab14	GGGGACATC	TGGGGCCAAGGGACCCTCGTCACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCC

Figure 3F - Heavy Chain DNA Sequence

Sequence Name	Constant Region
Ab1	AAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCC
Ab2	AAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCC
Ab3	AAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCC
Ab4	AAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCC
Ab5	AAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCC
Ab6	AAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCC
Ab7	AAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCC
Ab8	AAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCC
Ab9	AAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCC
Ab10	AAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCC
Ab11	AAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCC
Ab12	AAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCC
Ab13	AAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCC
Ab14	AAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCC

Figure 3G - Heavy Chain DNA Sequence

Sequence Name	Constant Region
Ab1	CTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC
Ab2	CTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC
Ab3	CTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC
Ab4	CTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC
Ab5	CTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC
Ab6	CTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC
Ab7	CTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC
Ab8	CTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC
Ab9	CTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC
Ab10	CTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC
Ab11	CTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC
Ab12	CTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC
Ab13	CTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC
Ab14	CTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC

Figure 3H - Heavy Chain DNA Sequence

Sequence Name	Constant Region
Ab1	TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAA
Ab2	TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAA
Ab3	TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACGCGAGAGTTGAGCCCAAATCTTGTGACAAA
Ab4	TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAA
Ab5	TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAA
Ab6	TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAA
Ab7	TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAA
Ab8	TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAA
Ab9	TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAA
Ab10	TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAA
Ab11	TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAA
Ab12	TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAA
Ab13	TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAA
Ab14	TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACGCGAGAGTTGAGCCCAAATCTTGTGACAAA

Figure 3I - Heavy Chain DNA Sequence

Sequence Name	Constant Region
Ab1	ACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATG
Ab2	ACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATG
Ab3	ACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATG
Ab4	ACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATG
Ab5	ACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATG
Ab6	ACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATG
Ab7	ACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATG
Ab8	ACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATG
Ab9	ACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATG
Ab10	ACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATG
Ab11	ACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATG
Ab12	ACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATG
Ab13	ACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATG
Ab14	ACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATG

Figure 3J - Heavy Chain DNA Sequence

Sequence Name	Constant Region
Ab1	ATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG
Ab2	ATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG
Ab3	ATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG
Ab4	ATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG
Ab5	ATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG
Ab6	ATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG
Ab7	ATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG
Ab8	ATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG
Ab9	ATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG
Ab10	ATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG
Ab11	ATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG
Ab12	ATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG
Ab13	ATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG
Ab14	ATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG

Figure 3K - Heavy Chain DNA Sequence

Sequence Name	Constant Region
Ab1	GAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGAC
Ab2	GAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGAC
Ab3	GAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGAC
Ab4	GAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGAC
Ab5	GAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGAC
Ab6	GAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGAC
Ab7	GAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGAC
Ab8	GAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGAC
Ab9	GAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGAC
Ab10	GAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGAC
Ab11	GAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGAC
Ab12	GAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGAC
Ab13	GAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGAC
Ab14	GAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGAC

Figure 3L - Heavy Chain DNA Sequence

Sequence Name	Constant Region
Ab1	TGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAG
Ab2	TGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAG
Ab3	TGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAG
Ab4	TGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAG
Ab5	TGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAG
Ab6	TGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAG
Ab7	TGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAG
Ab8	TGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAG
Ab9	TGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAG
Ab10	TGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAG
Ab11	TGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAG
Ab12	TGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAG
Ab13	TGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAG
Ab14	TGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAG

Figure 3M - Heavy Chain DNA Sequence

Sequence Name	Constant Region
Ab1	CCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTC
Ab2	CCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTC
Ab3	CCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTC
Ab4	CCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTC
Ab5	CCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTC
Ab6	CCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTC
Ab7	CCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTC
Ab8	CCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTC
Ab9	CCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTC
Ab10	CCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTC
Ab11	CCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTC
Ab12	CCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTC
Ab13	CCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTC
Ab14	CCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTC

Figure 3N - Heavy Chain DNA Sequence

Sequence Name	Constant Region
Ab1	TATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGC
Ab2	TATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGC
Ab3	TATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGC
Ab4	TATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGC
Ab5	TATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGC
Ab6	TATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGC
Ab7	TATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGC
Ab8	TATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGC
Ab9	TATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGC
Ab10	TATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGC
Ab11	TATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGC
Ab12	TATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGC
Ab13	TATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGC
Ab14	TATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGC

Figure 3O - Heavy Chain DNA Sequence

Sequence Name	Constant Region
Ab1	TCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTG
Ab2	TCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTG
Ab3	TCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTG
Ab4	TCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTG
Ab5	TCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTG
Ab6	TCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTG
Ab7	TCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTG
Ab8	TCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTG
Ab9	TCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTG
Ab10	TCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTG
Ab11	TCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTG
Ab12	TCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTG
Ab13	TCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTG
Ab14	TCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTG

Figure 3P - Heavy Chain DNA Sequence

Sequence Name	Constant Region
Ab1	CACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 11)
Ab2	CACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 51)
Ab3	CACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 91)
Ab4	CACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 131)
Ab5	CACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 171)
Ab6	CACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 211)
Ab7	CACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 251)
Ab8	CACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 291)
Ab9	CACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 331)
Ab10	CACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 371)
Ab11	CACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 411)
Ab12	CACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 451)
Ab13	CACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 491)
Ab14	CACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 531)

Figure 4A - Light Chain DNA Sequence

Sequence Name	FR1
Ab1	CAAGTGCTGACCCAGACTGCATCCCCCGTGTCTGCAGCTGTGGGAAGCACAGTCACCATCAATTGC
Ab2	CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGC
Ab3	CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGC
Ab4	CAAGTGCTGACCCAGACTCCATCCCCCGTGTCTGCAGCTGTGGGAAGCACAGTCACCATCAATTGC
Ab5	CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGC
Ab6	CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGC
Ab7	CAAGTGCTGACCCAGACTGCATCCCCCGTGTCTGCAGCTGTGGGAAGCACAGTCACCATCAATTGC
Ab8	CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGC
Ab9	CAAGTGCTGACCCAGACTCCATCCCCCGTGTCTGCAGCTGTGGGAAGCACAGTCACCATCAATTGC
Ab10	CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGC
Ab11	CAGGTGCTGACCCAGACTGCATCCCCCGTGTCTCCAGCTGTGGGAAGCACAGTCACCATCAATTGC
Ab12	CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGC
Ab13	GCCATCGTGATGACCCAGACTCCATCTTCCAAGTCTGTCCCTGTGGGAGACACAGTCACCATCAATTGC
Ab14	CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGC

Figure 4B - Light Chain DNA Sequence

Sequence Name	CDR1	FR2
Ab1	CAGGCCAGTCAGAGTGTTTATGATAACAACTACCTAGCC	TGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCAACTGATCTAT
Ab2	CAGGCCAGTCAGAGTGTTTATGATAACAACTACCTAGCC	TGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTAT
Ab3	CAGGCCAGTCAGAGTGTTTATGATAACAACTACCTAGCC	TGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTAT
Ab4	CAGGCCAGTCAGAGTGTTTATCATAACACCTACCTGGCC	TGGTATCAGCAGAAACCAGGGCAGCCTCCCAAACAACTGATCTAT
Ab5	CAGGCCAGTCAGAGTGTTTATCATAACACCTACCTGGCC	TGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTAT
Ab6	CAGGCCAGTCAGAGTGTTTATCATAACACCTACCTGGCC	TGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTAT
Ab7	CAGGCCAGTCAGAGTGTTTATAATTACAACTACCTTGCC	TGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCAACTGATCTAT
Ab8	CAGGCCAGTCAGAGTGTTTACAATTACAACTACCTTGCC	TGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTAT
Ab9	CAGGCCAGTCAGAATGTTTATAATAACAACTACCTAGCC	TGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCAACTGATCTAT
Ab10	CAGGCCAGTCAGAATGTTTACAATAACAACTACCTAGCC	TGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTAT
Ab11	CGGGCCAGTCAGAGTGTTTATTATAACAACTACCTAGCC	TGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCAACTGATCTAT
Ab12	CGGGCCAGTCAGAGTGTTTACTATAACAACTACCTAGCC	TGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTAT
Ab13	CAGGCCAGTGAGAGTCTTTATAATAACAACGCCTTGGCC	TGGTTTCAGCAGAAACCAGGGCAGCCTCCCAAGCGCCTGATCTAT
Ab14	CAGGCCAGTCAGAATGTTTACAATAACAACTACCTAGCC	TGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTAT

Figure 4C - Light Chain DNA Sequence

Sequence Name	CDR2	FR3
Ab1	TCTACATCCACTCTGGCATCT	GGGGTCTCATCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCA
Ab2	TCTACATCCACTCTGGCATCT	GGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCA
Ab3	TCTACATCCACTCTGGCATCT	GGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCA
Ab4	GATGCATCCACTCTGGCGTCT	GGGGTCCCATCGCGGTTCAGCGGCAGTGGATCTGGGACACAGTTCACTCTCACCA
Ab5	GATGCATCCACTCTGGCATCT	GGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCA
Ab6	GATGCATCCACTCTGGCATCT	GGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCA
Ab7	TCTACATCCACTCTGGCATCT	GGGGTCTCATCGCGATTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCA
Ab8	TCTACATCCACTCTGGCATCT	GGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCA
Ab9	TCTACGTCCACTCTGGCATCT	GGGGTCTCATCGCGATTCAGAGGCAGTGGATCTGGGACACAGTTCACTCTCACCA
Ab10	TCTACATCCACTCTGGCATCT	GGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCA
Ab11	TCTACATCCACTCTGGCATCT	GGGGTCTCATCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCA
Ab12	TCTACATCCACTCTGGCATCT	GGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCA
Ab13	GATGCATCCAAACTGGCATCT	GGGGTCCCATCGCGGTTCAGTGGCGGTGGGTCTGGGACACAGTTCACTCTCACCA
Ab14	TCTACATCCACTCTGGCATCT	GGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCA

Figure 4D - Light Chain DNA Sequence

Sequence Name	FR3	CDR3
Ab1	TCAGCGACCTGGAGTGTGCCGATGCTGCCACTTACTACTGT	CTAGGCAGTTATGATTGTAGTAGTGGTGATTGTTTTGTT
Ab2	TCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGT	CTAGGCAGTTATGATTGTAGTAGTGGTGATTGTTTTGTT
Ab3	TCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGT	CTAGGCAGTTATGATTGTAGTAGTGGTGATTGTTTTGTT
Ab4	TCAGCGGCGTGCAGTGTAACGATGCTGCCGCTTACTACTGT	CTGGGCAGTTATGATTGTACTAATGGTGATTGTTTTGTT
Ab5	TCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGT	CTGGGCAGTTATGATTGTACTAATGGTGATTGTTTTGTT
Ab6	TCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGT	CTGGGCAGTTATGATTGTACTAATGGTGATTGTTTTGTT
Ab7	TCAGCGACGTGCAGTGTGACGATGCTGCCACTTACTACTGT	CTAGGCAGTTATGACTGTAGTACTGGTGATTGTTTTGTT
Ab8	TCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGT	CTGGGCAGTTATGATTGTAGTACTGGTGATTGTTTTGTT
Ab9	TCAGCGACGTGCAGTGTGACGATGCTGCCACTTACTACTGT	CTAGGCAGTTATGATTGTAGTCGTGGTGATTGTTTTGTT
Ab10	TCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGT	CTGGGCAGTTATGATTGTAGTCGTGGTGATTGTTTTGTT
Ab11	TCAGCGACGTGCAGTGTGACGATGCTGCCACTTACTACTGT	CTAGGCAGTTATGATTGTAGTAATGGTGATTGTTTTGTT
Ab12	TCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGT	CTGGGCAGTTATGATTGTAGTAATGGTGATTGTTTTGTT
Ab13	TCAGTGGCGTGCAGTGTGACGATGCTGCCACTTACTACTGT	GGAGGCTACAGAAGTGATAGTGTTGATGGTGTTGCT
Ab14	TCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGT	CTGGGCAGTTATGATTGTAGTCGTGGTGATTGTTTTGTT

Figure 4E - Light Chain DNA Sequence

Sequence Name	FR4	Constant Region
Ab1	TTCGGCGGAGGGACCGAGGTGGTGGTCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTG
Ab2	TTCGGCGGAGGAACCAAGGTGGAAATCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTG
Ab3	TTCGGCGGAGGAACCAAGGTGGAAATCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTG
Ab4	TTCGGCGGAGGGACCGAGGTGGTGGTCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTG
Ab5	TTCGGCGGAGGAACCAAGGTGGAAATCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTG
Ab6	TTCGGCGGAGGAACCAAGGTGGAAATCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTG
Ab7	TTCGGCGGAGGGACCGAGGTGGTGGTCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTG
Ab8	TTCGGCGGAGGAACCAAGGTGGAAATCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTG
Ab9	TTCGGCGGAGGGACCGAGGTGGTGGTCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTG
Ab10	TTCGGCGGAGGAACCAAGGTGGAAATCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTG
Ab11	TTCGGCGGAGGGACCGAGGTGGTGGTCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTG
Ab12	TTCGGCGGAGGAACCAAGGTGGAAATCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTG
Ab13	TTCGCCGGAGGGACCGAGGTGGTGGTCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTG
Ab14	TTCGGCGGAGGAACCAAGGTGGAAATCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTG

Figure 4F - Light Chain DNA Sequence

Sequence Name	Constant Region
Ab1	AAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCC
Ab2	AAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCC
Ab3	AAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCC
Ab4	AAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCC
Ab5	AAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCC
Ab6	AAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCC
Ab7	AAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCC
Ab8	AAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCC
Ab9	AAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCC
Ab10	AAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCC
Ab11	AAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCC
Ab12	AAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCC
Ab13	AAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCC
Ab14	AAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCC

Figure 4G - Light Chain DNA Sequence

Sequence Name	Constant Region
Ab1	TCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAG
Ab2	TCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAG
Ab3	TCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAG
Ab4	TCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAG
Ab5	TCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAG
Ab6	TCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAG
Ab7	TCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAG
Ab8	TCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAG
Ab9	TCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAG
Ab10	TCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAG
Ab11	TCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAG
Ab12	TCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAG
Ab13	TCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAG
Ab14	TCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAG

Figure 4H - Light Chain DNA Sequence

Sequence Name	Constant Region
Ab1	CAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC
Ab2	CAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC
Ab3	CAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC
Ab4	CAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC
Ab5	CAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC
Ab6	CAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC
Ab7	CAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC
Ab8	CAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC
Ab9	CAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC
Ab10	CAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC
Ab11	CAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC
Ab12	CAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC
Ab13	CAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC
Ab14	CAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC

Figure 4I - Light Chain DNA Sequence

Sequence Name	
Ab1	AGGGGAGAGTGTTAG (SEQ ID NO: 31)
Ab2	AGGGGAGAGTGTTAG (SEQ ID NO: 71)
Ab3	AGGGGAGAGTGTTAG (SEQ ID NO: 111)
Ab4	AGGGGAGAGTGTTAG (SEQ ID NO: 151)
Ab5	AGGGGAGAGTGTTAG (SEQ ID NO: 191)
Ab6	AGGGGAGAGTGTTAG (SEQ ID NO: 231)
Ab7	AGGGGAGAGTGTTAG (SEQ ID NO: 271)
Ab8	AGGGGAGAGTGTTAG (SEQ ID NO: 311)
Ab9	AGGGGAGAGTGTTAG (SEQ ID NO: 351)
Ab10	AGGGGAGAGTGTTAG (SEQ ID NO: 391)
Ab11	AGGGGAGAGTGTTAG (SEQ ID NO: 431)
Ab12	AGGGGAGAGTGTTAG (SEQ ID NO: 471)
Ab13	AGGGGAGAGTGTTAG (SEQ ID NO: 511)
Ab14	AGGGGAGAGTGTTAG (SEQ ID NO: 551)

Figure 5

Heavy Chain Protein Sequence Features

Antibody	Variable Region Coordinates	SEQ ID NO:	CDR1 Coordinates	SEQ ID NO:	CDR2 Coordinates	SEQ ID NO:	CDR3 Coordinates	SEQ ID NO:
Ab1	1-109	2	30-34	4	49-64	6	96-98	8
Ab2	1-111	42	31-35	44	50-65	46	98-100	48
Ab3	1-111	82	31-35	84	50-65	86	98-100	88
Ab4	1-109	122	30-34	124	49-64	126	96-98	128
Ab5	1-111	162	31-35	164	50-65	166	98-100	168
Ab6	1-111	202	31-35	204	50-65	206	98-100	208
Ab7	1-110	242	31-35	244	50-65	246	97-99	248
Ab8	1-111	282	31-35	284	50-65	286	98-100	288
Ab9	1-109	322	30-34	324	49-64	326	96-98	328
Ab10	1-111	362	31-35	364	50-65	366	98-100	368
Ab11	1-109	402	30-34	404	49-64	406	96-98	408
Ab12	1-111	442	31-35	444	50-65	446	98-100	448
Ab13	1-111	482	30-34	484	49-65	486	97-100	488
Ab14	1-111	522	31-35	524	50-65	526	98-100	528

Figure 6

Heavy Chain Protein Sequence Features

Antibody	FR1 Coordinates	SEQ ID NO:	FR2 Coordinates	SEQ ID NO:	FR3 Coordinates	SEQ ID NO:	FR4 Coordinates	SEQ ID NO:	Constant Region Coordinates	SEQ ID NO:
Ab1	1-29	3	35-48	5	65-95	7	99-109	9	110-439	10
Ab2	1-30	43	36-49	45	66-97	47	101-111	49	112-441	50
Ab3	1-30	83	36-49	85	66-97	87	101-111	89	112-441	90
Ab4	1-29	123	35-48	125	65-95	127	99-109	129	110-439	130
Ab5	1-30	163	36-49	165	66-97	167	101-111	169	112-441	170
Ab6	1-30	203	36-49	205	66-97	207	101-111	209	112-441	210
Ab7	1-30	243	36-49	245	66-96	247	100-110	249	111-440	250
Ab8	1-30	283	36-49	285	66-97	287	101-111	289	112-441	290
Ab9	1-29	323	35-48	325	65-95	327	99-109	329	110-439	330
Ab10	1-30	363	36-49	365	66-97	367	101-111	369	112-441	370
Ab11	1-29	403	35-48	405	65-95	407	99-109	409	110-439	410
Ab12	1-30	443	36-49	445	66-97	447	101-111	449	112-441	450
Ab13	1-29	483	35-48	485	66-96	487	101-111	489	112-441	490
Ab14	1-30	523	36-49	525	66-97	527	101-111	529	112-441	530

Figure 7

Light Chain Protein Sequence Features

Antibody	Variable Region Coordinates	SEQ ID NO:	CDR1 Coordinates	SEQ ID NO:	CDR2 Coordinates	SEQ ID NO:	CDR3 Coordinates	SEQ ID NO:
Ab1	1-113	22	23-35	24	51-57	26	90-102	28
Ab2	1-113	62	23-35	64	51-57	66	90-102	68
Ab3	1-113	102	23-35	104	51-57	106	90-102	108
Ab4	1-113	142	23-35	144	51-57	146	90-102	148
Ab5	1-113	182	23-35	184	51-57	186	90-102	188
Ab6	1-113	222	23-35	224	51-57	226	90-102	228
Ab7	1-113	262	23-35	264	51-57	266	90-102	268
Ab8	1-113	302	23-35	304	51-57	306	90-102	308
Ab9	1-113	342	23-35	344	51-57	346	90-102	348
Ab10	1-113	382	23-35	384	51-57	386	90-102	388
Ab11	1-113	422	23-35	424	51-57	426	90-102	428
Ab12	1-113	462	23-35	464	51-57	466	90-102	468
Ab13	1-113	502	24-36	504	52-58	506	91-102	508
Ab14	1-113	542	23-35	544	51-57	546	90-102	548

Figure 8

Light Chain Protein Sequence Features

Antibody	FR1 Coordinates	SEQ ID NO:	FR2 Coordinates	SEQ ID NO:	FR3 Coordinates	SEQ ID NO:	FR4 Coordinates	SEQ ID NO:	Constant Region Coordinates	SEQ ID NO:
Ab1	1-22	23	36-50	25	58-89	27	103-113	29	114-219	30
Ab2	1-22	63	36-50	65	58-89	67	103-113	69	114-219	70
Ab3	1-22	103	36-50	105	58-89	107	103-113	109	114-219	110
Ab4	1-22	143	36-50	145	58-89	147	103-113	149	114-219	150
Ab5	1-22	183	36-50	185	58-89	187	103-113	189	114-219	190
Ab6	1-22	223	36-50	225	58-89	227	103-113	229	114-219	230
Ab7	1-22	263	36-50	265	58-89	267	103-113	269	114-219	270
Ab8	1-22	303	36-50	305	58-89	307	103-113	309	114-219	310
Ab9	1-22	343	36-50	345	58-89	347	103-113	349	114-219	350
Ab10	1-22	383	36-50	385	58-89	387	103-113	389	114-219	390
Ab11	1-22	423	36-50	425	58-89	427	103-113	429	114-219	430
Ab12	1-22	463	36-50	465	58-89	467	103-113	469	114-219	470
Ab13	1-23	503	37-51	505	59-90	507	103-113	509	114-219	510
Ab14	1-22	543	36-50	545	58-89	547	103-113	549	114-219	550

Figure 9

Heavy Chain DNA Sequence Features

Antibody	Variable Region Coordinates	SEQ ID NO:	CDR1 Coordinates	SEQ ID NO:	CDR2 Coordinates	SEQ ID NO:	CDR3 Coordinates	SEQ ID NO:
Ab1	1-327	12	88-102	14	145-192	16	286-294	18
Ab2	1-333	52	91-105	54	148-195	56	292-300	58
Ab3	1-333	92	91-105	94	148-195	96	292-300	98
Ab4	1-327	132	88-102	134	145-192	136	286-294	138
Ab5	1-333	172	91-105	174	148-195	176	292-300	178
Ab6	1-333	212	91-105	214	148-195	216	292-300	218
Ab7	1-330	252	91-105	254	148-195	256	289-297	258
Ab8	1-333	292	91-105	294	148-195	296	292-300	298
Ab9	1-327	332	88-102	334	145-192	336	286-294	338
Ab10	1-333	372	91-105	374	148-195	376	292-300	378
Ab11	1-327	412	88-102	414	145-192	416	286-294	418
Ab12	1-333	452	91-105	454	148-195	456	292-300	458
Ab13	1-333	492	88-102	494	145-195	496	289-300	498
Ab14	1-333	532	91-105	534	148-195	536	292-300	538

Figure 10

Heavy Chain DNA Sequence Features

Antibody	FR1 Coordinates	SEQ ID NO:	FR2 Coordinates	SEQ ID NO:	FR3 Coordinates	SEQ ID NO:	FR4 Coordinates	SEQ ID NO:	Constant Region Coordinates	SEQ ID NO:
Ab1	1-87	13	103-144	15	193-285	17	295-327	19	328-1320	20
Ab2	1-90	53	106-147	55	196-291	57	301-333	59	334-1326	60
Ab3	1-90	93	106-147	95	196-291	97	301-333	99	334-1326	100
Ab4	1-87	133	103-144	135	193-285	137	295-327	139	328-1320	140
Ab5	1-90	173	106-147	175	196-291	177	301-333	179	334-1326	180
Ab6	1-90	213	106-147	215	196-291	217	301-333	219	334-1326	220
Ab7	1-90	253	106-147	255	196-288	257	298-330	259	331-1323	260
Ab8	1-90	293	106-147	295	196-291	297	301-333	299	334-1326	300
Ab9	1-87	333	103-144	335	193-285	337	295-327	339	328-1320	340
Ab10	1-90	373	106-147	375	196-291	377	301-333	379	334-1326	380
Ab11	1-87	413	103-144	415	193-285	417	295-327	419	328-1320	420
Ab12	1-90	453	106-147	455	196-291	457	301-333	459	334-1326	460
Ab13	1-87	493	103-144	495	196-288	497	301-333	499	334-1326	500
Ab14	1-90	533	106-147	535	196-291	537	301-333	539	334-1326	540

Figure 11

Light Chain DNA Sequence Features

Antibody	Variable Region Coordinates	SEQ ID NO:	CDR1 Coordinates	SEQ ID NO:	CDR2 Coordinates	SEQ ID NO:	CDR3 Coordinates	SEQ ID NO:
Ab1	1-339	32	67-105	34	151-171	36	268-306	38
Ab2	1-339	72	67-105	74	151-171	76	268-306	78
Ab3	1-339	112	67-105	114	151-171	116	268-306	118
Ab4	1-339	152	67-105	154	151-171	156	268-306	158
Ab5	1-339	192	67-105	194	151-171	196	268-306	198
Ab6	1-339	232	67-105	234	151-171	236	268-306	238
Ab7	1-339	272	67-105	274	151-171	276	268-306	278
Ab8	1-339	312	67-105	314	151-171	316	268-306	318
Ab9	1-339	352	67-105	354	151-171	356	268-306	358
Ab10	1-339	392	67-105	394	151-171	396	268-306	398
Ab11	1-339	432	67-105	434	151-171	436	268-306	438
Ab12	1-339	472	67-105	474	151-171	476	268-306	478
Ab13	1-339	512	70-108	514	154-174	516	271-306	518
Ab14	1-339	552	67-105	554	151-171	556	268-306	558

Figure 12

Light Chain DNA Sequence Features

Antibody	FR1 Coordinates	SEQ ID NO:	FR2 Coordinates	SEQ ID NO:	FR3 Coordinates	SEQ ID NO:	FR4 Coordinates	SEQ ID NO:	Constant Region Coordinates	SEQ ID NO:
Ab1	1-66	33	106-150	35	172-267	37	307-339	39	340-660	40
Ab2	1-66	73	106-150	75	172-267	77	307-339	79	340-660	80
Ab3	1-66	113	106-150	115	172-267	117	307-339	119	340-660	120
Ab4	1-66	153	106-150	155	172-267	157	307-339	159	340-660	160
Ab5	1-66	193	106-150	195	172-267	197	307-339	199	340-660	200
Ab6	1-66	233	106-150	235	172-267	237	307-339	239	340-660	240
Ab7	1-66	273	106-150	275	172-267	277	307-339	279	340-660	280
Ab8	1-66	313	106-150	315	172-267	317	307-339	319	340-660	320
Ab9	1-66	353	106-150	355	172-267	357	307-339	359	340-660	360
Ab10	1-66	393	106-150	395	172-267	397	307-339	399	340-660	400
Ab11	1-66	433	106-150	435	172-267	437	307-339	439	340-660	440
Ab12	1-66	473	106-150	475	172-267	477	307-339	479	340-660	480
Ab13	1-69	513	109-153	515	175-270	517	307-339	519	340-660	520
Ab14	1-66	553	106-150	555	172-267	557	307-339	559	340-660	560

FIG. 13

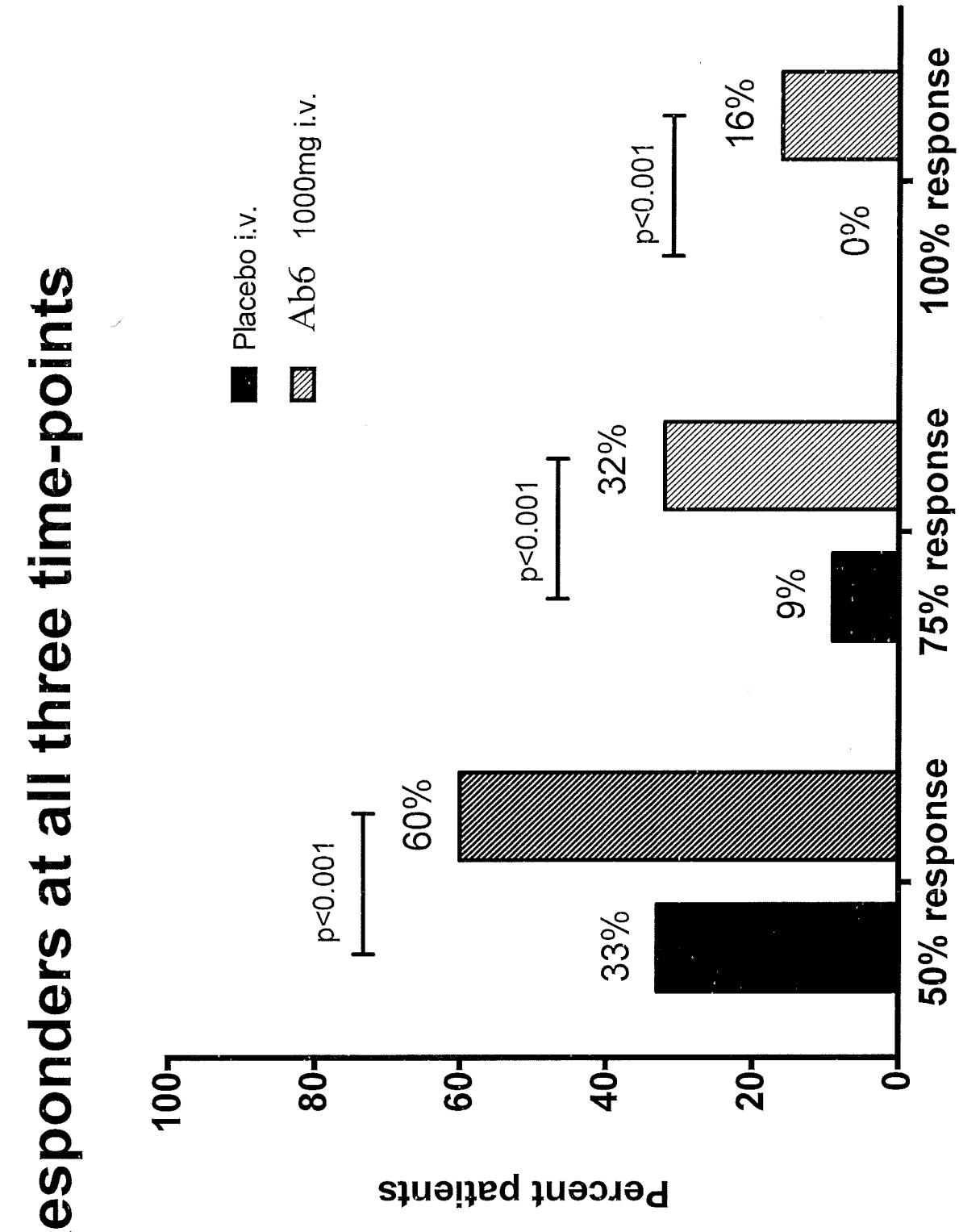
Responders at all three time-points
Placebo i.v.
Ab6 1000mg i.v.
Percent patients
100
80
60
40
20
0
p<0.001
60%
33%
p<0.001
32%
9%
p<0.001
16%
0%
50% response
75% response
100% response

FIG. 14

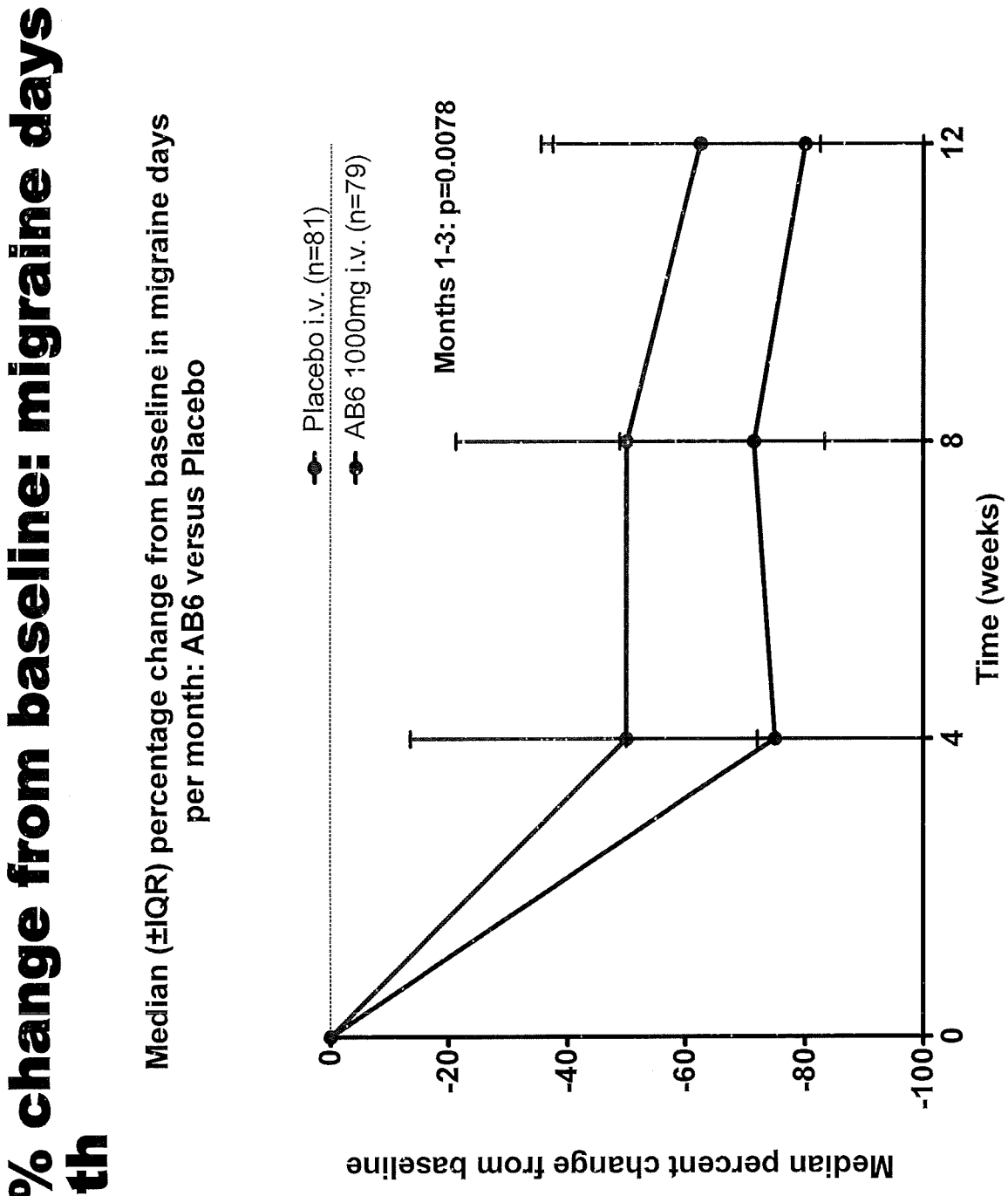
Median % change from baseline: migraine days per month
Median (±IQR) percentage change from baseline in migraine days per month: AB6 versus Placebo
Placebo i.v. (n=81)
AB6 1000mg i.v. (n=79)
Months 1-3: p=0.0078
Median percent change from baseline
0
-20
-40
-60
-80
-100
0
4
8
12
Time (weeks)

FIG. 15

Median % change from baseline: migraine episodes per month

Median (±IQR) percentage change from baseline in migraine episodes per month: AB6 versus Placebo

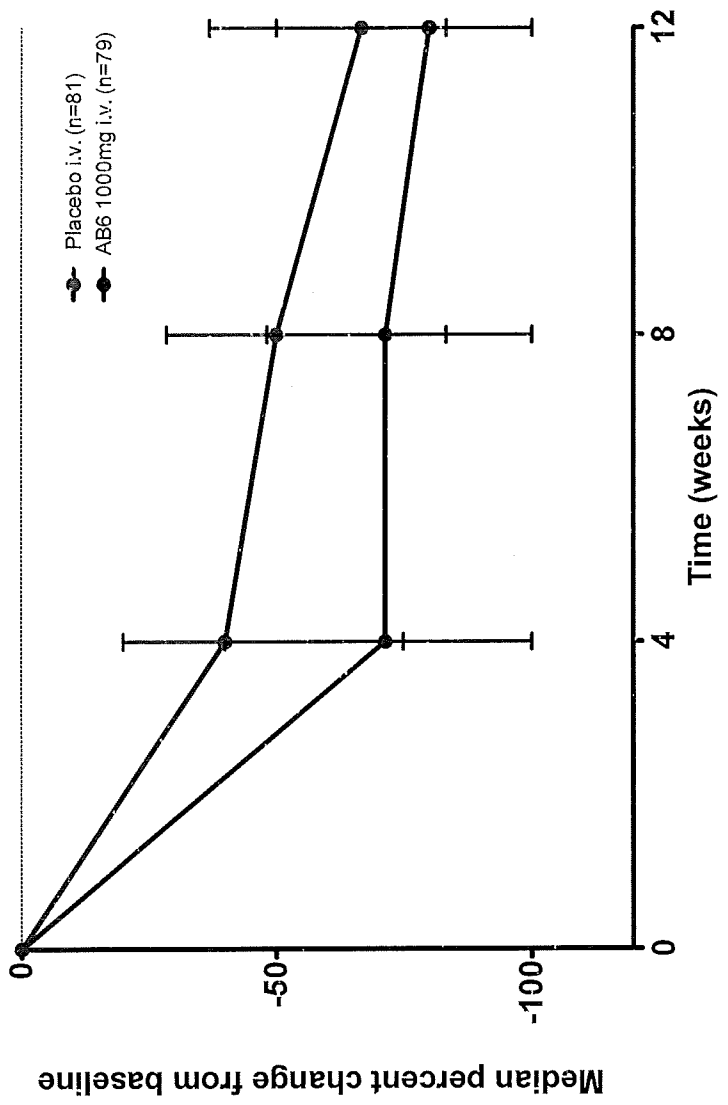

FIG. 16

Median % change from baseline: migraine hours per month

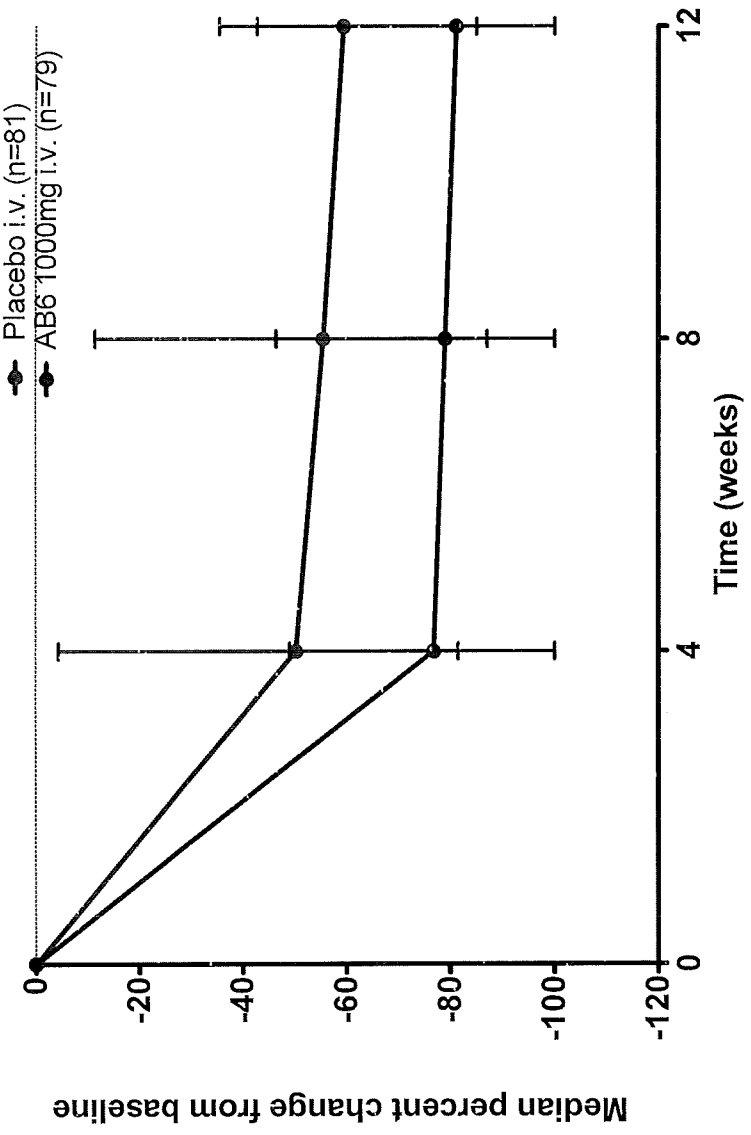

FIG. 17

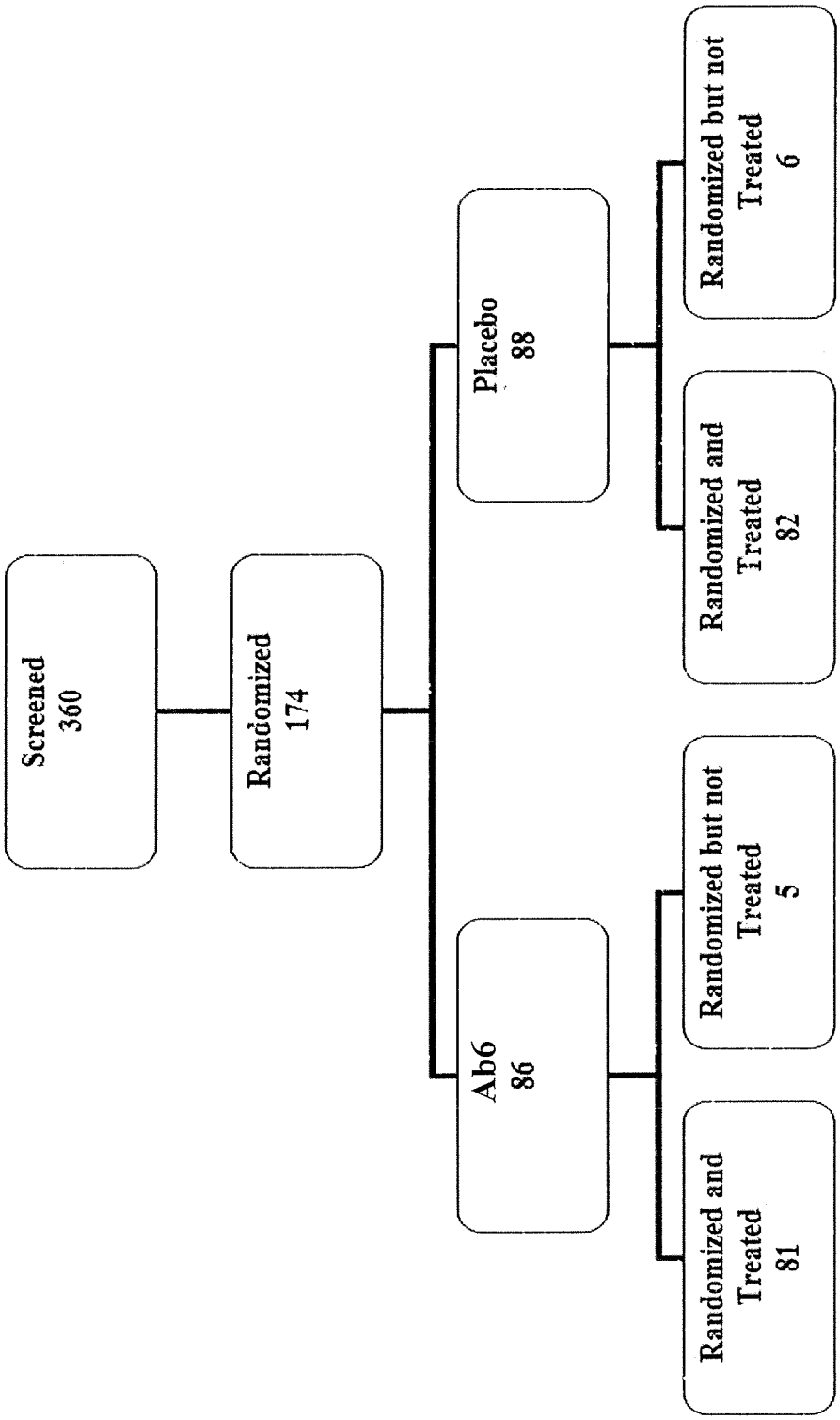
Screened
360
Randomized
174
Ab6
86
Placebo
88
Randomized and
Treated
81
Randomized but not
Treated
5
Randomized and
Treated
82
Randomized but not
Treated
6

FIG. 18

Mean Change Baseline HIT-6 score

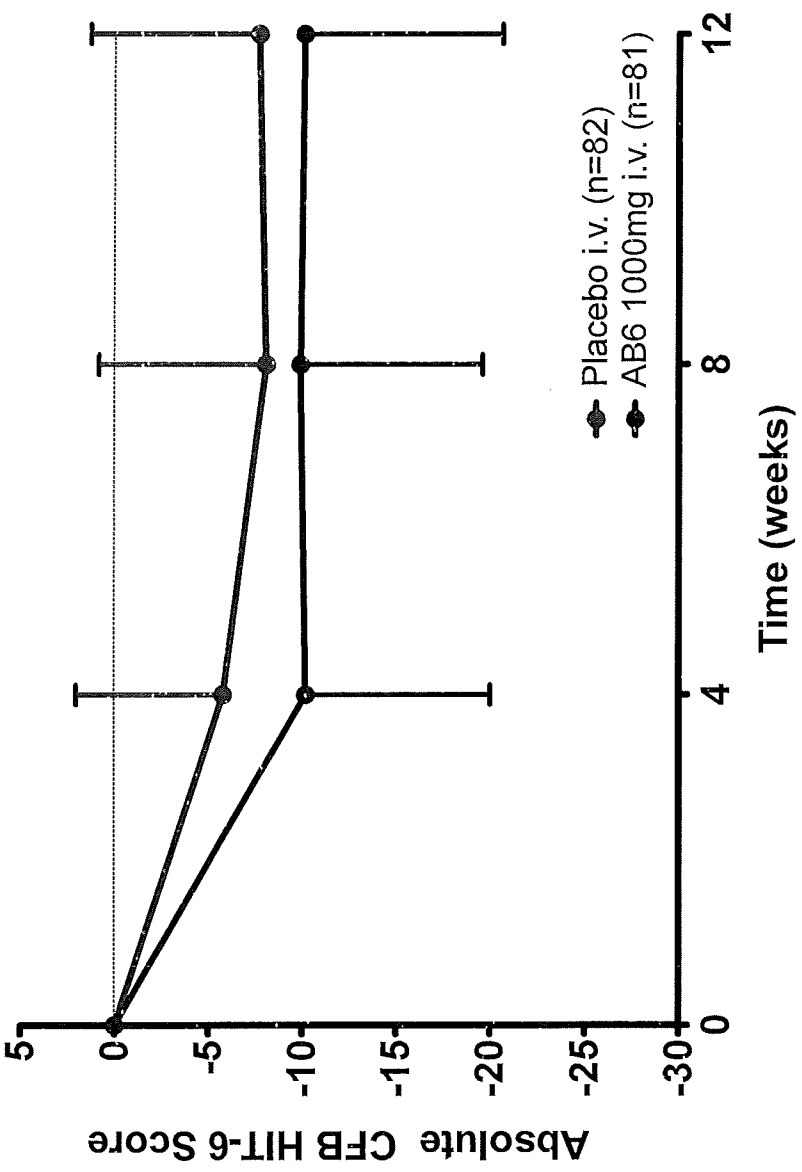

FIG. 19

HIT-6 Responder Analysis

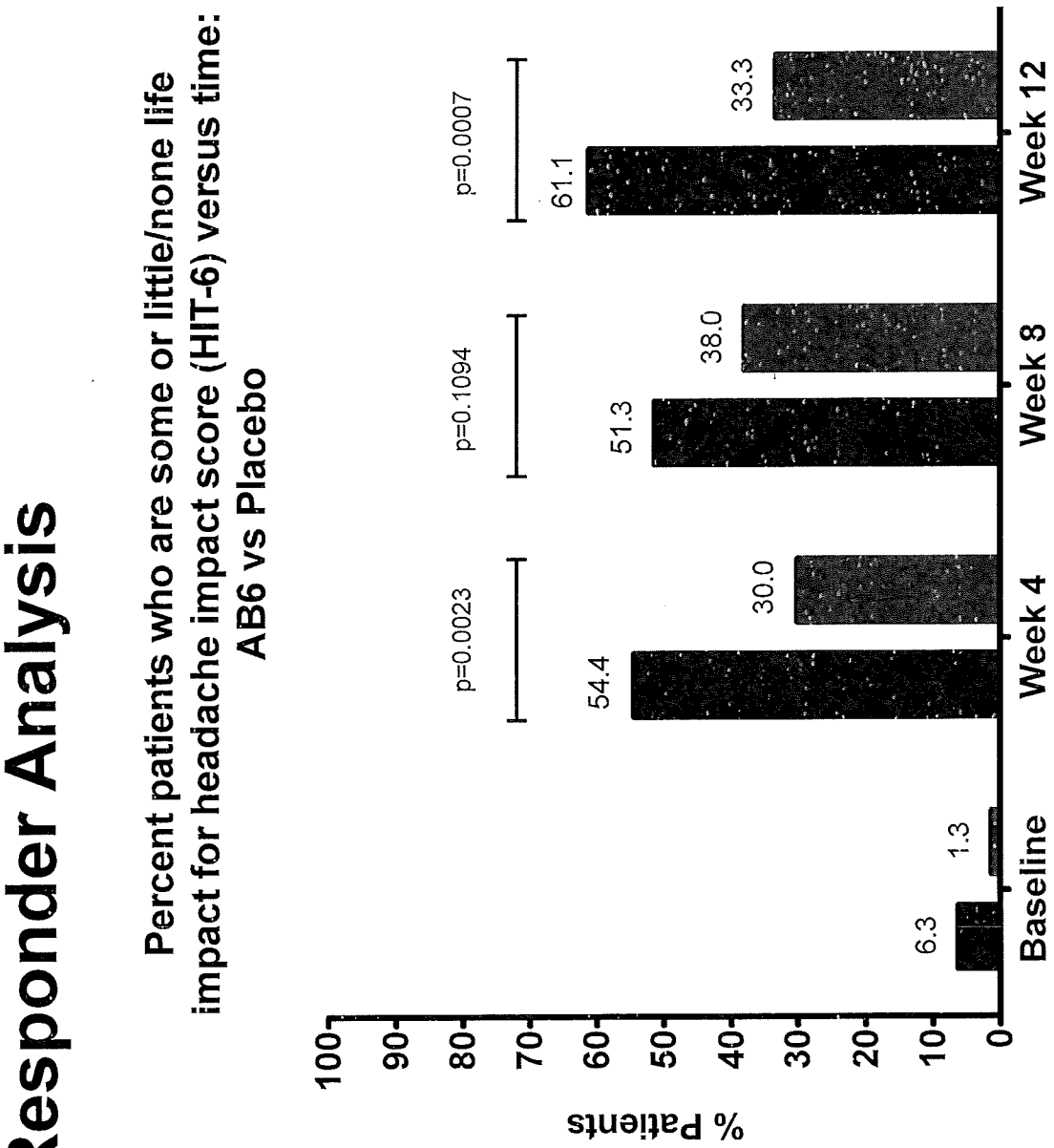

FIG. 20. PK Profile

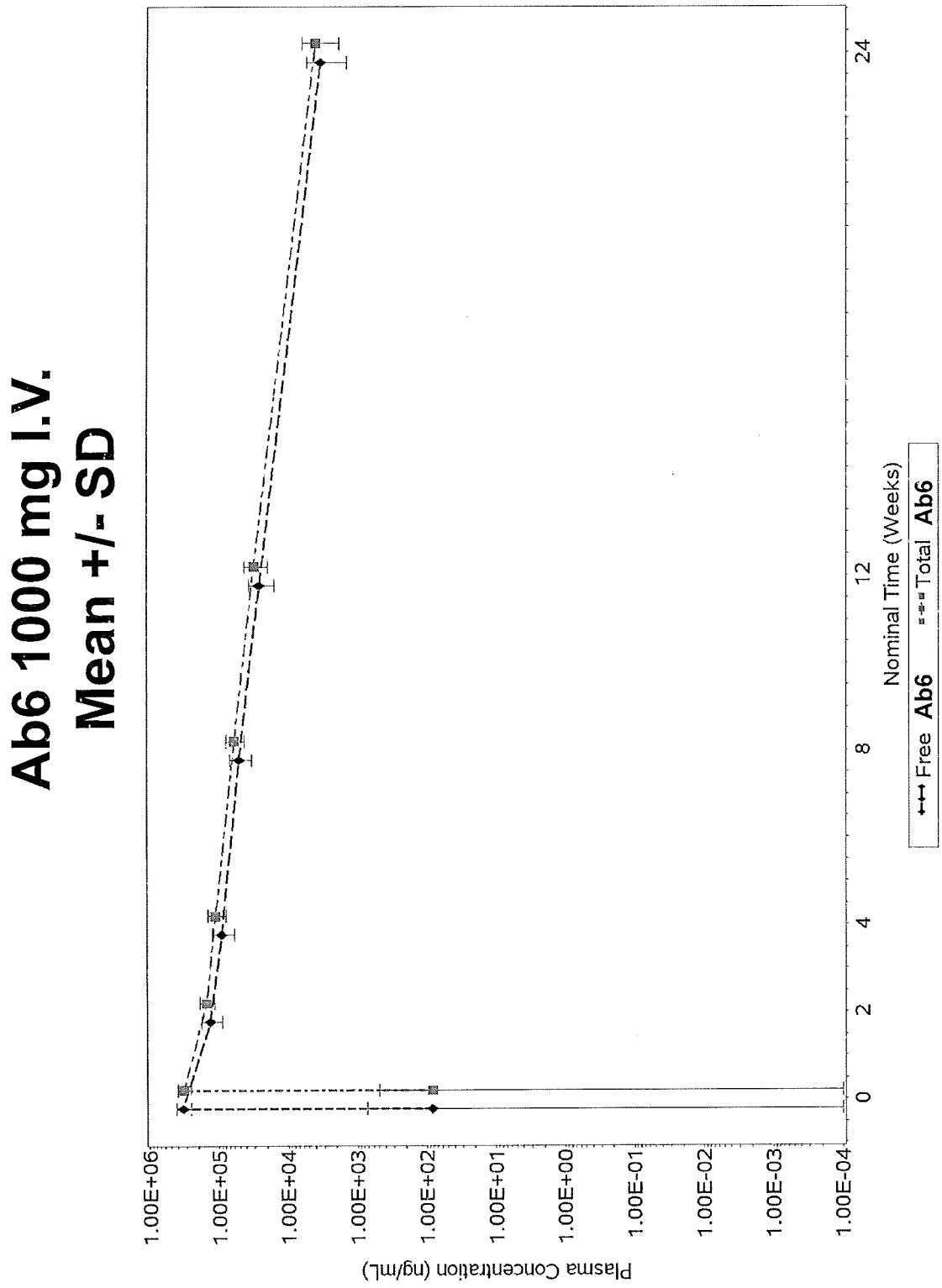

FIG. 21. PK Parameters

Plasma Free Ab6*

	C_{max} (µg/mL)	$AUC_{0-\infty}$ (mg*hr/mL)	Half-Life (Days)	Vz (L)	CL (mL/hr)
N	81	78	78	78	78
Mean	336	219	31	5.2	5.0
SD	80	64	8	2.1	1.5

* - Following 1000 mg Ab6 IV single-dose

FIG. 22

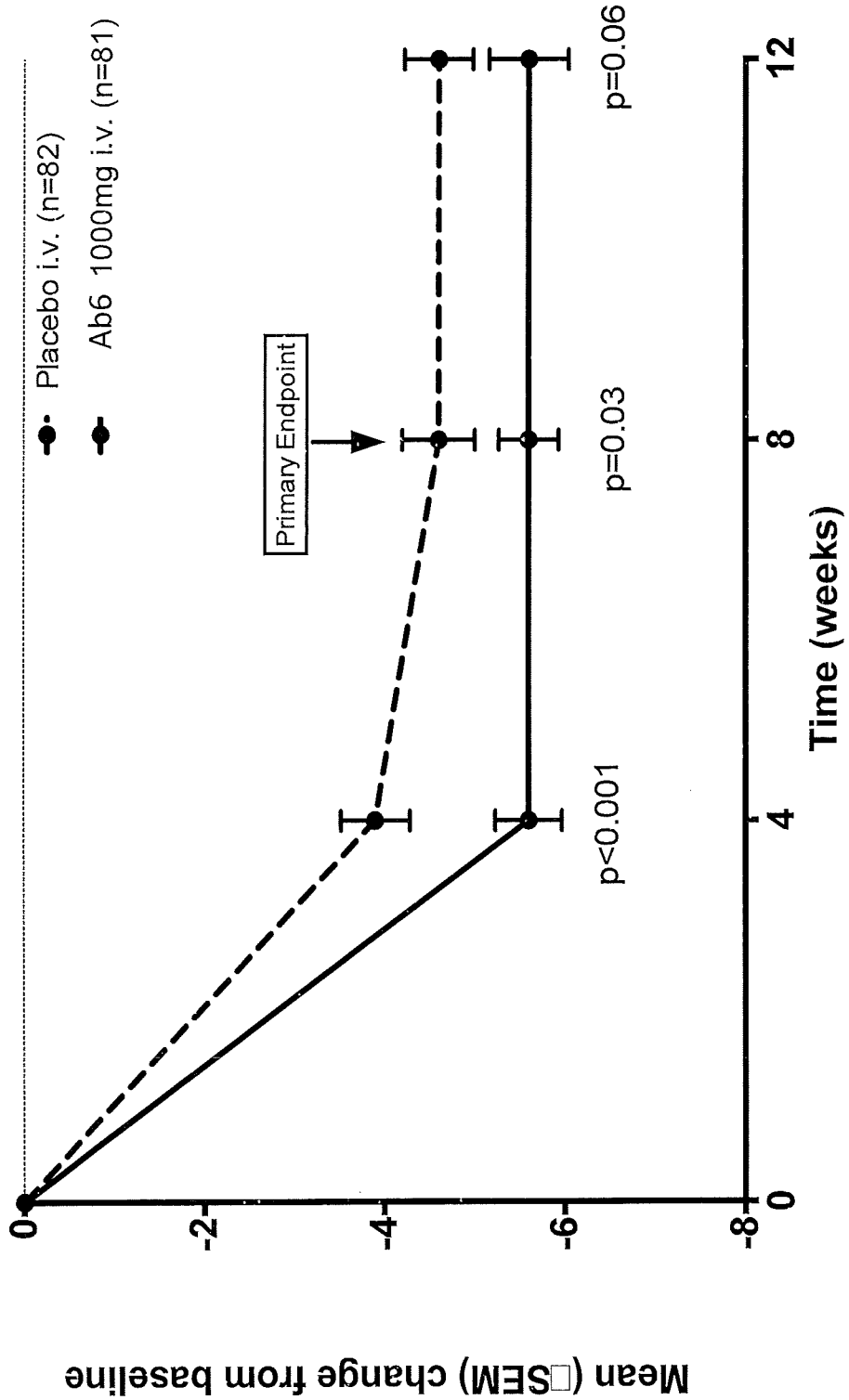
Placebo i.v. (n=82)
Ab6 1000mg i.v. (n=81)
Primary Endpoint
p<0.001
p=0.03
p=0.06
Mean (±SEM) change from baseline
0
-2
-4
-6
-8
0
4
8
12
Time (weeks)

FIG. 23

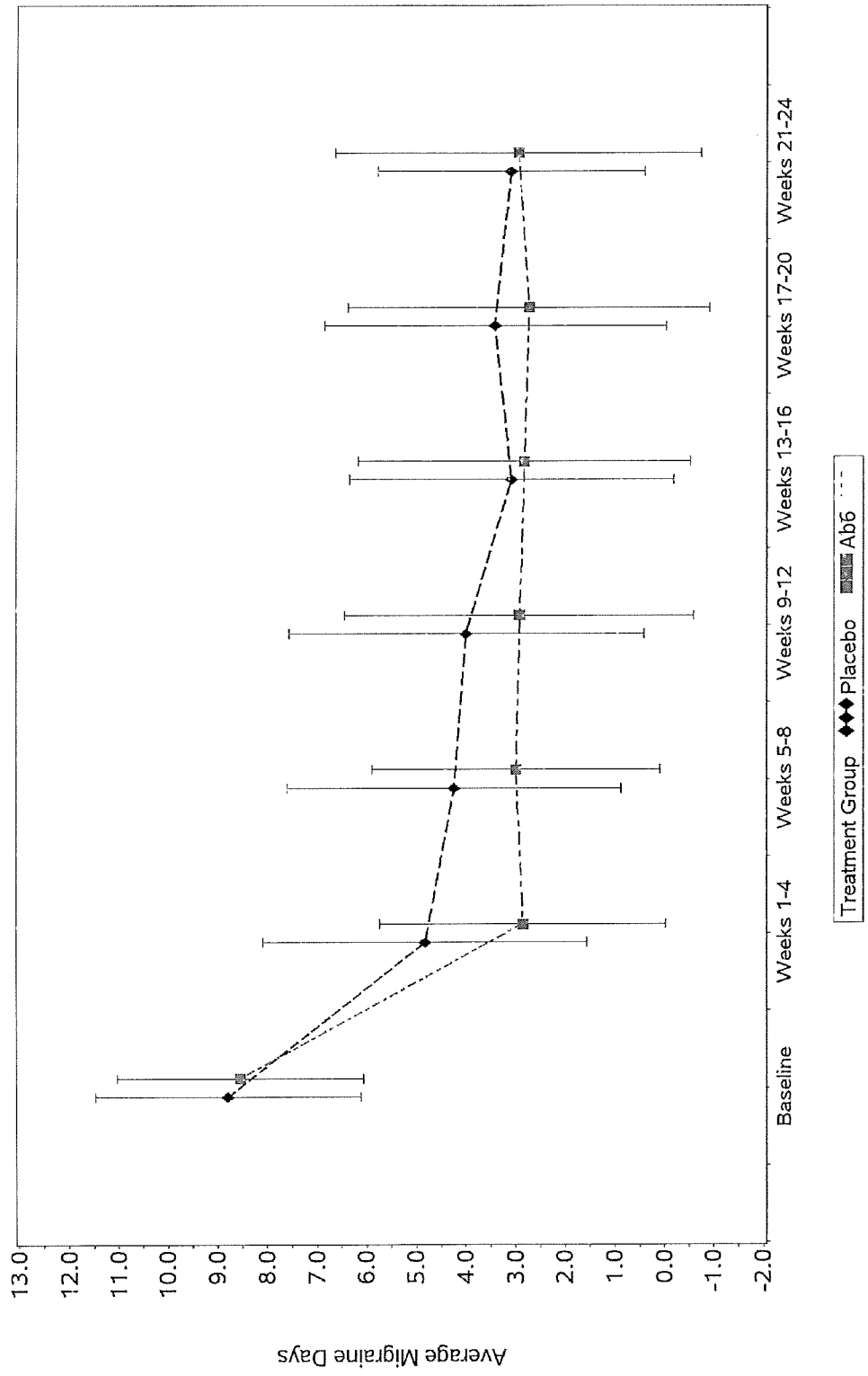
Average Migraine Days
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
-2.0
Baseline
Weeks 1-4
Weeks 5-8
Weeks 9-12
Weeks 13-16
Weeks 17-20
Weeks 21-24
Treatment Group
Placebo
Ab6

FIG. 24

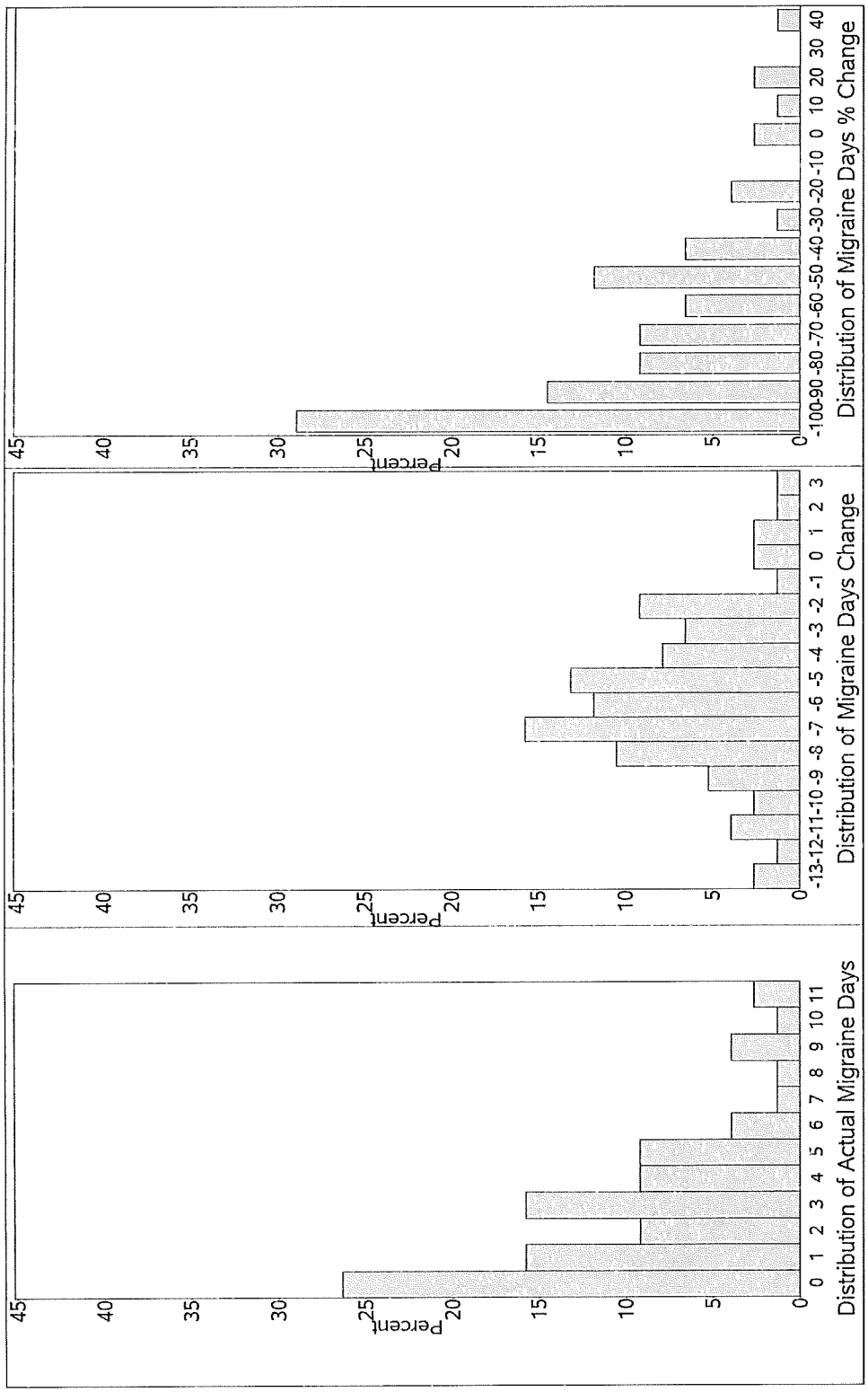
Distribution of Actual Migraine Days
Distribution of Migraine Days Change
Distribution of Migraine Days % Change
Percent
0 1 2 3 4 5 6 7 8 9 10 11
-13 -12 -11 -10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0 1 2 3
-100 -90 -80 -70 -60 -50 -40 -30 -20 -10 0 10 20 30 40
0 5 10 15 20 25 30 35 40 45

FIG. 25

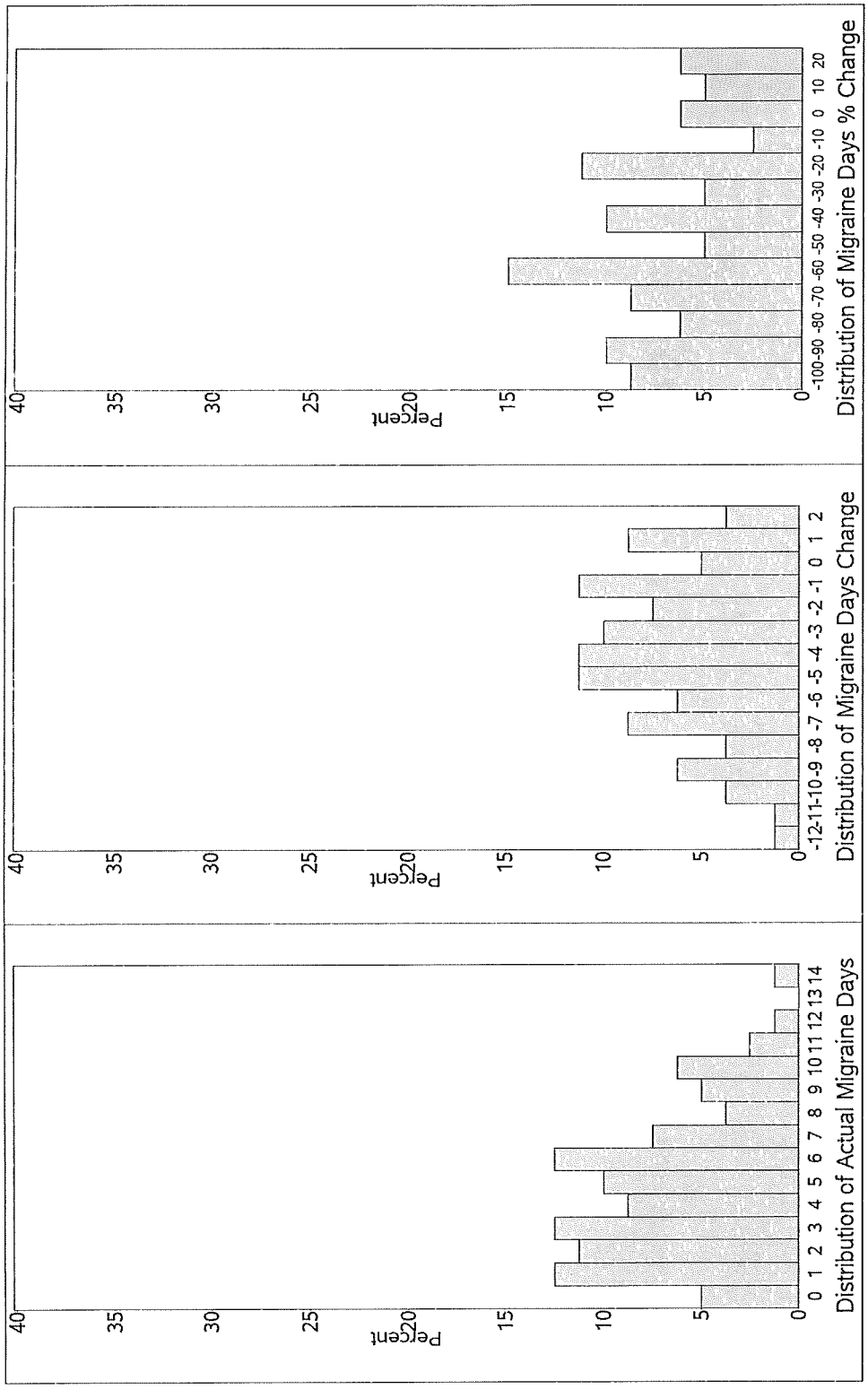
Distribution of Actual Migraine Days
Distribution of Migraine Days Change
Distribution of Migraine Days % Change
Percent
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
-12 -11 -10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0 1 2
-100 -90 -80 -70 -60 -50 -40 -30 -20 -10 0 10 20
0 5 10 15 20 25 30 35 40

FIG. 26

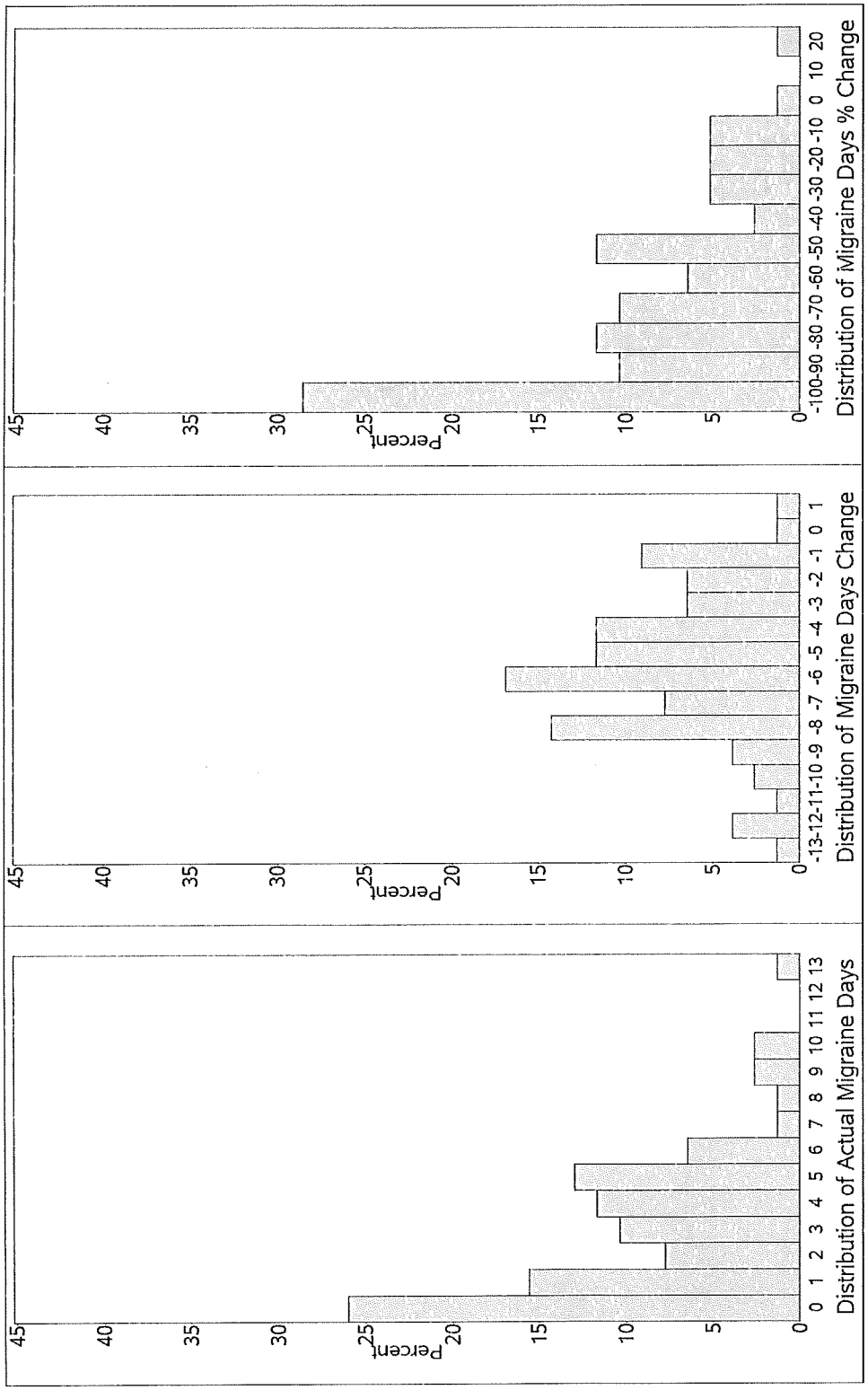
Distribution of Actual Migraine Days
Distribution of Migraine Days Change
Distribution of Migraine Days % Change
Percent
0 1 2 3 4 5 6 7 8 9 10 11 12 13
-13 -12 -11 -10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0 1
-100 -90 -80 -70 -60 -50 -40 -30 -20 -10 0 10 20
0 5 10 15 20 25 30 35 40 45

FIG. 27

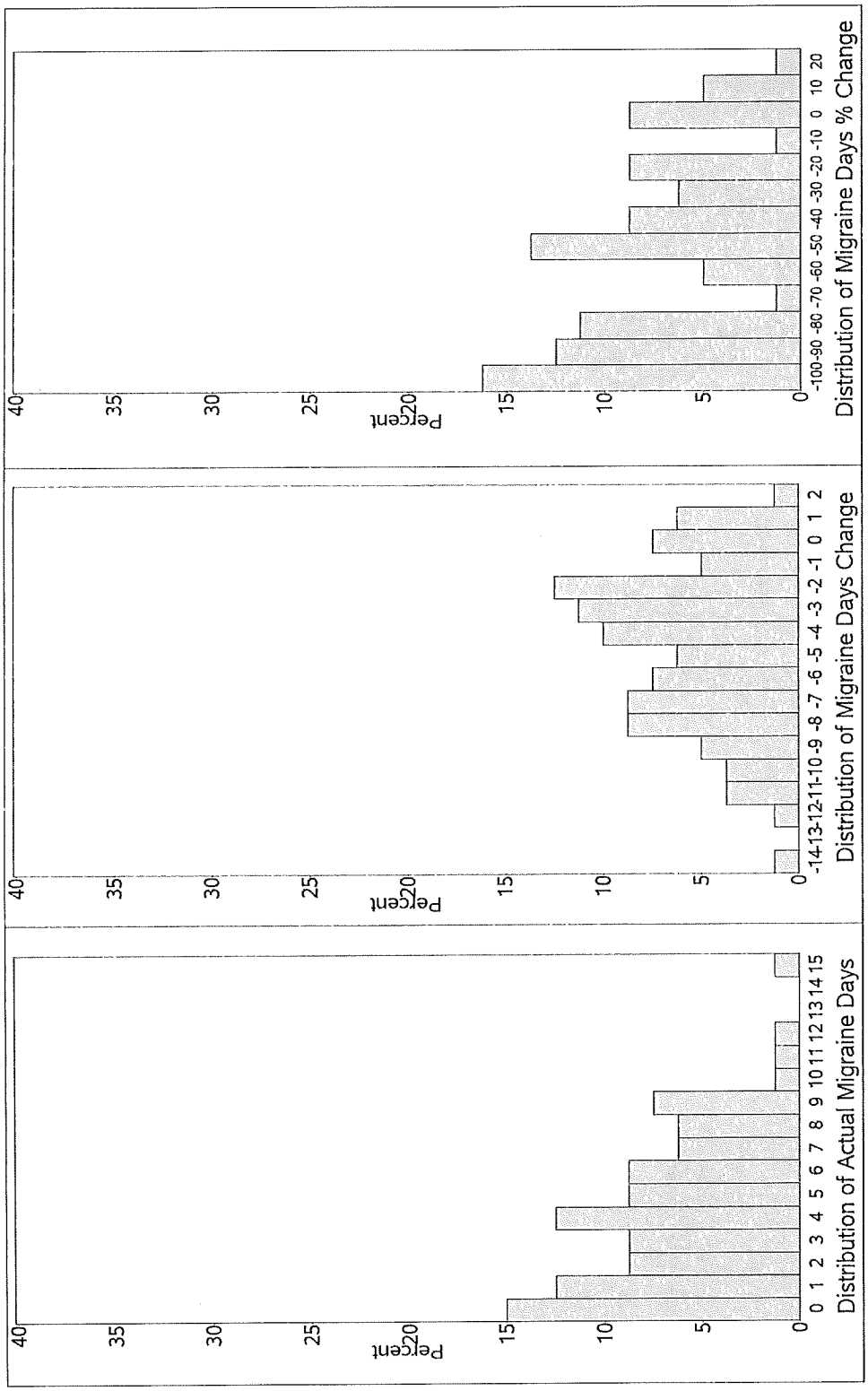
Distribution of Actual Migraine Days
Distribution of Migraine Days Change
Distribution of Migraine Days % Change
Percent
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
-14 -13 -12 -11 -10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0 1 2
-100 -90 -80 -70 -60 -50 -40 -30 -20 -10 0 10 20
0 5 10 15 20 25 30 35 40

FIG. 28

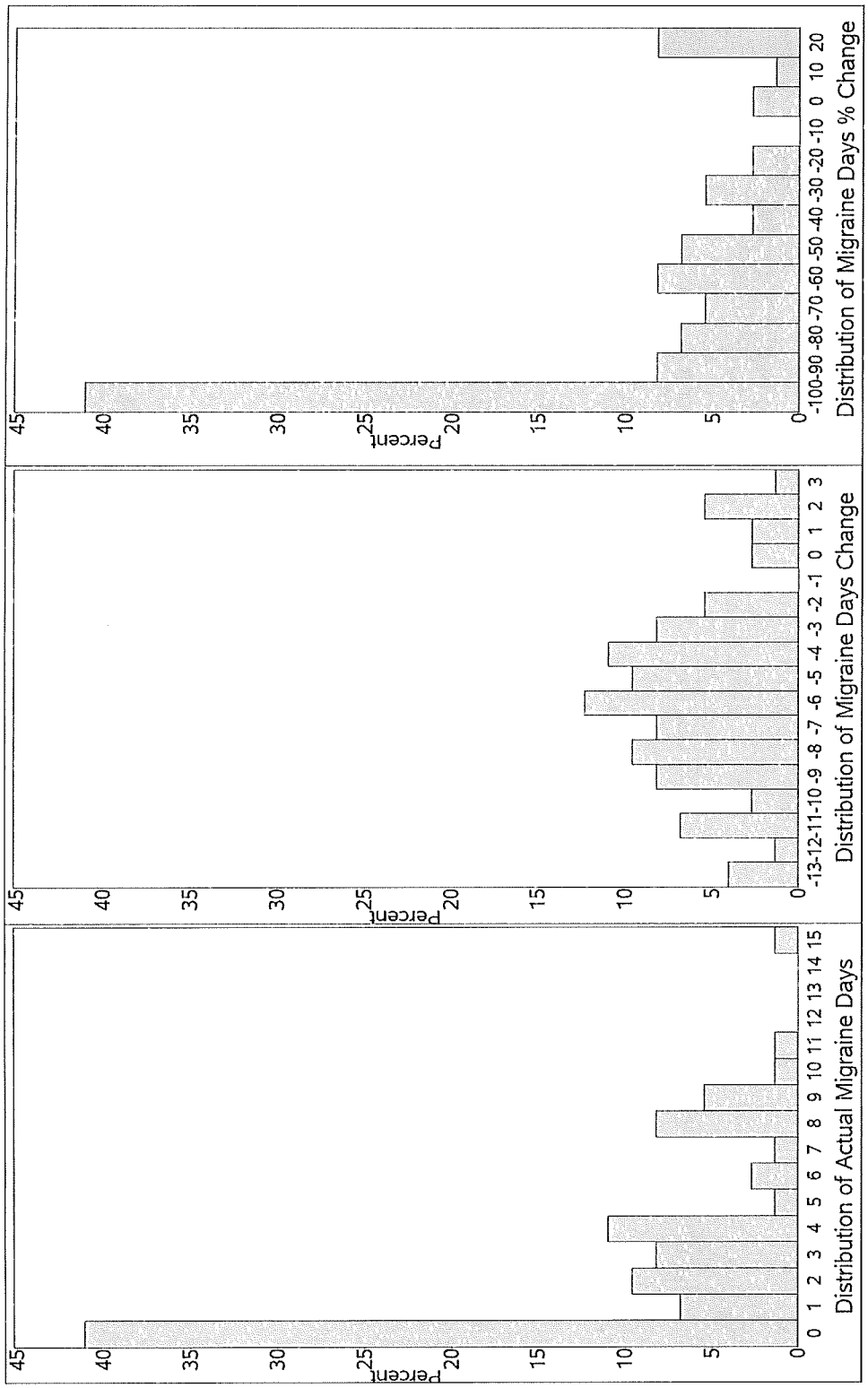
Percent
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Distribution of Actual Migraine Days
-13-12-11-10-9 -8 -7 -6 -5 -4 -3 -2 -1 0 1 2 3
Distribution of Migraine Days Change
-100-90 -80 -70 -60 -50 -40 -30 -20 -10 0 10 20
Distribution of Migraine Days % Change

FIG. 29

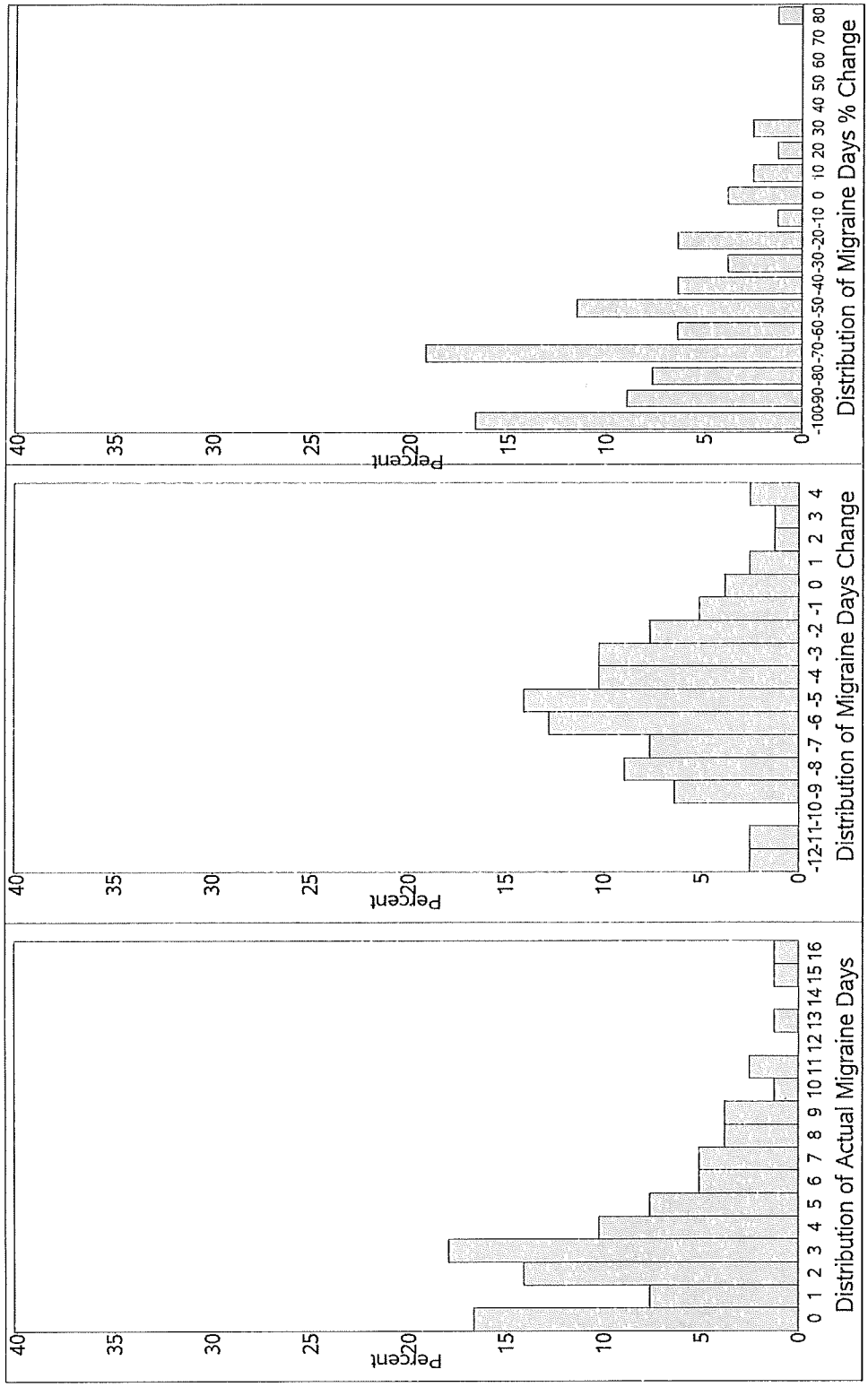
Distribution of Actual Migraine Days
Distribution of Migraine Days Change
Distribution of Migraine Days % Change
Percent
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
-12 -11 -10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0 1 2 3 4
-100 -90 -80 -70 -60 -50 -40 -30 -20 -10 0 10 20 30 40 50 60 70 80
0 5 10 15 20 25 30 35 40

FIG. 30

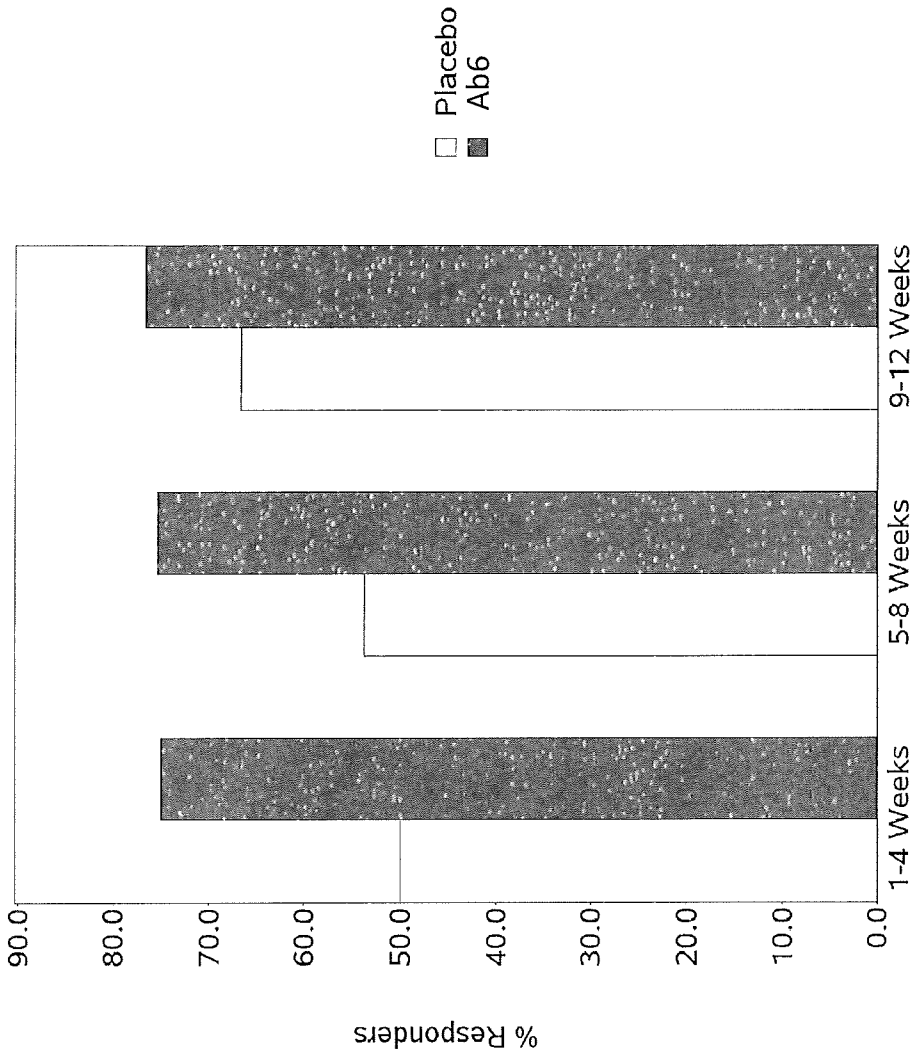
Placebo
Ab6
% Responders
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
1-4 Weeks
5-8 Weeks
9-12 Weeks

FIG. 31

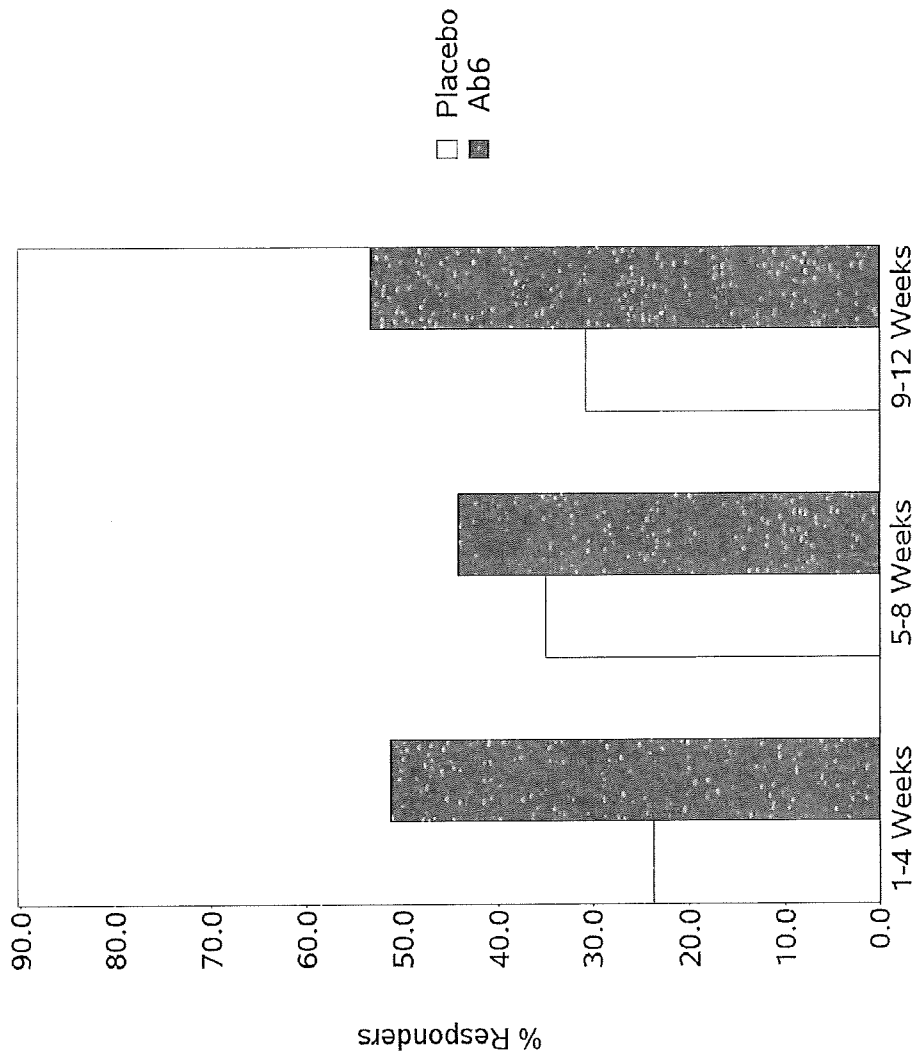
Placebo
Ab6
% Responders
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
1-4 Weeks
5-8 Weeks
9-12 Weeks

FIG. 32

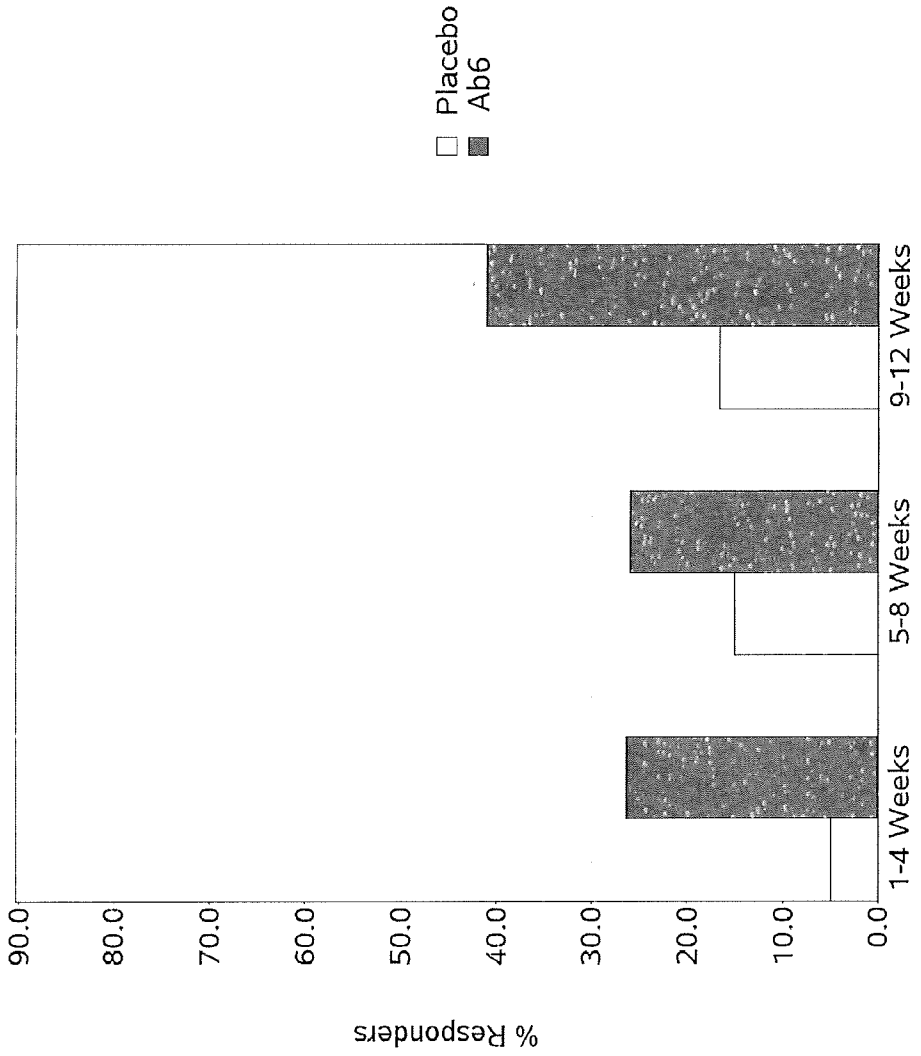
Placebo
Ab6
% Responders
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
1-4 Weeks
5-8 Weeks
9-12 Weeks

FIG. 33

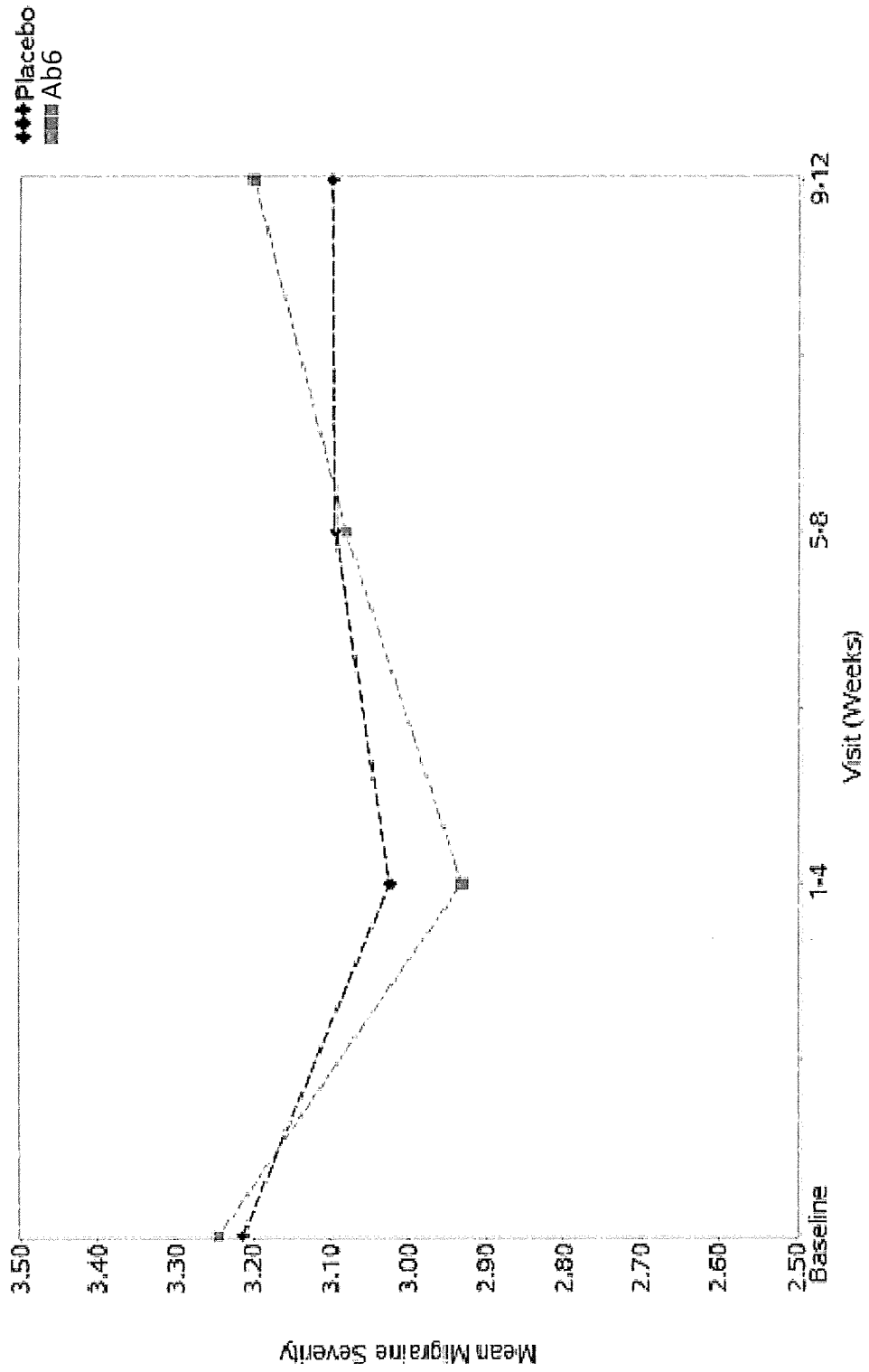
Placebo
Ab6
Mean Migraine Severity
3.50
3.40
3.30
3.20
3.10
3.00
2.90
2.80
2.70
2.60
2.50
Baseline
1-4
5-8
9-12
Visit (Weeks)

FIG. 34. Mean (±SD) Change from Baseline In Study Endpoints						
Endpoint	**Weeks 1-4**		**Weeks 5-8**		**Weeks 9-12**	
	Placebo i.v. (n=82)	**Ab6 1000mg i.v. (n=81)**	**Placebo i.v. (n=82)**	**Ab6 1000mg i.v. (n=81)**	**Placebo i.v. (n=82)**	**Ab6 1000mg i.v. (n=81)**
Migraine Days	-3.9 (3.5)	-5.6 (3.3)[1]	-4.6 (3.6)	-5.6 (3.0)[2]	-4.6 (3.5)	-5.6 (4.0)[3]
Migraine Episodes	-3.0 (2.7)	-3.7 (2.4)	-3.7 (2.9)	-3.8 (2.2)	-3.7 (2.8)	-3.9 (2.6)
Migraine Hours	-33.7 (41.8)	-58.0 (49.1)	-36.1 (45.9)	-54.4 (48.3)	-37.1 (40.0)	-54.6 (60.5)
Average Migraine Severity[4]	-0.16 (0.58)	-0.31 (0.58)	-0.10 (0.54)	-0.16 (0.50)	-0.08 (0.54)	-0.11 (0.43)
Headache Frequency	-4.0 (3.8)	-5.6 (3.4)	-5.0 (3.7)	-5.3 (3.5)	-5.1 (3.7)	-5.9 (3.8)
HIT-6 score	-5.8 (7.8)	-10.2 (9.8)	-8.1 (8.9)	-9.9 (9.7)	-7.7 (9.0)	-10.1 (10.6)
MSQ RFP	19.9 (23.8)	29.3 (24.3)	25.2 (24.8)	28.8 (24.7)	22.2 (23.1)	28.5 (24.5)
MSQ RFR	16.3 (23.2)	21.1 (23.9)	20.2 (22.1)	20.9 (23.3)	18.0 (20.5)	21.4 (23.1)
MSQ EF	19.4 (27.6)	25.1 (28.3)	21.2 (25.1)	23.8 (25.8)	21.1 (25.1)	23.1 (26.8)

[1]$p<0.001$; [2]$p=0.03$; [3]$p=0.06$; [4] Severity measured on a 4 point scale with 1= mild and 4 = severe

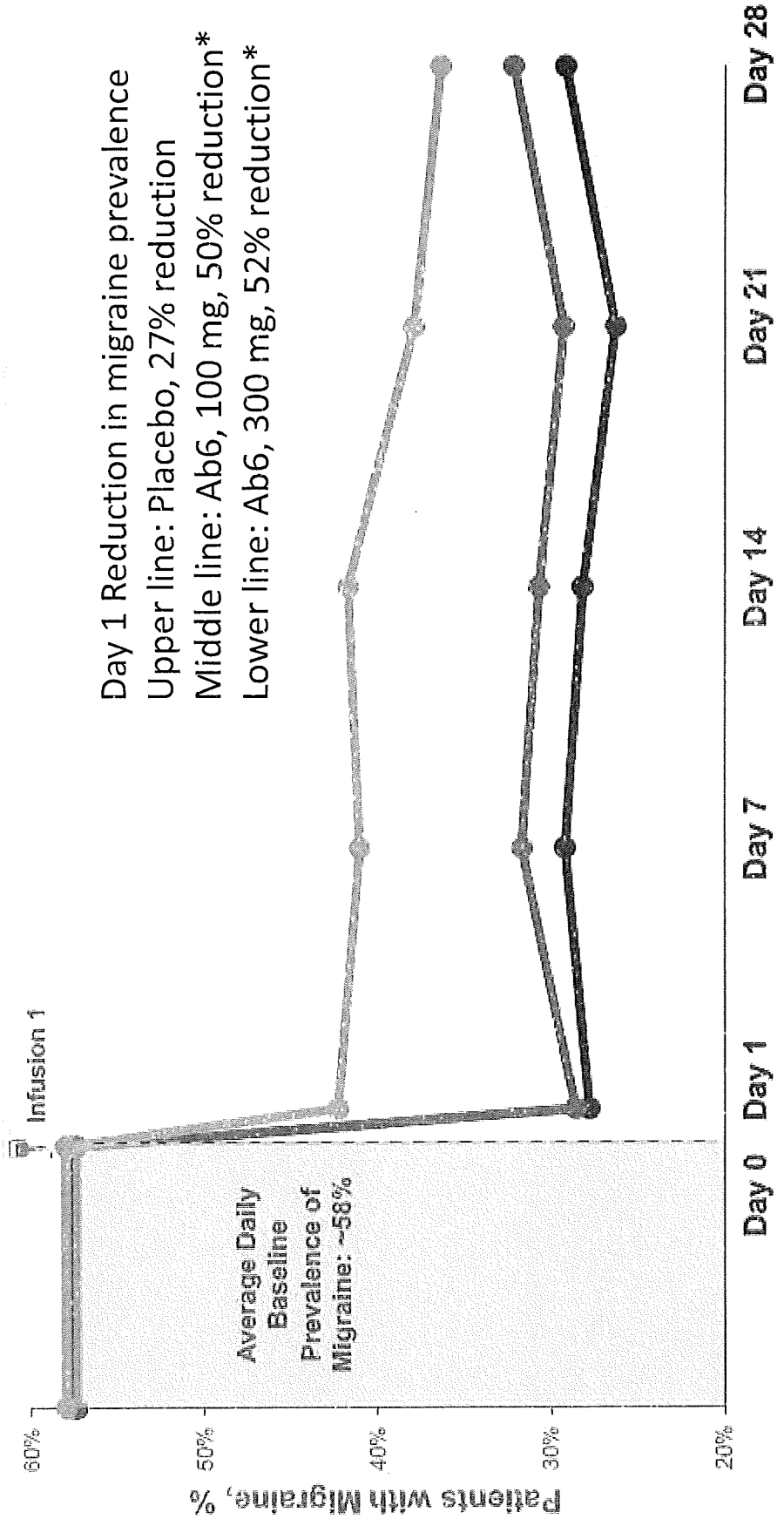
Day 1 Reduction in migraine prevalence
Upper line: Placebo, 27% reduction
Middle line: Ab6, 100 mg, 50% reduction*
Lower line: Ab6, 300 mg, 52% reduction*
Infusion 1
Average Daily Baseline Prevalence of Migraine: ~58%
Patients with Migraine, %
60%
50%
40%
30%
20%
Day 0
Day 1
Day 7
Day 14
Day 21
Day 28

FIG. 35

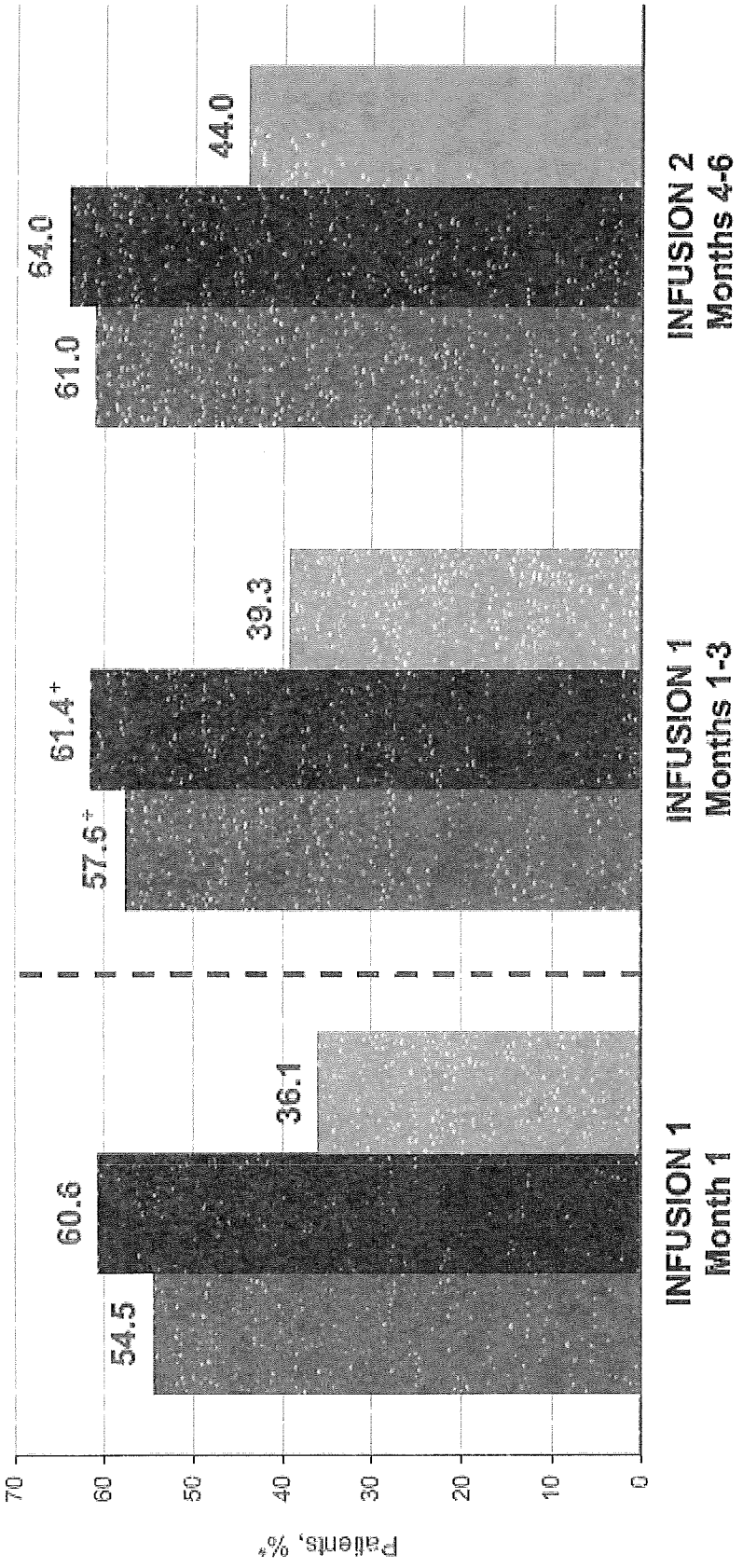

FIG. 36. Chronic migraine ≥ 50% responder rates

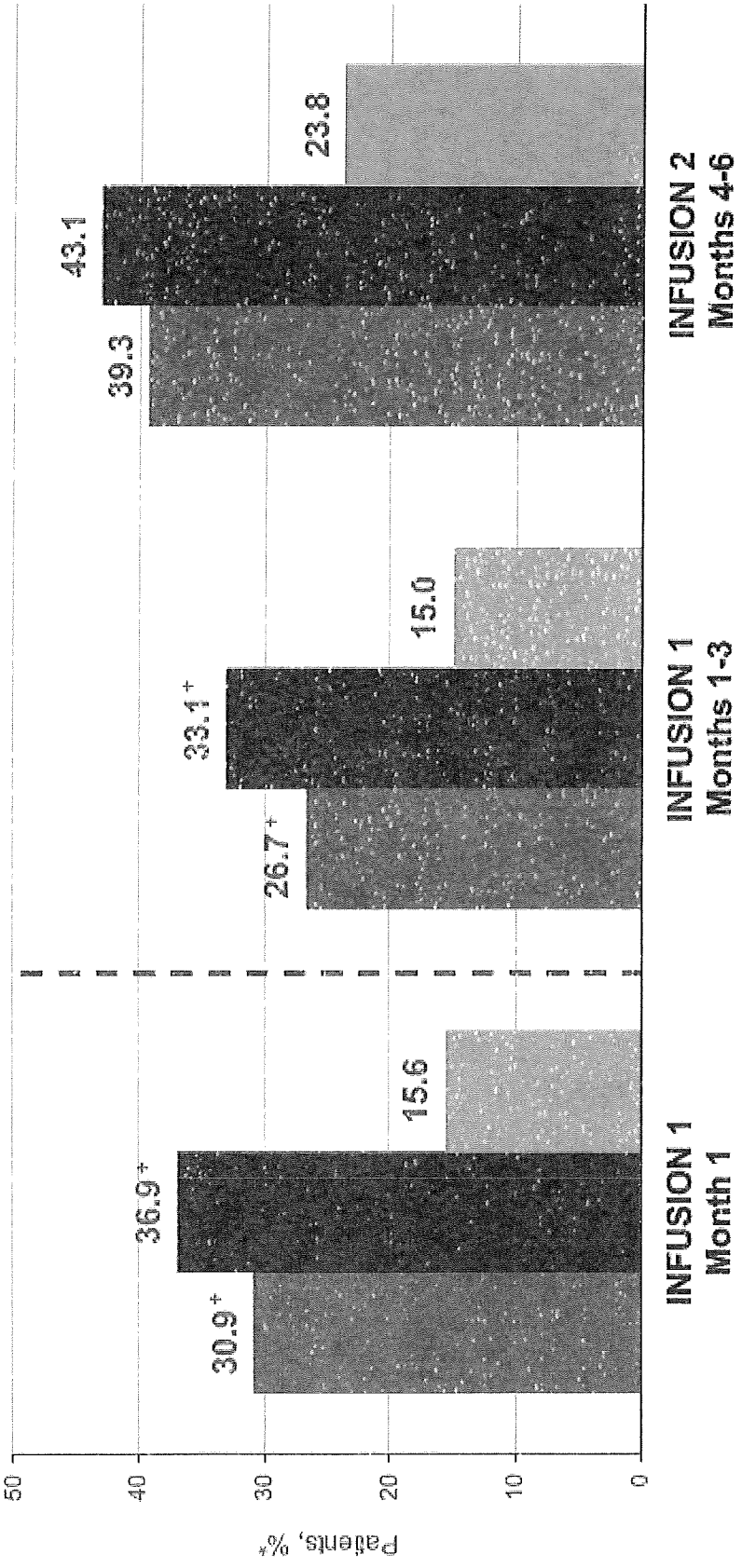

FIG. 37. Chronic migraine ≥ 75% responder rates

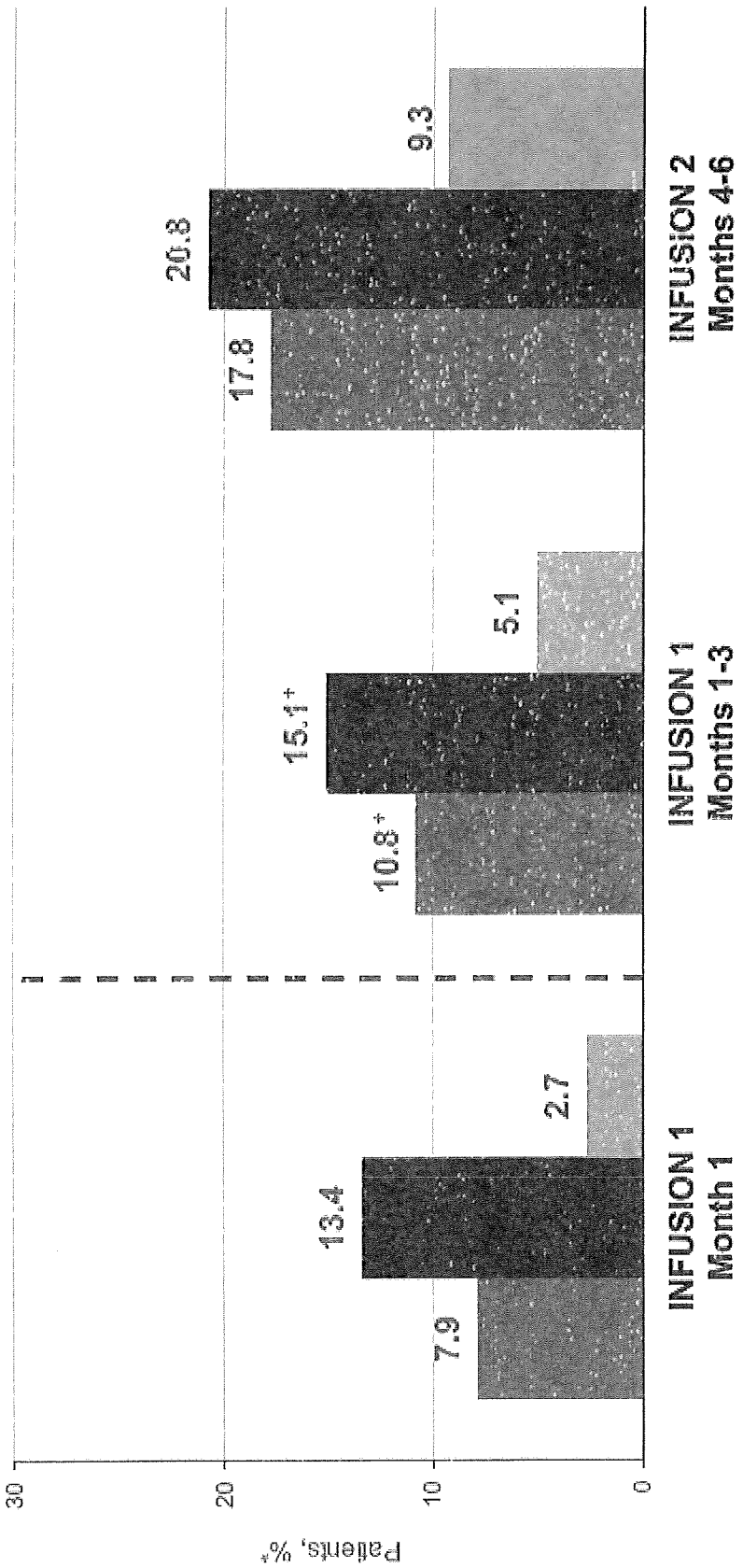

FIG. 38. Chronic migraine 100% responder rates

FIG. 39

	Placebo	100 mg	300 mg
Subjects, n	**366**	**356**	**350**
Mean age, years (SD)	39.6 (11.3)	41.0 (11.7)	41.0 (10.4)
Mean BMI, kg/m^2 (SD)	27.0 (5.6)	26.4 (5.0)	26.3 (5.0)
Female, %	89	86	90
Mean years from migraine diagnosis	17.0	18.3	19.0
Mean duration of chronic migraine, years (SD)	11.6 (10.9)	11.6 (11.7)	12.4 (11.2)
≥1 prophylactic medication, n (%)*	163 (44.5)	161 (45.2)	155 (44.3)
Mean migraine days/month (SD)	16.2 (4.6)	16.1 (4.6)	16.1 (4.8)
Mean headache days/month (SD)	20.6 (3.0)	20.4 (3.1)	20.4 (3.2)

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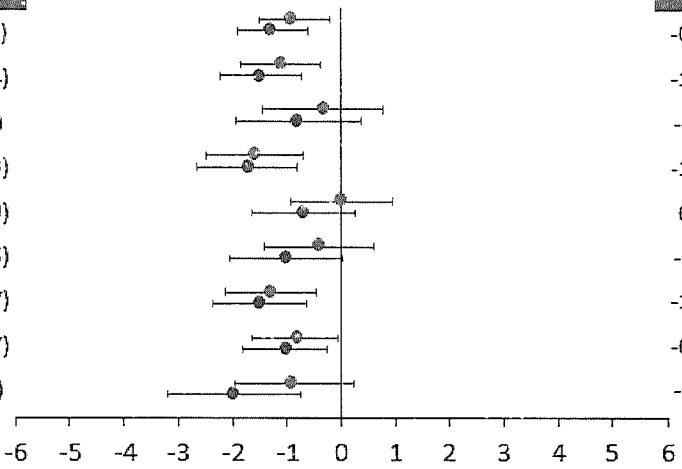
PCT/US2020/012790

FIG. 40. Difference from placebo in change from baseline in mean migraine days (MMD) over months 1-3 by baseline subgroup

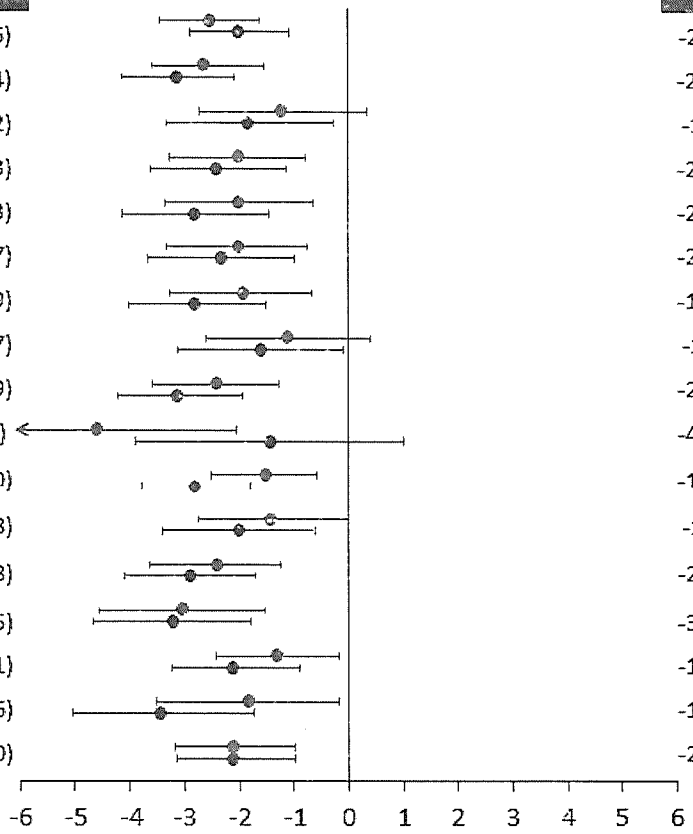
Variable	Subgroup	Change from baseline (sample size)			Difference from placebo (95% CI)	
		100 mg	300 mg	Placebo	100 mg	300 mg
All patients		-3.9 (n=221)	-4.3 (n=222)	-3.2 (n=222)	-0.9 (-1.50, -0.20)	-1.3 (-1.91, -0.59)
MMD frequency	≤9 days	-3.2 (n=142)	-3.6 (n=142)	-2.1 (n=144)	-1.1 (-1.85, -0.38)	-1.5 (-2.22, -0.73)
	>9 days	-5.1 (n=79)	-5.6 (n=80)	-4.8 (n=78)	-0.3 (-1.45, 0.78)	-0.8 (-1.94, 0.37)
Age at diagnosis	≤21 years	-4.4 (n=123)	-4.6 (n=122)	-2.9 (n=113)	-1.6 (-2.47, -0.69)	-1.7 (-2.66, -0.80)
	>21 years	-3.3 (n=98)	-4.0 (n=100)	-3.3 (n=109)	0.0 (-0.92, 0.95)	-0.7 (-1.65, 0.25)
Duration of migraine	≤15 years	-3.6 (n=106)	-4.2 (n=98)	-3.2 (n=115)	-0.4 (-1.40, 0.61)	-1.0 (-2.03, 0.03)
	>15 years	-4.2 (n=115)	-4.4 (n=124)	-2.9 (n=107)	-1.3 (-2.12, -0.47)	-1.5 (-2.36, -0.62)
Aura symptoms	Suffer from aura	-4.0 (n=167)	-4.2 (n=173)	-3.1 (n=167)	-0.8 (-1.63, -0.06)	-1.0 (-1.82, -0.25)
	No aura	-3.7 (n=54)	-4.8 (n=49)	-2.8 (n=55)	-0.9 (-1.96, 0.22)	-2.0 (-3.19, -0.76)



WO 2020/146535
PCT/US2020/012790

FIG. 41. Difference from placebo in change from baseline in mean migraine days (MMD) over months 1-3 by baseline subgroup

Variable	Subgroup	Change from baseline (sample size)			Difference from placebo (95% CI)	
		100 mg	300 mg	Placebo	100 mg	300 mg
All patients		-8.3 (n=350)	-7.8 (n=356)	-5.8 (n=366)	-2.5 (-3.44, -1.62)	-2.0 (-2.89, -1.07)
MMD frequency	<17 days	-6.8 (n=192)	-7.4 (n=193)	-4.3 (n=204)	-2.6 (-3.58, -1.53)	-3.1 (-4.12, -2.08)
	≥17 days	-8.9 (n=164)	-9.5 (n=157)	-7.7 (n=162)	-1.2 (-2.70, 0.35)	-1.8 (-3.32, -0.25)
Age at diagnosis	≤21 years	-7.5 (n=204)	-7.8 (n=193)	-5.5 (n=193)	-2.0 (-3.26, -0.78)	-2.4 (-3.60, -1.13)
	>21 years	-8.2 (n=152)	-8.9 (n=157)	-6.2 (n=173)	-2.0 (-3.35, -0.64)	-2.8 (-4.12, -1.43)
Duration of migraine	≤15 years	-8.0 (n=174)	-8.3 (n=158)	-6.0 (n=187)	-2.0 (-3.31, -0.74)	-2.3 (-3.65, -0.97)
	>15 years	-7.6 (n=182)	-8.4 (n=192)	-5.6 (n=179)	-1.9 (-3.25, -0.65)	-2.8 (-4.00, -1.50)
Aura symptoms	Suffer from aura	-7.1 (n=115)	-7.6 (n=128)	-6.0 (n=127)	-1.1 (-2.59, 0.40)	-1.6 (-3.11, -0.07)
	No aura	-8.1 (n=241)	-8.7 (n=222)	-5.7 (n=239)	-2.4 (-3.56, -1.27)	-3.1 (-4.20, -1.93)
Prior prophylactic medication use	Yes	-10.3 (n=51)	-7.2 (n=62)	-5.7 (n=46)	-4.6 (-7.19, -2.04)	-1.4 (-3.90, 1.02)
	No	-7.4 (n=305)	-8.6 (n=288)	-5.8 (n=320)	-1.5 (-2.51, -0.57)	-2.8 (-3.76, -1.79)
Concomitant prophylactic medication use	Yes	-6.4 (n=152)	-7.1 (n=147)	-5.1 (n=158)	-1.4 (-2.73, 0.01)	-2.0 (-3.39, -0.60)
	No	-8.8 (n=204)	-9.2 (n=203)	-6.4 (n=208)	-2.4 (-3.63, -1.23)	-2.9 (-4.08, -1.71)
Medication overuse	Yes	-8.4 (n=139)	-8.6 (n=147)	-5.4 (n=145)	-3.0 (-4.56, -1.52)	-3.2 (-4.66, -1.78)
	No	-7.4 (n=217)	-8.1 (n=203)	-6.1 (n=221)	-1.3 (-2.43, -0.16)	-2.1 (-3.24, -0.88)
Triptan use	≥33% of days	-7.7 (n=124)	-9.2 (n=125)	-5.9 (n=116)	-1.8 (-3.51, -0.18)	-3.4 (-5.05, -1.73)
	<33% of days	-7.9 (n=231)	-7.8 (n=225)	-5.8 (n=250)	-2.1 (-3.16, -0.98)	-2.1 (-3.13, -0.97)



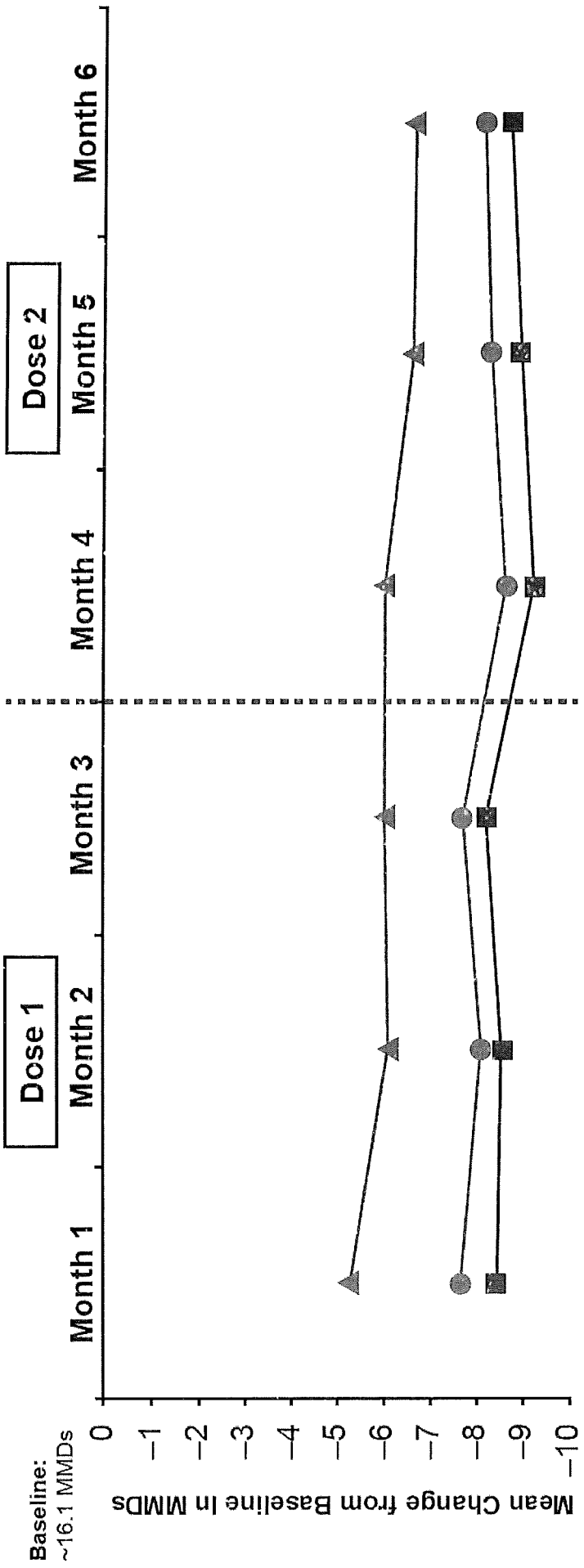

Mean Change from Baseline in MMDs
0
−1
−2
−3
−4
−5
−6
−7
−8
−9
−10
Baseline:
~16.1 MMDs
Month 1
Dose 1
Month 2
Month 3
Month 4
Dose 2
Month 5
Month 6

FIG. 42.

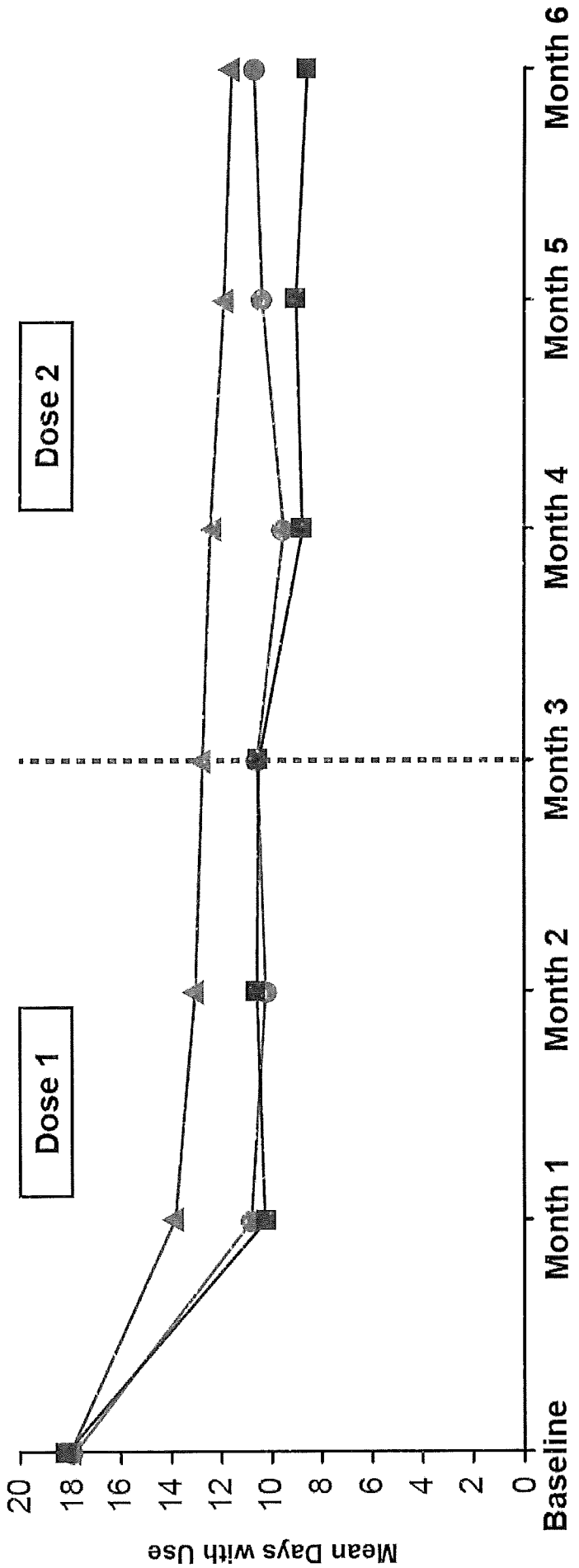

Mean Days with Use
20
18
16
14
12
10
8
6
4
2
0
Baseline
Month 1
Month 2
Month 3
Month 4
Month 5
Month 6
Dose 1
Dose 2

FIG. 43.

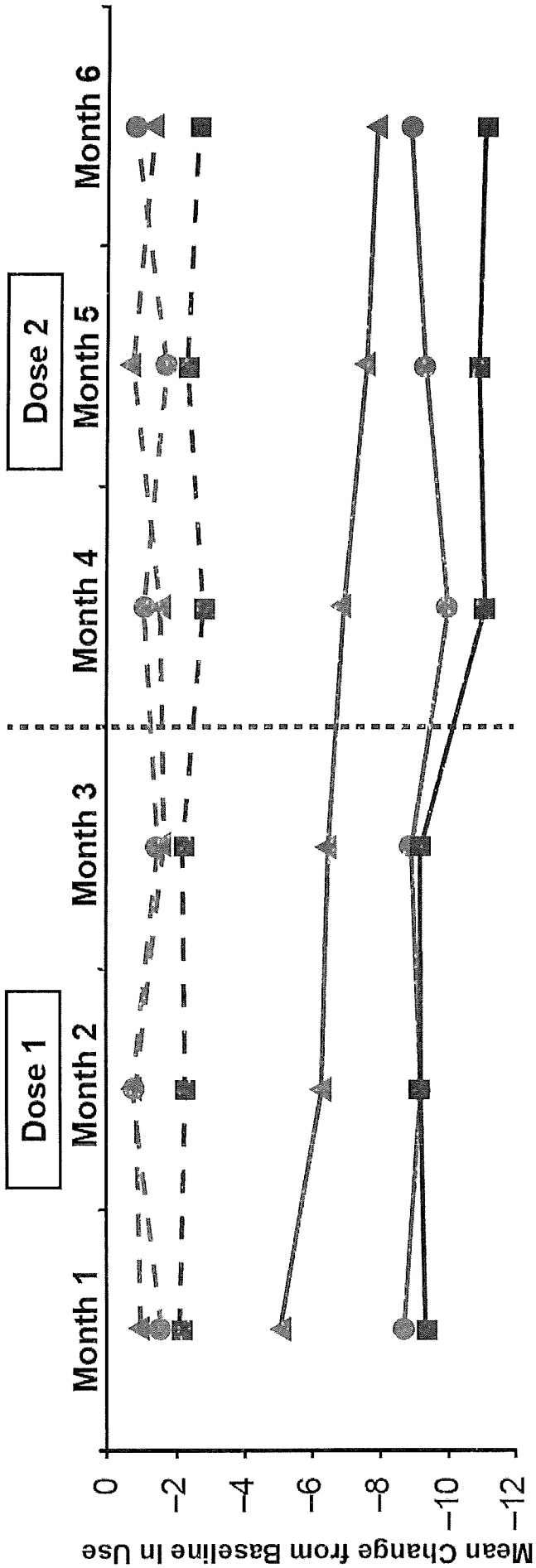

Dose 1
Dose 2
Month 1
Month 2
Month 3
Month 4
Month 5
Month 6
0
−2
−4
−6
−8
−10
−12
Mean Change from Baseline in Use

FIG. 44.

FIG. 45.

	Month 1			Month 6		
	Ab6 100 mg	Ab6 400 mg	Placebo	Ab6 100 mg	Ab6 400 mg	Placebo
Baseline use						
1–9 days/month, n	37	49	49	37	49	49
≥10 days/month, n	264	265	260	264	265	260
≥1 day/month, mean (SD)	18.3 (9.05)	18.4 (9.61)	17.9 (8.60)	18.3 (9.05)	18.4 (9.61)	17.9 (8.60)
Post-baseline use, mean (SD)						
≥1 day/month	10.7 (9.39)	10.2 (9.87)	13.8 (9.52)	10.8 (11.18)	8.6 (9.97)	11.5 (10.16)
Change from baseline, mean (SD)						
≥1 day/month	-7.8 (8.08)	-8.3 (7.64)	-4.5 (7.46)	-8.1 (9.90)	-9.6 (9.92)	-7.0 (9.39)
1–9 days/month	-1.5 (4.44)	-2.3 (4.34)	-1.0 (5.29)	-0.8 (6.63)	-2.6 (4.57)	-1.3 (4.83)
≥10 days/month	-8.7 (8.08)	-9.4 (7.62)	-5.1 (7.63)	-8.9 (9.88)	-11.1 (10.10)	-7.9 (9.64)
Percent change from baseline, mean (SD)						
≥1 day/month	-42.6 (39.98)	-47.0 (40.90)	-22.4 (52.02)	-40.7 (60.66)	-52.9 (48.97)	-34.7 (58.48)
1–9 days/month	-31.8 (67.95)	-47.3 (65.38)	-9.5 (100.52)	1.4 (132.84)	-45.0 (73.05)	-11.2 (108.44)
≥10 days/month	-44.1 (34.24)	-47.0 (34.73)	-24.8 (36.17)	-45.3 (44.91)	-54.5 (42.52)	-38.5 (44.63)

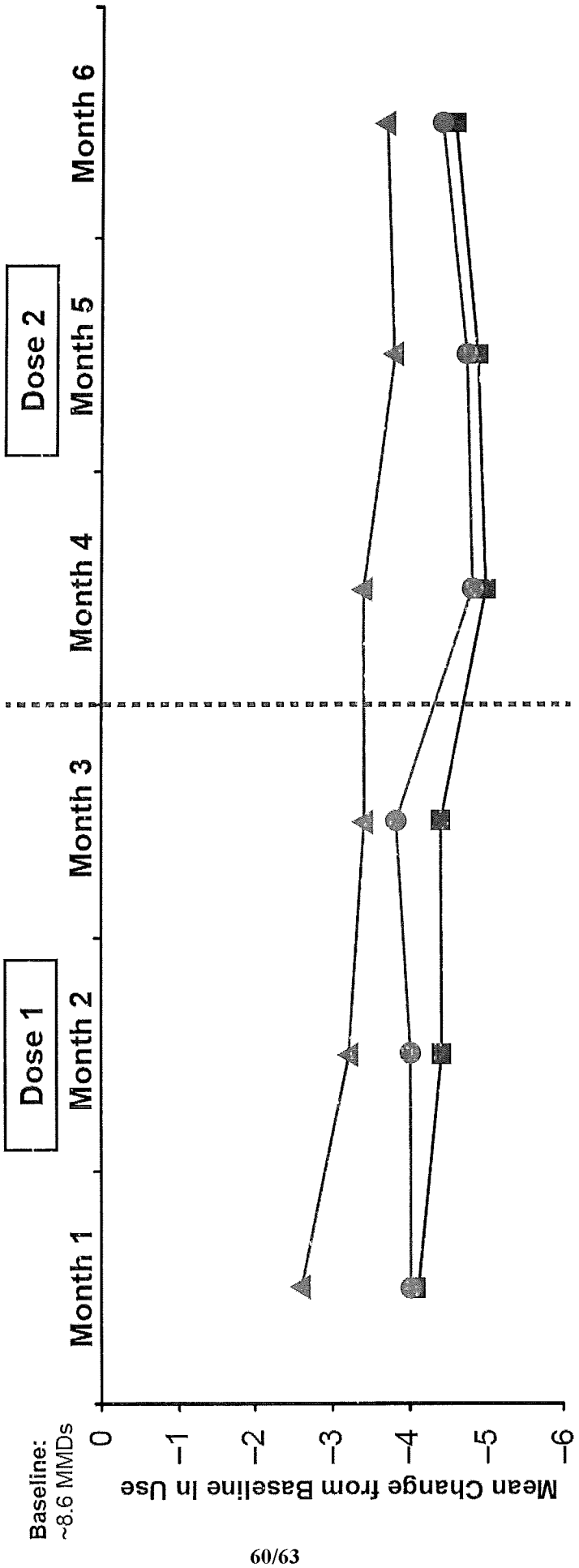

Baseline:
~8.6 MMDs
0
−1
−2
−3
−4
−5
−6
Mean Change from Baseline in Use
Month 1
Dose 1
Month 2
Month 3
Month 4
Dose 2
Month 5
Month 6

FIG. 46.

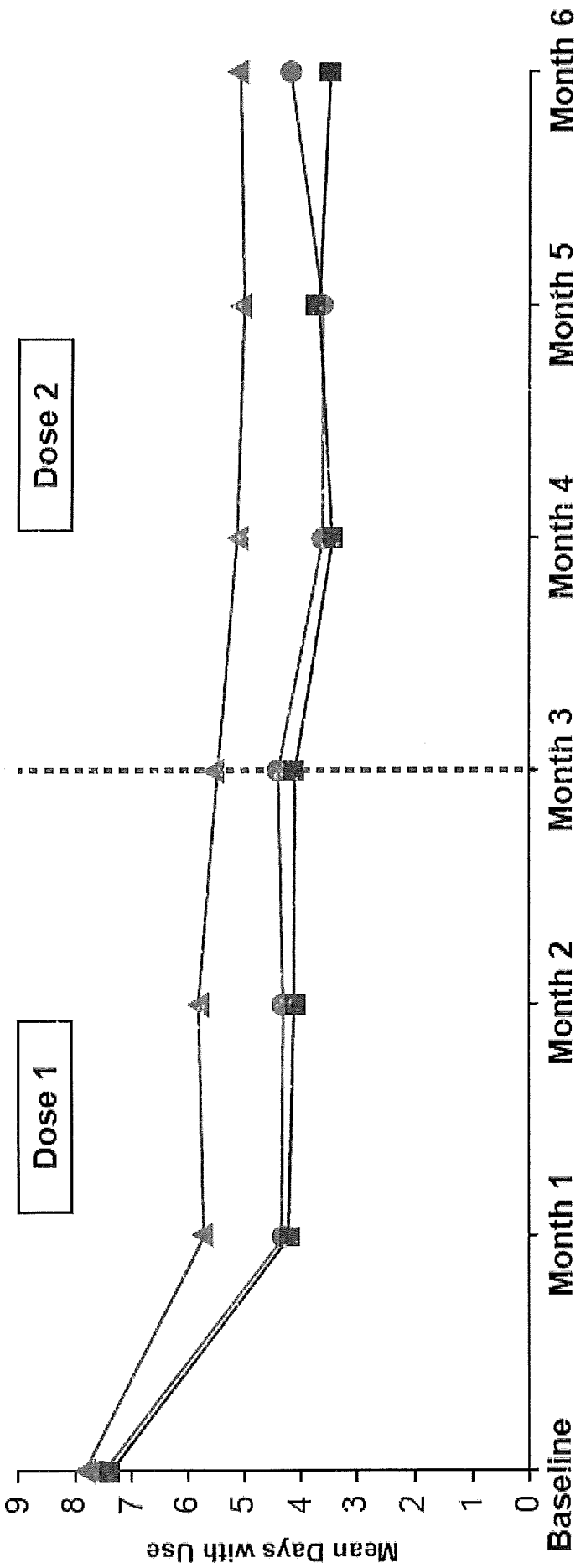

Mean Days with Use
0
1
2
3
4
5
6
7
8
9
Baseline
Month 1
Month 2
Month 3
Month 4
Month 5
Month 6
Dose 1
Dose 2

FIG. 47.

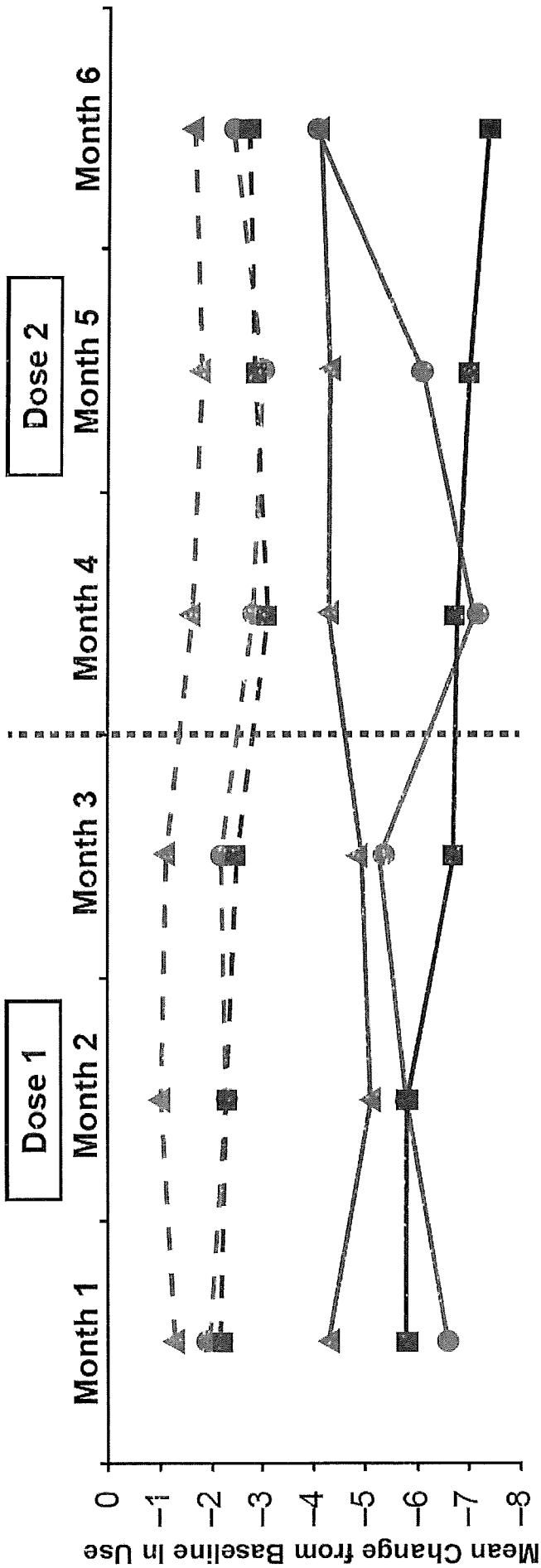

Mean Change from Baseline In Use
0
-1
-2
-3
-4
-5
-6
-7
-8
Month 1
Month 2
Month 3
Month 4
Month 5
Month 6
Dose 1
Dose 2

FIG. 48.

FIG. 49. Summary of Acute Medication Days by Subgroups of Episodic Migraine Patients with Baseline Acute Medication Use

	Month 1			Month 6		
	Ab6 100 mg	Ab6 400 mg	Placebo	Ab6 100 mg	Ab6 400 mg	Placebo
Baseline use						
1–9 days/month, n	117	111	108	117	111	108
≥10 days/month, n	42	41	44	42	41	44
≥1 day/month, mean (SD)	7.5 (4.97)	7.5 (4.58)	7.8 (4.98)	7.5 (4.97)	7.5 (4.58)	7.8 (4.98)
Post-baseline use, mean (SD)						
≥1 day/month	4.3 (3.99)	4.2 (4.45)	5.7 (5.04)	4.2 (5.87)	3.5 (3.92)	5.1 (5.19)
Change from baseline, mean (SD)						
≥1 day/month	-3.3 (4.14)	-3.2 (4.20)	-2.2 (4.68)	-2.8 (4.92)	-4.1 (4.60)	-2.3 (4.69)
1–9 days/month	-2.0 (2.91)	-2.2 (3.57)	-1.3 (3.10)	-2.4 (3.11)	-2.7 (3.83)	-1.6 (3.52)
≥10 days/month	-6.6 (5.11)	-5.8 (4.66)	-4.3 (6.82)	-4.0 (8.60)	-7.4 (4.60)	-4.1 (6.60)
Percent change from baseline, mean (SD)						
≥1 day/month	-36.9 (63.96)	-39.4 (77.71)	-22.4 (60.27)	-45.4 (62.28)	-50.9 (59.88)	-22.5 (95.61)
1–9 days/month	-33.9 (72.22)	-37.0 (88.45)	-19.7 (64.62)	-50.1 (59.65)	-48.2 (68.26)	-18.2 (107.55)
≥10 days/month	-45.1 (30.26)	-45.9 (34.95)	-29.1 (47.94)	-29.2 (69.14)	-57.2 (32.59)	-33.9 (52.53)

SEQUENCE LISTING

<110> Lundbeck A/S

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<130> 1143257.008803

<160> 567

<170> PatentIn version 3.5

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<213> Artificial

<220>
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Leu Thr Leu Thr Cys Thr Val Ser Gly Leu Asp Leu Ser Ser Tyr Tyr
            20                  25                  30


Met Gln Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile Gly
        35                  40                  45


Val Ile Gly Ile Asn Asp Asn Thr Tyr Tyr Ala Ser Trp Ala Lys Gly
    50                  55                  60


Arg Phe Thr Ile Ser Arg Ala Ser Ser Thr Thr Val Asp Leu Lys Met
65                  70                  75                  80


Thr Ser Leu Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg Gly
                85                  90                  95
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Asp Ile Trp Gly Pro Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
100 105 110

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
115 120 125

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
130 135 140

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
145 150 155 160

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
165 170 175

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
180 185 190

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu
195 200 205

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
210 215 220

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
225 230 235 240

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
245 250 255

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
260 265 270

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
275 280 285

Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
290 295 300

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
305 310 315 320

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
325 330 335

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
340 345 350

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
355 360 365

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
370 375 380

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
385 390 395 400

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
405 410 415

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
420 425 430

Leu Ser Leu Ser Pro Gly Lys
435

<210> 2
<211> 109
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 2

Gln Ser Leu Glu Glu Ser Gly Gly Arg Leu Val Thr Pro Gly Thr Pro
1 5 10 15

Leu Thr Leu Thr Cys Thr Val Ser Gly Leu Asp Leu Ser Ser Tyr Tyr
20 25 30

Met Gln Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile Gly
35 40 45

Val Ile Gly Ile Asn Asp Asn Thr Tyr Tyr Ala Ser Trp Ala Lys Gly
50 55 60

Arg Phe Thr Ile Ser Arg Ala Ser Ser Thr Thr Val Asp Leu Lys Met
65 70 75 80

Thr Ser Leu Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg Gly
85 90 95

Asp Ile Trp Gly Pro Gly Thr Leu Val Thr Val Ser Ser
100 105

<210> 3
<211> 29
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 3

Gln Ser Leu Glu Glu Ser Gly Gly Arg Leu Val Thr Pro Gly Thr Pro
1 5 10 15

Leu Thr Leu Thr Cys Thr Val Ser Gly Leu Asp Leu Ser
20 25

<210> 4
<211> 5
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 4

Ser Tyr Tyr Met Gln
1 5

<210> 5
<211> 14
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<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 5

Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile Gly
1 5 10

<210> 6
<211> 16
<212> PRT
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<220>

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<400> 6

Val Ile Gly Ile Asn Asp Asn Thr Tyr Tyr Ala Ser Trp Ala Lys Gly
1 5 10 15

<210> 7
<211> 31
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 7

Arg Phe Thr Ile Ser Arg Ala Ser Ser Thr Thr Val Asp Leu Lys Met
1 5 10 15

Thr Ser Leu Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg
20 25 30

<210> 8
<211> 3
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 8

Gly Asp Ile
1

<210> 9
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 9

Trp Gly Pro Gly Thr Leu Val Thr Val Ser Ser
1 5 10

<210> 10
<211> 330
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 10

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 11
<211> 1320
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<213> Artificial

<220>
<223> Engineered antibody sequence

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120

gggaaggggc tggaatggat cggagtcatt ggtattaatg ataacacata ctacgcgagc
180

tgggcgaaag gccgattcac catctccaga gcctcgtcga ccacggtgga tctgaaaatg
240

accagtctga caaccgagga cacggccacc tatttctgtg ccagagggga catctggggc
300

ccaggcaccc tcgtcaccgt ctcgagcgcc tccaccaagg gcccatcggt cttccccctg
360

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420

tacttccccg aaccggtgac ggtgtcgtgg aactcaggcg ccctgaccag cggcgtgcac
480

accttcccgg ctgtcctaca gtcctcagga ctctactccc tcagcagcgt ggtgaccgtg
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ccctccagca gcttgggcac ccagacctac atctgcaacg tgaatcacaa gcccagcaac
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aagctcaccg tggacaagag caggtggcag caggggaacg tcttctcatg ctccgtgatg
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1320

<210> 12

<211> 327
<212> DNA
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<220>
<223> Engineered antibody sequence

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tgcacagtct ctggactcga cctcagtagc tactacatgc aatgggtccg ccaggctcca
120

gggaaggggc tggaatggat cggagtcatt ggtattaatg ataacacata ctacgcgagc
180

tgggcgaaag gccgattcac catctccaga gcctcgtcga ccacggtgga tctgaaaatg
240

accagtctga caaccgagga cacggccacc tatttctgtg ccagagggga catctggggc
300

c c a g g c a c c c t c g t c a c c g t c t c g a g c
327

<210> 13
<211> 87
<212> DNA
<213> Artificial

<220>
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60

t g c a c a g t c t c t g g a c t c g a c c t c a g t
87

<210> 14
<211> 15

<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 14
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15

<210> 15
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<400> 15
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<210> 16
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<211> 93
<212> DNA
<213> Artificial

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60

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93

<210> 18
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<212> DNA
<213> Artificial

<220>
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<400> 18
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9

<210> 19
<211> 33
<212> DNA
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<400> 19
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ggcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg
120

tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca
180

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacccagacc
240

tacatctgca acgtgaatca caagcccagc aacaccaagg tggacaagag agttgagccc
300

aaatcttgtg acaaaactca cacatgccca ccgtgcccag cacctgaact cctgggggga
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ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct
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gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg
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tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacgcc
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agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag
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aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggaggag
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<210> 21
<211> 219
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<400> 21

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Thr Val Thr Ile Asn Cys Gln Ala Ser Gln Ser Val Tyr Asp Asn Asn
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Gln Leu
35 40 45

Ile Tyr Ser Thr Ser Thr Leu Ala Ser Gly Val Ser Ser Arg Phe Lys
50 55 60

Gly Ser Gly Ser Gly Thr Gln Phe Thr Leu Thr Ile Ser Asp Leu Glu
65 70 75 80

Cys Ala Asp Ala Ala Thr Tyr Tyr Cys Leu Gly Ser Tyr Asp Cys Ser
85 90 95

Ser Gly Asp Cys Phe Val Phe Gly Gly Gly Thr Glu Val Val Val Lys
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Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
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Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 22
<211> 113
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 22

Gln Val Leu Thr Gln Thr Ala Ser Pro Val Ser Ala Ala Val Gly Ser
1 5 10 15

Thr Val Thr Ile Asn Cys Gln Ala Ser Gln Ser Val Tyr Asp Asn Asn
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Gln Leu

35 40 45

Ile Tyr Ser Thr Ser Thr Leu Ala Ser Gly Val Ser Ser Arg Phe Lys
50 55 60

Gly Ser Gly Ser Gly Thr Gln Phe Thr Leu Thr Ile Ser Asp Leu Glu
65 70 75 80

Cys Ala Asp Ala Ala Thr Tyr Tyr Cys Leu Gly Ser Tyr Asp Cys Ser
85 90 95

Ser Gly Asp Cys Phe Val Phe Gly Gly Gly Thr Glu Val Val Val Lys
100 105 110

Arg

<210> 23
<211> 22
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

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Gln Val Leu Thr Gln Thr Ala Ser Pro Val Ser Ala Ala Val Gly Ser
1 5 10 15

Thr Val Thr Ile Asn Cys
20

<210> 24
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 24

Gln Ala Ser Gln Ser Val Tyr Asp Asn Asn Tyr Leu Ala
1 5 10

<210> 25
<211> 15
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 25

Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Gln Leu Ile Tyr
1 5 10 15

<210> 26
<211> 7
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<400> 26

Ser Thr Ser Thr Leu Ala Ser
1 5

<210> 27
<211> 32
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 27

Gly Val Ser Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Thr
1 5 10 15

Leu Thr Ile Ser Asp Leu Glu Cys Ala Asp Ala Ala Thr Tyr Tyr Cys
20 25 30

<210> 28
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 28

Leu Gly Ser Tyr Asp Cys Ser Ser Gly Asp Cys Phe Val
1 5 10

<210> 29
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 29

Phe Gly Gly Gly Thr Glu Val Val Val Lys Arg
1 5 10

<210> 30
<211> 106
<212> PRT
<213> Artificial

<220>

<223> Engineered antibody sequence

<400> 30

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1 5 10 15

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
20 25 30

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
35 40 45

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
50 55 60

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65 70 75 80

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
85 90 95

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> 31
<211> 660
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 31
caagtgctga cccagactgc atcccccgtg tctgcagctg tgggaagcac agtcaccatc 60

aattgccagg ccagtcagag tgtttatgat aacaactacc tagcctggta tcagcagaaa 120

ccagggcagc ctcccaagca actgatctat tctacatcca ctctggcatc tggggtctca 180

tcgcggttca aaggcagtgg atctgggaca cagttcactc tcaccatcag cgacctggag 240

tgtgccgatg ctgccactta ctactgtcta ggcagttatg attgtagtag tggtgattgt 300

tttgttttcg gcggagggac cgaggtggtg gtcaaacgta cggtggctgc accatctgtc 360

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 420

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 480

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 600

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgttag 660

<210> 32
<211> 339
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 32
caagtgctga cccagactgc atcccccgtg tctgcagctg tgggaagcac agtcaccatc 60

aattgccagg ccagtcagag tgtttatgat aacaactacc tagcctggta tcagcagaaa 120

ccagggcagc ctcccaagca actgatctat tctacatcca ctctggcatc tggggtctca 180

tcgcggttca aaggcagtgg atctgggaca cagttcactc tcaccatcag cgacctggag
240

tgtgccgatg ctgccactta ctactgtcta ggcagttatg attgtagtag tggtgattgt
300

tttgttttcg gcggagggac cgaggtggtg gtcaaacgt
339

<210> 33
<211> 66
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 33
caagtgctga cccagactgc atcccccgtg tctgcagctg tgggaagcac agtcaccatc
60

a a t t g c
66

<210> 34
<211> 39
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 34
caggccagtc agagtgttta tgataacaac tacctagcc
39

<210> 35
<211> 45
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 35
tggtatcagc agaaaccagg gcagcctccc aagcaactga tctat
45

<210> 36
<211> 21
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 36
t c t a c a t c c a c t c t g g c a t c t
21

<210> 37
<211> 96
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 37
ggggtctcat cgcggttcaa aggcagtgga tctgggacac agttcactct caccatcagc
60

gacctggagt gtgccgatgc tgccacttac tactgt
96

<210> 38
<211> 39
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 38
ctaggcagtt atgattgtag tagtggtgat tgttttgtt
39

<210> 39
<211> 33
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 39
ttcggcggag ggaccgaggt ggtggtcaaa cgt
33

<210> 40
<211> 321
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 40
acggtggctg caccatctgt cttcatcttc ccgccatctg atgagcagtt gaaatctgga
60

actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg
120

aaggtggata acgccctcca atcgggtaac tcccaggaga gtgtcacaga gcaggacagc
180

aaggacagca cctacagcct cagcagcacc ctgacgctga gcaaagcaga ctacgagaaa
240

cacaaagtct acgcctgcga agtcacccat cagggcctga gctcgcccgt cacaaagagc
300

ttcaacaggg gagagtgtta g
321

<210> 41
<211> 441
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 41

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Leu Asp Leu Ser Ser Tyr
20 25 30

Tyr Met Gln Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Val Ile Gly Ile Asn Asp Asn Thr Tyr Tyr Ala Ser Trp Ala Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Thr Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala
85 90 95

Arg Gly Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
100 105 110

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
115 120 125

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
130 135 140

```
Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
145                 150                 155                 160

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
                165                 170                 175

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
            180                 185                 190

Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg
        195                 200                 205

Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
    210                 215                 220

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
225                 230                 235                 240

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
                245                 250                 255

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
            260                 265                 270

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
        275                 280                 285

Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
    290                 295                 300

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
305                 310                 315                 320
```

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
325 330 335

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
340 345 350

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
355 360 365

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
370 375 380

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
385 390 395 400

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
405 410 415

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
420 425 430

Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440

<210> 42
<211> 111
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 42

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Leu Asp Leu Ser Ser Tyr
20 25 30

Tyr Met Gln Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Val Ile Gly Ile Asn Asp Asn Thr Tyr Tyr Ala Ser Trp Ala Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Thr Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala
85 90 95

Arg Gly Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105 110

<210> 43
<211> 30
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 43

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Leu Asp Leu Ser
20 25 30

<210> 44

<211> 5
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 44

Ser Tyr Tyr Met Gln
1 5

<210> 45
<211> 14
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 45

Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Gly
1 5 10

<210> 46
<211> 16
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 46

Val Ile Gly Ile Asn Asp Asn Thr Tyr Tyr Ala Ser Trp Ala Lys Gly
1 5 10 15

<210> 47
<211> 32
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 47

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Thr Thr Val Tyr Leu Gln
1 5 10 15

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala Arg
20 25 30

<210> 48
<211> 3
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 48

Gly Asp Ile
1

<210> 49
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 49

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
1 5 10

<210> 50
<211> 330
<212> PRT

<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 50

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 51
<211> 1326
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 51
gaggtgcagc ttgtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc
60

tcctgtgcag tctctggact cgacctcagt agctactaca tgcaatgggt ccgtcaggct
120

ccagggaagg ggctggagtg ggtcggagtc attggtatca atgataacac atactacgcg
180

agctgggcga aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt
240

caaatgaaca gcctgagagc tgaggacact gctgtgtatt tctgtgctag aggggacatc
300

tggggccaag ggaccctcgt caccgtctcg agcgcctcca ccaagggccc atcggtcttc
360

cccctggcac cctcctccaa gagcacctct gggggcacag cggccctggg ctgcctggtc
420

aaggactact tccccgaacc ggtgacggtg tcgtggaact caggcgccct gaccagcggc
480

gtgcacacct tcccggctgt cctacagtcc tcaggactct actccctcag cagcgtggtg
540

accgtgccct ccagcagctt gggcacccag acctacatct gcaacgtgaa tcacaagccc
600

agcaacacca aggtggacaa gagagttgag cccaaatctt gtgacaaaac tcacacatgc
660

ccaccgtgcc cagcacctga actcctgggg ggaccgtcag tcttcctctt cccccaaaa
720

cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg
780

agccacgaag accctgaggt caagttcaac tggtacgtgg acggcgtgga ggtgcataat
840

gccaagacaa agccgcggga ggagcagtac gccagcacgt accgtgtggt cagcgtcctc
900

accgtcctgc accaggactg gctgaatggc aaggagtaca agtgcaaggt ctccaacaaa
960

gccctcccag cccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca
1020

caggtgtaca ccctgccccc atcccgggag gagatgacca agaaccaggt cagcctgacc
1080

tgcctggtca aaggcttcta tcccagcgac atcgccgtgg agtgggagag caatgggcag
1140

ccggagaaca actacaagac cacgcctccc gtgctggact ccgacggctc cttcttcctc
1200

tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc
1260

gtgatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt
1320

a a a t g a
1326

<210> 52
<211> 333
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 52
gaggtgcagc ttgtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc
60

tcctgtgcag tctctggact cgacctcagt agctactaca tgcaatgggt ccgtcaggct 120

ccagggaagg ggctggagtg ggtcggagtc attggtatca atgataacac atactacgcg 180

agctgggcga aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt 240

caaatgaaca gcctgagagc tgaggacact gctgtgtatt tctgtgctag aggggacatc 300

tggggccaag ggaccctcgt caccgtctcg agc 333

<210> 53
<211> 90
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 53
gaggtgcagc ttgtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc 60

tcctgtgcag tctctggact cgacctcagt 90

<210> 54
<211> 15
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 54
agctactaca tgcaa 15

<210> 55
<211> 42
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 55
tgggtccgtc aggctccagg gaaggggctg gagtgggtcg ga
42

<210> 56
<211> 48
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 56
gtcattggta tcaatgataa cacatactac gcgagctggg cgaaaggc
48

<210> 57
<211> 96
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 57
cgattcacca tctccagaga caattccaag accacggtgt atcttcaaat gaacagcctg
60

agagctgagg acactgctgt gtatttctgt gctaga
96

<210> 58
<211> 9

<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 58
g g g g a c a t c
9

<210> 59
<211> 33
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 59
t g g g g c c a a g g g a c c c t c g t c a c c g t c t c g a g c
33

<210> 60
<211> 993
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 60
gcctccacca agggcccatc ggtcttcccc ctggcaccct cctccaagag cacctctggg
60

ggcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg
120

tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca
180

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacccagacc
240

tacatctgca acgtgaatca caagcccagc aacaccaagg tggacaagag agttgagccc
300

aaatcttgtg acaaaactca cacatgccca ccgtgcccag cacctgaact cctgggggga
360

ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct
420

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg
480

tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacgcc
540

agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag
600

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc
660

aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggaggag
720

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc
780

gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg
840

ctggactccg acggctcctt cttcctctac agcaagctca ccgtggacaa gagcaggtgg
900

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg
960

cagaagagcc tctccctgtc tccgggtaaa tga
993

<210> 61
<211> 219
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 61

Gln Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
1 5 10 15

Arg Val Thr Ile Asn Cys Gln Ala Ser Gln Ser Val Tyr Asp Asn Asn
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Gln Leu
35 40 45

Ile Tyr Ser Thr Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80

Pro Glu Asp Val Ala Thr Tyr Tyr Cys Leu Gly Ser Tyr Asp Cys Ser
85 90 95

Ser Gly Asp Cys Phe Val Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 62
<211> 113
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 62

Gln Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
1 5 10 15

Arg Val Thr Ile Asn Cys Gln Ala Ser Gln Ser Val Tyr Asp Asn Asn
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Gln Leu
35 40 45

Ile Tyr Ser Thr Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80

Pro Glu Asp Val Ala Thr Tyr Tyr Cys Leu Gly Ser Tyr Asp Cys Ser
85 90 95

Ser Gly Asp Cys Phe Val Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

Arg

<210> 63
<211> 22
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 63

Gln Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
1 5 10 15

Arg Val Thr Ile Asn Cys
20

<210> 64
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 64

Gln Ala Ser Gln Ser Val Tyr Asp Asn Asn Tyr Leu Ala
1 5 10

<210> 65
<211> 15
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 65

Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Gln Leu Ile Tyr
1 5 10 15

<210> 66
<211> 7
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 66

Ser Thr Ser Thr Leu Ala Ser
1 5

<210> 67
<211> 32
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 67

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Val Ala Thr Tyr Tyr Cys
20 25 30

<210> 68
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 68

Leu Gly Ser Tyr Asp Cys Ser Ser Gly Asp Cys Phe Val
1 5 10

<210> 69
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 69

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
1 5 10

<210> 70
<211> 106
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 70

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1 5 10 15

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
20 25 30

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
        35   40   45

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
    50   55   60

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65   70   75   80

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
                85   90   95

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
            100   105

<210> 71
<211> 660
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 71
caagtgctga cccagtctcc atcctccctg tctgcatctg taggagacag agtcaccatc
60

aattgccagg ccagtcagag tgtttatgat aacaactacc tagcctggta tcagcagaaa
120

ccagggaaag ttcctaagca actgatctat tctacatcca ctctggcatc tggggtccca
180

tctcgtttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagcctgcag
240

cctgaagatg ttgcaactta ttactgtcta ggcagttatg attgtagtag tggtgattgt
300

tttgttttcg gcggaggaac caaggtggaa atcaaacgta cggtggctgc accatctgtc 360

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 420

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 480

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 600

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgttag 660

<210> 72
<211> 339
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 72
caagtgctga cccagtctcc atcctccctg tctgcatctg taggagacag agtcaccatc 60

aattgccagg ccagtcagag tgtttatgat aacaactacc tagcctggta tcagcagaaa 120

ccagggaaag ttcctaagca actgatctat tctacatcca ctctggcatc tggggtccca 180

tctcgtttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagcctgcag 240

cctgaagatg ttgcaactta ttactgtcta ggcagttatg attgtagtag tggtgattgt 300

tttgttttcg gcggaggaac caaggtggaa atcaaacgt 339

<210> 73
<211> 66
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 73
caagtgctga cccagtctcc atcctccctg tctgcatctg taggagacag agtcaccatc 60

a a t t g c 66

<210> 74
<211> 39
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 74
caggccagtc agagtgttta tgataacaac tacctagcc 39

<210> 75
<211> 45
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 75
tggtatcagc agaaaccagg gaaagttcct aagcaactga tctat 45

<210> 76

<211> 21
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 76
t c t a c a t c c a c t c t g g c a t c t
21

<210> 77
<211> 96
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 77
ggggtcccat ctcgtttcag tggcagtgga tctgggacag atttcactct caccatcagc
60

agcctgcagc ctgaagatgt tgcaacttat tactgt
96

<210> 78
<211> 39
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 78
ctaggcagtt atgattgtag tagtggtgat tgttttgtt
39

<210> 79
<211> 33
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 79
ttcggcggag gaaccaaggt ggaaatcaaa cgt
33

<210> 80
<211> 321
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 80
acggtggctg caccatctgt cttcatcttc ccgccatctg atgagcagtt gaaatctgga
60

actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg
120

aaggtggata acgccctcca atcgggtaac tcccaggaga gtgtcacaga gcaggacagc
180

aaggacagca cctacagcct cagcagcacc ctgacgctga gcaaagcaga ctacgagaaa
240

cacaaagtct acgcctgcga agtcacccat cagggcctga gctcgcccgt cacaaagagc
300

ttcaacaggg gagagtgtta g
321

<210> 81
<211> 441
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 81

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Leu Asp Leu Ser Ser Tyr
20 25 30

Tyr Met Gln Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Val Ile Gly Ile Asn Asp Asn Thr Tyr Tyr Ala Ser Trp Ala Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Thr Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala
85 90 95

Arg Gly Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
100 105 110

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
115 120 125

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
130 135 140

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
145 150 155 160

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
165 170 175

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
180 185 190

Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Ala Arg
195 200 205

Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
210 215 220

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
225 230 235 240

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
245 250 255

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
260 265 270

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
275 280 285

Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
290 295 300

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
305 310 315 320

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
325 330 335

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
340 345 350

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
355 360 365

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
370 375 380

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
385 390 395 400

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
405 410 415

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
420 425 430

Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440

<210> 82
<211> 111
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 82

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Leu Asp Leu Ser Ser Tyr
20 25 30

Tyr Met Gln Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Val Ile Gly Ile Asn Asp Asn Thr Tyr Tyr Ala Ser Trp Ala Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Thr Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala
85 90 95

Arg Gly Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105 110

<210> 83
<211> 30
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 83

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Leu Asp Leu Ser
20 25 30

<210> 84
<211> 5
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 84

Ser Tyr Tyr Met Gln
1 5

<210> 85
<211> 14
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 85

Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Gly
1 5 10

<210> 86
<211> 16
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 86

Val Ile Gly Ile Asn Asp Asn Thr Tyr Tyr Ala Ser Trp Ala Lys Gly
1 5 10 15

<210> 87
<211> 32
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 87

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Thr Thr Val Tyr Leu Gln
1 5 10 15

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala Arg
            20   25   30

<210> 88
<211> 3
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 88

Gly Asp Ile
1

<210> 89
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 89

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
1   5   10

<210> 90
<211> 330
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 90

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1   5   10   15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Ala
85 90 95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 91
<211> 1326
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 91
gaggtgcagc ttgtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc
60

tcctgtgcag tctctggact cgacctcagt agctactaca tgcaatgggt ccgtcaggct
120

ccagggaagg ggctggagtg ggtcggagtc attggtatca atgataacac atactacgcg
180

agctgggcga aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt
240

caaatgaaca gcctgagagc tgaggacact gctgtgtatt tctgtgctag aggggacatc
300

tggggccaag ggaccctcgt caccgtctcg agcgcctcca ccaagggccc atcggtcttc
360

cccctggcac cctcctccaa gagcacctct gggggcacag cggccctggg ctgcctggtc
420

aaggactact tccccgaacc ggtgacggtg tcgtggaact caggcgccct gaccagcggc
480

gtgcacacct tcccggctgt cctacagtcc tcaggactct actccctcag cagcgtggtg
540

accgtgccct ccagcagctt gggcacccag acctacatct gcaacgtgaa tcacaagccc
600

agcaacacca aggtggacgc gagagttgag cccaaatctt gtgacaaaac tcacacatgc
660

ccaccgtgcc cagcacctga actcctgggg ggaccgtcag tcttcctctt ccccccaaaa
720

cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg
780

agccacgaag accctgaggt caagttcaac tggtacgtgg acggcgtgga ggtgcataat
840

gccaagacaa agccgcggga ggagcagtac gccagcacgt accgtgtggt cagcgtcctc
900

accgtcctgc accaggactg gctgaatggc aaggagtaca agtgcaaggt ctccaacaaa
960

gccctcccag cccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca
1020

caggtgtaca ccctgccccc atcccgggag gagatgacca agaaccaggt cagcctgacc
1080

tgcctggtca aaggcttcta tcccagcgac atcgccgtgg agtgggagag caatgggcag
1140

ccggagaaca actacaagac cacgcctccc gtgctggact ccgacggctc cttcttcctc
1200

tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc
1260

gtgatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt
1320

a a a t g a
1326

<210> 92
<211> 333
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 92
gaggtgcagc ttgtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc
60

tcctgtgcag tctctggact cgacctcagt agctactaca tgcaatgggt ccgtcaggct
120

ccagggaagg ggctggagtg ggtcggagtc attggtatca atgataacac atactacgcg
180

agctgggcga aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt
240

caaatgaaca gcctgagagc tgaggacact gctgtgtatt tctgtgctag aggggacatc 300

tggggccaag ggaccctcgt caccgtctcg agc 333

<210> 93
<211> 90
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 93
gaggtgcagc ttgtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc 60

tcctgtgcag tctctggact cgacctcagt 90

<210> 94
<211> 15
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 94
agctactaca tgcaa 15

<210> 95
<211> 42
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 95
tgggtccgtc aggctccagg gaaggggctg gagtgggtcg ga
42

<210> 96
<211> 48
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 96
gtcattggta tcaatgataa cacatactac gcgagctggg cgaaaggc
48

<210> 97
<211> 96
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 97
cgattcacca tctccagaga caattccaag accacggtgt atcttcaaat gaacagcctg
60

agagctgagg acactgctgt gtatttctgt gctaga
96

<210> 98
<211> 9
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 98
g g g g a c a t c
9

<210> 99
<211> 33
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 99
tggggccaag ggaccctcgt caccgtctcg agc
33

<210> 100
<211> 993
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 100
gcctccacca agggcccatc ggtcttcccc ctggcaccct cctccaagag cacctctggg
60

ggcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg
120

tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca
180

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacccagacc
240

tacatctgca acgtgaatca caagcccagc aacaccaagg tggacgcgag agttgagccc
300

aaatcttgtg acaaaactca cacatgccca ccgtgcccag cacctgaact cctgggggga
360

ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggaccccct
420

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg
480

tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacgcc
540

agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag
600

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc
660

aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggaggag
720

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc
780

gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg
840

ctggactccg acggctcctt cttcctctac agcaagctca ccgtggacaa gagcaggtgg
900

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg
960

cagaagagcc tctccctgtc tccgggtaaa tga
993

<210> 101
<211> 219
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 101

Gln Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
1 5 10 15

Arg Val Thr Ile Asn Cys Gln Ala Ser Gln Ser Val Tyr Asp Asn Asn
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Gln Leu
35 40 45

Ile Tyr Ser Thr Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80

Pro Glu Asp Val Ala Thr Tyr Tyr Cys Leu Gly Ser Tyr Asp Cys Ser
85 90 95

Ser Gly Asp Cys Phe Val Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser

195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 102
<211> 113
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 102

Gln Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
1 5 10 15

Arg Val Thr Ile Asn Cys Gln Ala Ser Gln Ser Val Tyr Asp Asn Asn
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Gln Leu
35 40 45

Ile Tyr Ser Thr Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80

Pro Glu Asp Val Ala Thr Tyr Tyr Cys Leu Gly Ser Tyr Asp Cys Ser
85 90 95

Ser Gly Asp Cys Phe Val Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

Arg

<210> 103
<211> 22
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 103

Gln Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
1 5 10 15

Arg Val Thr Ile Asn Cys
20

<210> 104
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 104

Gln Ala Ser Gln Ser Val Tyr Asp Asn Asn Tyr Leu Ala
1 5 10

<210> 105
<211> 15
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 105

Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Gln Leu Ile Tyr
1 5 10 15

<210> 106
<211> 7
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 106

Ser Thr Ser Thr Leu Ala Ser
1 5

<210> 107
<211> 32
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 107

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Val Ala Thr Tyr Tyr Cys
20 25 30

<210> 108
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 108

Leu Gly Ser Tyr Asp Cys Ser Ser Gly Asp Cys Phe Val
1 5 10

<210> 109
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 109

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
1 5 10

<210> 110
<211> 106
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 110

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1 5 10 15

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
20 25 30

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
35 40 45

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
50 55 60

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65 70 75 80

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
85 90 95

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> 111
<211> 660
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 111
caagtgctga cccagtctcc atcctccctg tctgcatctg taggagacag agtcaccatc 60

aattgccagg ccagtcagag tgtttatgat aacaactacc tagcctggta tcagcagaaa 120

ccagggaaag ttcctaagca actgatctat tctacatcca ctctggcatc tggggtccca 180

tctcgtttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagcctgcag 240

cctgaagatg ttgcaactta ttactgtcta ggcagttatg attgtagtag tggtgattgt 300

tttgttttcg gcggaggaac caaggtggaa atcaaacgta cggtggctgc accatctgtc 360

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 420

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 480

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 600

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgttag 660

<210> 112
<211> 339
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 112
caagtgctga cccagtctcc atcctccctg tctgcatctg taggagacag agtcaccatc 60

aattgccagg ccagtcagag tgtttatgat aacaactacc tagcctggta tcagcagaaa 120

ccagggaaag ttcctaagca actgatctat tctacatcca ctctggcatc tggggtccca 180

tctcgtttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagcctgcag 240

cctgaagatg ttgcaactta ttactgtcta ggcagttatg attgtagtag tggtgattgt 300

tttgttttcg gcggaggaac caaggtggaa atcaaacgt 339

<210> 113
<211> 66
<212> DNA
<213> Artificial

<220>

<223> Engineered antibody sequence

<400> 113
caagtgctga cccagtctcc atcctccctg tctgcatctg taggagacag agtcaccatc
60

a a t t g c
66

<210> 114
<211> 39
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 114
caggccagtc agagtgttta tgataacaac tacctagcc
39

<210> 115
<211> 45
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 115
tggtatcagc agaaaccagg gaaagttcct aagcaactga tctat
45

<210> 116
<211> 21
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 116

t c t a c a t c c a c t c t g g c a t c t
21

<210> 117
<211> 96
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 117
ggggtcccat ctcgtttcag tggcagtgga tctgggacag atttcactct caccatcagc
60

a g c c t g c a g c c t g a a g a t g t t g c a a c t t a t t a c t g t
96

<210> 118
<211> 39
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 118
c t a g g c a g t t a t g a t t g t a g t a g t g g t g a t t g t t t t g t t
39

<210> 119
<211> 33
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 119
t t c g g c g g a g g a a c c a a g g t g g a a a t c a a a c g t
33

<210> 120
<211> 321
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 120
acggtggctg caccatctgt cttcatcttc ccgccatctg atgagcagtt gaaatctgga
60

actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg
120

aaggtggata acgccctcca atcgggtaac tcccaggaga gtgtcacaga gcaggacagc
180

aaggacagca cctacagcct cagcagcacc ctgacgctga gcaaagcaga ctacgagaaa
240

cacaaagtct acgcctgcga agtcacccat cagggcctga gctcgcccgt cacaaagagc
300

t t c a a c a g g g g a g a g t g t t a g
321

<210> 121
<211> 439
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 121

Gln Ser Leu Glu Glu Ser Gly Gly Arg Leu Val Thr Pro Gly Thr Pro
1 5 10 15

Leu Thr Leu Thr Cys Ser Val Ser Gly Ile Asp Leu Ser Gly Tyr Tyr
20 25 30

Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile Gly
35 40 45

Val Ile Gly Ile Asn Gly Ala Thr Tyr Tyr Ala Ser Trp Ala Lys Gly
50 55 60

Arg Phe Thr Ile Ser Lys Thr Ser Ser Thr Thr Val Asp Leu Lys Met
65 70 75 80

Thr Ser Leu Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg Gly
85 90 95

Asp Ile Trp Gly Pro Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
100 105 110

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
115 120 125

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
130 135 140

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
145 150 155 160

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
165 170 175

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
180 185 190

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu
195 200 205

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
210 215 220

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
225 230 235 240

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
245 250 255

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
260 265 270

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
275 280 285

Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
290 295 300

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
305 310 315 320

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
325 330 335

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
340 345 350

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
355 360 365

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
370 375 380

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
385 390 395 400

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
405 410 415

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
420 425 430

Leu Ser Leu Ser Pro Gly Lys
435

<210> 122
<211> 109
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 122

Gln Ser Leu Glu Glu Ser Gly Gly Arg Leu Val Thr Pro Gly Thr Pro
1 5 10 15

Leu Thr Leu Thr Cys Ser Val Ser Gly Ile Asp Leu Ser Gly Tyr Tyr
20 25 30

Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile Gly
35 40 45

Val Ile Gly Ile Asn Gly Ala Thr Tyr Tyr Ala Ser Trp Ala Lys Gly
50 55 60

Arg Phe Thr Ile Ser Lys Thr Ser Ser Thr Thr Val Asp Leu Lys Met
65 70 75 80

Thr Ser Leu Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg Gly
85 90 95

Asp Ile Trp Gly Pro Gly Thr Leu Val Thr Val Ser Ser
100 105

<210> 123
<211> 29
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 123

Gln Ser Leu Glu Glu Ser Gly Gly Arg Leu Val Thr Pro Gly Thr Pro
1 5 10 15

Leu Thr Leu Thr Cys Ser Val Ser Gly Ile Asp Leu Ser
20 25

<210> 124
<211> 5
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 124

Gly Tyr Tyr Met Asn
1 5

<210> 125
<211> 14
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 125

Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile Gly
1 5 10

<210> 126
<211> 16
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 126

Val Ile Gly Ile Asn Gly Ala Thr Tyr Tyr Ala Ser Trp Ala Lys Gly
1 5 10 15

<210> 127
<211> 31
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 127

Arg Phe Thr Ile Ser Lys Thr Ser Ser Thr Thr Val Asp Leu Lys Met
1 5 10 15

Thr Ser Leu Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg
20 25 30

<210> 128
<211> 3
<212> PRT

<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 128

Gly Asp Ile
1

<210> 129
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 129

Trp Gly Pro Gly Thr Leu Val Thr Val Ser Ser
1 5 10

<210> 130
<211> 330
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 130

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 131
<211> 1320
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 131
cagtcgctgg aggagtccgg gggtcgcctg gtcacgcctg ggacacccct gacactcacc 60

tgttccgtct ctggcatcga cctcagtggc tactacatga actgggtccg ccaggctcca 120

gggaaggggc tggaatggat cggagtcatt ggtattaatg gtgccacata ctacgcgagc 180

tgggcgaaag gccgattcac catctccaaa acctcgtcga ccacggtgga tctgaaaatg
240

accagtctga caaccgagga cacggccacc tatttctgtg ccagagggga catctggggc
300

ccgggcaccc tcgtcaccgt ctcgagcgcc tccaccaagg gcccatcggt cttccccctg
360

gcaccctcct ccaagagcac ctctgggggc acagcggccc tgggctgcct ggtcaaggac
420

tacttccccg aaccggtgac ggtgtcgtgg aactcaggcg ccctgaccag cggcgtgcac
480

accttcccgg ctgtcctaca gtcctcagga ctctactccc tcagcagcgt ggtgaccgtg
540

ccctccagca gcttgggcac ccagacctac atctgcaacg tgaatcacaa gcccagcaac
600

accaaggtgg acaagagagt tgagcccaaa tcttgtgaca aaactcacac atgcccaccg
660

tgcccagcac ctgaactcct gggggggaccg tcagtcttcc tcttcccccc aaaacccaag
720

gacaccctca tgatctcccg gacccctgag gtcacatgcg tggtggtgga cgtgagccac
780

gaagaccctg aggtcaagtt caactggtac gtggacggcg tggaggtgca taatgccaag
840

acaaagccgc gggaggagca gtacgccagc acgtaccgtg tggtcagcgt cctcaccgtc
900

ctgcaccagg actggctgaa tggcaaggag tacaagtgca aggtctccaa caaagccctc
960

ccagccccca tcgagaaaac catctccaaa gccaaagggc agccccgaga accacaggtg
1020

tacaccctgc ccccatcccg ggaggagatg accaagaacc aggtcagcct gacctgcctg
1080

gtcaaaggct tctatcccag cgacatcgcc gtggagtggg agagcaatgg gcagccggag 1140

aacaactaca agaccacgcc tcccgtgctg gactccgacg gctccttctt cctctacagc 1200

aagctcaccg tggacaagag caggtggcag caggggaacg tcttctcatg ctccgtgatg 1260

catgaggctc tgcacaacca ctacacgcag aagagcctct ccctgtctcc gggtaaatga 1320

<210> 132
<211> 327
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 132
cagtcgctgg aggagtccgg gggtcgcctg gtcacgcctg ggacacccct gacactcacc 60

tgttccgtct ctggcatcga cctcagtggc tactacatga actgggtccg ccaggctcca 120

gggaaggggc tggaatggat cggagtcatt ggtattaatg gtgccacata ctacgcgagc 180

tgggcgaaag gccgattcac catctccaaa acctcgtcga ccacggtgga tctgaaaatg 240

accagtctga caaccgagga cacggccacc tatttctgtg ccagagggga catctggggc 300

c c g g g c a c c c t c g t c a c c g t c t c g a g c 327

<210> 133
<211> 87
<212> DNA

<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 133
cagtcgctgg aggagtccgg gggtcgcctg gtcacgcctg ggacacccct gacactcacc 60

tgttccgtct ctggcatcga cctcagt 87

<210> 134
<211> 15
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 134
ggctactaca tgaac 15

<210> 135
<211> 42
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 135
tgggtccgcc aggctccagg gaaggggctg gaatggatcg ga 42

<210> 136
<211> 48
<212> DNA
<213> Artificial

<220>

<223> Engineered antibody sequence

<400> 136
gtcattggta ttaatggtgc cacatactac gcgagctggg cgaaaggc 48

<210> 137
<211> 93
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 137
cgattcacca tctccaaaac ctcgtcgacc acggtggatc tgaaaatgac cagtctgaca 60

accgaggaca cggccaccta tttctgtgcc aga 93

<210> 138
<211> 9
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 138
g g g g a c a t c 9

<210> 139
<211> 33
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 139

tggggcccgg gcaccctcgt caccgtctcg agc
33

<210> 140
<211> 993
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 140
gcctccacca agggcccatc ggtcttcccc ctggcaccct cctccaagag cacctctggg
60

ggcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg
120

tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca
180

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacccagacc
240

tacatctgca acgtgaatca caagcccagc aacaccaagg tggacaagag agttgagccc
300

aaatcttgtg acaaaactca cacatgccca ccgtgcccag cacctgaact cctgggggga
360

ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggaccct
420

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg
480

tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacgcc
540

agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag
600

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc
660

aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggaggag
720

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc
780

gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg
840

ctggactccg acggctcctt cttcctctac agcaagctca ccgtggacaa gagcaggtgg
900

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg
960

c a g a a g a g c c t c t c c c t g t c t c c g g g t a a a t g a
993

<210> 141
<211> 219
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 141

Gln Val Leu Thr Gln Thr Pro Ser Pro Val Ser Ala Ala Val Gly Ser
1 5 10 15

Thr Val Thr Ile Asn Cys Gln Ala Ser Gln Ser Val Tyr His Asn Thr
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Gln Leu
35 40 45

Ile Tyr Asp Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Gln Phe Thr Leu Thr Ile Ser Gly Val Gln
65 70 75 80

Cys Asn Asp Ala Ala Ala Tyr Tyr Cys Leu Gly Ser Tyr Asp Cys Thr
85 90 95

Asn Gly Asp Cys Phe Val Phe Gly Gly Gly Thr Glu Val Val Val Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 142
<211> 113
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 142

Gln Val Leu Thr Gln Thr Pro Ser Pro Val Ser Ala Ala Val Gly Ser
1 5 10 15

Thr Val Thr Ile Asn Cys Gln Ala Ser Gln Ser Val Tyr His Asn Thr
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Gln Leu
35 40 45

Ile Tyr Asp Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Gln Phe Thr Leu Thr Ile Ser Gly Val Gln
65 70 75 80

Cys Asn Asp Ala Ala Ala Tyr Tyr Cys Leu Gly Ser Tyr Asp Cys Thr
85 90 95

Asn Gly Asp Cys Phe Val Phe Gly Gly Gly Thr Glu Val Val Val Lys
100 105 110

Arg

<210> 143
<211> 22
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 143

Gln Val Leu Thr Gln Thr Pro Ser Pro Val Ser Ala Ala Val Gly Ser
1 5 10 15

Thr Val Thr Ile Asn Cys
20

<210> 144
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 144

Gln Ala Ser Gln Ser Val Tyr His Asn Thr Tyr Leu Ala
1 5 10

<210> 145
<211> 15
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 145

Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Gln Leu Ile Tyr
1 5 10 15

<210> 146
<211> 7
<212> PRT
<213> Artificial

<220>

<223> Engineered antibody sequence

<400> 146

Asp Ala Ser Thr Leu Ala Ser
1 5

<210> 147
<211> 32
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 147

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Gln Phe Thr
1 5 10 15

Leu Thr Ile Ser Gly Val Gln Cys Asn Asp Ala Ala Ala Tyr Tyr Cys
20 25 30

<210> 148
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 148

Leu Gly Ser Tyr Asp Cys Thr Asn Gly Asp Cys Phe Val
1 5 10

<210> 149
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 149

Phe Gly Gly Gly Thr Glu Val Val Val Lys Arg
1 5 10

<210> 150
<211> 106
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 150

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1 5 10 15

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
20 25 30

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
35 40 45

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
50 55 60

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65 70 75 80

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
85 90 95

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> 151
<211> 660
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 151
caagtgctga cccagactcc atcccccgtg tctgcagctg tgggaagcac agtcaccatc
60

aattgccagg ccagtcagag tgtttatcat aacacctacc tggcctggta tcagcagaaa
120

ccagggcagc ctcccaaaca actgatctat gatgcatcca ctctggcgtc tggggtccca
180

tcgcggttca gcggcagtgg atctgggaca cagttcactc tcaccatcag cggcgtgcag
240

tgtaacgatg ctgccgctta ctactgtctg ggcagttatg attgtactaa tggtgattgt
300

tttgttttcg gcggagggac cgaggtggtg gtcaaacgta cggtggctgc accatctgtc
360

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg
420

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa
480

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc
540

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa
600

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgttag
660

<210> 152
<211> 339
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 152
caagtgctga cccagactcc atcccccgtg tctgcagctg tgggaagcac agtcaccatc
60

aattgccagg ccagtcagag tgtttatcat aacacctacc tggcctggta tcagcagaaa
120

ccagggcagc ctcccaaaca actgatctat gatgcatcca ctctggcgtc tggggtccca
180

tcgcggttca gcggcagtgg atctgggaca cagttcactc tcaccatcag cggcgtgcag
240

tgtaacgatg ctgccgctta ctactgtctg ggcagttatg attgtactaa tggtgattgt
300

tttgttttcg gcggagggac cgaggtggtg gtcaaacgt
339

<210> 153
<211> 66
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 153
caagtgctga cccagactcc atcccccgtg tctgcagctg tgggaagcac agtcaccatc
60

a a t t g c
66

<210> 154

<211> 39
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 154
caggccagtc agagtgttta tcataacacc tacctggcc
39

<210> 155
<211> 45
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 155
tggtatcagc agaaaccagg gcagcctccc aaacaactga tctat
45

<210> 156
<211> 21
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 156
g a t g c a t c c a c t c t g g c g t c t
21

<210> 157
<211> 96
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 157
ggggtcccat cgcggttcag cggcagtgga tctgggacac agttcactct caccatcagc
60

ggcgtgcagt gtaacgatgc tgccgcttac tactgt
96

<210> 158
<211> 39
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 158
ctgggcagtt atgattgtac taatggtgat tgttttgtt
39

<210> 159
<211> 33
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 159
ttcggcggag ggaccgaggt ggtggtcaaa cgt
33

<210> 160
<211> 321
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 160
acggtggctg caccatctgt cttcatcttc ccgccatctg atgagcagtt gaaatctgga
60

actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg
120

aaggtggata acgccctcca atcgggtaac tcccaggaga gtgtcacaga gcaggacagc
180

aaggacagca cctacagcct cagcagcacc ctgacgctga gcaaagcaga ctacgagaaa
240

cacaaagtct acgcctgcga agtcacccat cagggcctga gctcgcccgt cacaaagagc
300

t t c a a c a g g g g a g a g t g t t a g
321

<210> 161
<211> 441
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 161

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Ile Asp Leu Ser Gly Tyr
20 25 30

Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Val Ile Gly Ile Asn Gly Ala Thr Tyr Tyr Ala Ser Trp Ala Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Thr Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala
85 90 95

Arg Gly Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
100 105 110

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
115 120 125

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
130 135 140

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
145 150 155 160

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
165 170 175

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
180 185 190

Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg
195 200 205

Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
210 215 220

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
225 230 235 240

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
245 250 255

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
260 265 270

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
275 280 285

Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
290 295 300

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
305 310 315 320

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
325 330 335

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
340 345 350

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
355 360 365

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
370 375 380

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
385 390 395 400

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
405 410 415

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
420 425 430

Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440

<210> 162
<211> 111
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 162

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Ile Asp Leu Ser Gly Tyr
20 25 30

Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Val Ile Gly Ile Asn Gly Ala Thr Tyr Tyr Ala Ser Trp Ala Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Thr Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala
85 90 95

Arg Gly Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105 110

<210> 163
<211> 30
<212> PRT

<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 163

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Ile Asp Leu Ser
20 25 30

<210> 164
<211> 5
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 164

Gly Tyr Tyr Met Asn
1 5

<210> 165
<211> 14
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 165

Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Gly
1 5 10

<210> 166
<211> 16

<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 166

Val Ile Gly Ile Asn Gly Ala Thr Tyr Tyr Ala Ser Trp Ala Lys Gly
1 5 10 15

<210> 167
<211> 32
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 167

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Thr Thr Val Tyr Leu Gln
1 5 10 15

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala Arg
20 25 30

<210> 168
<211> 3
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 168

Gly Asp Ile
1

<210> 169

<211> 11
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 169

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
1 5 10

<210> 170
<211> 330
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 170

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 171
<211> 1326
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 171
gaggtgcagc ttgtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc
60

tcctgtgcag tctctggaat cgacctcagt ggctactaca tgaactgggt ccgtcaggct
120

ccagggaagg ggctggagtg ggtcggagtc attggtatta atggtgccac atactacgcg
180

agctgggcga aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt
240

caaatgaaca gcctgagagc tgaggacact gctgtgtatt tctgtgctag aggggacatc
300

tggggccaag ggaccctcgt caccgtctcg agcgcctcca ccaagggccc atcggtcttc
360

cccctggcac cctcctccaa gagcacctct gggggcacag cggccctggg ctgcctggtc
420

aaggactact tccccgaacc ggtgacggtg tcgtggaact caggcgccct gaccagcggc
480

gtgcacacct tcccggctgt cctacagtcc tcaggactct actccctcag cagcgtggtg
540

accgtgccct ccagcagctt gggcacccag acctacatct gcaacgtgaa tcacaagccc
600

agcaacacca aggtggacaa gagagttgag cccaaatctt gtgacaaaac tcacacatgc
660

ccaccgtgcc cagcacctga actcctgggg ggaccgtcag tcttcctctt cccccaaaa
720

cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg
780

agccacgaag accctgaggt caagttcaac tggtacgtgg acggcgtgga ggtgcataat
840

gccaagacaa agccgcggga ggagcagtac gccagcacgt accgtgtggt cagcgtcctc
900

accgtcctgc accaggactg gctgaatggc aaggagtaca agtgcaaggt ctccaacaaa
960

gccctcccag cccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca
1020

caggtgtaca ccctgccccc atcccgggag gagatgacca agaaccaggt cagcctgacc
1080

tgcctggtca aaggcttcta tcccagcgac atcgccgtgg agtgggagag caatgggcag
1140

ccggagaaca actacaagac cacgcctccc gtgctggact ccgacggctc cttcttcctc
1200

tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc
1260

gtgatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt
1320

a a a t g a
1326

<210> 172
<211> 333
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 172
gaggtgcagc ttgtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc
60

tcctgtgcag tctctggaat cgacctcagt ggctactaca tgaactgggt ccgtcaggct
120

ccagggaagg ggctggagtg ggtcggagtc attggtatta atggtgccac atactacgcg
180

agctgggcga aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt
240

caaatgaaca gcctgagagc tgaggacact gctgtgtatt tctgtgctag aggggacatc
300

tggggccaag ggaccctcgt caccgtctcg agc
333

<210> 173
<211> 90
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 173
gaggtgcagc ttgtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc
60

t c c t g t g c a g t c t c t g g a a t c g a c c t c a g t
90

<210> 174
<211> 15
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 174
g g c t a c t a c a t g a a c
15

<210> 175
<211> 42
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 175
tgggtccgtc aggctccagg gaaggggctg gagtgggtcg ga
42

<210> 176
<211> 48
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 176
gtcattggta ttaatggtgc cacatactac gcgagctggg cgaaaggc
48

<210> 177
<211> 96

<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 177
cgattcacca tctccagaga caattccaag accacggtgt atcttcaaat gaacagcctg 60

agagctgagg acactgctgt gtatttctgt gctaga 96

<210> 178
<211> 9
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 178
g g g g a c a t c 9

<210> 179
<211> 33
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 179
tggggccaag ggaccctcgt caccgtctcg agc 33

<210> 180
<211> 993
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 180
gcctccacca agggcccatc ggtcttcccc ctggcaccct cctccaagag cacctctggg
60

ggcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg
120

tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca
180

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacccagacc
240

tacatctgca acgtgaatca caagcccagc aacaccaagg tggacaagag agttgagccc
300

aaatcttgtg acaaaactca cacatgccca ccgtgcccag cacctgaact cctgggggga
360

ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct
420

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg
480

tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacgcc
540

agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag
600

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc
660

aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggaggag
720

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc
780

gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg
840

ctggactccg acggctcctt cttcctctac agcaagctca ccgtggacaa gagcaggtgg
900

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg
960

c a g a a g a g c c t c t c c c t g t c t c c g g g t a a a t g a
993

<210> 181
<211> 219
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 181

Gln Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
1 5 10 15

Arg Val Thr Ile Asn Cys Gln Ala Ser Gln Ser Val Tyr His Asn Thr
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Gln Leu
35 40 45

Ile Tyr Asp Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80

Pro Glu Asp Val Ala Thr Tyr Tyr Cys Leu Gly Ser Tyr Asp Cys Thr
85 90 95

Asn Gly Asp Cys Phe Val Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 182
<211> 113
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 182

Gln Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
1 5 10 15

Arg Val Thr Ile Asn Cys Gln Ala Ser Gln Ser Val Tyr His Asn Thr
            20   25   30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Gln Leu
        35   40   45

Ile Tyr Asp Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
    50   55   60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
65   70   75   80

Pro Glu Asp Val Ala Thr Tyr Tyr Cys Leu Gly Ser Tyr Asp Cys Thr
                85   90   95

Asn Gly Asp Cys Phe Val Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100   105   110

Arg

<210> 183
<211> 22
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 183

Gln Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
1   5   10   15

Arg Val Thr Ile Asn Cys
            20

<210> 184
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 184

Gln Ala Ser Gln Ser Val Tyr His Asn Thr Tyr Leu Ala
1 5 10

<210> 185
<211> 15
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 185

Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Gln Leu Ile Tyr
1 5 10 15

<210> 186
<211> 7
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 186

Asp Ala Ser Thr Leu Ala Ser
1 5

<210> 187

<211> 32
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 187

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Val Ala Thr Tyr Tyr Cys
20 25 30

<210> 188
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 188

Leu Gly Ser Tyr Asp Cys Thr Asn Gly Asp Cys Phe Val
1 5 10

<210> 189
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 189

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
1 5 10

<210> 190
<211> 106
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 190

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1 5 10 15

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
20 25 30

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
35 40 45

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
50 55 60

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65 70 75 80

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
85 90 95

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> 191
<211> 660
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 191
caagtgctga cccagtctcc atcctccctg tctgcatctg taggagacag agtcaccatc
60

aattgccagg ccagtcagag tgtttatcat aacacctacc tggcctggta tcagcagaaa
120

ccagggaaag ttcctaagca actgatctat gatgcatcca ctctggcatc tggggtccca
180

tctcgtttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagcctgcag
240

cctgaagatg ttgcaactta ttactgtctg ggcagttatg attgtactaa tggtgattgt
300

tttgttttcg gcggaggaac caaggtggaa atcaaacgta cggtggctgc accatctgtc
360

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg
420

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa
480

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc
540

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa
600

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgttag
660

<210> 192
<211> 339
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 192

caagtgctga cccagtctcc atcctccctg tctgcatctg taggagacag agtcaccatc
60

aattgccagg ccagtcagag tgtttatcat aacacctacc tggcctggta tcagcagaaa
120

ccagggaaag ttcctaagca actgatctat gatgcatcca ctctggcatc tggggtccca
180

tctcgtttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagcctgcag
240

cctgaagatg ttgcaactta ttactgtctg ggcagttatg attgtactaa tggtgattgt
300

tttgttttcg gcggaggaac caaggtggaa atcaaacgt
339

<210> 193
<211> 66
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 193
caagtgctga cccagtctcc atcctccctg tctgcatctg taggagacag agtcaccatc
60

a a t t g c
66

<210> 194
<211> 39
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 194
caggccagtc agagtgttta tcataacacc tacctggcc
39

<210> 195
<211> 45
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 195
tggtatcagc agaaaccagg gaaagttcct aagcaactga tctat
45

<210> 196
<211> 21
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 196
g a t g c a t c c a c t c t g g c a t c t
21

<210> 197
<211> 96
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 197
ggggtcccat ctcgtttcag tggcagtgga tctgggacag atttcactct caccatcagc
60

agcctgcagc ctgaagatgt tgcaacttat tactgt
96

<210> 198

<211> 39
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 198
ctgggcagtt atgattgtac taatggtgat tgttttgtt
39

<210> 199
<211> 33
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 199
ttcggcggag gaaccaaggt ggaaatcaaa cgt
33

<210> 200
<211> 321
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 200
acggtggctg caccatctgt cttcatcttc ccgccatctg atgagcagtt gaaatctgga
60

actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg
120

aaggtggata acgccctcca atcgggtaac tcccaggaga gtgtcacaga gcaggacagc
180

aaggacagca cctacagcct cagcagcacc ctgacgctga gcaaagcaga ctacgagaaa
240

cacaaagtct acgcctgcga agtcacccat cagggcctga gctcgcccgt cacaaagagc
300

t t c a a c a g g g g a g a g t g t t a g
321

<210> 201
<211> 441
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 201

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Ile Asp Leu Ser Gly Tyr
20 25 30

Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Val Ile Gly Ile Asn Gly Ala Thr Tyr Tyr Ala Ser Trp Ala Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Thr Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala
85 90 95

Arg Gly Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
100 105 110

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
115 120 125

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
130 135 140

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
145 150 155 160

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
165 170 175

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
180 185 190

Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Ala Arg
195 200 205

Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
210 215 220

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
225 230 235 240

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
245 250 255

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
260 265 270

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
275 280 285

Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
290 295 300

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
305 310 315 320

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
325 330 335

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
340 345 350

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
355 360 365

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
370 375 380

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
385 390 395 400

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
405 410 415

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
420 425 430

Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440

<210> 202
<211> 111
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 202

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Ile Asp Leu Ser Gly Tyr
20 25 30

Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Val Ile Gly Ile Asn Gly Ala Thr Tyr Tyr Ala Ser Trp Ala Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Thr Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala
85 90 95

Arg Gly Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105 110

<210> 203
<211> 30
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 203

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Ile Asp Leu Ser
20 25 30

<210> 204
<211> 5
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 204

Gly Tyr Tyr Met Asn
1 5

<210> 205
<211> 14
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 205

Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Gly
1 5 10

<210> 206
<211> 16
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 206

Val Ile Gly Ile Asn Gly Ala Thr Tyr Tyr Ala Ser Trp Ala Lys Gly

1 5 10 15

<210> 207
<211> 32
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 207

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Thr Thr Val Tyr Leu Gln
1 5 10 15

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala Arg
20 25 30

<210> 208
<211> 3
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 208

Gly Asp Ile
1

<210> 209
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 209

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
1 5 10

<210> 210
<211> 330
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 210

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Ala
85 90 95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 211
<211> 1326
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 211
gaggtgcagc ttgtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc
60

tcctgtgcag tctctggaat cgacctcagt ggctactaca tgaactgggt ccgtcaggct
120

ccagggaagg ggctggagtg ggtcggagtc attggtatta atggtgccac atactacgcg
180

agctgggcga aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt
240

caaatgaaca gcctgagagc tgaggacact gctgtgtatt tctgtgctag aggggacatc
300

tggggccaag ggaccctcgt caccgtctcg agcgcctcca ccaagggccc atcggtcttc
360

cccctggcac cctcctccaa gagcacctct gggggcacag cggccctggg ctgcctggtc
420

aaggactact tccccgaacc ggtgacggtg tcgtggaact caggcgccct gaccagcggc
480

gtgcacacct tcccggctgt cctacagtcc tcaggactct actccctcag cagcgtggtg
540

accgtgccct ccagcagctt gggcacccag acctacatct gcaacgtgaa tcacaagccc
600

agcaacacca aggtggacgc gagagttgag cccaaatctt gtgacaaaac tcacacatgc
660

ccaccgtgcc cagcacctga actcctgggg ggaccgtcag tcttcctctt cccccaaaa
720

cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg
780

agccacgaag accctgaggt caagttcaac tggtacgtgg acggcgtgga ggtgcataat
840

gccaagacaa agccgcggga ggagcagtac gccagcacgt accgtgtggt cagcgtcctc
900

accgtcctgc accaggactg gctgaatggc aaggagtaca agtgcaaggt ctccaacaaa
960

gccctcccag cccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca
1020

caggtgtaca ccctgccccc atcccgggag gagatgacca agaaccaggt cagcctgacc
1080

tgcctggtca aaggcttcta tcccagcgac atcgccgtgg agtgggagag caatgggcag
1140

ccggagaaca actacaagac cacgcctccc gtgctggact ccgacggctc cttcttcctc
1200

tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc
1260

gtgatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt
1320

a a a t g a
1326

<210> 212
<211> 333
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 212
gaggtgcagc ttgtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc
60

tcctgtgcag tctctggaat cgacctcagt ggctactaca tgaactgggt ccgtcaggct
120

ccagggaagg ggctggagtg ggtcggagtc attggtatta atggtgccac atactacgcg
180

agctgggcga aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt
240

caaatgaaca gcctgagagc tgaggacact gctgtgtatt tctgtgctag aggggacatc
300

tggggccaag ggaccctcgt caccgtctcg agc
333

<210> 213
<211> 90
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 213
gaggtgcagc ttgtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc
60

tcctgtgcag tctctggaat cgacctcagt
90

<210> 214
<211> 15
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 214
g g c t a c t a c a t g a a c
15

<210> 215
<211> 42
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 215
tgggtccgtc aggctccagg gaaggggctg gagtgggtcg ga
42

<210> 216
<211> 48
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 216
gtcattggta ttaatggtgc cacatactac gcgagctggg cgaaaggc
48

<210> 217
<211> 96
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 217
cgattcacca tctccagaga caattccaag accacggtgt atcttcaaat gaacagcctg
60

agagctgagg acactgctgt gtatttctgt gctaga
96

<210> 218
<211> 9
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 218
g g g g a c a t c
9

<210> 219
<211> 33
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 219
tggggccaag ggaccctcgt caccgtctcg agc
33

<210> 220
<211> 993
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 220
gcctccacca agggcccatc ggtcttcccc ctggcaccct cctccaagag cacctctggg
60

ggcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg
120

tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca
180

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacccagacc
240

tacatctgca acgtgaatca caagcccagc aacaccaagg tggacgcgag agttgagccc
300

aaatcttgtg acaaaactca cacatgccca ccgtgcccag cacctgaact cctgggggga
360

ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct
420

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg
480

tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacgcc
540

agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag
600

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc
660

aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggaggag
720

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc
780

gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg
840

ctggactccg acggctcctt cttcctctac agcaagctca ccgtggacaa gagcaggtgg
900

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg
960

cagaagagcc tctccctgtc tccgggtaaa tga
993

<210> 221
<211> 219
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 221

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Gln Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
1               5                  10                  15


Arg Val Thr Ile Asn Cys Gln Ala Ser Gln Ser Val Tyr His Asn Thr
            20                  25                  30


Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Gln Leu
        35                  40                  45


Ile Tyr Asp Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
    50                  55                  60


Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
65                  70                  75                  80


Pro Glu Asp Val Ala Thr Tyr Tyr Cys Leu Gly Ser Tyr Asp Cys Thr
                85                  90                  95


Asn Gly Asp Cys Phe Val Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110


Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125


Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
```

130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 222
<211> 113
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 222

Gln Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
1 5 10 15

Arg Val Thr Ile Asn Cys Gln Ala Ser Gln Ser Val Tyr His Asn Thr
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Gln Leu
35 40 45

Ile Tyr Asp Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
    50   55   60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
65   70   75   80

Pro Glu Asp Val Ala Thr Tyr Tyr Cys Leu Gly Ser Tyr Asp Cys Thr
                85   90   95

Asn Gly Asp Cys Phe Val Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100   105   110

Arg

<210> 223
<211> 22
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 223

Gln Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
1   5   10   15

Arg Val Thr Ile Asn Cys
            20

<210> 224
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 224

Gln Ala Ser Gln Ser Val Tyr His Asn Thr Tyr Leu Ala
1 5 10

<210> 225
<211> 15
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 225

Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Gln Leu Ile Tyr
1 5 10 15

<210> 226
<211> 7
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 226

Asp Ala Ser Thr Leu Ala Ser
1 5

<210> 227
<211> 32
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 227

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Val Ala Thr Tyr Tyr Cys
20 25 30

<210> 228
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 228

Leu Gly Ser Tyr Asp Cys Thr Asn Gly Asp Cys Phe Val
1 5 10

<210> 229
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 229

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
1 5 10

<210> 230
<211> 106
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 230

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1 5 10 15

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
20 25 30

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
35 40 45

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
50 55 60

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65 70 75 80

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
85 90 95

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> 231
<211> 660
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 231
caagtgctga cccagtctcc atcctccctg tctgcatctg taggagacag agtcaccatc 60

aattgccagg ccagtcagag tgtttatcat aacacctacc tggcctggta tcagcagaaa 120

ccagggaaag ttcctaagca actgatctat gatgcatcca ctctggcatc tggggtccca 180

tctcgtttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagcctgcag 240

cctgaagatg ttgcaactta ttactgtctg ggcagttatg attgtactaa tggtgattgt 300

tttgttttcg gcggaggaac caaggtggaa atcaaacgta cggtggctgc accatctgtc 360

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 420

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 480

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 600

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgttag 660

<210> 232
<211> 339
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 232
caagtgctga cccagtctcc atcctccctg tctgcatctg taggagacag agtcaccatc 60

aattgccagg ccagtcagag tgtttatcat aacacctacc tggcctggta tcagcagaaa 120

ccagggaaag ttcctaagca actgatctat gatgcatcca ctctggcatc tggggtccca 180

tctcgtttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagcctgcag 240

cctgaagatg ttgcaactta ttactgtctg ggcagttatg attgtactaa tggtgattgt
300

tttgttttcg gcggaggaac caaggtggaa atcaaacgt
339

<210> 233
<211> 66
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 233
caagtgctga cccagtctcc atcctccctg tctgcatctg taggagacag agtcaccatc
60

a a t t g c
66

<210> 234
<211> 39
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 234
caggccagtc agagtgttta tcataacacc tacctggcc
39

<210> 235
<211> 45
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 235
tggtatcagc agaaaccagg gaaagttcct aagcaactga tctat
45

<210> 236
<211> 21
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 236
g a t g c a t c c a c t c t g g c a t c t
21

<210> 237
<211> 96
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 237
ggggtcccat ctcgtttcag tggcagtgga tctgggacag atttcactct caccatcagc
60

agcctgcagc ctgaagatgt tgcaacttat tactgt
96

<210> 238
<211> 39
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 238
ctgggcagtt atgattgtac taatggtgat tgttttgtt
39

<210> 239
<211> 33
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 239
ttcggcggag gaaccaaggt ggaaatcaaa cgt
33

<210> 240
<211> 321
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 240
acggtggctg caccatctgt cttcatcttc ccgccatctg atgagcagtt gaaatctgga
60

actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg
120

aaggtggata acgccctcca atcgggtaac tcccaggaga gtgtcacaga gcaggacagc
180

aaggacagca cctacagcct cagcagcacc ctgacgctga gcaaagcaga ctacgagaaa
240

cacaaagtct acgcctgcga agtcacccat cagggcctga gctcgcccgt cacaaagagc
300

ttcaacaggg gagagtgtta g
321

<210> 241
<211> 440

<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 241

Gln Glu Gln Leu Lys Glu Ser Gly Gly Arg Leu Val Thr Pro Gly Thr
1 5 10 15

Ser Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser Asn His
20 25 30

Tyr Met Gln Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Val Val Gly Ile Asn Gly Arg Thr Tyr Tyr Ala Ser Trp Ala Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Thr Ser Ser Thr Thr Val Asp Leu Lys
65 70 75 80

Met Thr Arg Leu Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg
85 90 95

Gly Asp Ile Trp Gly Pro Gly Thr Leu Val Thr Val Ser Ser Ala Ser
100 105 110

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
115 120 125

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
130 135 140

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val

145 150 155 160

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
165 170 175

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
180 185 190

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val
195 200 205

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
210 215 220

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
225 230 235 240

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
245 250 255

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
260 265 270

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
275 280 285

Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
290 295 300

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
305 310 315 320

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
325 330 335

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
340 345 350

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
355 360 365

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
370 375 380

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
385 390 395 400

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
405 410 415

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
420 425 430

Ser Leu Ser Leu Ser Pro Gly Lys
435 440

<210> 242
<211> 110
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 242

Gln Glu Gln Leu Lys Glu Ser Gly Gly Arg Leu Val Thr Pro Gly Thr
1 5 10 15

Ser Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser Asn His

20 25 30

Tyr Met Gln Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Val Val Gly Ile Asn Gly Arg Thr Tyr Tyr Ala Ser Trp Ala Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Thr Ser Ser Thr Thr Val Asp Leu Lys
65 70 75 80

Met Thr Arg Leu Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg
85 90 95

Gly Asp Ile Trp Gly Pro Gly Thr Leu Val Thr Val Ser Ser
100 105 110

<210> 243
<211> 30
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 243

Gln Glu Gln Leu Lys Glu Ser Gly Gly Arg Leu Val Thr Pro Gly Thr
1 5 10 15

Ser Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser
20 25 30

<210> 244
<211> 5
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 244

Asn His Tyr Met Gln
1 5

<210> 245
<211> 14
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 245

Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile Gly
1 5 10

<210> 246
<211> 16
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 246

Val Val Gly Ile Asn Gly Arg Thr Tyr Tyr Ala Ser Trp Ala Lys Gly
1 5 10 15

<210> 247
<211> 31
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 247

Arg Phe Thr Ile Ser Arg Thr Ser Ser Thr Thr Val Asp Leu Lys Met
1 5 10 15

Thr Arg Leu Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg
20 25 30

<210> 248
<211> 3
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 248

Gly Asp Ile
1

<210> 249
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 249

Trp Gly Pro Gly Thr Leu Val Thr Val Ser Ser
1 5 10

<210> 250
<211> 330
<212> PRT
<213> Artificial

<220>

<223> Engineered antibody sequence

<400> 250

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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
```

165 170 175

Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 251
<211> 1323

<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 251
caggagcagc tgaaggagtc cgggggtcgc ctggtcacgc ctgggacatc cctgacactc
60

acctgcaccg tctctggaat cgacctcagt aaccactaca tgcaatgggt ccgccaggct
120

ccagggaagg ggctggagtg gatcggagtc gttggtatta atggtcgcac atactacgcg
180

agctgggcga aaggccgatt caccatctcc agaacctcgt cgaccacggt ggatctgaaa
240

atgaccaggc tgacaaccga ggacacggcc acctatttct gtgccagagg ggacatctgg
300

ggcccaggca ccctggtcac cgtctcgagc gcctccacca agggcccatc ggtcttcccc
360

ctggcaccct cctccaagag cacctctggg ggcacagcgg ccctgggctg cctggtcaag
420

gactacttcc ccgaaccggt gacggtgtcg tggaactcag gcgccctgac cagcggcgtg
480

cacaccttcc cggctgtcct acagtcctca ggactctact ccctcagcag cgtggtgacc
540

gtgccctcca gcagcttggg cacccagacc tacatctgca acgtgaatca caagcccagc
600

aacaccaagg tggacaagag agttgagccc aaatcttgtg acaaaactca cacatgccca
660

ccgtgcccag cacctgaact cctgggggga ccgtcagtct tcctcttccc cccaaaaccc
720

aaggacaccc tcatgatctc ccggacccct gaggtcacat gcgtggtggt ggacgtgagc
780

cacgaagacc ctgaggtcaa gttcaactgg tacgtggacg gcgtggaggt gcataatgcc
840

aagacaaagc cgcgggagga gcagtacgcc agcacgtacc gtgtggtcag cgtcctcacc
900

gtcctgcacc aggactggct gaatggcaag gagtacaagt gcaaggtctc caacaaagcc
960

ctcccagccc ccatcgagaa aaccatctcc aaagccaaag ggcagccccg agaaccacag
1020

gtgtacaccc tgcccccatc ccgggaggag atgaccaaga accaggtcag cctgacctgc
1080

ctggtcaaag gcttctatcc cagcgacatc gccgtggagt gggagagcaa tgggcagccg
1140

gagaacaact acaagaccac gcctcccgtg ctggactccg acggctcctt cttcctctac
1200

agcaagctca ccgtggacaa gagcaggtgg cagcagggga acgtcttctc atgctccgtg
1260

atgcatgagg ctctgcacaa ccactacacg cagaagagcc tctccctgtc tccgggtaaa
1320

t g a
1323

<210> 252
<211> 330
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 252
caggagcagc tgaaggagtc cgggggtcgc ctggtcacgc ctgggacatc cctgacactc
60

acctgcaccg tctctggaat cgacctcagt aaccactaca tgcaatgggt ccgccaggct
120

ccagggaagg ggctggagtg gatcggagtc gttggtatta atggtcgcac atactacgcg 180

agctgggcga aaggccgatt caccatctcc agaacctcgt cgaccacggt ggatctgaaa 240

atgaccaggc tgacaaccga ggacacggcc acctatttct gtgccagagg ggacatctgg 300

g g c c c a g g c a c c c t g g t c a c c g t c t c g a g c 330

<210> 253
<211> 90
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 253
caggagcagc tgaaggagtc cgggggtcgc ctggtcacgc ctgggacatc cctgacactc 60

a c c t g c a c c g t c t c t g g a a t c g a c c t c a g t 90

<210> 254
<211> 15
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 254
a a c c a c t a c a t g c a a 15

<210> 255
<211> 42

<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 255
tgggtccgcc aggctccagg gaaggggctg gagtggatcg ga
42

<210> 256
<211> 48
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 256
gtcgttggta ttaatggtcg cacatactac gcgagctggg cgaaaggc
48

<210> 257
<211> 93
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 257
cgattcacca tctccagaac ctcgtcgacc acggtggatc tgaaaatgac caggctgaca
60

accgaggaca cggccaccta tttctgtgcc aga
93

<210> 258
<211> 9
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 258
g g g g a c a t c
9

<210> 259
<211> 33
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 259
t g g g g c c c a g g c a c c c t g g t c a c c g t c t c g a g c
33

<210> 260
<211> 993
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 260
gcctccacca agggcccatc ggtcttcccc ctggcaccct cctccaagag cacctctggg
60

ggcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg
120

tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca
180

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacccagacc
240

tacatctgca acgtgaatca caagcccagc aacaccaagg tggacaagag agttgagccc
300

aaatcttgtg acaaaactca cacatgccca ccgtgcccag cacctgaact cctgggggga
360

ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct
420

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg
480

tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacgcc
540

agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag
600

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc
660

aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggaggag
720

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc
780

gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg
840

ctggactccg acggctcctt cttcctctac agcaagctca ccgtggacaa gagcaggtgg
900

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg
960

cagaagagcc tctccctgtc tccgggtaaa tga
993

<210> 261
<211> 219
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 261

Gln Val Leu Thr Gln Thr Ala Ser Pro Val Ser Ala Ala Val Gly Ser
1 5 10 15

Thr Val Thr Ile Asn Cys Gln Ala Ser Gln Ser Val Tyr Asn Tyr Asn
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Gln Leu
35 40 45

Ile Tyr Ser Thr Ser Thr Leu Ala Ser Gly Val Ser Ser Arg Phe Lys
50 55 60

Gly Ser Gly Ser Gly Thr Gln Phe Thr Leu Thr Ile Ser Asp Val Gln
65 70 75 80

Cys Asp Asp Ala Ala Thr Tyr Tyr Cys Leu Gly Ser Tyr Asp Cys Ser
85 90 95

Thr Gly Asp Cys Phe Val Phe Gly Gly Gly Thr Glu Val Val Val Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 262
<211> 113
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 262

Gln Val Leu Thr Gln Thr Ala Ser Pro Val Ser Ala Ala Val Gly Ser
1 5 10 15

Thr Val Thr Ile Asn Cys Gln Ala Ser Gln Ser Val Tyr Asn Tyr Asn
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Gln Leu
35 40 45

Ile Tyr Ser Thr Ser Thr Leu Ala Ser Gly Val Ser Ser Arg Phe Lys
50 55 60

Gly Ser Gly Ser Gly Thr Gln Phe Thr Leu Thr Ile Ser Asp Val Gln
65 70 75 80

Cys Asp Asp Ala Ala Thr Tyr Tyr Cys Leu Gly Ser Tyr Asp Cys Ser
85 90 95

Thr Gly Asp Cys Phe Val Phe Gly Gly Gly Thr Glu Val Val Val Lys
100 105 110

Arg

<210> 263
<211> 22
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 263

Gln Val Leu Thr Gln Thr Ala Ser Pro Val Ser Ala Ala Val Gly Ser
1 5 10 15

Thr Val Thr Ile Asn Cys
20

<210> 264
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 264

Gln Ala Ser Gln Ser Val Tyr Asn Tyr Asn Tyr Leu Ala
1 5 10

<210> 265
<211> 15
<212> PRT

<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 265

Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Gln Leu Ile Tyr
1 5 10 15

<210> 266
<211> 7
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 266

Ser Thr Ser Thr Leu Ala Ser
1 5

<210> 267
<211> 32
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 267

Gly Val Ser Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Thr
1 5 10 15

Leu Thr Ile Ser Asp Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
20 25 30

<210> 268
<211> 13

<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 268

Leu Gly Ser Tyr Asp Cys Ser Thr Gly Asp Cys Phe Val
1 5 10

<210> 269
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 269

Phe Gly Gly Gly Thr Glu Val Val Val Lys Arg
1 5 10

<210> 270
<211> 106
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 270

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1 5 10 15

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
20 25 30

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser

35 40 45

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
50 55 60

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65 70 75 80

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
85 90 95

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> 271
<211> 660
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 271
caagtgctga cccagactgc atcccccgtg tctgcagctg tgggaagcac agtcaccatc 60

aattgccagg ccagtcagag tgtttataat tacaactacc ttgcctggta tcagcagaaa 120

ccagggcagc ctcccaagca actgatctat tctacatcca ctctggcatc tggggtctca 180

tcgcgattca aaggcagtgg atctgggaca cagttcactc tcaccatcag cgacgtgcag 240

tgtgacgatg ctgccactta ctactgtcta ggcagttatg actgtagtac tggtgattgt 300

tttgttttcg gcggagggac cgaggtggtg gtcaaacgta cggtggctgc accatctgtc 360

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 420

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 480

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 600

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgttag 660

<210> 272
<211> 339
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 272
caagtgctga cccagactgc atcccccgtg tctgcagctg tgggaagcac agtcaccatc 60

aattgccagg ccagtcagag tgtttataat tacaactacc ttgcctggta tcagcagaaa 120

ccagggcagc ctcccaagca actgatctat tctacatcca ctctggcatc tggggtctca 180

tcgcgattca aaggcagtgg atctgggaca cagttcactc tcaccatcag cgacgtgcag 240

tgtgacgatg ctgccactta ctactgtcta ggcagttatg actgtagtac tggtgattgt 300

tttgttttcg gcggagggac cgaggtggtg gtcaaacgt 339

<210> 273
<211> 66
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 273
caagtgctga cccagactgc atcccccgtg tctgcagctg tgggaagcac agtcaccatc
60

a a t t g c
66

<210> 274
<211> 39
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 274
caggccagtc agagtgttta taattacaac taccttgcc
39

<210> 275
<211> 45
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 275
tggtatcagc agaaaccagg gcagcctccc aagcaactga tctat
45

<210> 276
<211> 21
<212> DNA

<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 276
tctacatcca ctctggcatc t
21

<210> 277
<211> 96
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 277
ggggtctcat cgcgattcaa aggcagtgga tctgggacac agttcactct caccatcagc
60

gacgtgcagt gtgacgatgc tgccacttac tactgt
96

<210> 278
<211> 39
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 278
ctaggcagtt atgactgtag tactggtgat tgttttgtt
39

<210> 279
<211> 33
<212> DNA
<213> Artificial

<220>

<223> Engineered antibody sequence

<400> 279
ttcggcggag ggaccgaggt ggtggtcaaa cgt
33

<210> 280
<211> 321
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 280
acggtggctg caccatctgt cttcatcttc ccgccatctg atgagcagtt gaaatctgga
60

actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg
120

aaggtggata acgccctcca atcgggtaac tcccaggaga gtgtcacaga gcaggacagc
180

aaggacagca cctacagcct cagcagcacc ctgacgctga gcaaagcaga ctacgagaaa
240

cacaaagtct acgcctgcga agtcacccat cagggcctga gctcgcccgt cacaaagagc
300

ttcaacaggg gagagtgtta g
321

<210> 281
<211> 441
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 281

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Ile Asp Leu Ser Asn His
20 25 30

Tyr Met Gln Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Val Val Gly Ile Asn Gly Arg Thr Tyr Tyr Ala Ser Trp Ala Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Thr Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala
85 90 95

Arg Gly Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
100 105 110

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
115 120 125

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
130 135 140

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
145 150 155 160

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
165 170 175

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr

180 185 190

Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg
195 200 205

Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
210 215 220

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
225 230 235 240

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
245 250 255

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
260 265 270

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
275 280 285

Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
290 295 300

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
305 310 315 320

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
325 330 335

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
340 345 350

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
355 360 365

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
370 375 380

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
385 390 395 400

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
405 410 415

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
420 425 430

Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440

<210> 282
<211> 111
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 282

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Ile Asp Leu Ser Asn His
20 25 30

Tyr Met Gln Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Val Val Gly Ile Asn Gly Arg Thr Tyr Tyr Ala Ser Trp Ala Lys

50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Thr Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala
85 90 95

Arg Gly Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105 110

<210> 283
<211> 30
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 283

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Ile Asp Leu Ser
20 25 30

<210> 284
<211> 5
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 284

Asn His Tyr Met Gln
1 5

<210> 285
<211> 14
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 285

Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Gly
1 5 10

<210> 286
<211> 16
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 286

Val Val Gly Ile Asn Gly Arg Thr Tyr Tyr Ala Ser Trp Ala Lys Gly
1 5 10 15

<210> 287
<211> 32
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 287

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Thr Thr Val Tyr Leu Gln
1 5 10 15

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala Arg

20 25 30

<210> 288
<211> 3
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 288

Gly Asp Ile
1

<210> 289
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 289

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
1 5 10

<210> 290
<211> 330
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 290

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn

195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 291
<211> 1326
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 291
gaggtgcagc ttgtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc
60

tcctgtgcag tctctggaat cgacctcagt aaccactaca tgcaatgggt ccgtcaggct 120

ccagggaagg ggctggagtg ggtcggagtc gttggtatca atggtcgcac atactacgcg 180

agctgggcga aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt 240

caaatgaaca gcctgagagc tgaggacact gctgtgtatt tctgtgctag aggggacatc 300

tggggccaag ggaccctcgt caccgtctcg agcgcctcca ccaagggccc atcggtcttc 360

cccctggcac cctcctccaa gagcacctct gggggcacag cggccctggg ctgcctggtc 420

aaggactact tccccgaacc ggtgacggtg tcgtggaact caggcgccct gaccagcggc 480

gtgcacacct tcccggctgt cctacagtcc tcaggactct actccctcag cagcgtggtg 540

accgtgccct ccagcagctt gggcacccag acctacatct gcaacgtgaa tcacaagccc 600

agcaacacca aggtggacaa gagagttgag cccaaatctt gtgacaaaac tcacacatgc 660

ccaccgtgcc cagcacctga actcctgggg ggaccgtcag tcttcctctt ccccccaaaa 720

cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg 780

agccacgaag accctgaggt caagttcaac tggtacgtgg acggcgtgga ggtgcataat 840

gccaagacaa agccgcggga ggagcagtac gccagcacgt accgtgtggt cagcgtcctc 900

accgtcctgc accaggactg gctgaatggc aaggagtaca agtgcaaggt ctccaacaaa 960

gccctcccag cccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca
1020

caggtgtaca ccctgccccc atcccgggag gagatgacca agaaccaggt cagcctgacc
1080

tgcctggtca aaggcttcta tcccagcgac atcgccgtgg agtgggagag caatgggcag
1140

ccggagaaca actacaagac cacgcctccc gtgctggact ccgacggctc cttcttcctc
1200

tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc
1260

gtgatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt
1320

a a a t g a
1326

<210> 292
<211> 333
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 292
gaggtgcagc ttgtggagtc tgggggaggc ttggtccagc ctgggggggtc cctgagactc
60

tcctgtgcag tctctggaat cgacctcagt aaccactaca tgcaatgggt ccgtcaggct
120

ccagggaagg ggctggagtg ggtcggagtc gttggtatca atggtcgcac atactacgcg
180

agctgggcga aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt
240

caaatgaaca gcctgagagc tgaggacact gctgtgtatt tctgtgctag aggggacatc
300

tggggccaag ggaccctcgt caccgtctcg agc
333

<210> 293
<211> 90
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 293
gaggtgcagc ttgtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc
60

tcctgtgcag tctctggaat cgacctcagt
90

<210> 294
<211> 15
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 294
aaccactaca tgcaa
15

<210> 295
<211> 42
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 295
tgggtccgtc aggctccagg gaaggggctg gagtgggtcg ga
42

<210> 296
<211> 48
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 296
gtcgttggta tcaatggtcg cacatactac gcgagctggg cgaaaggc 48

<210> 297
<211> 96
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 297
cgattcacca tctccagaga caattccaag accacggtgt atcttcaaat gaacagcctg 60

agagctgagg acactgctgt gtatttctgt gctaga 96

<210> 298
<211> 9
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 298
g g g g a c a t c 9

<210> 299

<211> 33
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 299
tggggccaag ggaccctcgt caccgtctcg agc
33

<210> 300
<211> 993
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 300
gcctccacca agggcccatc ggtcttcccc ctggcaccct cctccaagag cacctctggg
60

ggcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg
120

tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca
180

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacccagacc
240

tacatctgca acgtgaatca caagcccagc aacaccaagg tggacaagag agttgagccc
300

aaatcttgtg acaaaactca cacatgccca ccgtgcccag cacctgaact cctgggggga
360

ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggaccct
420

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg
480

tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacgcc
540

agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag
600

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc
660

aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggaggag
720

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc
780

gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg
840

ctggactccg acggctcctt cttcctctac agcaagctca ccgtggacaa gagcaggtgg
900

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg
960

c a g a a g a g c c t c t c c c t g t c t c c g g g t a a a t g a
993

<210> 301
<211> 219
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 301

Gln Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
1 5 10 15

Arg Val Thr Ile Asn Cys Gln Ala Ser Gln Ser Val Tyr Asn Tyr Asn
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Gln Leu
35 40 45

Ile Tyr Ser Thr Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80

Pro Glu Asp Val Ala Thr Tyr Tyr Cys Leu Gly Ser Tyr Asp Cys Ser
85 90 95

Thr Gly Asp Cys Phe Val Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 302
<211> 113
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 302

Gln Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
1 5 10 15

Arg Val Thr Ile Asn Cys Gln Ala Ser Gln Ser Val Tyr Asn Tyr Asn
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Gln Leu
35 40 45

Ile Tyr Ser Thr Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80

Pro Glu Asp Val Ala Thr Tyr Tyr Cys Leu Gly Ser Tyr Asp Cys Ser
85 90 95

Thr Gly Asp Cys Phe Val Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

Arg

<210> 303
<211> 22
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 303

Gln Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
1 5 10 15

Arg Val Thr Ile Asn Cys
20

<210> 304
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 304

Gln Ala Ser Gln Ser Val Tyr Asn Tyr Asn Tyr Leu Ala
1 5 10

<210> 305
<211> 15
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 305

Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Gln Leu Ile Tyr
1 5 10 15

<210> 306
<211> 7
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 306

Ser Thr Ser Thr Leu Ala Ser
1 5

<210> 307
<211> 32
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 307

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Val Ala Thr Tyr Tyr Cys
20 25 30

<210> 308
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 308

Leu Gly Ser Tyr Asp Cys Ser Thr Gly Asp Cys Phe Val

1 5 10

<210> 309
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 309

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
1 5 10

<210> 310
<211> 106
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 310

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1 5 10 15

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
20 25 30

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
35 40 45

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
50 55 60

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65 70 75 80

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
85 90 95

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> 311
<211> 660
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 311
caagtgctga cccagtctcc atcctccctg tctgcatctg taggagacag agtcaccatc 60

aattgccagg ccagtcagag tgtttacaat tacaactacc ttgcctggta tcagcagaaa 120

ccagggaaag ttcctaagca actgatctat tctacatcca ctctggcatc tggggtccca 180

tctcgtttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagcctgcag 240

cctgaagatg ttgcaactta ttactgtctg ggcagttatg attgtagtac tggtgattgt 300

tttgttttcg gcggaggaac caaggtggaa atcaaacgta cggtggctgc accatctgtc 360

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 420

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 480

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 600

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgttag 660

<210> 312
<211> 339
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 312
caagtgctga cccagtctcc atcctccctg tctgcatctg taggagacag agtcaccatc 60

aattgccagg ccagtcagag tgtttacaat tacaactacc ttgcctggta tcagcagaaa 120

ccagggaaag ttcctaagca actgatctat tctacatcca ctctggcatc tggggtccca 180

tctcgtttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagcctgcag 240

cctgaagatg ttgcaactta ttactgtctg ggcagttatg attgtagtac tggtgattgt 300

tttgttttcg gcggaggaac caaggtggaa atcaaacgt 339

<210> 313
<211> 66
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 313

caagtgctga cccagtctcc atcctccctg tctgcatctg taggagacag agtcaccatc
60

a a t t g c
66

<210> 314
<211> 39
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 314
caggccagtc agagtgttta caattacaac taccttgcc
39

<210> 315
<211> 45
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 315
tggtatcagc agaaaccagg gaaagttcct aagcaactga tctat
45

<210> 316
<211> 21
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 316
t c t a c a t c c a c t c t g g c a t c t
21

<210> 317
<211> 96
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 317
ggggtcccat ctcgtttcag tggcagtgga tctgggacag atttcactct caccatcagc
60

agcctgcagc ctgaagatgt tgcaacttat tactgt
96

<210> 318
<211> 39
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 318
ctgggcagtt atgattgtag tactggtgat tgttttgtt
39

<210> 319
<211> 33
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 319
ttcggcggag gaaccaaggt ggaaatcaaa cgt
33

<210> 320
<211> 321

<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 320
acggtggctg caccatctgt cttcatcttc ccgccatctg atgagcagtt gaaatctgga
60

actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg
120

aaggtggata acgccctcca atcgggtaac tcccaggaga gtgtcacaga gcaggacagc
180

aaggacagca cctacagcct cagcagcacc ctgacgctga gcaaagcaga ctacgagaaa
240

cacaaagtct acgcctgcga agtcacccat cagggcctga gctcgcccgt cacaaagagc
300

t t c a a c a g g g g a g a g t g t t a g
321

<210> 321
<211> 439
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 321

Gln Ser Leu Glu Glu Ser Gly Gly Arg Leu Val Thr Pro Gly Thr Pro
1 5 10 15

Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Gly Leu Ser Ser Tyr Tyr
20 25 30

Met Gln Trp Val Arg Gln Ser Pro Gly Arg Gly Leu Glu Trp Ile Gly

35 40 45

Val Ile Gly Ser Asp Gly Lys Thr Tyr Tyr Ala Thr Trp Ala Lys Gly
50 55 60

Arg Phe Thr Ile Ser Lys Thr Ser Ser Thr Thr Val Asp Leu Arg Met
65 70 75 80

Ala Ser Leu Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Thr Arg Gly
85 90 95

Asp Ile Trp Gly Pro Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
100 105 110

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
115 120 125

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
130 135 140

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
145 150 155 160

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
165 170 175

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
180 185 190

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu
195 200 205

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
210 215 220

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
225 230 235 240

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
245 250 255

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
260 265 270

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
275 280 285

Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
290 295 300

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
305 310 315 320

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
325 330 335

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
340 345 350

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
355 360 365

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
370 375 380

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
385 390 395 400

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
405 410 415

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
420 425 430

Leu Ser Leu Ser Pro Gly Lys
435

<210> 322
<211> 109
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 322

Gln Ser Leu Glu Glu Ser Gly Gly Arg Leu Val Thr Pro Gly Thr Pro
1 5 10 15

Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Gly Leu Ser Ser Tyr Tyr
20 25 30

Met Gln Trp Val Arg Gln Ser Pro Gly Arg Gly Leu Glu Trp Ile Gly
35 40 45

Val Ile Gly Ser Asp Gly Lys Thr Tyr Tyr Ala Thr Trp Ala Lys Gly
50 55 60

Arg Phe Thr Ile Ser Lys Thr Ser Ser Thr Thr Val Asp Leu Arg Met
65 70 75 80

Ala Ser Leu Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Thr Arg Gly
85 90 95

Asp Ile Trp Gly Pro Gly Thr Leu Val Thr Val Ser Ser
100 105

<210> 323
<211> 29
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 323

Gln Ser Leu Glu Glu Ser Gly Gly Arg Leu Val Thr Pro Gly Thr Pro
1 5 10 15

Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Gly Leu Ser
20 25

<210> 324
<211> 5
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 324

Ser Tyr Tyr Met Gln
1 5

<210> 325
<211> 14
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 325

Trp Val Arg Gln Ser Pro Gly Arg Gly Leu Glu Trp Ile Gly
1 5 10

<210> 326
<211> 16
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 326

Val Ile Gly Ser Asp Gly Lys Thr Tyr Tyr Ala Thr Trp Ala Lys Gly
1 5 10 15

<210> 327
<211> 31
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 327

Arg Phe Thr Ile Ser Lys Thr Ser Ser Thr Thr Val Asp Leu Arg Met
1 5 10 15

Ala Ser Leu Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Thr Arg
20 25 30

<210> 328
<211> 3
<212> PRT
<213> Artificial

<220>

<223> Engineered antibody sequence

<400> 328

Gly Asp Ile
1

<210> 329
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 329

Trp Gly Pro Gly Thr Leu Val Thr Val Ser Ser
1 5 10

<210> 330
<211> 330
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 330

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser

```
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240
```

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 331
<211> 1320
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 331
cagtcgctgg aggagtccgg gggtcgcctg gtcacgcctg ggacacccct gacactcacc
60

tgcacagtct ctggaatcgg cctcagtagc tactacatgc agtgggtccg ccagtctcca
120

gggaggggc tggaatggat cggagtcatt ggtagtgatg gtaagacata ctacgcgacc
180

tgggcgaaag gccgattcac catctccaag acctcgtcga ccacggtgga tctgagaatg
240

gccagtctga caaccgagga cacggccacc tatttctgta ccagagggga catctggggc
300

ccggggaccc tcgtcaccgt ctcgagcgcc tccaccaagg gcccatcggt cttccccctg
360

gcaccctcct ccaagagcac ctctgggggc acagcggccc tgggctgcct ggtcaaggac
420

tacttccccg aaccggtgac ggtgtcgtgg aactcaggcg ccctgaccag cggcgtgcac
480

accttcccgg ctgtcctaca gtcctcagga ctctactccc tcagcagcgt ggtgaccgtg
540

ccctccagca gcttgggcac ccagacctac atctgcaacg tgaatcacaa gcccagcaac
600

accaaggtgg acaagagagt tgagcccaaa tcttgtgaca aaactcacac atgcccaccg
660

tgcccagcac ctgaactcct gggggggaccg tcagtcttcc tcttcccccc aaaacccaag
720

gacaccctca tgatctcccg gacccctgag gtcacatgcg tggtggtgga cgtgagccac
780

gaagaccctg aggtcaagtt caactggtac gtggacggcg tggaggtgca taatgccaag
840

acaaagccgc gggaggagca gtacgccagc acgtaccgtg tggtcagcgt cctcaccgtc
900

ctgcaccagg actggctgaa tggcaaggag tacaagtgca aggtctccaa caaagccctc
960

ccagccccca tcgagaaaac catctccaaa gccaaagggc agccccgaga accacaggtg
1020

tacaccctgc ccccatcccg ggaggagatg accaagaacc aggtcagcct gacctgcctg
1080

gtcaaaggct tctatcccag cgacatcgcc gtggagtggg agagcaatgg gcagccggag
1140

aacaactaca agaccacgcc tcccgtgctg gactccgacg gctccttctt cctctacagc 1200

aagctcaccg tggacaagag caggtggcag caggggaacg tcttctcatg ctccgtgatg 1260

catgaggctc tgcacaacca ctacacgcag aagagcctct ccctgtctcc gggtaaatga 1320

<210> 332
<211> 327
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 332
cagtcgctgg aggagtccgg gggtcgcctg gtcacgcctg ggacacccct gacactcacc 60

tgcacagtct ctggaatcgg cctcagtagc tactacatgc agtgggtccg ccagtctcca 120

gggaggggggc tggaatggat cggagtcatt ggtagtgatg gtaagacata ctacgcgacc 180

tgggcgaaag gccgattcac catctccaag acctcgtcga ccacggtgga tctgagaatg 240

gccagtctga caaccgagga cacggccacc tatttctgta ccagagggga catctggggc 300

c c g g g g a c c c t c g t c a c c g t c t c g a g c 327

<210> 333
<211> 87
<212> DNA
<213> Artificial

<220>

<223> Engineered antibody sequence

<400> 333
cagtcgctgg aggagtccgg gggtcgcctg gtcacgcctg ggacacccct gacactcacc 60

tgcacagtct ctggaatcgg cctcagt 87

<210> 334
<211> 15
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 334
agctactaca tgcag 15

<210> 335
<211> 42
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 335
tgggtccgcc agtctccagg gaggggctg gaatggatcg ga 42

<210> 336
<211> 48
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 336

gtcattggta gtgatggtaa gacatactac gcgacctggg cgaaaggc
48

<210> 337
<211> 93
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 337
cgattcacca tctccaagac ctcgtcgacc acggtggatc tgagaatggc cagtctgaca
60

accgaggaca cggccaccta tttctgtacc aga
93

<210> 338
<211> 9
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 338
g g g g a c a t c
9

<210> 339
<211> 33
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 339
tggggcccgg ggaccctcgt caccgtctcg agc
33

<210> 340
<211> 993
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 340
gcctccacca agggcccatc ggtcttcccc ctggcaccct cctccaagag cacctctggg
60

ggcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg
120

tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca
180

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacccagacc
240

tacatctgca acgtgaatca caagcccagc aacaccaagg tggacaagag agttgagccc
300

aaatcttgtg acaaaactca cacatgccca ccgtgcccag cacctgaact cctgggggga
360

ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct
420

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg
480

tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacgcc
540

agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag
600

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc
660

aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggaggag
720

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc
780

gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg
840

ctggactccg acggctcctt cttcctctac agcaagctca ccgtggacaa gagcaggtgg
900

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg
960

c a g a a g a g c c t c t c c c t g t c t c c g g g t a a a t g a
993

<210> 341
<211> 219
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 341

Gln Val Leu Thr Gln Thr Pro Ser Pro Val Ser Ala Ala Val Gly Ser
1 5 10 15

Thr Val Thr Ile Asn Cys Gln Ala Ser Gln Asn Val Tyr Asn Asn Asn
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Gln Leu
35 40 45

Ile Tyr Ser Thr Ser Thr Leu Ala Ser Gly Val Ser Ser Arg Phe Arg
50 55 60

Gly Ser Gly Ser Gly Thr Gln Phe Thr Leu Thr Ile Ser Asp Val Gln
65 70 75 80

Cys Asp Asp Ala Ala Thr Tyr Tyr Cys Leu Gly Ser Tyr Asp Cys Ser
85 90 95

Arg Gly Asp Cys Phe Val Phe Gly Gly Gly Thr Glu Val Val Val Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 342
<211> 113
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 342

Gln Val Leu Thr Gln Thr Pro Ser Pro Val Ser Ala Ala Val Gly Ser
1 5 10 15

Thr Val Thr Ile Asn Cys Gln Ala Ser Gln Asn Val Tyr Asn Asn Asn
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Gln Leu
35 40 45

Ile Tyr Ser Thr Ser Thr Leu Ala Ser Gly Val Ser Ser Arg Phe Arg
50 55 60

Gly Ser Gly Ser Gly Thr Gln Phe Thr Leu Thr Ile Ser Asp Val Gln
65 70 75 80

Cys Asp Asp Ala Ala Thr Tyr Tyr Cys Leu Gly Ser Tyr Asp Cys Ser
85 90 95

Arg Gly Asp Cys Phe Val Phe Gly Gly Gly Thr Glu Val Val Val Lys
100 105 110

Arg

<210> 343
<211> 22
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 343

Gln Val Leu Thr Gln Thr Pro Ser Pro Val Ser Ala Ala Val Gly Ser
1 5 10 15

Thr Val Thr Ile Asn Cys
20

<210> 344
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 344

Gln Ala Ser Gln Asn Val Tyr Asn Asn Asn Tyr Leu Ala
1 5 10

<210> 345
<211> 15
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 345

Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Gln Leu Ile Tyr
1 5 10 15

<210> 346
<211> 7
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 346

Ser Thr Ser Thr Leu Ala Ser
1 5

<210> 347
<211> 32
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 347

Gly Val Ser Ser Arg Phe Arg Gly Ser Gly Ser Gly Thr Gln Phe Thr
1 5 10 15

Leu Thr Ile Ser Asp Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
20 25 30

<210> 348
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 348

Leu Gly Ser Tyr Asp Cys Ser Arg Gly Asp Cys Phe Val
1 5 10

<210> 349
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 349

Phe Gly Gly Gly Thr Glu Val Val Val Lys Arg
1 5 10

<210> 350
<211> 106
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 350

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1 5 10 15

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
20 25 30

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
35 40 45

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
50 55 60

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65 70 75 80

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
85 90 95

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> 351

<211> 660
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 351
caagtgctga cccagactcc atcccccgtg tctgcagctg tgggaagcac agtcaccatc
60

aattgccagg ccagtcagaa tgtttataat aacaactacc tagcctggta tcagcagaaa
120

ccagggcagc ctcccaagca actgatctat tctacgtcca ctctggcatc tggggtctca
180

tcgcgattca gaggcagtgg atctgggaca cagttcactc tcaccatcag cgacgtgcag
240

tgtgacgatg ctgccactta ctactgtcta ggcagttatg attgtagtcg tggtgattgt
300

tttgttttcg gcggagggac cgaggtggtg gtcaaacgta cggtggctgc accatctgtc
360

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg
420

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa
480

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc
540

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa
600

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgttag
660

<210> 352
<211> 339
<212> DNA

<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 352
caagtgctga cccagactcc atcccccgtg tctgcagctg tgggaagcac agtcaccatc
60

aattgccagg ccagtcagaa tgtttataat aacaactacc tagcctggta tcagcagaaa
120

ccagggcagc ctcccaagca actgatctat tctacgtcca ctctggcatc tggggtctca
180

tcgcgattca gaggcagtgg atctgggaca cagttcactc tcaccatcag cgacgtgcag
240

tgtgacgatg ctgccactta ctactgtcta ggcagttatg attgtagtcg tggtgattgt
300

tttgttttcg gcggagggac cgaggtggtg gtcaaacgt
339

<210> 353
<211> 66
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 353
caagtgctga cccagactcc atcccccgtg tctgcagctg tgggaagcac agtcaccatc
60

a a t t g c
66

<210> 354
<211> 39
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 354
caggccagtc agaatgttta taataacaac tacctagcc 39

<210> 355
<211> 45
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 355
tggtatcagc agaaaccagg gcagcctccc aagcaactga tctat 45

<210> 356
<211> 21
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 356
t c t a c g t c c a c t c t g g c a t c t 21

<210> 357
<211> 96
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 357
ggggtctcat cgcgattcag aggcagtgga tctgggacac agttcactct caccatcagc 60

gacgtgcagt gtgacgatgc tgccacttac tactgt
96

<210> 358
<211> 39
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 358
ctaggcagtt atgattgtag tcgtggtgat tgttttgtt
39

<210> 359
<211> 33
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 359
ttcggcggag ggaccgaggt ggtggtcaaa cgt
33

<210> 360
<211> 321
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 360
acggtggctg caccatctgt cttcatcttc ccgccatctg atgagcagtt gaaatctgga
60

actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg
120

aaggtggata acgccctcca atcgggtaac tcccaggaga gtgtcacaga gcaggacagc 180

aaggacagca cctacagcct cagcagcacc ctgacgctga gcaaagcaga ctacgagaaa 240

cacaaagtct acgcctgcga agtcacccat cagggcctga gctcgcccgt cacaaagagc 300

t t c a a c a g g g g a g a g t g t t a g 321

<210> 361
<211> 441
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 361

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Ile Gly Leu Ser Ser Tyr
20 25 30

Tyr Met Gln Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Val Ile Gly Ser Asp Gly Lys Thr Tyr Tyr Ala Thr Trp Ala Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Thr Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Thr

85 90 95

Arg Gly Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
100 105 110

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
115 120 125

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
130 135 140

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
145 150 155 160

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
165 170 175

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
180 185 190

Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg
195 200 205

Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
210 215 220

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
225 230 235 240

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
245 250 255

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
260 265 270

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
275 280 285

Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
290 295 300

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
305 310 315 320

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
325 330 335

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
340 345 350

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
355 360 365

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
370 375 380

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
385 390 395 400

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
405 410 415

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
420 425 430

Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440

<210> 362
<211> 111
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 362

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Ile Gly Leu Ser Ser Tyr
20 25 30

Tyr Met Gln Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Val Ile Gly Ser Asp Gly Lys Thr Tyr Tyr Ala Thr Trp Ala Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Thr Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Thr
85 90 95

Arg Gly Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105 110

<210> 363
<211> 30
<212> PRT
<213> Artificial

<220>

<223> Engineered antibody sequence

<400> 363

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Ile Gly Leu Ser
20 25 30

<210> 364
<211> 5
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 364

Ser Tyr Tyr Met Gln
1 5

<210> 365
<211> 14
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 365

Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Gly
1 5 10

<210> 366
<211> 16
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 366

Val Ile Gly Ser Asp Gly Lys Thr Tyr Tyr Ala Thr Trp Ala Lys Gly
1 5 10 15

<210> 367
<211> 32
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 367

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Thr Thr Val Tyr Leu Gln
1 5 10 15

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Thr Arg
20 25 30

<210> 368
<211> 3
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 368

Gly Asp Ile
1

<210> 369
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 369

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
1 5 10

<210> 370
<211> 330
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 370

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys

100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 371
<211> 1326
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 371
gaggtgcagc ttgtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc
60

tcctgtgcag tctctggaat cggcctcagt agctactaca tgcaatgggt ccgtcaggct
120

ccagggaagg ggctggagtg ggtcggagtc attggtagtg atggtaagac atactacgcg
180

acctgggcga aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt
240

caaatgaaca gcctgagagc tgaggacact gctgtgtatt tctgtaccag aggggacatc
300

tggggccaag ggaccctcgt caccgtctcg agcgcctcca ccaagggccc atcggtcttc
360

cccctggcac cctcctccaa gagcacctct gggggcacag cggccctggg ctgcctggtc
420

aaggactact tccccgaacc ggtgacggtg tcgtggaact caggcgccct gaccagcggc
480

gtgcacacct tcccggctgt cctacagtcc tcaggactct actccctcag cagcgtggtg
540

accgtgccct ccagcagctt gggcacccag acctacatct gcaacgtgaa tcacaagccc
600

agcaacacca aggtggacaa gagagttgag cccaaatctt gtgacaaaac tcacacatgc
660

ccaccgtgcc cagcacctga actcctgggg ggaccgtcag tcttcctctt ccccccaaaa
720

cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg
780

agccacgaag accctgaggt caagttcaac tggtacgtgg acggcgtgga ggtgcataat
840

gccaagacaa agccgcggga ggagcagtac gccagcacgt accgtgtggt cagcgtcctc
900

accgtcctgc accaggactg gctgaatggc aaggagtaca agtgcaaggt ctccaacaaa
960

gccctcccag cccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca
1020

caggtgtaca ccctgccccc atcccgggag gagatgacca agaaccaggt cagcctgacc
1080

tgcctggtca aaggcttcta tcccagcgac atcgccgtgg agtgggagag caatgggcag
1140

ccggagaaca actacaagac cacgcctccc gtgctggact ccgacggctc cttcttcctc
1200

tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc
1260

gtgatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt
1320

a a a t g a
1326

<210> 372
<211> 333
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 372
gaggtgcagc ttgtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc
60

tcctgtgcag tctctggaat cggcctcagt agctactaca tgcaatgggt ccgtcaggct
120

ccagggaagg ggctggagtg ggtcggagtc attggtagtg atggtaagac atactacgcg
180

acctgggcga aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt
240

caaatgaaca gcctgagagc tgaggacact gctgtgtatt tctgtaccag aggggacatc
300

tggggccaag ggaccctcgt caccgtctcg agc
333

<210> 373
<211> 90
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 373
gaggtgcagc ttgtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc
60

tcctgtgcag tctctggaat cggcctcagt
90

<210> 374
<211> 15
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 374
agctactaca tgcaa
15

<210> 375
<211> 42
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 375
tgggtccgtc aggctccagg gaaggggctg gagtgggtcg ga
42

<210> 376
<211> 48
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 376
gtcattggta gtgatggtaa gacatactac gcgacctggg cgaaaggc
48

<210> 377
<211> 96
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 377
cgattcacca tctccagaga caattccaag accacggtgt atcttcaaat gaacagcctg 60

agagctgagg acactgctgt gtatttctgt accaga 96

<210> 378
<211> 9
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 378
g g g g a c a t c 9

<210> 379
<211> 33
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 379
tggggccaag ggaccctcgt caccgtctcg agc 33

<210> 380
<211> 993
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 380
gcctccacca agggcccatc ggtcttcccc ctggcaccct cctccaagag cacctctggg
60

ggcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg
120

tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca
180

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacccagacc
240

tacatctgca acgtgaatca caagcccagc aacaccaagg tggacaagag agttgagccc
300

aaatcttgtg acaaaactca cacatgccca ccgtgcccag cacctgaact cctgggggga
360

ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggaccct
420

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg
480

tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacgcc
540

agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag
600

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc
660

aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggaggag
720

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc
780

gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg
840

ctggactccg acggctcctt cttcctctac agcaagctca ccgtggacaa gagcaggtgg
900

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg
960

c a g a a g a g c c t c t c c c t g t c t c c g g g t a a a t g a
993

<210> 381
<211> 219
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 381

Gln Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
1 5 10 15

Arg Val Thr Ile Asn Cys Gln Ala Ser Gln Asn Val Tyr Asn Asn Asn
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Gln Leu
35 40 45

Ile Tyr Ser Thr Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80

Pro Glu Asp Val Ala Thr Tyr Tyr Cys Leu Gly Ser Tyr Asp Cys Ser
85 90 95

Arg Gly Asp Cys Phe Val Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115   120   125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130   135   140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145   150   155   160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165   170   175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180   185   190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195   200   205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210   215

<210> 382
<211> 113
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 382

Gln Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
1   5   10   15

Arg Val Thr Ile Asn Cys Gln Ala Ser Gln Asn Val Tyr Asn Asn Asn
            20   25   30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Gln Leu
35 40 45

Ile Tyr Ser Thr Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80

Pro Glu Asp Val Ala Thr Tyr Tyr Cys Leu Gly Ser Tyr Asp Cys Ser
85 90 95

Arg Gly Asp Cys Phe Val Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

Arg

<210> 383
<211> 22
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 383

Gln Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
1 5 10 15

Arg Val Thr Ile Asn Cys
20

<210> 384

<211> 13
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 384

Gln Ala Ser Gln Asn Val Tyr Asn Asn Asn Tyr Leu Ala
1 5 10

<210> 385
<211> 15
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 385

Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Gln Leu Ile Tyr
1 5 10 15

<210> 386
<211> 7
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 386

Ser Thr Ser Thr Leu Ala Ser
1 5

<210> 387
<211> 32
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 387

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Val Ala Thr Tyr Tyr Cys
20 25 30

<210> 388
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 388

Leu Gly Ser Tyr Asp Cys Ser Arg Gly Asp Cys Phe Val
1 5 10

<210> 389
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 389

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
1 5 10

<210> 390
<211> 106
<212> PRT

<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 390

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1 5 10 15

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
20 25 30

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
35 40 45

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
50 55 60

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65 70 75 80

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
85 90 95

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> 391
<211> 660
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 391
caagtgctga cccagtctcc atcctccctg tctgcatctg taggagacag agtcaccatc
60

aattgccagg ccagtcagaa tgtttacaat aacaactacc tagcctggta tcagcagaaa 120

ccagggaaag ttcctaagca actgatctat tctacatcca ctctggcatc tggggtccca 180

tctcgtttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagcctgcag 240

cctgaagatg ttgcaactta ttactgtctg ggcagttatg attgtagtcg tggtgattgt 300

tttgttttcg gcggaggaac caaggtggaa atcaaacgta cggtggctgc accatctgtc 360

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 420

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 480

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 600

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgttag 660

<210> 392
<211> 339
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 392
caagtgctga cccagtctcc atcctccctg tctgcatctg taggagacag agtcaccatc 60

aattgccagg ccagtcagaa tgtttacaat aacaactacc tagcctggta tcagcagaaa 120

ccagggaaag ttcctaagca actgatctat tctacatcca ctctggcatc tggggtccca
180

tctcgtttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagcctgcag
240

cctgaagatg ttgcaactta ttactgtctg ggcagttatg attgtagtcg tggtgattgt
300

tttgttttcg gcggaggaac caaggtggaa atcaaacgt
339

<210> 393
<211> 66
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 393
caagtgctga cccagtctcc atcctccctg tctgcatctg taggagacag agtcaccatc
60

a a t t g c
66

<210> 394
<211> 39
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 394
caggccagtc agaatgttta caataacaac tacctagcc
39

<210> 395
<211> 45

<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 395
tggtatcagc agaaaccagg gaaagttcct aagcaactga tctat
45

<210> 396
<211> 21
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 396
t c t a c a t c c a c t c t g g c a t c t
21

<210> 397
<211> 96
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 397
ggggtcccat ctcgtttcag tggcagtgga tctgggacag atttcactct caccatcagc
60

agcctgcagc ctgaagatgt tgcaacttat tactgt
96

<210> 398
<211> 39
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 398
ctgggcagtt atgattgtag tcgtggtgat tgttttgtt 39

<210> 399
<211> 33
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 399
ttcggcggag gaaccaaggt ggaaatcaaa cgt 33

<210> 400
<211> 321
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 400
acggtggctg caccatctgt cttcatcttc ccgccatctg atgagcagtt gaaatctgga 60

actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg 120

aaggtggata acgccctcca atcgggtaac tcccaggaga gtgtcacaga gcaggacagc 180

aaggacagca cctacagcct cagcagcacc ctgacgctga gcaaagcaga ctacgagaaa 240

cacaaagtct acgcctgcga agtcacccat cagggcctga gctcgcccgt cacaaagagc 300

t t c a a c a g g g g a g a g t g t t a g
321

<210> 401
<211> 439
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 401

Gln Ser Leu Glu Glu Ser Gly Gly Arg Leu Val Thr Pro Gly Gly Ser
1 5 10 15

Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Val Thr Asn Tyr Tyr
20 25 30

Met Gln Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile Gly
35 40 45

Val Ile Gly Val Asn Gly Lys Arg Tyr Tyr Ala Ser Trp Ala Lys Gly
50 55 60

Arg Phe Thr Ile Ser Lys Thr Ser Ser Thr Thr Val Asp Leu Lys Met
65 70 75 80

Thr Ser Leu Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg Gly
85 90 95

Asp Ile Trp Gly Pro Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
100 105 110

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
115 120 125

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
130 135 140

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
145 150 155 160

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
165 170 175

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
180 185 190

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu
195 200 205

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
210 215 220

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
225 230 235 240

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
245 250 255

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
260 265 270

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
275 280 285

Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
290 295 300

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
305 310 315 320

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
325 330 335

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
340 345 350

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
355 360 365

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
370 375 380

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
385 390 395 400

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
405 410 415

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
420 425 430

Leu Ser Leu Ser Pro Gly Lys
435

<210> 402
<211> 109
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 402

Gln Ser Leu Glu Glu Ser Gly Gly Arg Leu Val Thr Pro Gly Gly Ser
1 5 10 15

Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Val Thr Asn Tyr Tyr
20 25 30

Met Gln Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile Gly
35 40 45

Val Ile Gly Val Asn Gly Lys Arg Tyr Tyr Ala Ser Trp Ala Lys Gly
50 55 60

Arg Phe Thr Ile Ser Lys Thr Ser Ser Thr Thr Val Asp Leu Lys Met
65 70 75 80

Thr Ser Leu Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg Gly
85 90 95

Asp Ile Trp Gly Pro Gly Thr Leu Val Thr Val Ser Ser
100 105

<210> 403
<211> 29
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 403

Gln Ser Leu Glu Glu Ser Gly Gly Arg Leu Val Thr Pro Gly Gly Ser
1 5 10 15

Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Val Thr
20 25

<210> 404
<211> 5
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 404

Asn Tyr Tyr Met Gln
1 5

<210> 405
<211> 14
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 405

Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile Gly
1 5 10

<210> 406
<211> 16
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 406

Val Ile Gly Val Asn Gly Lys Arg Tyr Tyr Ala Ser Trp Ala Lys Gly
1 5 10 15

<210> 407

<211> 31
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 407

Arg Phe Thr Ile Ser Lys Thr Ser Ser Thr Thr Val Asp Leu Lys Met
1 5 10 15

Thr Ser Leu Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg
20 25 30

<210> 408
<211> 3
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 408

Gly Asp Ile
1

<210> 409
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 409

Trp Gly Pro Gly Thr Leu Val Thr Val Ser Ser
1 5 10

<210> 410
<211> 330
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 410

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15


Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30


Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45


Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60


Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80


Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95


Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110


Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125


Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140
```

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 411
<211> 1320
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 411
cagtcgctgg aggagtccgg gggtcgcctg gtcacgcctg gaggatccct gacactcacc
60

tgcacagtct ctggaatcga cgtcactaac tactatatgc aatgggtccg ccaggctcca
120

gggaaggggc tggaatggat cggagtcatt ggtgtgaatg gtaagagata ctacgcgagc
180

tgggcgaaag gccgattcac catctccaaa acctcgtcga ccacggtgga tctgaaaatg
240

accagtctga caaccgagga cacggccacc tatttctgtg ccagaggcga catctggggc
300

ccggggaccc tcgtcaccgt ctcgagcgcc tccaccaagg gcccatcggt cttccccctg
360

gcaccctcct ccaagagcac ctctgggggc acagcggccc tgggctgcct ggtcaaggac
420

tacttccccg aaccggtgac ggtgtcgtgg aactcaggcg ccctgaccag cggcgtgcac
480

accttcccgg ctgtcctaca gtcctcagga ctctactccc tcagcagcgt ggtgaccgtg
540

ccctccagca gcttgggcac ccagacctac atctgcaacg tgaatcacaa gcccagcaac
600

accaaggtgg acaagagagt tgagcccaaa tcttgtgaca aaactcacac atgcccaccg
660

tgcccagcac ctgaactcct gggggggaccg tcagtcttcc tcttcccccc aaaacccaag 720

gacaccctca tgatctcccg gacccctgag gtcacatgcg tggtggtgga cgtgagccac 780

gaagaccctg aggtcaagtt caactggtac gtggacggcg tggaggtgca taatgccaag 840

acaaagccgc gggaggagca gtacgccagc acgtaccgtg tggtcagcgt cctcaccgtc 900

ctgcaccagg actggctgaa tggcaaggag tacaagtgca aggtctccaa caaagccctc 960

ccagccccca tcgagaaaac catctccaaa gccaaagggc agccccgaga accacaggtg 1020

tacaccctgc ccccatcccg ggaggagatg accaagaacc aggtcagcct gacctgcctg 1080

gtcaaaggct tctatcccag cgacatcgcc gtggagtggg agagcaatgg gcagccggag 1140

aacaactaca agaccacgcc tcccgtgctg gactccgacg gctccttctt cctctacagc 1200

aagctcaccg tggacaagag caggtggcag caggggaacg tcttctcatg ctccgtgatg 1260

catgaggctc tgcacaacca ctacacgcag aagagcctct ccctgtctcc gggtaaatga 1320

<210> 412
<211> 327
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 412
cagtcgctgg aggagtccgg gggtcgcctg gtcacgcctg gaggatccct gacactcacc 60

tgcacagtct ctggaatcga cgtcactaac tactatatgc aatgggtccg ccaggctcca 120

gggaaggggc tggaatggat cggagtcatt ggtgtgaatg gtaagagata ctacgcgagc 180

tgggcgaaag gccgattcac catctccaaa acctcgtcga ccacggtgga tctgaaaatg 240

accagtctga caaccgagga cacggccacc tatttctgtg ccagaggcga catctggggc 300

c c g g g g a c c c t c g t c a c c g t c t c g a g c 327

<210> 413
<211> 87
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 413
cagtcgctgg aggagtccgg gggtcgcctg gtcacgcctg gaggatccct gacactcacc 60

t g c a c a g t c t c t g g a a t c g a c g t c a c t 87

<210> 414
<211> 15
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 414
a a c t a c t a t a t g c a a 15

<210> 415
<211> 42
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 415
tgggtccgcc aggctccagg gaaggggctg gaatggatcg ga
42

<210> 416
<211> 48
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 416
gtcattggtg tgaatggtaa gagatactac gcgagctggg cgaaaggc
48

<210> 417
<211> 93
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 417
cgattcacca tctccaaaac ctcgtcgacc acggtggatc tgaaaatgac cagtctgaca
60

accgaggaca cggccaccta tttctgtgcc aga
93

<210> 418
<211> 9

<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 418
g g c g a c a t c
9

<210> 419
<211> 33
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 419
t g g g g c c c g g g g a c c c t c g t c a c c g t c t c g a g c
33

<210> 420
<211> 993
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 420
gcctccacca agggcccatc ggtcttcccc ctggcaccct cctccaagag cacctctggg
60

ggcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg
120

tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca
180

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacccagacc
240

tacatctgca acgtgaatca caagcccagc aacaccaagg tggacaagag agttgagccc
300

aaatcttgtg acaaaactca cacatgccca ccgtgcccag cacctgaact cctgggggga
360

ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct
420

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg
480

tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacgcc
540

agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag
600

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc
660

aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggaggag
720

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc
780

gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg
840

ctggactccg acggctcctt cttcctctac agcaagctca ccgtggacaa gagcaggtgg
900

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg
960

cagaagagcc tctccctgtc tccgggtaaa tga
993

<210> 421
<211> 219
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 421

Gln Val Leu Thr Gln Thr Ala Ser Pro Val Ser Pro Ala Val Gly Ser
1 5 10 15

Thr Val Thr Ile Asn Cys Arg Ala Ser Gln Ser Val Tyr Tyr Asn Asn
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Gln Leu
35 40 45

Ile Tyr Ser Thr Ser Thr Leu Ala Ser Gly Val Ser Ser Arg Phe Lys
50 55 60

Gly Ser Gly Ser Gly Thr Gln Phe Thr Leu Thr Ile Ser Asp Val Gln
65 70 75 80

Cys Asp Asp Ala Ala Thr Tyr Tyr Cys Leu Gly Ser Tyr Asp Cys Ser
85 90 95

Asn Gly Asp Cys Phe Val Phe Gly Gly Gly Thr Glu Val Val Val Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 422
<211> 113
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 422

Gln Val Leu Thr Gln Thr Ala Ser Pro Val Ser Pro Ala Val Gly Ser
1 5 10 15

Thr Val Thr Ile Asn Cys Arg Ala Ser Gln Ser Val Tyr Tyr Asn Asn
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Gln Leu
35 40 45

Ile Tyr Ser Thr Ser Thr Leu Ala Ser Gly Val Ser Ser Arg Phe Lys
50 55 60

Gly Ser Gly Ser Gly Thr Gln Phe Thr Leu Thr Ile Ser Asp Val Gln
65 70 75 80

Cys Asp Asp Ala Ala Thr Tyr Tyr Cys Leu Gly Ser Tyr Asp Cys Ser
85 90 95

Asn Gly Asp Cys Phe Val Phe Gly Gly Gly Thr Glu Val Val Val Lys
100 105 110

Arg

<210> 423
<211> 22
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 423

Gln Val Leu Thr Gln Thr Ala Ser Pro Val Ser Pro Ala Val Gly Ser
1 5 10 15

Thr Val Thr Ile Asn Cys
20

<210> 424
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 424

Arg Ala Ser Gln Ser Val Tyr Tyr Asn Asn Tyr Leu Ala
1 5 10

<210> 425
<211> 15
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 425

Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Gln Leu Ile Tyr
1 5 10 15

<210> 426
<211> 7
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 426

Ser Thr Ser Thr Leu Ala Ser
1 5

<210> 427
<211> 32
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 427

Gly Val Ser Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Thr
1 5 10 15

Leu Thr Ile Ser Asp Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
20 25 30

<210> 428
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 428

Leu Gly Ser Tyr Asp Cys Ser Asn Gly Asp Cys Phe Val
1 5 10

<210> 429
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 429

Phe Gly Gly Gly Thr Glu Val Val Val Lys Arg
1 5 10

<210> 430
<211> 106
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 430

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1 5 10 15

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
20 25 30

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
35 40 45

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
50 55 60

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65 70 75 80

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
85 90 95

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> 431
<211> 660
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 431
caggtgctga cccagactgc atcccccgtg tctccagctg tgggaagcac agtcaccatc 60

aattgccggg ccagtcagag tgtttattat aacaactacc tagcctggta tcagcagaaa 120

ccagggcagc ctcccaagca actgatctat tctacatcca ctctggcatc tggggtctca 180

tcgcggttca aaggcagtgg atctgggaca cagttcactc tcaccatcag cgacgtgcag 240

tgtgacgatg ctgccactta ctactgtcta ggcagttatg attgtagtaa tggtgattgt 300

tttgttttcg gcggagggac cgaggtggtg gtcaaacgta cggtggctgc accatctgtc 360

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 420

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 480

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 600

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgttag 660

<210> 432
<211> 339
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 432
caggtgctga cccagactgc atcccccgtg tctccagctg tgggaagcac agtcaccatc 60

aattgccggg ccagtcagag tgtttattat aacaactacc tagcctggta tcagcagaaa 120

ccagggcagc ctcccaagca actgatctat tctacatcca ctctggcatc tggggtctca 180

tcgcggttca aaggcagtgg atctgggaca cagttcactc tcaccatcag cgacgtgcag 240

tgtgacgatg ctgccactta ctactgtcta ggcagttatg attgtagtaa tggtgattgt 300

tttgttttcg gcggagggac cgaggtggtg gtcaaacgt 339

<210> 433
<211> 66
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 433
caggtgctga cccagactgc atcccccgtg tctccagctg tgggaagcac agtcaccatc 60

a a t t g c 66

<210> 434
<211> 39
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 434
cgggccagtc agagtgttta ttataacaac tacctagcc 39

<210> 435
<211> 45
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 435
tggtatcagc agaaaccagg gcagcctccc aagcaactga tctat 45

<210> 436

<211> 21
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 436
t c t a c a t c c a c t c t g g c a t c t
21

<210> 437
<211> 96
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 437
ggggtctcat cgcggttcaa aggcagtgga tctgggacac agttcactct caccatcagc
60

gacgtgcagt gtgacgatgc tgccacttac tactgt
96

<210> 438
<211> 39
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 438
ctaggcagtt atgattgtag taatggtgat tgttttgtt
39

<210> 439
<211> 33
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 439
ttcggcggag ggaccgaggt ggtggtcaaa cgt
33

<210> 440
<211> 321
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 440
acggtggctg caccatctgt cttcatcttc ccgccatctg atgagcagtt gaaatctgga
60

actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg
120

aaggtggata acgccctcca atcgggtaac tcccaggaga gtgtcacaga gcaggacagc
180

aaggacagca cctacagcct cagcagcacc ctgacgctga gcaaagcaga ctacgagaaa
240

cacaaagtct acgcctgcga agtcacccat cagggcctga gctcgcccgt cacaaagagc
300

ttcaacaggg gagagtgtta g
321

<210> 441
<211> 441
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 441

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Ile Asp Val Thr Asn Tyr
20 25 30

Tyr Met Gln Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Val Ile Gly Val Asn Gly Lys Arg Tyr Tyr Ala Ser Trp Ala Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Thr Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala
85 90 95

Arg Gly Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
100 105 110

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
115 120 125

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
130 135 140

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
145 150 155 160

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
165 170 175

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
180 185 190

Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg
195 200 205

Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
210 215 220

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
225 230 235 240

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
245 250 255

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
260 265 270

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
275 280 285

Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
290 295 300

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
305 310 315 320

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
325 330 335

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
340 345 350

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
355 360 365

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
370 375 380

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
385 390 395 400

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
405 410 415

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
420 425 430

Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440

<210> 442
<211> 111
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 442

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Ile Asp Val Thr Asn Tyr
20 25 30

Tyr Met Gln Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Val Ile Gly Val Asn Gly Lys Arg Tyr Tyr Ala Ser Trp Ala Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Thr Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala
85 90 95

Arg Gly Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105 110

<210> 443
<211> 30
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 443

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Ile Asp Val Thr
20 25 30

<210> 444
<211> 5
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 444

Asn Tyr Tyr Met Gln
1 5

<210> 445
<211> 14
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 445

Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Gly
1 5 10

<210> 446
<211> 16
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 446

Val Ile Gly Val Asn Gly Lys Arg Tyr Tyr Ala Ser Trp Ala Lys Gly
1 5 10 15

<210> 447
<211> 32
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 447

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Thr Thr Val Tyr Leu Gln
1 5 10 15

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala Arg
            20   25   30

<210> 448
<211> 3
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 448

Gly Asp Ile
1

<210> 449
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 449

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
1   5   10

<210> 450
<211> 330
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 450

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1   5   10   15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 451
<211> 1326
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 451
gaggtgcagc ttgtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc
60

tcctgtgcag tctctggaat cgacgtcact aactactaca tgcaatgggt ccgtcaggct
120

ccagggaagg ggctggagtg ggtcggagtc attggtgtga atggtaagag atactacgcg
180

agctgggcga aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt
240

caaatgaaca gcctgagagc tgaggacact gctgtgtatt tctgtgccag aggggacatc
300

tggggccaag ggaccctcgt caccgtctcg agcgcctcca ccaagggccc atcggtcttc
360

cccctggcac cctcctccaa gagcacctct gggggcacag cggccctggg ctgcctggtc
420

aaggactact tccccgaacc ggtgacggtg tcgtggaact caggcgccct gaccagcggc
480

gtgcacacct tcccggctgt cctacagtcc tcaggactct actccctcag cagcgtggtg
540

accgtgccct ccagcagctt gggcacccag acctacatct gcaacgtgaa tcacaagccc
600

agcaacacca aggtggacaa gagagttgag cccaaatctt gtgacaaaac tcacacatgc
660

ccaccgtgcc cagcacctga actcctgggg ggaccgtcag tcttcctctt ccccccaaaa
720

cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg
780

agccacgaag accctgaggt caagttcaac tggtacgtgg acggcgtgga ggtgcataat
840

gccaagacaa agccgcggga ggagcagtac gccagcacgt accgtgtggt cagcgtcctc
900

accgtcctgc accaggactg gctgaatggc aaggagtaca agtgcaaggt ctccaacaaa
960

gccctcccag cccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca
1020

caggtgtaca ccctgccccc atcccgggag gagatgacca agaaccaggt cagcctgacc
1080

tgcctggtca aaggcttcta tcccagcgac atcgccgtgg agtgggagag caatgggcag
1140

ccggagaaca actacaagac cacgcctccc gtgctggact ccgacggctc cttcttcctc
1200

tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc
1260

gtgatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt
1320

a a a t g a
1326

<210> 452
<211> 333
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 452
gaggtgcagc ttgtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc
60

tcctgtgcag tctctggaat cgacgtcact aactactaca tgcaatgggt ccgtcaggct
120

ccagggaagg ggctggagtg ggtcggagtc attggtgtga atggtaagag atactacgcg
180

agctgggcga aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt
240

caaatgaaca gcctgagagc tgaggacact gctgtgtatt tctgtgccag aggggacatc 300

tggggccaag ggaccctcgt caccgtctcg agc 333

<210> 453
<211> 90
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 453
gaggtgcagc ttgtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc 60

tcctgtgcag tctctggaat cgacgtcact 90

<210> 454
<211> 15
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 454
aactactaca tgcaa 15

<210> 455
<211> 42
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 455
tgggtccgtc aggctccagg gaaggggctg gagtgggtcg ga
42

<210> 456
<211> 48
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 456
gtcattggtg tgaatggtaa gagatactac gcgagctggg cgaaaggc
48

<210> 457
<211> 96
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 457
cgattcacca tctccagaga caattccaag accacggtgt atcttcaaat gaacagcctg
60

agagctgagg acactgctgt gtatttctgt gccaga
96

<210> 458
<211> 9
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 458
g g g g a c a t c
9

<210> 459
<211> 33
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 459
tggggccaag ggaccctcgt caccgtctcg agc
33

<210> 460
<211> 993
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 460
gcctccacca agggcccatc ggtcttcccc ctggcaccct cctccaagag cacctctggg
60

ggcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg
120

tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca
180

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacccagacc
240

tacatctgca acgtgaatca caagcccagc aacaccaagg tggacaagag agttgagccc
300

aaatcttgtg acaaaactca cacatgccca ccgtgcccag cacctgaact cctgggggga
360

ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggaccccct
420

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg
480

tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacgcc
540

agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag
600

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc
660

aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggaggag
720

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc
780

gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg
840

ctggactccg acggctcctt cttcctctac agcaagctca ccgtggacaa gagcaggtgg
900

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg
960

cagaagagcc tctccctgtc tccgggtaaa tga
993

<210> 461
<211> 219
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 461

Gln Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
1 5 10 15

Arg Val Thr Ile Asn Cys Arg Ala Ser Gln Ser Val Tyr Tyr Asn Asn
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Gln Leu
35 40 45

Ile Tyr Ser Thr Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80

Pro Glu Asp Val Ala Thr Tyr Tyr Cys Leu Gly Ser Tyr Asp Cys Ser
85 90 95

Asn Gly Asp Cys Phe Val Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser

195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 462
<211> 113
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 462

Gln Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
1 5 10 15

Arg Val Thr Ile Asn Cys Arg Ala Ser Gln Ser Val Tyr Tyr Asn Asn
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Gln Leu
35 40 45

Ile Tyr Ser Thr Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80

Pro Glu Asp Val Ala Thr Tyr Tyr Cys Leu Gly Ser Tyr Asp Cys Ser
85 90 95

Asn Gly Asp Cys Phe Val Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

Arg

<210> 463
<211> 22
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 463

Gln Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
1 5 10 15

Arg Val Thr Ile Asn Cys
20

<210> 464
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 464

Arg Ala Ser Gln Ser Val Tyr Tyr Asn Asn Tyr Leu Ala
1 5 10

<210> 465
<211> 15
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 465

Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Gln Leu Ile Tyr
1 5 10 15

<210> 466
<211> 7
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 466

Ser Thr Ser Thr Leu Ala Ser
1 5

<210> 467
<211> 32
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 467

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Val Ala Thr Tyr Tyr Cys
20 25 30

<210> 468
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 468

Leu Gly Ser Tyr Asp Cys Ser Asn Gly Asp Cys Phe Val
1 5 10

<210> 469
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 469

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
1 5 10

<210> 470
<211> 106
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 470

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1 5 10 15

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
20 25 30

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
35 40 45

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
50 55 60

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65 70 75 80

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
85 90 95

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> 471
<211> 660
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 471
caagtgctga cccagtctcc atcctccctg tctgcatctg taggagacag agtcaccatc 60

aattgccggg ccagtcagag tgtttactat aacaactacc tagcctggta tcagcagaaa 120

ccagggaaag ttcctaagca actgatctat tctacatcca ctctggcatc tggggtccca 180

tctcgtttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagcctgcag 240

cctgaagatg ttgcaactta ttactgtctg ggcagttatg attgtagtaa tggtgattgt 300

tttgttttcg gcggaggaac caaggtggaa atcaaacgta cggtggctgc accatctgtc 360

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 420

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 480

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 600

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgttag 660

<210> 472
<211> 339
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 472
caagtgctga cccagtctcc atcctccctg tctgcatctg taggagacag agtcaccatc 60

aattgccggg ccagtcagag tgtttactat aacaactacc tagcctggta tcagcagaaa 120

ccagggaaag ttcctaagca actgatctat tctacatcca ctctggcatc tggggtccca 180

tctcgtttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagcctgcag 240

cctgaagatg ttgcaactta ttactgtctg ggcagttatg attgtagtaa tggtgattgt 300

tttgttttcg gcggaggaac caaggtggaa atcaaacgt 339

<210> 473
<211> 66
<212> DNA
<213> Artificial

<220>

<223> Engineered antibody sequence

<400> 473
caagtgctga cccagtctcc atcctccctg tctgcatctg taggagacag agtcaccatc
60

a a t t g c
66

<210> 474
<211> 39
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 474
cgggccagtc agagtgttta ctataacaac tacctagcc
39

<210> 475
<211> 45
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 475
tggtatcagc agaaaccagg gaaagttcct aagcaactga tctat
45

<210> 476
<211> 21
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 476

t c t a c a t c c a c t c t g g c a t c t
21

<210> 477
<211> 96
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 477
ggggtcccat ctcgtttcag tggcagtgga tctgggacag atttcactct caccatcagc
60

a g c c t g c a g c c t g a a g a t g t t g c a a c t t a t t a c t g t
96

<210> 478
<211> 39
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 478
c t g g g c a g t t a t g a t t g t a g t a a t g g t g a t t g t t t t g t t
39

<210> 479
<211> 33
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 479
t t c g g c g g a g g a a c c a a g g t g g a a a t c a a a c g t
33

<210> 480
<211> 321
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 480
acggtggctg caccatctgt cttcatcttc ccgccatctg atgagcagtt gaaatctgga
60

actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg
120

aaggtggata acgccctcca atcgggtaac tcccaggaga gtgtcacaga gcaggacagc
180

aaggacagca cctacagcct cagcagcacc ctgacgctga gcaaagcaga ctacgagaaa
240

cacaaagtct acgcctgcga agtcacccat cagggcctga gctcgcccgt cacaaagagc
300

t t c a a c a g g g g a g a g t g t t a g
321

<210> 481
<211> 441
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 481

Gln Ser Val Glu Glu Ser Gly Gly Gly Leu Val Gln Pro Glu Gly Ser
1 5 10 15

Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Asp Phe Ser Ser Asn Ala
20 25 30

Met Trp Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile Gly
35 40 45

Cys Ile Tyr Asn Gly Asp Gly Ser Thr Tyr Tyr Ala Ser Trp Val Asn
50 55 60

Gly Arg Phe Ser Ile Ser Lys Thr Ser Ser Thr Thr Val Thr Leu Gln
65 70 75 80

Leu Asn Ser Leu Thr Val Ala Asp Thr Ala Thr Tyr Tyr Cys Ala Arg
85 90 95

Asp Leu Asp Leu Trp Gly Pro Gly Thr Leu Val Thr Val Ser Ser Ala
100 105 110

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
115 120 125

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
130 135 140

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
145 150 155 160

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
165 170 175

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
180 185 190

Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg
195 200 205

Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
210 215 220

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
225 230 235 240

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
245 250 255

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
260 265 270

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
275 280 285

Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
290 295 300

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
305 310 315 320

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
325 330 335

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
340 345 350

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
355 360 365

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
370 375 380

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
385 390 395 400

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
405 410 415

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
420 425 430

Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440

<210> 482
<211> 111
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 482

Gln Ser Val Glu Glu Ser Gly Gly Gly Leu Val Gln Pro Glu Gly Ser
1 5 10 15

Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Asp Phe Ser Ser Asn Ala
20 25 30

Met Trp Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile Gly
35 40 45

Cys Ile Tyr Asn Gly Asp Gly Ser Thr Tyr Tyr Ala Ser Trp Val Asn
50 55 60

Gly Arg Phe Ser Ile Ser Lys Thr Ser Ser Thr Thr Val Thr Leu Gln
65 70 75 80

Leu Asn Ser Leu Thr Val Ala Asp Thr Ala Thr Tyr Tyr Cys Ala Arg
85 90 95

Asp Leu Asp Leu Trp Gly Pro Gly Thr Leu Val Thr Val Ser Ser
100 105 110

<210> 483
<211> 29
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 483

Gln Ser Val Glu Glu Ser Gly Gly Gly Leu Val Gln Pro Glu Gly Ser
1 5 10 15

Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Asp Phe Ser
20 25

<210> 484
<211> 5
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 484

Ser Asn Ala Met Trp
1 5

<210> 485
<211> 14
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 485

Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile Gly
1 5 10

<210> 486
<211> 17
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 486

Cys Ile Tyr Asn Gly Asp Gly Ser Thr Tyr Tyr Ala Ser Trp Val Asn
1 5 10 15

Gly

<210> 487
<211> 31
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 487

Arg Phe Ser Ile Ser Lys Thr Ser Ser Thr Thr Val Thr Leu Gln Leu
1 5 10 15

Asn Ser Leu Thr Val Ala Asp Thr Ala Thr Tyr Tyr Cys Ala Arg
20 25 30

<210> 488
<211> 4
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 488

Asp Leu Asp Leu
1

<210> 489
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 489

Trp Gly Pro Gly Thr Leu Val Thr Val Ser Ser
1 5 10

<210> 490
<211> 330
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 490

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 491
<211> 1326
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 491
cagtcggtgg aggagtccgg gggaggcctg gtccagcctg agggatccct gacactcacc
60

tgcacagcct ctggattcga cttcagtagc aatgcaatgt ggtgggtccg ccaggctcca
120

gggaaggggc tggagtggat cggatgcatt tacaatggtg atggcagcac atactacgcg
180

agctgggtga atggccgatt ctccatctcc aaaacctcgt cgaccacggt gactctgcaa
240

ctgaatagtc tgacagtcgc ggacacggcc acgtattatt gtgcgagaga tcttgacttg
300

tggggcccgg gcaccctcgt caccgtctcg agcgcctcca ccaagggccc atcggtcttc
360

cccctggcac cctcctccaa gagcacctct gggggcacag cggccctggg ctgcctggtc
420

aaggactact tccccgaacc ggtgacggtg tcgtggaact caggcgccct gaccagcggc
480

gtgcacacct tcccggctgt cctacagtcc tcaggactct actccctcag cagcgtggtg
540

accgtgccct ccagcagctt gggcacccag acctacatct gcaacgtgaa tcacaagccc
600

agcaacacca aggtggacaa gagagttgag cccaaatctt gtgacaaaac tcacacatgc
660

ccaccgtgcc cagcacctga actcctgggg ggaccgtcag tcttcctctt ccccccaaaa
720

cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg
780

agccacgaag accctgaggt caagttcaac tggtacgtgg acggcgtgga ggtgcataat
840

gccaagacaa agccgcggga ggagcagtac gccagcacgt accgtgtggt cagcgtcctc
900

accgtcctgc accaggactg gctgaatggc aaggagtaca agtgcaaggt ctccaacaaa
960

gccctcccag cccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca
1020

caggtgtaca ccctgccccc atcccgggag gagatgacca agaaccaggt cagcctgacc
1080

tgcctggtca aaggcttcta tcccagcgac atcgccgtgg agtgggagag caatgggcag
1140

ccggagaaca actacaagac cacgcctccc gtgctggact ccgacggctc cttcttcctc
1200

tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc
1260

gtgatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt
1320

a a a t g a
1326

<210> 492
<211> 333
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 492
cagtcggtgg aggagtccgg gggaggcctg gtccagcctg agggatccct gacactcacc
60

tgcacagcct ctggattcga cttcagtagc aatgcaatgt ggtgggtccg ccaggctcca
120

gggaaggggc tggagtggat cggatgcatt tacaatggtg atggcagcac atactacgcg
180

agctgggtga atggccgatt ctccatctcc aaaacctcgt cgaccacggt gactctgcaa
240

ctgaatagtc tgacagtcgc ggacacggcc acgtattatt gtgcgagaga tcttgacttg
300

tggggcccgg gcaccctcgt caccgtctcg agc
333

<210> 493
<211> 87
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 493
cagtcggtgg aggagtccgg gggaggcctg gtccagcctg agggatccct gacactcacc
60

tgcacagcct ctggattcga cttcagt
87

<210> 494
<211> 15
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 494
agcaatgcaa tgtgg
15

<210> 495
<211> 42
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 495
tgggtccgcc aggctccagg gaaggggctg gagtggatcg ga
42

<210> 496
<211> 51
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 496
tgcatttaca atggtgatgg cagcacatac tacgcgagct gggtgaatgg c
51

<210> 497
<211> 93
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 497
cgattctcca tctccaaaac ctcgtcgacc acggtgactc tgcaactgaa tagtctgaca
60

gtcgcggaca cggccacgta ttattgtgcg aga
93

<210> 498
<211> 12
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 498
gatcttgact g
12

<210> 499

<211> 33
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 499
tggggcccgg gcaccctcgt caccgtctcg agc
33

<210> 500
<211> 993
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 500
gcctccacca agggcccatc ggtcttcccc ctggcaccct cctccaagag cacctctggg
60

ggcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg
120

tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca
180

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacccagacc
240

tacatctgca acgtgaatca caagcccagc aacaccaagg tggacaagag agttgagccc
300

aaatcttgtg acaaaactca cacatgccca ccgtgcccag cacctgaact cctgggggga
360

ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggaccct
420

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg
480

tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacgcc
540

agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag
600

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc
660

aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggaggag
720

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc
780

gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg
840

ctggactccg acggctcctt cttcctctac agcaagctca ccgtggacaa gagcaggtgg
900

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg
960

c a g a a g a g c c t c t c c c t g t c t c c g g g t a a a t g a
993

<210> 501
<211> 219
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 501

Ala Ile Val Met Thr Gln Thr Pro Ser Ser Lys Ser Val Pro Val Gly
1 5 10 15

Asp Thr Val Thr Ile Asn Cys Gln Ala Ser Glu Ser Leu Tyr Asn Asn
20 25 30

Asn Ala Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro Lys Arg
35 40 45

Leu Ile Tyr Asp Ala Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe
50 55 60

Ser Gly Gly Gly Ser Gly Thr Gln Phe Thr Leu Thr Ile Ser Gly Val
65 70 75 80

Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys Gly Gly Tyr Arg Ser Asp
85 90 95

Ser Val Asp Gly Val Ala Phe Ala Gly Gly Thr Glu Val Val Val Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 502
<211> 113
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 502

Ala Ile Val Met Thr Gln Thr Pro Ser Ser Lys Ser Val Pro Val Gly
1 5 10 15

Asp Thr Val Thr Ile Asn Cys Gln Ala Ser Glu Ser Leu Tyr Asn Asn
20 25 30

Asn Ala Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro Lys Arg
35 40 45

Leu Ile Tyr Asp Ala Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe
50 55 60

Ser Gly Gly Gly Ser Gly Thr Gln Phe Thr Leu Thr Ile Ser Gly Val
65 70 75 80

Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys Gly Gly Tyr Arg Ser Asp
85 90 95

Ser Val Asp Gly Val Ala Phe Ala Gly Gly Thr Glu Val Val Val Lys
100 105 110

Arg

<210> 503
<211> 23
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 503

Ala Ile Val Met Thr Gln Thr Pro Ser Ser Lys Ser Val Pro Val Gly
1 5 10 15

Asp Thr Val Thr Ile Asn Cys
20

<210> 504
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 504

Gln Ala Ser Glu Ser Leu Tyr Asn Asn Asn Ala Leu Ala
1 5 10

<210> 505
<211> 15
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 505

Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro Lys Arg Leu Ile Tyr
1 5 10 15

<210> 506
<211> 7
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 506

Asp Ala Ser Lys Leu Ala Ser
1 5

<210> 507
<211> 32
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 507

Gly Val Pro Ser Arg Phe Ser Gly Gly Gly Ser Gly Thr Gln Phe Thr
1 5 10 15

Leu Thr Ile Ser Gly Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
20 25 30

<210> 508
<211> 12
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 508

Gly Gly Tyr Arg Ser Asp Ser Val Asp Gly Val Ala

1 5 10

<210> 509
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 509

Phe Ala Gly Gly Thr Glu Val Val Val Lys Arg
1 5 10

<210> 510
<211> 106
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 510

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1 5 10 15

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
20 25 30

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
35 40 45

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
50 55 60

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65 70 75 80

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
85 90 95

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> 511
<211> 660
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 511
gccatcgtga tgacccagac tccatcttcc aagtctgtcc ctgtgggaga cacagtcacc 60

atcaattgcc aggccagtga gagtctttat aataacaacg ccttggcctg gtttcagcag 120

aaaccagggc agcctcccaa gcgcctgatc tatgatgcat ccaaactggc atctggggtc 180

ccatcgcggt tcagtggcgg tgggtctggg acacagttca ctctcaccat cagtggcgtg 240

cagtgtgacg atgctgccac ttactactgt ggaggctaca gaagtgatag tgttgatggt 300

gttgctttcg ccggagggac cgaggtggtg gtcaaacgta cggtggctgc accatctgtc 360

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 420

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 480

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 600

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgttag 660

<210> 512
<211> 339
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 512
gccatcgtga tgacccagac tccatcttcc aagtctgtcc ctgtgggaga cacagtcacc 60

atcaattgcc aggccagtga gagtctttat aataacaacg ccttggcctg gtttcagcag 120

aaaccagggc agcctcccaa gcgcctgatc tatgatgcat ccaaactggc atctggggtc 180

ccatcgcggt tcagtggcgg tgggtctggg acacagttca ctctcaccat cagtggcgtg 240

cagtgtgacg atgctgccac ttactactgt ggaggctaca gaagtgatag tgttgatggt 300

gttgctttcg ccggagggac cgaggtggtg gtcaaacgt 339

<210> 513
<211> 69
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 513

gccatcgtga tgacccagac tccatcttcc aagtctgtcc ctgtgggaga cacagtcacc
60

a t c a a t t g c
69

<210> 514
<211> 39
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 514
caggccagtg agagtcttta taataacaac gccttggcc
39

<210> 515
<211> 45
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 515
tggtttcagc agaaaccagg gcagcctccc aagcgcctga tctat
45

<210> 516
<211> 21
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 516
g a t g c a t c c a a a c t g g c a t c t
21

<210> 517
<211> 96
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 517
ggggtcccat cgcggttcag tggcggtggg tctgggacac agttcactct caccatcagt 60

ggcgtgcagt gtgacgatgc tgccacttac tactgt 96

<210> 518
<211> 36
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 518
ggaggctaca gaagtgatag tgttgatggt gttgct 36

<210> 519
<211> 33
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 519
ttcgccggag ggaccgaggt ggtggtcaaa cgt 33

<210> 520
<211> 321

<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 520
acggtggctg caccatctgt cttcatcttc ccgccatctg atgagcagtt gaaatctgga
60

actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg
120

aaggtggata acgccctcca atcgggtaac tcccaggaga gtgtcacaga gcaggacagc
180

aaggacagca cctacagcct cagcagcacc ctgacgctga gcaaagcaga ctacgagaaa
240

cacaaagtct acgcctgcga agtcacccat cagggcctga gctcgcccgt cacaaagagc
300

t t c a a c a g g g g a g a g t g t t a g
321

<210> 521
<211> 441
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 521

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Ile Gly Leu Ser Ser Tyr
20 25 30

Tyr Met Gln Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

35 40 45

Gly Val Ile Gly Ser Asp Gly Lys Thr Tyr Tyr Ala Thr Trp Ala Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Thr Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Thr
85 90 95

Arg Gly Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
100 105 110

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
115 120 125

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
130 135 140

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
145 150 155 160

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
165 170 175

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
180 185 190

Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Ala Arg
195 200 205

Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
210 215 220

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
225 230 235 240

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
245 250 255

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
260 265 270

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
275 280 285

Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
290 295 300

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
305 310 315 320

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
325 330 335

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
340 345 350

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
355 360 365

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
370 375 380

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
385 390 395 400

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
405 410 415

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
420 425 430

Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440

<210> 522
<211> 111
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 522

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Ile Gly Leu Ser Ser Tyr
20 25 30

Tyr Met Gln Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Val Ile Gly Ser Asp Gly Lys Thr Tyr Tyr Ala Thr Trp Ala Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Thr Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Thr
85 90 95

Arg Gly Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105 110

<210> 523
<211> 30
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 523

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Ile Gly Leu Ser
20 25 30

<210> 524
<211> 5
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 524

Ser Tyr Tyr Met Gln
1 5

<210> 525
<211> 14
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 525

Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Gly
1 5 10

<210> 526
<211> 16
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 526

Val Ile Gly Ser Asp Gly Lys Thr Tyr Tyr Ala Thr Trp Ala Lys Gly
1 5 10 15

<210> 527
<211> 32
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 527

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Thr Thr Val Tyr Leu Gln
1 5 10 15

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Thr Arg
20 25 30

<210> 528
<211> 3
<212> PRT
<213> Artificial

<220>

<223> Engineered antibody sequence

<400> 528

Gly Asp Ile
1

<210> 529
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 529

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
1 5 10

<210> 530
<211> 330
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 530

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser

```
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Ala
                85                  90                  95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240
```

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 531
<211> 1326
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 531
gaggtgcagc ttgtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc
60

tcctgtgcag tctctggaat cggcctcagt agctactaca tgcaatgggt ccgtcaggct
120

ccagggaagg ggctggagtg ggtcggagtc attggtagtg atggtaagac atactacgcg
180

acctgggcga aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt
240

caaatgaaca gcctgagagc tgaggacact gctgtgtatt tctgtaccag aggggacatc
300

tggggccaag ggaccctcgt caccgtctcg agcgcctcca ccaagggccc atcggtcttc
360

cccctggcac cctcctccaa gagcacctct gggggcacag cggccctggg ctgcctggtc
420

aaggactact tccccgaacc ggtgacggtg tcgtggaact caggcgccct gaccagcggc
480

gtgcacacct tcccggctgt cctacagtcc tcaggactct actccctcag cagcgtggtg
540

accgtgccct ccagcagctt gggcacccag acctacatct gcaacgtgaa tcacaagccc
600

agcaacacca aggtggacgc gagagttgag cccaaatctt gtgacaaaac tcacacatgc
660

ccaccgtgcc cagcacctga actcctgggg ggaccgtcag tcttcctctt ccccccaaaa
720

cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg
780

agccacgaag accctgaggt caagttcaac tggtacgtgg acggcgtgga ggtgcataat
840

gccaagacaa agccgcggga ggagcagtac gccagcacgt accgtgtggt cagcgtcctc
900

accgtcctgc accaggactg gctgaatggc aaggagtaca agtgcaaggt ctccaacaaa
960

gccctcccag cccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca
1020

caggtgtaca ccctgccccc atcccgggag gagatgacca agaaccaggt cagcctgacc
1080

tgcctggtca aaggcttcta tcccagcgac atcgccgtgg agtgggagag caatgggcag
1140

ccggagaaca actacaagac cacgcctccc gtgctggact ccgacggctc cttcttcctc
1200

tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc
1260

gtgatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt
1320

a a a t g a
1326

<210> 532
<211> 333
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 532
gaggtgcagc ttgtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc
60

tcctgtgcag tctctggaat cggcctcagt agctactaca tgcaatgggt ccgtcaggct
120

ccagggaagg ggctggagtg ggtcggagtc attggtagtg atggtaagac atactacgcg
180

acctgggcga aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt
240

caaatgaaca gcctgagagc tgaggacact gctgtgtatt tctgtaccag aggggacatc
300

t g g g g c c a a g g g a c c c t c g t c a c c g t c t c g a g c
333

<210> 533
<211> 90
<212> DNA

<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 533
gaggtgcagc ttgtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc
60

t c c t g t g c a g t c t c t g g a a t c g g c c t c a g t
90

<210> 534
<211> 15
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 534
a g c t a c t a c a t g c a a
15

<210> 535
<211> 42
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 535
tgggtccgtc aggctccagg gaaggggctg gagtgggtcg ga
42

<210> 536
<211> 48
<212> DNA
<213> Artificial

<220>

<223> Engineered antibody sequence

<400> 536
gtcattggta gtgatggtaa gacatactac gcgacctggg cgaaaggc 48

<210> 537
<211> 96
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 537
cgattcacca tctccagaga caattccaag accacggtgt atcttcaaat gaacagcctg 60

agagctgagg acactgctgt gtatttctgt accaga 96

<210> 538
<211> 9
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 538
g g g g a c a t c 9

<210> 539
<211> 33
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 539

tggggccaag ggaccctcgt caccgtctcg agc
33

<210> 540
<211> 993
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 540
gcctccacca agggcccatc ggtcttcccc ctggcaccct cctccaagag cacctctggg
60

ggcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg
120

tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca
180

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacccagacc
240

tacatctgca acgtgaatca caagcccagc aacaccaagg tggacgcgag agttgagccc
300

aaatcttgtg acaaaactca cacatgccca ccgtgcccag cacctgaact cctgggggga
360

ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggaccct
420

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg
480

tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacgcc
540

agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag
600

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc
660

aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggaggag 720

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc 780

gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg 840

ctggactccg acggctcctt cttcctctac agcaagctca ccgtggacaa gagcaggtgg 900

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg 960

c a g a a g a g c c t c t c c c t g t c t c c g g g t a a a t g a 993

<210> 541
<211> 219
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 541

Gln Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
1 5 10 15

Arg Val Thr Ile Asn Cys Gln Ala Ser Gln Asn Val Tyr Asn Asn Asn
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Gln Leu
35 40 45

Ile Tyr Ser Thr Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80

Pro Glu Asp Val Ala Thr Tyr Tyr Cys Leu Gly Ser Tyr Asp Cys Ser
85 90 95

Arg Gly Asp Cys Phe Val Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 542
<211> 113
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 542

Gln Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
1 5 10 15

Arg Val Thr Ile Asn Cys Gln Ala Ser Gln Asn Val Tyr Asn Asn Asn
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Gln Leu
35 40 45

Ile Tyr Ser Thr Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80

Pro Glu Asp Val Ala Thr Tyr Tyr Cys Leu Gly Ser Tyr Asp Cys Ser
85 90 95

Arg Gly Asp Cys Phe Val Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

Arg

<210> 543
<211> 22
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 543

Gln Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
1 5 10 15

Arg Val Thr Ile Asn Cys
20

<210> 544
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 544

Gln Ala Ser Gln Asn Val Tyr Asn Asn Asn Tyr Leu Ala
1 5 10

<210> 545
<211> 15
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 545

Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Gln Leu Ile Tyr
1 5 10 15

<210> 546
<211> 7
<212> PRT
<213> Artificial

<220>

<223> Engineered antibody sequence

<400> 546

Ser Thr Ser Thr Leu Ala Ser
1 5

<210> 547
<211> 32
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 547

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Val Ala Thr Tyr Tyr Cys
20 25 30

<210> 548
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 548

Leu Gly Ser Tyr Asp Cys Ser Arg Gly Asp Cys Phe Val
1 5 10

<210> 549
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 549

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
1 5 10

<210> 550
<211> 106
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 550

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1 5 10 15

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
20 25 30

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
35 40 45

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
50 55 60

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65 70 75 80

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
85 90 95

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> 551
<211> 660
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 551
caagtgctga cccagtctcc atcctccctg tctgcatctg taggagacag agtcaccatc
60

aattgccagg ccagtcagaa tgtttacaat aacaactacc tagcctggta tcagcagaaa
120

ccagggaaag ttcctaagca actgatctat tctacatcca ctctggcatc tggggtccca
180

tctcgtttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagcctgcag
240

cctgaagatg ttgcaactta ttactgtctg ggcagttatg attgtagtcg tggtgattgt
300

tttgttttcg gcggaggaac caaggtggaa atcaaacgta cggtggctgc accatctgtc
360

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg
420

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa
480

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc
540

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa
600

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgttag
660

<210> 552
<211> 339
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 552
caagtgctga cccagtctcc atcctccctg tctgcatctg taggagacag agtcaccatc
60

aattgccagg ccagtcagaa tgtttacaat aacaactacc tagcctggta tcagcagaaa
120

ccagggaaag ttcctaagca actgatctat tctacatcca ctctggcatc tggggtccca
180

tctcgtttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagcctgcag
240

cctgaagatg ttgcaactta ttactgtctg ggcagttatg attgtagtcg tggtgattgt
300

tttgttttcg gcggaggaac caaggtggaa atcaaacgt
339

<210> 553
<211> 66
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 553
caagtgctga cccagtctcc atcctccctg tctgcatctg taggagacag agtcaccatc
60

a a t t g c
66

<210> 554

<211> 39
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 554
caggccagtc agaatgttta caataacaac tacctagcc
39

<210> 555
<211> 45
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 555
tggtatcagc agaaaccagg gaaagttcct aagcaactga tctat
45

<210> 556
<211> 21
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 556
t c t a c a t c c a c t c t g g c a t c t
21

<210> 557
<211> 96
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 557
ggggtcccat ctcgtttcag tggcagtgga tctgggacag atttcactct caccatcagc
60

agcctgcagc ctgaagatgt tgcaacttat tactgt
96

<210> 558
<211> 39
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 558
ctgggcagtt atgattgtag tcgtggtgat tgttttgtt
39

<210> 559
<211> 33
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 559
ttcggcggag gaaccaaggt ggaaatcaaa cgt
33

<210> 560
<211> 321
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 560
acggtggctg caccatctgt cttcatcttc ccgccatctg atgagcagtt gaaatctgga
60

actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg
120

aaggtggata acgccctcca atcgggtaac tcccaggaga gtgtcacaga gcaggacagc
180

aaggacagca cctacagcct cagcagcacc ctgacgctga gcaaagcaga ctacgagaaa
240

cacaaagtct acgcctgcga agtcacccat cagggcctga gctcgcccgt cacaaagagc
300

t t c a a c a g g g g a g a g t g t t a g
321

<210> 561
<211> 37
<212> PRT
<213> Homo sapiens

<220>
<223> C-term amidated

<400> 561

Ala Cys Asp Thr Ala Thr Cys Val Thr His Arg Leu Ala Gly Leu Leu
1 5 10 15

Ser Arg Ser Gly Gly Val Val Lys Asn Asn Phe Val Pro Thr Asn Val
20 25 30

Gly Ser Lys Ala Phe
35

<210> 562
<211> 37
<212> PRT
<213> Homo sapiens

<220>

<223> C-term amidated

<400> 562

Ala Cys Asn Thr Ala Thr Cys Val Thr His Arg Leu Ala Gly Leu Leu
1 5 10 15

Ser Arg Ser Gly Gly Met Val Lys Ser Asn Phe Val Pro Thr Asn Val
20 25 30

Gly Ser Lys Ala Phe
35

<210> 563
<211> 106
<212> PRT
<213> Homo sapiens

<400> 563

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1 5 10 15

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
20 25 30

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
35 40 45

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
50 55 60

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65 70 75 80

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
85 90 95

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> 564
<211> 330
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 564

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro

115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 565
<211> 329
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 565

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys

100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
325

<210> 566
<211> 440
<212> PRT
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 566

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Ile Asp Leu Ser Gly Tyr
20 25 30

Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Val Ile Gly Ile Asn Gly Ala Thr Tyr Tyr Ala Ser Trp Ala Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Thr Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala

85 90 95

Arg Gly Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
100 105 110

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
115 120 125

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
130 135 140

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
145 150 155 160

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
165 170 175

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
180 185 190

Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Ala Arg
195 200 205

Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
210 215 220

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
225 230 235 240

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
245 250 255

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
260 265 270

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
275 280 285

Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
290 295 300

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
305 310 315 320

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
325 330 335

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
340 345 350

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
355 360 365

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
370 375 380

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
385 390 395 400

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
405 410 415

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
420 425 430

Lys Ser Leu Ser Leu Ser Pro Gly
435 440

<210> 567
<211> 1323
<212> DNA
<213> Artificial

<220>
<223> Engineered antibody sequence

<400> 567
gaggtgcagc ttgtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc
60

tcctgtgcag tctctggaat cgacctcagt ggctactaca tgaactgggt ccgtcaggct
120

ccagggaagg ggctggagtg ggtcggagtc attggtatta atggtgccac atactacgcg
180

agctgggcga aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt
240

caaatgaaca gcctgagagc tgaggacact gctgtgtatt tctgtgctag aggggacatc
300

tggggccaag ggaccctcgt caccgtctcg agcgcctcca ccaagggccc atcggtcttc
360

cccctggcac cctcctccaa gagcacctct gggggcacag cggccctggg ctgcctggtc
420

aaggactact tccccgaacc ggtgacggtg tcgtggaact caggcgccct gaccagcggc
480

gtgcacacct tcccggctgt cctacagtcc tcaggactct actccctcag cagcgtggtg
540

accgtgccct ccagcagctt gggcacccag acctacatct gcaacgtgaa tcacaagccc
600

agcaacacca aggtggacgc gagagttgag cccaaatctt gtgacaaaac tcacacatgc
660

ccaccgtgcc cagcacctga actcctgggg ggaccgtcag tcttcctctt cccccaaaa
720

cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg
780

agccacgaag accctgaggt caagttcaac tggtacgtgg acggcgtgga ggtgcataat
840

gccaagacaa agccgcggga ggagcagtac gccagcacgt accgtgtggt cagcgtcctc
900

accgtcctgc accaggactg gctgaatggc aaggagtaca agtgcaaggt ctccaacaaa
960

gccctcccag cccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca
1020

caggtgtaca ccctgccccc atcccgggag gagatgacca agaaccaggt cagcctgacc
1080

tgcctggtca aaggcttcta tcccagcgac atcgccgtgg agtgggagag caatgggcag
1140

ccggagaaca actacaagac cacgcctccc gtgctggact ccgacggctc cttcttcctc
1200

tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc
1260

gtgatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt
1320

t g a
1323