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(54) Titre : TRAITEMENT DE MAUX DE TETE DUS A UN USAGE ABUSIF DE MEDICAMENTS A L'AIDE D'ANTICORPS ANTI-CGRP OU ANTI-CGRP-R

(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	SYMQ	WVRQAPGKGLEWIG	VIGINDNTYYASWAKG
Ab2	EVQLVESGGGLVQPGGSLRLSCAVSGLDLS	SYMQ	WVRQAPGKGLEWVG	VIGINDNTYYASWAKG
Ab3	EVQLVESGGGLVQPGGSLRLSCAVSGLDLS	SYMQ	WVRQAPGKGLEWVG	VIGINDNTYYASWAKG
Ab4	QSLEESGGRLVTPGTPLTLCSVSGIDLS	GYMN	WVRQAPGKGLEWIG	VIGINGATYYASWAKG
Ab5	EVQLVESGGGLVQPGGSLRLSCAVSGIDLS	GYMN	WVRQAPGKGLEWVG	VIGINGATYYASWAKG
Ab6	EVQLVESGGGLVQPGGSLRLSCAVSGIDLS	GYMN	WVRQAPGKGLEWVG	VIGINGATYYASWAKG
Ab7	QEQLKESGGRLVTPGTSLTLTCTVSGIDLS	NHMQ	WVRQAPGKGLEWIG	VVGINGRTYYASWAKG
Ab8	EVQLVESGGGLVQPGGSLRLSCAVSGIDLS	NHMQ	WVRQAPGKGLEWVG	VVGINGRTYYASWAKG
Ab9	QSLEESGGRLVTPGTPLTLCTVSGIGLS	SYMQ	WVRQSPGRGLEWIG	VIGSDGKTYYATWAKG
Ab10	EVQLVESGGGLVQPGGSLRLSCAVSGIGLS	SYMQ	WVRQAPGKGLEWVG	VIGSDGKTYYATWAKG
Ab11	QSLEESGGRLVTPGGSLTLTCTVSGIDVT	NYMQ	WVRQAPGKGLEWIG	VIGVNGKRYYASWAKG
Ab12	EVQLVESGGGLVQPGGSLRLSCAVSGIDVT	NYMQ	WVRQAPGKGLEWVG	VIGVNGKRYYASWAKG
Ab13	QSVEESGGGLVQPEGSLTLCTASGFDF	SNAMW	WVRQAPGKGLEWIG	CIYNGDGSTYYASWVNG
Ab14	EVQLVESGGGLVQPGGSLRLSCAVSGIGLS	SYMQ	WVRQAPGKGLEWVG	VIGSDGKTYYATWAKG

(57) Abrégé/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.



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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	QSLEESGGRLVTPGTPLTLCTVSGLDLS	SYMQ	WVRQAPGKGLEWIG	VIGINDNTYYASWAKG
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Ab4	QSLEESGGRLVTPGTPLTLCTVSGIDLS	GYMN	WVRQAPGKGLEWIG	VIGINGATYYASWAKG
Ab5	EVQLVESGGGLVQPGGSLRLSCAVSGIDLS	GYMN	WVRQAPGKGLEWVG	VIGINGATYYASWAKG
Ab6	EVQLVESGGGLVQPGGSLRLSCAVSGIDLS	GYMN	WVRQAPGKGLEWVG	VIGINGATYYASWAKG
Ab7	QEQLKESGGRLVTPGTSLTCTVSGIDLS	NHMQ	WVRQAPGKGLEWIG	VVGINGRTYYASWAKG
Ab8	EVQLVESGGGLVQPGGSLRLSCAVSGIDLS	NHMQ	WVRQAPGKGLEWVG	VVGINGRTYYASWAKG
Ab9	QSLEESGGRLVTPGTPLTLCTVSGIDLS	SYMQ	WVRQSPGRGLEWIG	VIGSDGKTYYATWAKG
Ab10	EVQLVESGGGLVQPGGSLRLSCAVSGIGLS	SYMQ	WVRQAPGKGLEWVG	VIGSDGKTYYATWAKG
Ab11	QSLEESGGRLVTPGGSLTLCTVSGIDVT	NYMQ	WVRQAPGKGLEWIG	VIGVNGKRYYASWAKG
Ab12	EVQLVESGGGLVQPGGSLRLSCAVSGIDVT	NYMQ	WVRQAPGKGLEWVG	VIGVNGKRYYASWAKG
Ab13	QSVEESGGGLVQPEGSLTLCTASGFDES	SNAMW	WVRQAPGKGLEWIG	CIYNGDGSTYYASWVNG
Ab14	EVQLVESGGGLVQPGGSLRLSCAVSGIGLS	SYMQ	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.

WO 2020/146535 A1

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# WO 2020/146535 A1



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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))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
- *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, dipropanoylemorphine, 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] In 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  $\pm$  20% of at least about (284  $\pm$  44 hours).

[0080] In other exemplary embodiments, the anti-human CGRP antibody used in the aforementioned methods binds to human  $\alpha$ - and  $\beta$ -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')<sub>2</sub>, 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 ( $\pm$  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 ( $\pm$  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 ( $\pm$  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  $C_{max}$  ( $\mu\text{g/mL}$ ),  $AUC_{0-\infty}$  ( $\text{mg}^*\text{hr/mL}$ ), half-life (days),  $V_z$  (L) and  $C_L$  ( $\text{mL}/\text{hr}$ ).

[0115] **FIG. 22** shows the change (mean  $\pm$  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 ( $\pm$  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  $\geq 50\%$  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  $\geq 75\%$  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, Cephalgia. 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<sub>2</sub> (SEQ ID NO: 561), wherein the terminal phenylalanine is amidated;

[0155] CGRP-beta: ACNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF-NH<sub>2</sub> (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<sup>R</sup> 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 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 metallothioneine 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')<sub>2</sub> 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')<sub>2</sub>, 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<sub>ab</sub> region; the stem portion of the "Y" configuration is designated the F<sub>c</sub> 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  $\gamma$ ,  $\mu$ ,  $\alpha$ ,  $\delta$ , and  $\epsilon$  (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  $\kappa$  (kappa) or  $\lambda$  (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<sub>0-t</sub>” refers to the area under the concentration-time curve from time=0 to last quantifiable concentration. “AUC<sub>0-inf</sub>” refers to the area under the concentration-time curve from time=0 extrapolated to infinity.

[0192] “I<sub>max</sub>” 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:

QVLTQSPSSLSASVGDRVTINCQASQSVYHNTYLAWYQQKPGKVPKQLIYDASTLASGVPSRFSGSGSGTDFLTISLQPEDVATYYCLGSYDCTNGDCFVFGGGTKVEIKR (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:

QVLTQSPSSLSASVGDRVTINCQASQSVYHNTYLAWYQQKPGKVPKQLIYDASTLASGVPSRFSGSGSGTDFLTISLQPEDVATYYCLGSYDCTNGDCFVFGGGTKVEIKRTVAAPSVFIFPPS

DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTTLSK  
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:

EVQLVESGGGLVQPGGSLRLSCAVSGIDLSGYMNWVRQAPGKGLEWVGVIGINGATYYAS  
WAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCARGDIWGQGTLTVSS (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:

EVQLVESGGGLVQPGGSLRLSCAVSGIDLSGYMNWVRQAPGKGLEWVGVIGINGATYYAS  
WAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCARGDIWGQGTLTVSSASTKGPSVFPLA  
PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPALQSSGLYSLSSVVTVPSSS  
LGTQTYICNVNHPKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR  
TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLN  
GKEYKCKVSNKALPAPIEKTIASKAKGQPREPVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA  
VEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ  
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:

EVQLVESGGGLVQPGGSLRLSCAVSGIDLSGYMNWVRQAPGKGLEWVGVIGINGATYYAS  
WAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCARGDIWGQGTLTVSSASTKGPSVFPLA  
PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPALQSSGLYSLSSVVTVPSSS  
LGTQTYICNVNHPKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR  
TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLN  
GKEYKCKVSNKALPAPIEKTIASKAKGQPREPVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA  
VEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ  
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')<sub>2</sub>, 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] TVAAPSVFIFPPSDEQLKSGTASVVCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (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] ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEM

TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQG  
NVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 564).

[0216] ASTKGPSVFPLAPSSKSTSGTAALGCLVKDYFPEPVTVWSNSGALTSGVHTFPA  
VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELL  
GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY  
ASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEM  
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQG  
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. Sulphydryl 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 ( $^{125}\text{I}$ ), Carbon 14 ( $^{14}\text{C}$ ), Sulfur 35 ( $^{35}\text{S}$ ), Tritium ( $^3\text{H}$ ) and Phosphorus 32 ( $^{32}\text{P}$ ).

[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, cyclophosphamide, 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 antimyotic 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, colchicine, 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 ( $^{32}\text{P}$ ), Scandium-47 ( $^{47}\text{Sc}$ ), Copper-67 ( $^{67}\text{Cu}$ ), Gallium-67 ( $^{67}\text{Ga}$ ), Yttrium-88 ( $^{88}\text{Y}$ ), Yttrium-90 ( $^{90}\text{Y}$ ), Iodine-125 ( $^{125}\text{I}$ ), Iodine-131 ( $^{131}\text{I}$ ), Samarium-153 ( $^{153}\text{Sm}$ ), Lutetium-177 ( $^{177}\text{Lu}$ ), Rhenium-186 ( $^{186}\text{Re}$ ) or Rhenium-188 ( $^{188}\text{Re}$ ), and alpha-emitters such as Astatine-211 ( $^{211}\text{At}$ ), Lead-212 ( $^{212}\text{Pb}$ ), Bismuth-212 ( $^{212}\text{Bi}$ ) or -213 ( $^{213}\text{Bi}$ ) or Actinium-225 ( $^{225}\text{Ac}$ ).

[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<sub>H</sub> 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<sub>L</sub> 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  $5 \times 10^{-7}$  M,  $10^{-7}$  M,  $5 \times 10^{-8}$  M,  $10^{-8}$  M,  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M,  $5 \times 10^{-13}$  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,  $5 \times 10^{-12}$  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<sup>-1</sup>,  $5 \times 10^{-5}$  S<sup>-1</sup>,  $10^{-5}$  S<sup>-1</sup>,  $5 \times 10^{-6}$  S<sup>-1</sup>,  $10^{-6}$  S<sup>-1</sup>,  $5 \times 10^{-7}$  S<sup>-1</sup>, or  $10^{-7}$  S<sup>-1</sup>.

[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] CAAGTGCTGaccagtctccatcctccctgtcatctgttaggagacagagtaccatcAA TtgcCAGGCCA GTCAGAGTGTATCATAACACCTACCTGGCCtggtatcagcagaaaccaggaaagtccctaagCAActgatcta tGATGCATCCACTCTGGCATCTgggtccatctcgttcagtggcagtggatctggacagattcacttcaccatcagcagc ctgcagcctgaagatgttcaacttattactgtCTGGCAGTTATGATTGACTAATGGTATTGTTTGTtgc gcgaggaaccaaggtgaaatcaaacgt (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] CAAGTGCTGaccagtctccatcctccctgtcatctgttaggagacagagtaccatcAA TtgcCAGGCCA GTCAGAGTGTATCATAACACCTACCTGGCCtggtatcagcagaaaccaggaaagtccctaagCAActgatcta tGATGCATCCACTCTGGCATCTgggtccatctcgttcagtggcagtggatctggacagattcacttcaccatcagcagc ctgcagcctgaagatgttcaacttattactgtCTGGCAGTTATGATTGACTAATGGTATTGTTTGTtgc gcgaggaaccaaggtgaaatcaaacgtACGGTGGCTGCACCATCTGTCTTCATCTCCGCCATCTGAT GAGCAGTTGAAATCTGGAACCTGCCTCTGTTGTGCCTGCTGAATAACTCTATCCCAGA GAGGCCAAAGTACAGTGGAAAGGTGGATAACGCCCTCCAATCGGGTAACCTCCAGGAGAG TGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGA GCAAAGCAGACTACGAGAACACAAAGTCTACGCCCTGCGAAGTCACCCATCAGGGCCTG AGCTCGCCCGTCACAAAGAGCTTCAACAGGGAGAGTGTAG (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] gaggtgcagctTgtggagtctggggaggctggccagcctgggggtccctgagactctctgtcaGTCtctggaAT CGACCTCagGGCTACTACATGAACtgggtccgtcaggtccaggaaaggggctggagtggtcGGAGTCATTGG TATTAATGGTGCACATACTACGCGAGCTGGCGAAAGGCegattcaccatctccagagacaattccaagA CCACGGTGtatctcaaatgaacagectgagagactgctgtatTTCtgtGCTAGAGGGACATCtgggccc aagggaccctgtcaccgtcTCGAGC (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] gaggtgcagctTgtggagtctggggaggctggccagcctgggggtccctgagactctctgtcaGTCtctggaAT CGACCTCagGGCTACTACATGAACtgggtccgtcaggtccaggaaaggggctggagtggtcGGAGTCATTGG TATTAATGGTGCACATACTACGCGAGCTGGCGAAAGGCegattcaccatctccagagacaattccaagA CCACGGTGtatctcaaatgaacagectgagagactgctgtatTTCtgtGCTAGAGGGACATCtgggccc

aaggggaccctcgtcaccgtcTCGAGCGCCTCCACCAAGGGCCATCGGTCTTCCCCCTGGCAcCCTCC  
 TCCaAGAGCACCTCTGGGGGCACAGCGGCCCTGGCCTGGTCAAGGACTACTTCCC  
 GAACCGGTGACGGTGTGGAACTCAGGCGCCCTGACCAGCGCGTGCACACCTTCCC  
 GGCTGTCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTACCGTGCCCTCCAG  
 CAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGG  
 TGGACGCGAGAGTTGAGCCAAATCTTGTGACAAAACACACATGCCACCCTGCCA  
 GCACCTGAACTCCTGGGGGACCGTCAGTCTCCTCTTCCCCAAAACCCAAGGACACC  
 CTCATGATCTCCCgGACCCCTGAGGTACATGCGTGGTGGACGTGAGCCACGAAGAC  
 CCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA  
 GCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTACCGTCCTCACCGTCTGC  
 ACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAGGGTCTCAACAAAGCCCTCCA  
 GCCCCCCATCGAGAAAACCATCTCAAAGCCAAGGGCAGCCCCGAGAACCCACAGGTGTA  
 CACCCCTGCCCTCATCCGGGAGGAGATGACCAAGAACCCAGGTACGCCGCTGACCTGCTGG  
 TCAAAGGCTTCTATCCCAGCGACATGCCGTGGAGTGGGAGAGCAATGGCAGCCGGAG  
 AACAACTACAAGACCACGCCCTCCGTGCTGGACTCCGACGGCTCCTCTCCTACAGC  
 AAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGAACGTCTCTCATGCTCCGTGAT  
 GCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGTAAATG  
 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:

gaggtgcagctTgtggagtctggggagggctggccagcctgggggtccctgagactctcctgtcaGTCtctggaATCGACCTCa  
 gtGGCTACTACATGAACAtgggtccgtcaggcgtccaggaaaggggctggagtggcGGAGTCATTGGTATTAAAT  
 GGTGCCACATACTACGCGAGCTGGCGAAAGGCcgattcaccatctccagagacaattccaagACCACGGT  
 GtatctcaaatgaacagcctgagagctgaggacactgctgttatTTCtgtGCTAGAGGGGACATCtggggccaaggaccctc  
 gtcaccgtcTCGAGCGCCTCCACCAAGGGCCATCGGTCTTCCCCCTGGCAcCCTCCTCCaAGA  
 GCACCTCTGGGGCACAGCGGCCCTGGCCTGGCTGCCTGGTCAAGGACTACTCCCCGAACCG  
 GTGACGGTGTGGAACTCAGGCGCCCTGACCAGCGCGTGCACACCTCCGGCTGTC  
 CTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTACCGTGCCTCCAGCAGCTTG  
 GGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACGC  
 GAGAGTTGAGCCAAATCTTGTGACAAAACACACATGCCACCCTGCCAGCACCTG  
 AACTCCTGGGGGACCGTCAGTCTCCTCTTCCCCAAAACCCAAGGACACCCTCATG  
 TCTCCCgGACCCCTGAGGTACATGCGTGGTGGACGTGAGCCACGAAGACCCCTGAGG  
 TCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGG  
 GAGGAGCAGTACGCCAGCAGTACCGTGTGGTACCGTCCTCACCGTCTGCACCAGGA  
 CTGGCTGAATGGCAAGGAGTACAAGTGCAGGTCTCAACAAAGCCCTCCAGCCCCA  
 TCGAGAAAACCATCTCCAAAGCCAAGGGCAGCCCCGAGAACCCACAGGTGTACACCCTG

CCCCCATCCCAGGGAGGAGATGACCAAGAACCAAGGTCAGCCTGACCTGCCTGGTCAAAGG  
 CTTCTATCCCAGCGACATCGCCGTGGAGTGGAGAGCAATGGGCAGCCGGAGAACAACT  
 ACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCCTACAGCAAGCTCA  
 CCGTGGACAAGAGCAGGTGGCAGCAGGGAACGTCTCATGCTCCGTATGCATGAG  
 GCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCGTCTCCGGGTTGA (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<sub>L</sub> or V<sub>H</sub> 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); Boulian, 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, 19<sup>th</sup> 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 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, propionic acid derivatives, enolic acid derivatives, anthralic acid derivatives (fenamates), selective COX-2 inhibitors (coxibs), 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, dipropanoylemorphine, 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 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, propionic acid derivatives, enolic acid derivatives, anthralic acid derivatives (fenamates), selective COX-2 inhibitors (coxibs), 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<sub>L</sub> and light chain polypeptides respectively in SEQ ID NO: 222 and SEQ ID NO: 221, and contains the V<sub>H</sub> 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**

<b>Characteristic</b>	<b>Placebo iv (n=82)</b>	<b>Ab6 1000mg iv (n=81)</b>
<b>Mean ±SD Age (years)</b>	39.0 (9.6)	38.6 (10.8)
<b>Mean ±SD Weight (kg)</b>	75.4 (14.4)	75.0 (16.5)
<b>Female Gender</b>	66 (80%)	67 (83%)
<b>Race:</b>		
<b>Caucasian</b>	66 (80.5%)	66 (81.5%)
<b>African American</b>	9 (11.0%)	10 (12.4%)
<b>Asian</b>	3 (3.7%)	4 (5.0%)
<b>Other</b>	4 (4.8%)	1 (1.1%)
<b>Baseline (per 28 days):</b>		
<b>Mean ±SD Migraine Days</b>	8.8 (2.7)	8.4 (2.1)
<b>Mean ±SD Migraine Episodes</b>	6.7 (2.4)	6.0 (2.2)
<b>Mean ±SD Headache Frequency</b>	9.6 (2.8)	9.2 (2.6)
<b>Mean ±SD Migraine Hours</b>	72.2 (51.0)	80.1 (49.1)
<b>Mean ±SD HIT-6 Score</b>	64.5 (4.44)	63.8 (5.21)
<b>Mean ±SD MSQ RFP Score</b>	49.0 (17.9)	49.5 (21.2)
<b>Mean ±SD MSQ RFR Score</b>	61.9 (22.7)	63.9 (24.0)
<b>Mean ±SD MSQ EF Score</b>	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 interim 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 ( $\pm$  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 ( $\pm$  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 ( $\pm$  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  $C_{max}$  ( $\mu$ g/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 results 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  $\geq$  50% reduction in migraine frequency were considered to be a 50% responder. Subjects with  $\geq$  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, and 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  $\geq 10$  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  $\geq 1$  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  $\geq 1$ , 1–9, and  $\geq 10$  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  $\geq 10$  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  $\geq 1$ , 1–9, and  $\geq 10$  days of acute medication use at baseline. With the exception of Ab6 100 mg at Month 6 in patients with  $\geq 10$  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 ( $\geq 10$  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 consists 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 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, 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 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, propionic acid derivatives, enolic acid derivatives, anthralic acid derivatives (fenamates), selective COX-2 inhibitors (coxibs), 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	FR1	CDR1	FR2	CDR2
Ab1	QSLEESGGRLVTPGTPPLTLCTVSGLDSL	SYMQ	WVRQAPGKGLEWIG	VIGINDNTYYASWAKG
Ab2	EVQLVESGGGLVQPGGSLRLSCAVSGLDSL	SYMQ	WVRQAPGKGLEWVG	VIGINDNTYYASWAKG
Ab3	EVQLVESGGRLVTPGTPPLTLCTVSGLDSL	SYMQ	WVRQAPGKGLEWVG	VIGINDNTYYASWAKG
Ab4	QSLEESGGRLVQPGGSLRLSCAVSGLDSL	GYMN	WVRQAPGKGLEWIG	VIGINGATYYASWAKG
Ab5	EVQLVESGGGLVQPGGSLRLSCAVSGLDSL	GYMN	WVRQAPGKGLEWVG	VIGINGATYYASWAKG
Ab6	EVQLVESGGGLVQPGGSLRLSCAVSGLDSL	GYMN	WVRQAPGKGLEWVG	VIGINGATYYASWAKG
Ab7	QEQLKESSGGRLLVTPGTSITLTLCTVSGLDSL	NHYMQ	WVRQAPGKGLEWIG	VVGINGRTYYASWAKG
Ab8	EVQLVESGGGLVQPGGSLRLSCAVSGLDSL	NHYMQ	WVRQAPGKGLEWVG	VVGINGRTYYASWAKG
Ab9	QSLEESGGRLVTPGTPPLTLCTVSGLIGLS	SYMQ	WVRQSPGRGLEWIG	VIGSDGKTYYATWAKG
Ab10	EVQLVESGGGLVQPGGSLRLSCAVSGLIGLS	SYMQ	WVRQAPGKGLEWVG	VIGSDGKTYYATWAKG
Ab11	QSLEESGGRLVTPGGSITLTLCTVSGIDVT	NYMQ	WVRQAPGKGLEWIG	VIGVNGKRYYASWAKG
Ab12	EVQLVESGGGLVQPGGSLRLSCAVSGIDVT	NYMQ	WVRQAPGKGLEWVG	VIGVNGKRYYASWAKG
Ab13	QSVEESGGGLVQPEGSLITLCTASGFDES	SNAMM	WVRQAPGKGLEWIG	CIYNGDGSTYYASWNG
Ab14	EVQLVESGGGLVQPGGSLRLSCAVSGLIGLS	SYMQ	WVRQAPGKGLEWVG	VIGSDGKTYYATWAKG

Figure 1B - Heavy Chain Protein Sequence

Sequence	FR3	CDR3	FR4
Ab1	RFTISRASSTTVIDLKMTSLTTEDTATYFCAR	GDI	WGPGBTLVTVSS
Ab2	RFTISRDNSSKTTVYIQLMNSLRAEDTAVYFCAR	GDI	WGQGTLTVTVSS
Ab3	RFTISRDNSSKTTVYIQLMNSLRAEDTAVYFCAR	GDI	WGQGTLTVTVSS
Ab4	RFTISRTSSSTTVIDLKMTSLTTEDTATYFCAR	GDI	WGPGTLTVTVSS
Ab5	RFTISRDNSSKTTVYIQLMNSLRAEDTAVYFCAR	GDI	WGQGTLTVTVSS
Ab6	RFTISRDNSSKTTVYIQLMNSLRAEDTAVYFCAR	GDI	WGQGTLTVTVSS
Ab7	RFTISRTSSSTTVIDLKMTSLTTEDTATYFCAR	GDI	WGPGTLTVTVSS
Ab8	RFTISRTSSSTTVIDLKMTSLTTEDTATYFCAR	GDI	WGQGTLTVTVSS
Ab9	RFTISRTSSSTTVIDLKMTSLTTEDTATYFCAR	GDI	WGQGTLTVTVSS
Ab10	RFTISRTSSSTTVIDLKMTSLTTEDTATYFCAR	GDI	WGQGTLTVTVSS
Ab11	RFTISRTSSSTTVIDLKMTSLTTEDTATYFCAR	GDI	WGPGTLTVTVSS
Ab12	RFTISRTSSSTTVIDLKMTSLTTEDTATYFCAR	DLDL	WGPGTLTVTVSS
Ab13	RFTISRTSSSTTVIDLKMTSLTTEDTATYFCAR	GDI	WGQGTLTVTVSS
Ab14	RFTISRTSSSTTVIDLKMTSLTTEDTATYFCAR	GDI	WGQGTLTVTVSS

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	NHKPSNTKVDKRVEPKSCKDKTHTCPPCPAPAPLLGGPSVFLFPPKPKDILMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA	
Ab2	NHKPSNTKVDKRVEPKSCKDKTHTCPPCPAPAPLLGGPSVFLFPPKPKDILMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA	
Ab3	NHKPSNTKVDKRVEPKSCKDKTHTCPPCPAPAPLLGGPSVFLFPPKPKDILMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA	
Ab4	NHKPSNTKVDKRVEPKSCKDKTHTCPPCPAPAPLLGGPSVFLFPPKPKDILMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA	
Ab5	NHKPSNTKVDKRVEPKSCKDKTHTCPPCPAPAPLLGGPSVFLFPPKPKDILMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA	
Ab6	NHKPSNTKVDKRVEPKSCKDKTHTCPPCPAPAPLLGGPSVFLFPPKPKDILMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA	
Ab7	NHKPSNTKVDKRVEPKSCKDKTHTCPPCPAPAPLLGGPSVFLFPPKPKDILMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA	
Ab8	NHKPSNTKVDKRVEPKSCKDKTHTCPPCPAPAPLLGGPSVFLFPPKPKDILMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA	
Ab9	NHKPSNTKVDKRVEPKSCKDKTHTCPPCPAPAPLLGGPSVFLFPPKPKDILMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA	
Ab10	NHKPSNTKVDKRVEPKSCKDKTHTCPPCPAPAPLLGGPSVFLFPPKPKDILMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA	
Ab11	NHKPSNTKVDKRVEPKSCKDKTHTCPPCPAPAPLLGGPSVFLFPPKPKDILMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA	
Ab12	NHKPSNTKVDKRVEPKSCKDKTHTCPPCPAPAPLLGGPSVFLFPPKPKDILMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA	
Ab13	NHKPSNTKVDKRVEPKSCKDKTHTCPPCPAPAPLLGGPSVFLFPPKPKDILMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA	
Ab14	NHKPSNTKVDKRVEPKSCKDKTHTCPPCPAPAPLLGGPSVFLFPPKPKDILMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA	

Figure 1E - Heavy Chain Protein Sequence

Sequence Name	Constant Region
Ab1	KTKPREEQYASTYRVRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVTLPSSREEMTKNQVSILTCLVKGFF
Ab2	KTKPREEQYASTYRVRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVTLPSSREEMTKNQVSILTCLVKGFF
Ab3	KTKPREEQYASTYRVRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVTLPSSREEMTKNQVSILTCLVKGFF
Ab4	KTKPREEQYASTYRVRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVTLPSSREEMTKNQVSILTCLVKGFF
Ab5	KTKPREEQYASTYRVRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVTLPSSREEMTKNQVSILTCLVKGFF
Ab6	KTKPREEQYASTYRVRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVTLPSSREEMTKNQVSILTCLVKGFF
Ab7	KTKPREEQYASTYRVRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVTLPSSREEMTKNQVSILTCLVKGFF
Ab8	KTKPREEQYASTYRVRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVTLPSSREEMTKNQVSILTCLVKGFF
Ab9	KTKPREEQYASTYRVRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVTLPSSREEMTKNQVSILTCLVKGFF
Ab10	KTKPREEQYASTYRVRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVTLPSSREEMTKNQVSILTCLVKGFF
Ab11	KTKPREEQYASTYRVRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVTLPSSREEMTKNQVSILTCLVKGFF
Ab12	KTKPREEQYASTYRVRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVTLPSSREEMTKNQVSILTCLVKGFF
Ab13	KTKPREEQYASTYRVRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVTLPSSREEMTKNQVSILTCLVKGFF
Ab14	KTKPREEQYASTYRVRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVTLPSSREEMTKNQVSILTCLVKGFF

Figure 1F - Heavy Chain Protein Sequence

Sequence Name	Constant Region
Ab1	YPSDIAVEWESNGOPENNYKTTPPVLDSDGSFFLYSKLTVDKSRMQLQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1)
Ab2	YPSDIAVEWESNGOPENNYKTTPPVLDSDGSFFLYSKLTVDKSRMQLQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 41)
Ab3	YPSDIAVEWESNGOPENNYKTTPPVLDSDGSFFLYSKLTVDKSRMQLQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 81)
Ab4	YPSDIAVEWESNGOPENNYKTTPPVLDSDGSFFLYSKLTVDKSRMQLQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 121)
Ab5	YPSDIAVEWESNGOPENNYKTTPPVLDSDGSFFLYSKLTVDKSRMQLQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 161)
Ab6	YPSDIAVEWESNGOPENNYKTTPPVLDSDGSFFLYSKLTVDKSRMQLQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 201)
Ab7	YPSDIAVEWESNGOPENNYKTTPPVLDSDGSFFLYSKLTVDKSRMQLQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 241)
Ab8	YPSDIAVEWESNGOPENNYKTTPPVLDSDGSFFLYSKLTVDKSRMQLQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 281)
Ab9	YPSDIAVEWESNGOPENNYKTTPPVLDSDGSFFLYSKLTVDKSRMQLQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 321)
Ab10	YPSDIAVEWESNGOPENNYKTTPPVLDSDGSFFLYSKLTVDKSRMQLQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 361)
Ab11	YPSDIAVEWESNGOPENNYKTTPPVLDSDGSFFLYSKLTVDKSRMQLQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 401)
Ab12	YPSDIAVEWESNGOPENNYKTTPPVLDSDGSFFLYSKLTVDKSRMQLQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 441)
Ab13	YPSDIAVEWESNGOPENNYKTTPPVLDSDGSFFLYSKLTVDKSRMQLQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 481)
Ab14	YPSDIAVEWESNGOPENNYKTTPPVLDSDGSFFLYSKLTVDKSRMQLQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 521)

Figure 2A - Light Chain Protein Sequence

Sequence	FR1	CDR1	FR2	CDR2
Ab1	QVLTQTA SPVSA AVGSTV TINC	QASQSVYD NNYLA	WYQQKPGQ PPKQLIY	STSTLAS
Ab2	QVLTQSP SSLSASV GDRV TINC	QASQSVYD NNYLA	WYQQKPGK VPKQLIY	STSTLAS
Ab3	QVLTQSP SSLSASV GDRV TINC	QASQSVYD NNYLA	WYQQKPGK VPKQLIY	STSTLAS
Ab4	QVLTQTP SPVSA AVGSTV TINC	QASQSVYH NTYLA	WYQQKPGQ PPKQLIY	DASTLAS
Ab5	QVLTQSP SSLSASV GDRV TINC	QASQSVYH NTYLA	WYQQKPGK VPKQLIY	DASTLAS
Ab6	QVLTQSP SSLSASV GDRV TINC	QASQSVYH NTYLA	WYQQKPGK VPKQLIY	DASTLAS
Ab7	QVLTQTA SPVSA AVGSTV TINC	QASQSVYNN NYLA	WYQQKPGQ PPKQLIY	STSTLAS
Ab8	QVLTQSP SSLSASV GDRV TINC	QASQSVYNN NYLA	WYQQKPGK VPKQLIY	STSTLAS
Ab9	QVLTQTP SPVSA AVGSTV TINC	QASQNVYNN NNYLA	WYQQKPGQ PPKQLIY	STSTLAS
Ab10	QVLTQSP SSLSASV GDRV TINC	QASQNVYNN NNYLA	WYQQKPGK VPKQLIY	STSTLAS
Ab11	QVLTQTA SPVSP AVGSTV TINC	RASQSVYNN NYLA	WYQQKPGQ PPKQLIY	STSTLAS
Ab12	QVLTQSP SSLSASV GDRV TINC	RASQSVYNN NYLA	WYQQKPGK VPKQLIY	STSTLAS
Ab13	QVLTQTP SSKSVP VGDT TINC	QASESLYNN NALA	WFQQKPGQ PPKRLIY	DASKLAS
Ab14	QVLTQSP SSLSASV GDRV TINC	QASQNVYNN NNYLA	WYQQKPGK VPKQLIY	STSTLAS

Figure 2B - Light Chain Protein Sequence

Sequence	FR3	CDR3	FR4
Ab1	GVSSRFKG SGSGTQFTL TISDLECA DAATYYC	LGSYDCSSG DCFV	FGGGTEVV VKR
Ab2	GVPSSRF SGSGSGTDF TLTISLQ PEDVATYYC	LGSYDCSSG DCFV	FGGGTKVE IKR
Ab3	GVPSSRF SGSGSGTDF TLTISLQ PEDVATYYC	LGSYDCSSG DCFV	FGGGTKVE IKR
Ab4	GVPSSRF SGSGSGTDF TLTISLQ PEDVATYYC	LGSYDCTN GDCFV	FGGGTEVV VKR
Ab5	GVPSSRF SGSGSGTDF TLTISLQ PEDVATYYC	LGSYDCTN GDCFV	FGGGTKVE IKR
Ab6	GVPSSRF SGSGSGTDF TLTISLQ PEDVATYYC	LGSYDCTN GDCFV	FGGGTKVE IKR
Ab7	GVPSSRF SGSGSGTDF TLTISLQ PEDVATYYC	LGSYDCTN GDCFV	FGGGTEVV VKR
Ab8	GVPSSRF SGSGSGTDF TLTISLQ PEDVATYYC	LGSYDCTN GDCFV	FGGGTKVE IKR
Ab9	GVPSSRF SGSGSGTDF TLTISLQ PEDVATYYC	LGSYDCTN GDCFV	FGGGTEVV VKR
Ab10	GVPSSRF SGSGSGTDF TLTISLQ PEDVATYYC	LGSYDCTN GDCFV	FGGGTKVE IKR
Ab11	GVPSSRF SGSGSGTDF TLTISLQ PEDVATYYC	LGSYDCSNG DCFV	FGGGTEVV VKR
Ab12	GVPSSRF SGGGSGTQF TLTISLQ PEDVATYYC	LGSYDCSNG DCFV	FGGGTKVE IKR
Ab13	GVPSSRF SGGGSGTQF TLTISLQ PEDVATYYC	GGRSDSV DGV	FAGGTEVV VKR
Ab14	GVPSSRF SGSGSGTDF TLTISLQ PEDVATYYC	LGSYDCSNG DCFV	FGGGTKVE IKR

Figure 2C – Light Chain Protein Sequence

Sequence Name	Constant Region
Ab1	TVAAPSVFIFPPSDEQLKSGTASVVCILLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSISSLSSTLTSKADYEKHKVYA
Ab2	TVAAPSVFIFPPSDEQLKSGTASVVCILLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSISSLSSTLTSKADYEKHKVYA
Ab3	TVAAPSVFIFPPSDEQLKSGTASVVCILLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSISSLSSTLTSKADYEKHKVYA
Ab4	TVAAPSVFIFPPSDEQLKSGTASVVCILLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSISSLSSTLTSKADYEKHKVYA
Ab5	TVAAPSVFIFPPSDEQLKSGTASVVCILLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSISSLSSTLTSKADYEKHKVYA
Ab6	TVAAPSVFIFPPSDEQLKSGTASVVCILLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSISSLSSTLTSKADYEKHKVYA
Ab7	TVAAPSVFIFPPSDEQLKSGTASVVCILLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSISSLSSTLTSKADYEKHKVYA
Ab8	TVAAPSVFIFPPSDEQLKSGTASVVCILLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSISSLSSTLTSKADYEKHKVYA
Ab9	TVAAPSVFIFPPSDEQLKSGTASVVCILLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSISSLSSTLTSKADYEKHKVYA
Ab10	TVAAPSVFIFPPSDEQLKSGTASVVCILLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSISSLSSTLTSKADYEKHKVYA
Ab11	TVAAPSVFIFPPSDEQLKSGTASVVCILLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSISSLSSTLTSKADYEKHKVYA
Ab12	TVAAPSVFIFPPSDEQLKSGTASVVCILLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSISSLSSTLTSKADYEKHKVYA
Ab13	TVAAPSVFIFPPSDEQLKSGTASVVCILLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSISSLSSTLTSKADYEKHKVYA
Ab14	TVAAPSVFIFPPSDEQLKSGTASVVCILLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSISSLSSTLTSKADYEKHKVYA

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	CAGTCGCTGGAGGACTCCGGGGTGCCTGGTCAACGCCCTGACACTCACCTGCACAGTCTGGACTCTGACCTCAGT	
Ab2	GAGGTGCAGCTTGTGGAGTCTGGGGAGGCTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCCTGAGACTCTGGACTCGACCTCAGT	
Ab3	GAGGTGCAGCTTGTGGAGTCTGGGGAGGCTGGTCCAGCCTGGTCAACGCCCTGACACTCACCTGTTCCGGTCAAGCTCAGT	
Ab4	CAGTCGCTGGAGGACTCCGGGGTGCCTGGTCAACGCCCTGACACTCACCTGTTCCGGTCAAGCTCAGT	
Ab5	GAGGTGCAGCTTGTGGAGTCTGGGGAGGCTGGTCCAGCCTGGTCAACGCCCTGACACTCACCTGTTCCGGTCAAGCTCAGT	
Ab6	CAGGAGCAGCTGAAGGAGTCCGGGGTGGCTGGTCAACGCCCTGACACTCACCTGTTCCGGTCAAGCTCAGT	
Ab7	GAGGTGCAGCTTGTGGAGTCTGGGGAGGCTGGTCCAGCCTGGTCAACGCCCTGACACTCACCTGTTCCGGTCAAGCTCAGT	
Ab8	CAGTCGCTGGAGTCTGGGGAGGCTGGTCAACGCCCTGACACTCACCTGTTCCGGTCAACGCCCTGACACTCACCTGTTCCGGTCAAGCTCAGT	
Ab9	GAGGTGCAGCTTGTGGAGTCTGGGGAGGCTGGTCAACGCCCTGGTCAACGCCCTGGAGGATCCCTGACACTCACCTGTTCCGGTCAAGCTCAGT	
Ab10	CAGTCGCTGGAGTCTGGGGAGGCTGGTCAACGCCCTGGAGGATCCCTGACACTCACCTGTTCCGGTCAAGCTCAGT	
Ab11	GAGGTGCAGCTTGTGGAGTCTGGGGAGGCTGGTCAACGCCCTGGAGGATCCCTGACACTCACCTGTTCCGGTCAAGCTCAGT	
Ab12	CAGTCGCTGGAGGACTCCGGGGAGGCTGGTCAACGCCCTGGAGGATCCCTGACACTCACCTGTTCCGGTCAAGCTCAGT	
Ab13	GAGGTGCAGCTTGTGGAGTCTGGGGAGGCTGGTCAACGCCCTGGAGGATCCCTGACACTCACCTGTTCCGGTCAAGCTCAGT	
Ab14	GAGGTGCAGCTTGTGGAGTCTGGGGAGGCTGGTCAACGCCCTGGAGGATCCCTGACACTCACCTGTTCCGGTCAAGCTCAGT	

Figure 3B - Heavy Chain DNA Sequence

Sequence	Name	CDR1	FR2
Ab1	AGCTACTACATGCCAA	GGGGTCCGCCAGGCTCCAGGGAAAGGGGCTGGAATGGATCGGA	TGGGTCCGCTCAGGCTCCAGGGAAAGGGGCTGGAGTGGTCGGA
Ab2	AGCTACTACATGCCAA	TGGGTCCGCTCAGGCTCCAGGGAAAGGGGCTGGAGTGGTCGGA	TGGGTCCGCCAGGCTCCAGGGAAAGGGGCTGGAGTGGTCGGA
Ab3	AGCTACTACATGCCAA	TGGGTCCGCCAGGCTCCAGGGAAAGGGGCTGGAGTGGTCGGA	TGGGTCCGCCAGGCTCCAGGGAAAGGGGCTGGAGTGGTCGGA
Ab4	GGCTACTACATGCCAA	TGGGTCCGCCAGGCTCCAGGGAAAGGGGCTGGAGTGGTCGGA	TGGGTCCGCCAGGCTCCAGGGAAAGGGGCTGGAGTGGTCGGA
Ab5	GGCTACTACATGCCAA	TGGGTCCGCCAGGCTCCAGGGAAAGGGGCTGGAGTGGTCGGA	TGGGTCCGCCAGGCTCCAGGGAAAGGGGCTGGAGTGGTCGGA
Ab6	GGCTACTACATGCCAA	TGGGTCCGCCAGGCTCCAGGGAAAGGGGCTGGAGTGGTCGGA	TGGGTCCGCCAGGCTCCAGGGAAAGGGGCTGGAGTGGTCGGA
Ab7	AACCCACTACATGCCAA	TGGGTCCGCCAGGCTCCAGGGAAAGGGGCTGGAGTGGTCGGA	TGGGTCCGCCAGGCTCCAGGGAAAGGGGCTGGAGTGGTCGGA
Ab8	AACCCACTACATGCCAA	TGGGTCCGCCAGGCTCCAGGGAAAGGGGCTGGAGTGGTCGGA	TGGGTCCGCCAGGCTCCAGGGAAAGGGGCTGGAGTGGTCGGA
Ab9	AGCTACTACATGCCAG	TGGGTCCGCCAGGCTCCAGGGAAAGGGGCTGGAGTGGTCGGA	TGGGTCCGCCAGGCTCCAGGGAAAGGGGCTGGAGTGGTCGGA
Ab10	AGCTACTACATGCCAA	TGGGTCCGCCAGGCTCCAGGGAAAGGGGCTGGAGTGGTCGGA	TGGGTCCGCCAGGCTCCAGGGAAAGGGGCTGGAGTGGTCGGA
Ab11	AACTACTATATGCCAA	TGGGTCCGCCAGGCTCCAGGGAAAGGGGCTGGAGTGGTCGGA	TGGGTCCGCCAGGCTCCAGGGAAAGGGGCTGGAGTGGTCGGA
Ab12	AACTACTACATGCCAA	TGGGTCCGCCAGGCTCCAGGGAAAGGGGCTGGAGTGGTCGGA	TGGGTCCGCCAGGCTCCAGGGAAAGGGGCTGGAGTGGTCGGA
Ab13	AGCAATGCAATGTGG	TGGGTCCGCCAGGCTCCAGGGAAAGGGGCTGGAGTGGTCGGA	TGGGTCCGCCAGGCTCCAGGGAAAGGGGCTGGAGTGGTCGGA
Ab14	AGCTACTACATGCCAA	TGGGTCCGCCAGGCTCCAGGGAAAGGGGCTGGAGTGGTCGGA	TGGGTCCGCCAGGCTCCAGGGAAAGGGGCTGGAGTGGTCGGA

Figure 3C - Heavy Chain DNA Sequence

Sequence	Name	CDR2
Ab1		GTCATTGGTATTAAATGATAAACACATACTACGGGAGCTGGCGAAAGGC
Ab2		GTCATTGGTATAATGATAAACACATACTACGGGAGCTGGCGAAAGGC
Ab3		GTCATTGGTATTAAATGATAAACACATACTACGGGAGCTGGCGAAAGGC
Ab4		GTCATTGGTATTAAATGTTGCCACATACTACGGGAGCTGGCGAAAGGC
Ab5		GTCATTGGTATTAAATGTTGCCACATACTACGGGAGCTGGCGAAAGGC
Ab6		GTCATTGGTATTAAATGTTGCCACATACTACGGGAGCTGGCGAAAGGC
Ab7		GTCATTGGTATTAAATGTTGCCACATACTACGGGAGCTGGCGAAAGGC
Ab8		GTCATTGGTATTAAATGTTGCCACATACTACGGGAGCTGGCGAAAGGC
Ab9		GTCATTGGTATTAAATGTTGCCACATACTACGGGAGCTGGCGAAAGGC
Ab10		GTCATTGGTATTAAATGTTGCCACATACTACGGGAGCTGGCGAAAGGC
Ab11		GTCATTGGTATTAAATGTTGCCACATACTACGGGAGCTGGCGAAAGGC
Ab12		GTCATTGGTATTAAATGTTGCCACATACTACGGGAGCTGGCGAAAGGC
Ab13		TGCATTTACAAATGGTATTAAAGACATACTACGGGACCTGGTGGTGAATGGC
Ab14		GTCATTGGTATTAAATGGTATTAAAGACATACTACGGGACCTGGCGAAAGGC

Figure 3D - Heavy Chain DNA Sequence

Sequence	Name	FR3
Ab1		CGATTCAACCATTCTCCAGAGACAATTCCAAGAACCCACGGTGGATCTGAAAATGACCAACGGAGCTGGCCACCTATTCTGTGCCAGA
Ab2		CGATTCAACCATTCTCCAGAGACAATTCCAAGAACCCACGGTGTATCTTCAAATGACCAACGGCTGAGGCTGAGGACACTGCTGTGCTAGA
Ab3		CGATTCAACCATTCTCCAGAGACAATTCCAAGAACCCACGGTGTATCTTCAAATGACCAACGGCTGAGGCTGAGGACACTGCTGTGCTAGA
Ab4		CGATTCAACCATTCTCCAGAGACAATTCCAAGAACCCACGGTGTATCTTCAAATGACCAACGGCTGAGGCTGAGGACACTGCTGTGCTAGA
Ab5		CGATTCAACCATTCTCCAGAGACAATTCCAAGAACCCACGGTGTATCTTCAAATGACCAACGGCTGAGGCTGAGGACACTGCTGTGCTAGA
Ab6		CGATTCAACCATTCTCCAGAGACAATTCCAAGAACCCACGGTGTATCTTCAAATGACCAACGGCTGAGGCTGAGGACACTGCTGTGCTAGA
Ab7		CGATTCAACCATTCTCCAGAGACAATTCCAAGAACCCACGGTGTATCTTCAAATGACCAACGGCTGAGGCTGAGGACACTGCTGTGCTAGA
Ab8		CGATTCAACCATTCTCCAGAGACAATTCCAAGAACCCACGGTGTATCTTCAAATGACCAACGGCTGAGGCTGAGGACACTGCTGTGCTAGA
Ab9		CGATTCAACCATTCTCCAGAGACAATTCCAAGAACCCACGGTGTATCTTCAAATGACCAACGGCTGAGGCTGAGGACACTGCTGTGCTAGA
Ab10		CGATTCAACCATTCTCCAGAGACAATTCCAAGAACCCACGGTGTATCTTCAAATGACCAACGGCTGAGGCTGAGGACACTGCTGTGCTAGA
Ab11		CGATTCAACCATTCTCCAGAGACAATTCCAAGAACCCACGGTGTATCTTCAAATGACCAACGGCTGAGGCTGAGGACACTGCTGTGCTAGA
Ab12		CGATTCAACCATTCTCCAGAGACAATTCCAAGAACCCACGGTGTATCTTCAAATGACCAACGGCTGAGGACACTGCTGTGCTAGA
Ab13		CGATTCAACCATTCTCCAGAGACAATTCCAAGAACCCACGGTGTATCTTCAAATGACCAACGGCTGAGGACACTGCTGTGCTAGA
Ab14		CGATTCAACCATTCTCCAGAGACAATTCCAAGAACCCACGGTGTATCTTCAAATGACCAACGGCTGAGGACACTGCTGTGCTAGA

Figure 3E - Heavy Chain DNA Sequence

Sequence Name	Sequence	FR4	Constant Region
CDR3	TGGGGCCCAGGACCCCTCGTCACCGTCTCGAGC	TGGGGCCCAGGACCCCTCGTCACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCC
Ab1	GGGACATC	TGGGGCCAAGGGAACCTCTGTACCCGTCCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCC
Ab2	GGGACATC	TGGGGCCAAGGGAACCTCTGTACCCGTCCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCC
Ab3	GGGACATC	TGGGGCCCCGGGACCCCTCGTCACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCC
Ab4	GGGACATC	TGGGGCCAAGGGAACCTCTGTACCCGTCCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCC
Ab5	GGGACATC	TGGGGCCAAGGGAACCTCTGTACCCGTCCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCC
Ab6	GGGACATC	TGGGGCCCCGGGACCCCTCGTCACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCC
Ab7	GGGACATC	TGGGGCCAAGGGAACCTCTGTACCCGTCCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCC
Ab8	GGGACATC	TGGGGCCCCGGGACCCCTCGTCACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCC
Ab9	GGGACATC	TGGGGCCAAGGGAACCTCTGTACCCGTCCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCC
Ab10	GGGACATC	TGGGGCCCCGGGACCCCTCGTCACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCC
Ab11	GGGACATC	TGGGGCCAAGGGAACCTCTGTACCCGTCCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCC
Ab12	GGGACATC	TGGGGCCCCGGGACCCCTCGTCACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCC
Ab13	GATCTTGACTTG	TGGGGCCCCGGGACCCCTCGTCACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCC
Ab14	GGGACATC	TGGGGCCCCGGGACCCCTCGTCACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCC

Figure 3F - Heavy Chain DNA Sequence

Sequence Name	Constant Region
Ab1	AAGAGCACCTCTGGGGCACAGGGCCCTGGCTGGTCAAGGACTACTTCCCGAACCGGTGACGGTGTCTGGAACTCAGGGCC
Ab2	AAGAGCACCTCTGGGGCACAGGGCCCTGGCTGGTCAAGGACTACTTCCCGAACCGGTGACGGTGTCTGGAACTCAGGC
Ab3	AAGAGCACCTCTGGGGCACAGGGCCCTGGCTGGTCAAGGACTACTTCCCGAACCGGTGACGGTGTCTGGAACTCAGGGCC
Ab4	AAGAGCACCTCTGGGGCACAGGGCCCTGGCTGGTCAAGGACTACTTCCCGAACCGGTGACGGTGTCTGGAACTCAGGGCC
Ab5	AAGAGCACCTCTGGGGCACAGGGCCCTGGCTGGTCAAGGACTACTTCCCGAACCGGTGACGGTGTCTGGAACTCAGGGCC
Ab6	AAGAGCACCTCTGGGGCACAGGGCCCTGGCTGGTCAAGGACTACTTCCCGAACCGGTGACGGTGTCTGGAACTCAGGGCC
Ab7	AAGAGCACCTCTGGGGCACAGGGCCCTGGCTGGTCAAGGACTACTTCCCGAACCGGTGACGGTGTCTGGAACTCAGGGCC
Ab8	AAGAGCACCTCTGGGGCACAGGGCCCTGGCTGGTCAAGGACTACTTCCCGAACCGGTGACGGTGTCTGGAACTCAGGGCC
Ab9	AAGAGCACCTCTGGGGCACAGGGCCCTGGCTGGTCAAGGACTACTTCCCGAACCGGTGACGGTGTCTGGAACTCAGGGCC
Ab10	AAGAGCACCTCTGGGGCACAGGGCCCTGGCTGGTCAAGGACTACTTCCCGAACCGGTGACGGTGTCTGGAACTCAGGGCC
Ab11	AAGAGCACCTCTGGGGCACAGGGCCCTGGCTGGTCAAGGACTACTTCCCGAACCGGTGACGGTGTCTGGAACTCAGGGCC
Ab12	AAGAGCACCTCTGGGGCACAGGGCCCTGGCTGGTCAAGGACTACTTCCCGAACCGGTGACGGTGTCTGGAACTCAGGGCC
Ab13	AAGAGCACCTCTGGGGCACAGGGCCCTGGCTGGTCAAGGACTACTTCCCGAACCGGTGACGGTGTCTGGAACTCAGGGCC
Ab14	AAGAGCACCTCTGGGGCACAGGGCCCTGGCTGGTCAAGGACTACTTCCCGAACCGGTGACGGTGTCTGGAACTCAGGGCC

Figure 3G – Heavy Chain DNA Sequence

Sequence Name	Constant Region
Ab1	CTGACCCAGCGCGTGCACACCTTCCGGCTGTCCCTACAGTCAGGACTCTACTCCCTCAGCAGCGTGGTGAACCGTGCCTCCAGCAGC
Ab2	CTGACCCAGCGCGTGCACACCTTCCGGCTGTCCCTACAGTCAGGACTCTACTCCCTCAGCAGCGTGGTGAACCGTGCCTCCAGCAGC
Ab3	CTGACCCAGCGCGTGCACACCTTCCGGCTGTCCCTACAGTCAGGACTCTACTCCCTCAGCAGCGTGGTGAACCGTGCCTCCAGCAGC
Ab4	CTGACCCAGCGCGTGCACACCTTCCGGCTGTCCCTACAGTCAGGACTCTACTCCCTCAGCAGCGTGGTGAACCGTGCCTCCAGCAGC
Ab5	CTGACCCAGCGCGTGCACACCTTCCGGCTGTCCCTACAGTCAGGACTCTACTCCCTCAGCAGCGTGGTGAACCGTGCCTCCAGCAGC
Ab6	CTGACCCAGCGCGTGCACACCTTCCGGCTGTCCCTACAGTCAGGACTCTACTCCCTCAGCAGCGTGGTGAACCGTGCCTCCAGCAGC
Ab7	CTGACCCAGCGCGTGCACACCTTCCGGCTGTCCCTACAGTCAGGACTCTACTCCCTCAGCAGCGTGGTGAACCGTGCCTCCAGCAGC
Ab8	CTGACCCAGCGCGTGCACACCTTCCGGCTGTCCCTACAGTCAGGACTCTACTCCCTCAGCAGCGTGGTGAACCGTGCCTCCAGCAGC
Ab9	CTGACCCAGCGCGTGCACACCTTCCGGCTGTCCCTACAGTCAGGACTCTACTCCCTCAGCAGCGTGGTGAACCGTGCCTCCAGCAGC
Ab10	CTGACCCAGCGCGTGCACACCTTCCGGCTGTCCCTACAGTCAGGACTCTACTCCCTCAGCAGCGTGGTGAACCGTGCCTCCAGCAGC
Ab11	CTGACCCAGCGCGTGCACACCTTCCGGCTGTCCCTACAGTCAGGACTCTACTCCCTCAGCAGCGTGGTGAACCGTGCCTCCAGCAGC
Ab12	CTGACCCAGCGCGTGCACACCTTCCGGCTGTCCCTACAGTCAGGACTCTACTCCCTCAGCAGCGTGGTGAACCGTGCCTCCAGCAGC
Ab13	CTGACCCAGCGCGTGCACACCTTCCGGCTGTCCCTACAGTCAGGACTCTACTCCCTCAGCAGCGTGGTGAACCGTGCCTCCAGCAGC
Ab14	CTGACCCAGCGCGTGCACACCTTCCGGCTGTCCCTACAGTCAGGACTCTACTCCCTCAGCAGCGTGGTGAACCGTGCCTCCAGCAGC

Figure 3H – Heavy Chain DNA Sequence

Sequence Name	Constant Region
Ab1	TTGGGCACCCAGACCTACATCTGCAACAGTGAATCACAAAGCCCAGAACACCAAGGGGACAAGAGAGTTGAGCCAAATCTTGTGACAAA
Ab2	TTGGGCACCCAGACCTACATCTGCAACAGTGAATCACAAAGCCCAGAACACCAAGGGGACAAGAGAGTTGAGCCAAATCTTGTGACAAA
Ab3	TTGGGCACCCAGACCTACATCTGCAACAGTGAATCACAAAGCCCAGAACACCAAGGGGACAAGAGAGTTGAGCCAAATCTTGTGACAAA
Ab4	TTGGGCACCCAGACCTACATCTGCAACAGTGAATCACAAAGCCCAGAACACCAAGGGGACAAGAGAGTTGAGCCAAATCTTGTGACAAA
Ab5	TTGGGCACCCAGACCTACATCTGCAACAGTGAATCACAAAGCCCAGAACACCAAGGGGACAAGAGAGTTGAGCCAAATCTTGTGACAAA
Ab6	TTGGGCACCCAGACCTACATCTGCAACAGTGAATCACAAAGCCCAGAACACCAAGGGGACAAGAGAGTTGAGCCAAATCTTGTGACAAA
Ab7	TTGGGCACCCAGACCTACATCTGCAACAGTGAATCACAAAGCCCAGAACACCAAGGGGACAAGAGAGTTGAGCCAAATCTTGTGACAAA
Ab8	TTGGGCACCCAGACCTACATCTGCAACAGTGAATCACAAAGCCCAGAACACCAAGGGGACAAGAGAGTTGAGCCAAATCTTGTGACAAA
Ab9	TTGGGCACCCAGACCTACATCTGCAACAGTGAATCACAAAGCCCAGAACACCAAGGGGACAAGAGAGTTGAGCCAAATCTTGTGACAAA
Ab10	TTGGGCACCCAGACCTACATCTGCAACAGTGAATCACAAAGCCCAGAACACCAAGGGGACAAGAGAGTTGAGCCAAATCTTGTGACAAA
Ab11	TTGGGCACCCAGACCTACATCTGCAACAGTGAATCACAAAGCCCAGAACACCAAGGGGACAAGAGAGTTGAGCCAAATCTTGTGACAAA
Ab12	TTGGGCACCCAGACCTACATCTGCAACAGTGAATCACAAAGCCCAGAACACCAAGGGGACAAGAGAGTTGAGCCAAATCTTGTGACAAA
Ab13	TTGGGCACCCAGACCTACATCTGCAACAGTGAATCACAAAGCCCAGAACACCAAGGGGACAAGAGAGTTGAGCCAAATCTTGTGACAAA
Ab14	TTGGGCACCCAGACCTACATCTGCAACAGTGAATCACAAAGCCCAGAACACCAAGGGGACAAGAGAGTTGAGCCAAATCTTGTGACAAA

Figure 3I – Heavy Chain DNA Sequence

Sequence	Constant Region
Ab1	ACTCACACATGCCAACCCGTGCCAGCACCTGAACACTCCTGGGGACCCGTCAAGTCTTCCTTCCCCAAAACCAAGGACACCCCTCATG
Ab2	ACTCACACATGCCAACCCGTGCCAGCACCTGAACACTCCTGGGGACCCGTCAAGTCTTCCTTCCCCAAAACCAAGGACACCCCTCATG
Ab3	ACTCACACATGCCAACCCGTGCCAGCACCTGAACACTCCTGGGGACCCGTCAAGTCTTCCTTCCCCAAAACCAAGGACACCCCTCATG
Ab4	ACTCACACATGCCAACCCGTGCCAGCACCTGAACACTCCTGGGGACCCGTCAAGTCTTCCTTCCCCAAAACCAAGGACACCCCTCATG
Ab5	ACTCACACATGCCAACCCGTGCCAGCACCTGAACACTCCTGGGGACCCGTCAAGTCTTCCTTCCCCAAAACCAAGGACACCCCTCATG
Ab6	ACTCACACATGCCAACCCGTGCCAGCACCTGAACACTCCTGGGGACCCGTCAAGTCTTCCTTCCCCAAAACCAAGGACACCCCTCATG
Ab7	ACTCACACATGCCAACCCGTGCCAGCACCTGAACACTCCTGGGGACCCGTCAAGTCTTCCTTCCCCAAAACCAAGGACACCCCTCATG
Ab8	ACTCACACATGCCAACCCGTGCCAGCACCTGAACACTCCTGGGGACCCGTCAAGTCTTCCTTCCCCAAAACCAAGGACACCCCTCATG
Ab9	ACTCACACATGCCAACCCGTGCCAGCACCTGAACACTCCTGGGGACCCGTCAAGTCTTCCTTCCCCAAAACCAAGGACACCCCTCATG
Ab10	ACTCACACATGCCAACCCGTGCCAGCACCTGAACACTCCTGGGGACCCGTCAAGTCTTCCTTCCCCAAAACCAAGGACACCCCTCATG
Ab11	ACTCACACATGCCAACCCGTGCCAGCACCTGAACACTCCTGGGGACCCGTCAAGTCTTCCTTCCCCAAAACCAAGGACACCCCTCATG
Ab12	ACTCACACATGCCAACCCGTGCCAGCACCTGAACACTCCTGGGGACCCGTCAAGTCTTCCTTCCCCAAAACCAAGGACACCCCTCATG
Ab13	ACTCACACATGCCAACCCGTGCCAGCACCTGAACACTCCTGGGGACCCGTCAAGTCTTCCTTCCCCAAAACCAAGGACACCCCTCATG
Ab14	ACTCACACATGCCAACCCGTGCCAGCACCTGAACACTCCTGGGGACCCGTCAAGTCTTCCTTCCCCAAAACCAAGGACACCCCTCATG

Figure 3J – Heavy Chain DNA Sequence

Sequence	Constant Region
Ab1	ATCTCCCGGAAACCCCTGAGGTACATGCCGTGAGGTACATGCCGTGAGGTGAGCAGCACGAAGACCCCTGAGGTCAAGTTCAACTGGTACGGCGCTG
Ab2	ATCTCCCGGAAACCCCTGAGGTACATGCCGTGAGGTGAGCAGCACGAAGACCCCTGAGGTCAAGTTCAACTGGTACGGCGCTG
Ab3	ATCTCCCGGAAACCCCTGAGGTACATGCCGTGAGGTGAGCAGCACGAAGACCCCTGAGGTCAAGTTCAACTGGTACGGCGCTG
Ab4	ATCTCCCGGAAACCCCTGAGGTACATGCCGTGAGGTGAGCAGCACGAAGACCCCTGAGGTCAAGTTCAACTGGTACGGCGCTG
Ab5	ATCTCCCGGAAACCCCTGAGGTACATGCCGTGAGGTGAGCAGCACGAAGACCCCTGAGGTCAAGTTCAACTGGTACGGCGCTG
Ab6	ATCTCCCGGAAACCCCTGAGGTACATGCCGTGAGGTGAGCAGCACGAAGACCCCTGAGGTCAAGTTCAACTGGTACGGCGCTG
Ab7	ATCTCCCGGAAACCCCTGAGGTACATGCCGTGAGGTGAGCAGCACGAAGACCCCTGAGGTCAAGTTCAACTGGTACGGCGCTG
Ab8	ATCTCCCGGAAACCCCTGAGGTACATGCCGTGAGGTGAGCAGCACGAAGACCCCTGAGGTCAAGTTCAACTGGTACGGCGCTG
Ab9	ATCTCCCGGAAACCCCTGAGGTACATGCCGTGAGGTGAGCAGCACGAAGACCCCTGAGGTCAAGTTCAACTGGTACGGCGCTG
Ab10	ATCTCCCGGAAACCCCTGAGGTACATGCCGTGAGGTGAGCAGCACGAAGACCCCTGAGGTCAAGTTCAACTGGTACGGCGCTG
Ab11	ATCTCCCGGAAACCCCTGAGGTACATGCCGTGAGGTGAGCAGCACGAAGACCCCTGAGGTCAAGTTCAACTGGTACGGCGCTG
Ab12	ATCTCCCGGAAACCCCTGAGGTACATGCCGTGAGGTGAGCAGCACGAAGACCCCTGAGGTCAAGTTCAACTGGTACGGCGCTG
Ab13	ATCTCCCGGAAACCCCTGAGGTACATGCCGTGAGGTGAGCAGCACGAAGACCCCTGAGGTCAAGTTCAACTGGTACGGCGCTG
Ab14	ATCTCCCGGAAACCCCTGAGGTACATGCCGTGAGGTGAGCAGCACGAAGACCCCTGAGGTCAAGTTCAACTGGTACGGCGCTG

Figure 3K – Heavy Chain DNA Sequence

Sequence Name	Constant Region
Ab1	GAGGTGCATAATGCCAAGACAAAGCCGGGGAGGAGCAGTACGCCAGCACGTACCGTACCGTGTGGTCAGCGTCTCACCCTGCACCGAC
Ab2	GAGGTGCATAATGCCAAGACAAAGCCGGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCTCACCCTGCACCGAC
Ab3	GAGGTGCATAATGCCAAGACAAAGCCGGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCTCACCCTGCACCGAC
Ab4	GAGGTGCATAATGCCAAGACAAAGCCGGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCTCACCCTGCACCGAC
Ab5	GAGGTGCATAATGCCAAGACAAAGCCGGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCTCACCCTGCACCGAC
Ab6	GAGGTGCATAATGCCAAGACAAAGCCGGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCTCACCCTGCACCGAC
Ab7	GAGGTGCATAATGCCAAGACAAAGCCGGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCTCACCCTGCACCGAC
Ab8	GAGGTGCATAATGCCAAGACAAAGCCGGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCTCACCCTGCACCGAC
Ab9	GAGGTGCATAATGCCAAGACAAAGCCGGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCTCACCCTGCACCGAC
Ab10	GAGGTGCATAATGCCAAGACAAAGCCGGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCTCACCCTGCACCGAC
Ab11	GAGGTGCATAATGCCAAGACAAAGCCGGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCTCACCCTGCACCGAC
Ab12	GAGGTGCATAATGCCAAGACAAAGCCGGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCTCACCCTGCACCGAC
Ab13	GAGGTGCATAATGCCAAGACAAAGCCGGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCTCACCCTGCACCGAC
Ab14	GAGGTGCATAATGCCAAGACAAAGCCGGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCTCACCCTGCACCGAC

Figure 3L – Heavy Chain DNA Sequence

Sequence Name	Constant Region
Ab1	TGGCTGAATGCCAAGGAGTACAAGGTCAAGGTCTCCAAACAAAGCCCTCCAGCCCCATCGAGAAAACCATCTCCAAAGCCAAGGGCAG
Ab2	TGGCTGAATGCCAAGGAGTACAAGGTCAAGGTCTCCAAACAAAGCCCTCCAGCCCCATCGAGAAAACCATCTCCAAAGCCAAGGGCAG
Ab3	TGGCTGAATGCCAAGGAGTACAAGGTCAAGGTCTCCAAACAAAGCCCTCCAGCCCCATCGAGAAAACCATCTCCAAAGCCAAGGGCAG
Ab4	TGGCTGAATGCCAAGGAGTACAAGGTCAAGGTCTCCAAACAAAGCCCTCCAGCCCCATCGAGAAAACCATCTCCAAAGCCAAGGGCAG
Ab5	TGGCTGAATGCCAAGGAGTACAAGGTCAAGGTCTCCAAACAAAGCCCTCCAGCCCCATCGAGAAAACCATCTCCAAAGCCAAGGGCAG
Ab6	TGGCTGAATGCCAAGGAGTACAAGGTCAAGGTCTCCAAACAAAGCCCTCCAGCCCCATCGAGAAAACCATCTCCAAAGCCAAGGGCAG
Ab7	TGGCTGAATGCCAAGGAGTACAAGGTCAAGGTCTCCAAACAAAGCCCTCCAGCCCCATCGAGAAAACCATCTCCAAAGCCAAGGGCAG
Ab8	TGGCTGAATGCCAAGGAGTACAAGGTCAAGGTCTCCAAACAAAGCCCTCCAGCCCCATCGAGAAAACCATCTCCAAAGCCAAGGGCAG
Ab9	TGGCTGAATGCCAAGGAGTACAAGGTCTCCAAACAAAGCCCTCCAGCCCCATCGAGAAAACCATCTCCAAAGCCAAGGGCAG
Ab10	TGGCTGAATGCCAAGGAGTACAAGGTCTCCAAACAAAGCCCTCCAGCCCCATCGAGAAAACCATCTCCAAAGCCAAGGGCAG
Ab11	TGGCTGAATGCCAAGGAGTACAAGGTCTCCAAACAAAGCCCTCCAGCCCCATCGAGAAAACCATCTCCAAAGCCAAGGGCAG
Ab12	TGGCTGAATGCCAAGGAGTACAAGGTCTCCAAACAAAGCCCTCCAGCCCCATCGAGAAAACCATCTCCAAAGCCAAGGGCAG
Ab13	TGGCTGAATGCCAAGGAGTACAAGGTCTCCAAACAAAGCCCTCCAGCCCCATCGAGAAAACCATCTCCAAAGCCAAGGGCAG
Ab14	TGGCTGAATGCCAAGGAGTACAAGGTCTCCAAACAAAGCCCTCCAGCCCCATCGAGAAAACCATCTCCAAAGCCAAGGGCAG

Figure 3M – Heavy Chain DNA Sequence

Sequence Name	Constant Region
Ab1	CCCCGAGAACACAGGTGTACACCCATCCGGGAGGATGACCAAGAACCAACTACAGGTCAGCCCTGACCTGCCCTGGTCAAAGGCTTC
Ab2	CCCCGAGAACACAGGTGTACACCCATCCGGGAGGATGACCAAGAACCAACTACAGGTCAGCCCTGACCTGCCCTGGTCAAAGGCTTC
Ab3	CCCCGAGAACACAGGTGTACACCCATCCGGGAGGATGACCAAGAACCAACTACAGGTCAGCCCTGACCTGCCCTGGTCAAAGGCTTC
Ab4	CCCCGAGAACACAGGTGTACACCCATCCGGGAGGATGACCAAGAACCAACTACAGGTCAGCCCTGACCTGCCCTGGTCAAAGGCTTC
Ab5	CCCCGAGAACACAGGTGTACACCCATCCGGGAGGATGACCAAGAACCAACTACAGGTCAGCCCTGACCTGCCCTGGTCAAAGGCTTC
Ab6	CCCCGAGAACACAGGTGTACACCCATCCGGGAGGATGACCAAGAACCAACTACAGGTCAGCCCTGACCTGCCCTGGTCAAAGGCTTC
Ab7	CCCCGAGAACACAGGTGTACACCCATCCGGGAGGATGACCAAGAACCAACTACAGGTCAGCCCTGACCTGCCCTGGTCAAAGGCTTC
Ab8	CCCCGAGAACACAGGTGTACACCCATCCGGGAGGATGACCAAGAACCAACTACAGGTCAGCCCTGACCTGCCCTGGTCAAAGGCTTC
Ab9	CCCCGAGAACACAGGTGTACACCCATCCGGGAGGATGACCAAGAACCAACTACAGGTCAGCCCTGACCTGCCCTGGTCAAAGGCTTC
Ab10	CCCCGAGAACACAGGTGTACACCCATCCGGGAGGATGACCAAGAACCAACTACAGGTCAGCCCTGACCTGCCCTGGTCAAAGGCTTC
Ab11	CCCCGAGAACACAGGTGTACACCCATCCGGGAGGATGACCAAGAACCAACTACAGGTCAGCCCTGACCTGCCCTGGTCAAAGGCTTC
Ab12	CCCCGAGAACACAGGTGTACACCCATCCGGGAGGATGACCAAGAACCAACTACAGGTCAGCCCTGACCTGCCCTGGTCAAAGGCTTC
Ab13	CCCCGAGAACACAGGTGTACACCCATCCGGGAGGATGACCAAGAACCAACTACAGGTCAGCCCTGACCTGCCCTGGTCAAAGGCTTC
Ab14	CCCCGAGAACACAGGTGTACACCCATCCGGGAGGATGACCAAGAACCAACTACAGGTCAGCCCTGACCTGCCCTGGTCAAAGGCTTC

Figure 3N – Heavy Chain DNA Sequence

Sequence Name	Constant Region
Ab1	TATCCCAGGGACATGCCGTGGAGGGAGAACAACTACAGGCAATGGCGAGCCCTCCCCGGTGGACTCCGACGGC
Ab2	TATCCCAGGGACATGCCGTGGAGGGAGAACAACTACAGGCAATGGCGAGCCCTCCCCGGTGGACTCCGACGGC
Ab3	TATCCCAGGGACATGCCGTGGAGGGAGAACAACTACAGGCAATGGCGAGCCCTCCCCGGTGGACTCCGACGGC
Ab4	TATCCCAGGGACATGCCGTGGAGGGAGAACAACTACAGGCAATGGCGAGCCCTCCCCGGTGGACTCCGACGGC
Ab5	TATCCCAGGGACATGCCGTGGAGGGAGAACAACTACAGGCAATGGCGAGCCCTCCCCGGTGGACTCCGACGGC
Ab6	TATCCCAGGGACATGCCGTGGAGGGAGAACAACTACAGGCAATGGCGAGCCCTCCCCGGTGGACTCCGACGGC
Ab7	TATCCCAGGGACATGCCGTGGAGGGAGAACAACTACAGGCAATGGCGAGCCCTCCCCGGTGGACTCCGACGGC
Ab8	TATCCCAGGGACATGCCGTGGAGGGAGAACAACTACAGGCAATGGCGAGCCCTCCCCGGTGGACTCCGACGGC
Ab9	TATCCCAGGGACATGCCGTGGAGGGAGAACAACTACAGGCAATGGCGAGCCCTCCCCGGTGGACTCCGACGGC
Ab10	TATCCCAGGGACATGCCGTGGAGGGAGAACAACTACAGGCAATGGCGAGCCCTCCCCGGTGGACTCCGACGGC
Ab11	TATCCCAGGGACATGCCGTGGAGGGAGAACAACTACAGGCAATGGCGAGCCCTCCCCGGTGGACTCCGACGGC
Ab12	TATCCCAGGGACATGCCGTGGAGGGAGAACAACTACAGGCAATGGCGAGCCCTCCCCGGTGGACTCCGACGGC
Ab13	TATCCCAGGGACATGCCGTGGAGGGAGAACAACTACAGGCAATGGCGAGCCCTCCCCGGTGGACTCCGACGGC
Ab14	TATCCCAGGGACATGCCGTGGAGGGAGAACAACTACAGGCAATGGCGAGCCCTCCCCGGTGGACTCCGACGGC

Figure 30 - Heavy Chain DNA Sequence

Sequence Name	Constant Region
Ab1	TCCCTCTTCTCTACAGGAAGCTCACCGTGGACAAAGGAGCAGGTTGGCAGCAGGGAAACGCTTCTCATGCTCCGTGATGCATGAGGCTCTG
Ab2	TCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAAGGAGCAGGTTGGCAGCAGGGAAACGCTTCTCATGCTCCGTGATGCATGAGGCTCTG
Ab3	TCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAAGGAGCAGGTTGGCAGCAGGGAAACGCTTCTCATGCTCCGTGATGCATGAGGCTCTG
Ab4	TCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAAGGAGCAGGTTGGCAGCAGGGAAACGCTTCTCATGCTCCGTGATGCATGAGGCTCTG
Ab5	TCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAAGGAGCAGGTTGGCAGCAGGGAAACGCTTCTCATGCTCCGTGATGCATGAGGCTCTG
Ab6	TCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAAGGAGCAGGTTGGCAGCAGGGAAACGCTTCTCATGCTCCGTGATGCATGAGGCTCTG
Ab7	TCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAAGGAGCAGGTTGGCAGCAGGGAAACGCTTCTCATGCTCCGTGATGCATGAGGCTCTG
Ab8	TCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAAGGAGCAGGTTGGCAGCAGGGAAACGCTTCTCATGCTCCGTGATGCATGAGGCTCTG
Ab9	TCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAAGGAGCAGGTTGGCAGCAGGGAAACGCTTCTCATGCTCCGTGATGCATGAGGCTCTG
Ab10	TCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAAGGAGCAGGTTGGCAGCAGGGAAACGCTTCTCATGCTCCGTGATGCATGAGGCTCTG
Ab11	TCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAAGGAGCAGGTTGGCAGCAGGGAAACGCTTCTCATGCTCCGTGATGCATGAGGCTCTG
Ab12	TCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAAGGAGCAGGTTGGCAGCAGGGAAACGCTTCTCATGCTCCGTGATGCATGAGGCTCTG
Ab13	TCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAAGGAGCAGGTTGGCAGCAGGGAAACGCTTCTCATGCTCCGTGATGCATGAGGCTCTG
Ab14	TCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAAGGAGCAGGTTGGCAGCAGGGAAACGCTTCTCATGCTCCGTGATGCATGAGGCTCTG

Figure 3P – Heavy Chain DNA Sequence

Sequence Name	Constant Region	SEQ ID NO:
Ab1	CACAAACCACTACACGGCAGAAAGAGCCTCTCCCTGTCTCCGGGTAATGA	11)
Ab2	CACAAACCACTACACGGCAGAAAGAGCCTCTCCCTGTCTCCGGGTAATGA	51)
Ab3	CACAAACCACTACACGGCAGAAAGAGCCTCTCCCTGTCTCCGGGTAATGA	91)
Ab4	CACAAACCACTACACGGCAGAAAGAGCCTCTCCCTGTCTCCGGGTAATGA	131)
Ab5	CACAAACCACTACACGGCAGAAAGAGCCTCTCCCTGTCTCCGGGTAATGA	171)
Ab6	CACAAACCACTACACGGCAGAAAGAGCCTCTCCCTGTCTCCGGGTAATGA	211)
Ab7	CACAAACCACTACACGGCAGAAAGAGCCTCTCCCTGTCTCCGGGTAATGA	251)
Ab8	CACAAACCACTACACGGCAGAAAGAGCCTCTCCCTGTCTCCGGGTAATGA	291)
Ab9	CACAAACCACTACACGGCAGAAAGAGCCTCTCCCTGTCTCCGGGTAATGA	331)
Ab10	CACAAACCACTACACGGCAGAAAGAGCCTCTCCCTGTCTCCGGGTAATGA	371)
Ab11	CACAAACCACTACACGGCAGAAAGAGCCTCTCCCTGTCTCCGGGTAATGA	411)
Ab12	CACAAACCACTACACGGCAGAAAGAGCCTCTCCCTGTCTCCGGGTAATGA	451)
Ab13	CACAAACCACTACACGGCAGAAAGAGCCTCTCCCTGTCTCCGGGTAATGA	491)
Ab14	CACAAACCACTACACGGCAGAAAGAGCCTCTCCCTGTCTCCGGGTAATGA	531)

Figure 4A - Light Chain DNA Sequence

Sequence	FR1
Name	
Ab1	CAAGTGCTGACCCAGACTGCATCCCCGGTGTCTGCAGCTGTGGAAAGCACAGTCACCATCAATTGC
Ab2	CAAGTGCTGACCCAGTCTCCATCCTCCCTGTGCATCTGTAGGAGACAGAGTCACCATCAATTGC
Ab3	CAAGTGCTGACCCAGTCTCCATCCTCCCGTGTGCATCTGTAGGAGACAGAGTCACCATCAATTGC
Ab4	CAAGTGCTGACCCAGTCTCCATCCTCCCGTGTGCATCTGTAGGAGACAGAGTCACCATCAATTGC
Ab5	CAAGTGCTGACCCAGTCTCCATCCTCCCGTGTGCATCTGTAGGAGACAGAGTCACCATCAATTGC
Ab6	CAAGTGCTGACCCAGTCTCCATCCTCCCGTGTGCATCTGTAGGAGACAGAGTCACCATCAATTGC
Ab7	CAAGTGCTGACCCAGTCTCCATCCTCCCGTGTGCATCTGTAGGAGACAGAGTCACCATCAATTGC
Ab8	CAAGTGCTGACCCAGTCTCCATCCTCCCGTGTGCATCTGTAGGAGACAGAGTCACCATCAATTGC
Ab9	CAAGTGCTGACCCAGACTCCATCCCCGGTGTCTGCAGCTGTGGAAAGCACAGTCACCATCAATTGC
Ab10	CAAGTGCTGACCCAGTCTCCATCCCCGGTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGC
Ab11	CAAGTGCTGACCCAGTCTCCATCCCCGGTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGC
Ab12	CAAGTGCTGACCCAGACTCCATCCCCGGTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGC
Ab13	CAAGTGCTGACCCAGACTCCATCTCCAAAGTCTGTCCCTGTGGAGACACAGTCACCATCAATTGC
Ab14	CAAGTGCTGACCCAGTCTCCATCTCCAAAGTCTGTCCCTGTGGAGACACAGTCACCATCAATTGC

Figure 4B - Light Chain DNA Sequence

Sequence	FR2
Name	
Ab1	TGGTATCAGCAGAAACCCAGGGCAGCCTCCAAAGCAACTGATCTAT
Ab2	TGGTATCAGCAGAAACCCAGGGAAAGTTCTAAAGCAACTGATCTAT
Ab3	TGGTATCAGCAGAAACCCAGGGCAGCCTCCAAACAACGATCTAT
Ab4	TGGTATCAGCAGAAACCCAGGGAAAGTTCTAAAGCAACTGATCTAT
Ab5	TGGTATCAGCAGAAACCCAGGGCAGCCTCCAAACAACGATCTAT
Ab6	TGGTATCAGCAGAAACCCAGGGAAAGTTCTAAAGCAACTGATCTAT
Ab7	TGGTATCAGCAGAAACCCAGGGCAGCCTCCAAACAACGATCTAT
Ab8	TGGTATCAGCAGAAACCCAGGGCAGCCTCCAAACAACGATCTAT
Ab9	TGGTATCAGCAGAAACCCAGGGCAGCCTCCAAAGCAACTGATCTAT
Ab10	TGGTATCAGCAGAAACCCAGGGCAGCCTCCAAAGCAACTGATCTAT
Ab11	TGGTATCAGCAGAAACCCAGGGCAGCCTCCAAAGCAACTGATCTAT
Ab12	TGGTATCAGCAGAAACCCAGGGCAGCCTCCAAAGCAACTGATCTAT
Ab13	TGGTATCAGCAGAAACCCAGGGCAGCCTCCAAAGCAACTGATCTAT
Ab14	TGGTATCAGCAGAAACCCAGGGCAGCCTCCAAAGCAACTGATCTAT

Figure 4C - Light Chain DNA Sequence

Sequence	Name	CDR2	FR3
	Ab1	TCTACATCCACTCTGGCATCT	GGGGTCTCATCGGGTTCAAAGGCAGTGGATCTGGACACAGTTCACTCTACCA
	Ab2	TCTACATCCACTCTGGCATCT	GGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGACAGATTCACTCTACCA
	Ab3	TCTACATCCACTCTGGCATCT	GGGGTCCCATCGGGTTCAGTGGCAGTGGATCTGGACACAGTTCACTCTACCA
	Ab4	GATGCATCCACTCTGGCTCT	GGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGACAGATTCACTCTACCA
	Ab5	GATGCATCCACTCTGGCATCT	GGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGACAGATTCACTCTACCA
	Ab6	GATGCATCCACTCTGGCATCT	GGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGACAGATTCACTCTACCA
	Ab7	TCTACATCCACTCTGGCATCT	GGGGTCTCATCGCATTAAAGGCAGTGGATCTGGACACAGTTCACTCTACCA
	Ab8	TCTACATCCACTCTGGCATCT	GGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGACAGATTCACTCTACCA
	Ab9	TCTACGTCCACTCTGGCATCT	GGGGTCTCATCGCATTAAAGGCAGTGGATCTGGACACAGATTCACTCTACCA
	Ab10	TCTACATCCACTCTGGCATCT	GGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGACAGATTCACTCTACCA
	Ab11	TCTACATCCACTCTGGCATCT	GGGGTCTCATCGGGTCAAAGGCAGTGGATCTGGACACAGTTCACTCTACCA
	Ab12	TCTACATCCACTCTGGCATCT	GGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGACAGATTCACTCTACCA
	Ab13	GATGCATCCAAACTGGCATCT	GGGGTCCCATCGGGTTCAGTGGCAGTGGATCTGGACAGATTCACTCTACCA
	Ab14	TCTACATCCACTCTGGCATCT	GGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGACAGATTCACTCTACCA

Figure 4D - Light Chain DNA Sequence

Sequence	Name	FR3	CDR3
	Ab1	TCAGGCACCTGGAGTGTGCCACCTTACTACTGT	CTAGGCAGTTATGATTGTAGTAGTGGTGGATTGTTTGT
	Ab2	TCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGT	CTAGGCAGTTATGATTGTAGTAGTGGTGGATTGTTTGT
	Ab3	TCAGGGGGTGCAGTGTAAAGATGTTGCAACTTATTACTGT	CTAGGCAGTTATGATTGTACTAATGGTGGATTGTTTGT
	Ab4	TCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGT	CTAGGCAGTTATGATTGTACTAATGGTGGATTGTTTGT
	Ab5	TCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGT	CTAGGCAGTTATGATTGTACTAATGGTGGATTGTTTGT
	Ab6	TCAGGCACGTGCAGTGTAAAGATGTTGCAACTTATTACTGT	CTAGGCAGTTATGATTGTACTAATGGTGGATTGTTTGT
	Ab7	TCAGGCACGTGCAGTGTAAAGATGTTGCAACTTATTACTGT	CTAGGCAGTTATGATTGTACTAATGGTGGATTGTTTGT
	Ab8	TCAGGCACGTGCAGTGTAAAGATGTTGCAACTTATTACTGT	CTAGGCAGTTATGATTGTACTAATGGTGGATTGTTTGT
	Ab9	TCAGGCACGTGCAGTGTAAAGATGTTGCAACTTATTACTGT	CTAGGCAGTTATGATTGTACTAATGGTGGATTGTTTGT
	Ab10	TCAGGCACGTGCAGTGTAAAGATGTTGCAACTTATTACTGT	CTAGGCAGTTATGATTGTACTAATGGTGGATTGTTTGT
	Ab11	TCAGGCACGTGCAGCCTGAAGATGTTGCAACTTATTACTGT	CTAGGCAGTTATGATTGTACTAATGGTGGATTGTTTGT
	Ab12	TCAGTGGCTGCAGTGTAAAGATGTTGCAACTTATTACTGT	GGAGGCTACAGAAGTGTAGTAGTGGTGGATTGTTGCT
	Ab13	TCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGT	CTAGGCAGTTATGATTGTACTAATGGTGGATTGTTTGT
	Ab14		

Figure 4E – Light Chain DNA Sequence

Sequence Name	FR4	Constant Region
Ab1	TTCGGGGAGGGACCGAGGTGGTGGTCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTGCCATCTGATGAGCAGTTG
Ab2	TTCGGGGAGGAACCAAGGTGGAAATCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTGCCATCTGATGAGCAGTTG
Ab3	TTCGGGGAGGAACCAAGGTGGAAATCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTGCCATCTGATGAGCAGTTG
Ab4	TTCGGGGAGGGACCGAGGTGGTGGTCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTGCCATCTGATGAGCAGTTG
Ab5	TTCGGGGAGGAACCAAGGTGGAAATCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTGCCATCTGATGAGCAGTTG
Ab6	TTCGGGGAGGAACCAAGGTGGAAATCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTGCCATCTGATGAGCAGTTG
Ab7	TTCGGGGAGGGACCGAGGTGGTGGTCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTGCCATCTGATGAGCAGTTG
Ab8	TTCGGGGAGGAACCCAGGTGGAAATCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTGCCATCTGATGAGCAGTTG
Ab9	TTCGGGGAGGGACCGAGGTGGTCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTGCCATCTGATGAGCAGTTG
Ab10	TTCGGGGAGGAACCAAGGTGGAAATCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTGCCATCTGATGAGCAGTTG
Ab11	TTCGGGGAGGGACCGAGGTGGTCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTGCCATCTGATGAGCAGTTG
Ab12	TTCGGGGAGGAACCAAGGTGGAAATCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTGCCATCTGATGAGCAGTTG
Ab13	TTCGGGGAGGGACCGAGGTGGTGGTCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTGCCATCTGATGAGCAGTTG
Ab14	TTCGGGGAGGAACCAAGGTGGAAATCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTGCCATCTGATGAGCAGTTG

Figure 4F – Light Chain DNA Sequence

Sequence Name	Constant Region
Ab1	AAATCTGGAAACTGCCTCTGTTGCGCTGCTGAATAACTCTATCCAGAGGGCCAAGGTACAGGGAAAGGGATAACGCC
Ab2	AAATCTGGAAACTGCCTCTGTTGCGCTGCTGAATAACTCTATCCAGAGGGCCAAGGTACAGGGAAAGGGATAACGCC
Ab3	AAATCTGGAAACTGCCTCTGTTGCGCTGCTGAATAACTCTATCCAGAGGGCCAAGGTACAGGGAAAGGGATAACGCC
Ab4	AAATCTGGAAACTGCCTCTGTTGCGCTGCTGAATAACTCTATCCAGAGGGCCAAGGTACAGGGAAAGGGATAACGCC
Ab5	AAATCTGGAAACTGCCTCTGTTGCGCTGCTGAATAACTCTATCCAGAGGGCCAAGGTACAGGGAAAGGGATAACGCC
Ab6	AAATCTGGAAACTGCCTCTGTTGCGCTGCTGAATAACTCTATCCAGAGGGCCAAGGTACAGGGAAAGGGATAACGCC
Ab7	AAATCTGGAAACTGCCTCTGTTGCGCTGCTGAATAACTCTATCCAGAGGGCCAAGGTACAGGGAAAGGGATAACGCC
Ab8	AAATCTGGAAACTGCCTCTGTTGCGCTGCTGAATAACTCTATCCAGAGGGCCAAGGTACAGGGAAAGGGATAACGCC
Ab9	AAATCTGGAAACTGCCTCTGTTGCGCTGCTGAATAACTCTATCCAGAGGGCCAAGGTACAGGGAAAGGGATAACGCC
Ab10	AAATCTGGAAACTGCCTCTGTTGCGCTGCTGAATAACTCTATCCAGAGGGCCAAGGTACAGGGAAAGGGATAACGCC
Ab11	AAATCTGGAAACTGCCTCTGTTGCGCTGCTGAATAACTCTATCCAGAGGGCCAAGGTACAGGGAAAGGGATAACGCC
Ab12	AAATCTGGAAACTGCCTCTGTTGCGCTGCTGAATAACTCTATCCAGAGGGCCAAGGTACAGGGAAAGGGATAACGCC
Ab13	AAATCTGGAAACTGCCTCTGTTGCGCTGCTGAATAACTCTATCCAGAGGGCCAAGGTACAGGGAAAGGGATAACGCC
Ab14	AAATCTGGAAACTGCCTCTGTTGCGCTGCTGAATAACTCTATCCAGAGGGCCAAGGTACAGGGAAAGGGATAACGCC

Figure 4G - Light Chain DNA Sequence

Sequence Name	Constant Region
Ab1	TCCATCGGGTAACTCCCAAGGAGAGTTGTCACAGAGGACAGCAAGGACACCTACAGGCCCTCAGGAGCACCTCAGGCCCTGACGGCTGAG
Ab2	TCCATCGGGTAACTCCCAGGAGAGTTGTCACAGAGGACAGCAAGGACACCTACAGGCCCTCAGGAGCACCTCAGGCCCTGACGGCTGAG
Ab3	TCCATCGGGTAACTCCCAGGAGAGTTGTCACAGAGGACAGCAAGGACACCTACAGGCCCTCAGGAGCACCTCAGGCCCTGACGGCTGAG
Ab4	TCCATCGGGTAACTCCCAGGAGAGTTGTCACAGAGGACAGCAAGGACACCTACAGGCCCTCAGGAGCACCTCAGGCCCTGACGGCTGAG
Ab5	TCCATCGGGTAACTCCCAGGAGAGTTGTCACAGAGGACAGCAAGGACACCTACAGGCCCTCAGGAGCACCTCAGGCCCTGACGGCTGAG
Ab6	TCCATCGGGTAACTCCCAGGAGAGTTGTCACAGAGGACAGCAAGGACACCTACAGGCCCTCAGGAGCACCTCAGGCCCTGACGGCTGAG
Ab7	TCCATCGGGTAACTCCCAGGAGAGTTGTCACAGAGGACAGCAAGGACACCTACAGGCCCTCAGGAGCACCTCAGGCCCTGACGGCTGAG
Ab8	TCCATCGGGTAACTCCCAGGAGAGTTGTCACAGAGGACAGCAAGGACACCTACAGGCCCTCAGGAGCACCTCAGGCCCTGACGGCTGAG
Ab9	TCCATCGGGTAACTCCCAGGAGAGTTGTCACAGAGGACAGCAAGGACACCTACAGGCCCTCAGGAGCACCTCAGGCCCTGACGGCTGAG
Ab10	TCCATCGGGTAACTCCCAGGAGAGTTGTCACAGAGGACAGCAAGGACACCTACAGGCCCTCAGGAGCACCTCAGGCCCTGACGGCTGAG
Ab11	TCCATCGGGTAACTCCCAGGAGAGTTGTCACAGAGGACAGCAAGGACACCTACAGGCCCTCAGGAGCACCTCAGGCCCTGACGGCTGAG
Ab12	TCCATCGGGTAACTCCCAGGAGAGTTGTCACAGAGGACAGCAAGGACACCTACAGGCCCTCAGGAGCACCTCAGGCCCTGACGGCTGAG
Ab13	TCCATCGGGTAACTCCCAGGAGAGTTGTCACAGAGGACAGCAAGGACACCTACAGGCCCTCAGGAGCACCTCAGGCCCTGACGGCTGAG
Ab14	TCCATCGGGTAACTCCCAGGAGAGTTGTCACAGAGGACAGCAAGGACACCTACAGGCCCTCAGGAGCACCTCAGGCCCTGACGGCTGAG

Figure 4H - Light Chain DNA Sequence

Sequence Name	Constant Region
Ab1	CAAAGCAGACTACGAGAACACAAAGTCTACGCCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC
Ab2	CAAAGCAGACTACGAGAACACAAAGTCTACGCCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC
Ab3	CAAAGCAGACTACGAGAACACAAAGTCTACGCCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC
Ab4	CAAAGCAGACTACGAGAACACAAAGTCTACGCCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC
Ab5	CAAAGCAGACTACGAGAACACAAAGTCTACGCCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC
Ab6	CAAAGCAGACTACGAGAACACAAAGTCTACGCCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC
Ab7	CAAAGCAGACTACGAGAACACAAAGTCTACGCCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC
Ab8	CAAAGCAGACTACGAGAACACAAAGTCTACGCCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC
Ab9	CAAAGCAGACTACGAGAACACAAAGTCTACGCCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC
Ab10	CAAAGCAGACTACGAGAACACAAAGTCTACGCCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC
Ab11	CAAAGCAGACTACGAGAACACAAAGTCTACGCCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC
Ab12	CAAAGCAGACTACGAGAACACAAAGTCTACGCCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC
Ab13	CAAAGCAGACTACGAGAACACAAAGTCTACGCCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC
Ab14	CAAAGCAGACTACGAGAACACAAAGTCTACGCCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC

Figure 4I - Light Chain DNA Sequence

Sequence Name	Sequence	ID NO:
Ab1	AGGGGAGAGTGTAG	31)
Ab2	AGGGGAGAGTGTAG	71)
Ab3	AGGGGAGAGTGTAG	111)
Ab4	AGGGGAGAGTGTAG	151)
Ab5	AGGGGAGAGTGTAG	191)
Ab6	AGGGGAGAGTGTAG	231)
Ab7	AGGGGAGAGTGTAG	271)
Ab8	AGGGGAGAGTGTAG	311)
Ab9	AGGGGAGAGTGTAG	351)
Ab10	AGGGGAGAGTGTAG	391)
Ab11	AGGGGAGAGTGTAG	431)
Ab12	AGGGGAGAGTGTAG	471)
Ab13	AGGGGAGAGTGTAG	511)
Ab14	AGGGGAGAGTGTAG	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		FR2		FR3		FR4		Constant Region		SEQ ID NO:
	Coordinates	SEQ ID NO:	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	SEQ ID	CDR1 NO: Coordinates	SEQ ID	CDR2 NO: Coordinates	SEQ ID	CDR3 NO: Coordinates	SEQ ID
	Coordinates							
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: Coordinates	FR2 SEQ ID NO: Coordinates	SEQ ID NO: Coordinates	FR3 SEQ ID NO: Coordinates	SEQ ID NO: Coordinates	FR4 SEQ ID NO: Coordinates	SEQ ID NO: Coordinates	Constant Region SEQ ID NO: Coordinates	SEQ ID NO: Coordinates
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

Heavy Chain DNA Sequence Features							
Antibody	Variable Region Coordinates	SEQ ID NO: Coordinates					
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		SEQ									
	FR1 Coordinates	SEQ ID	FR2 Coordinates	SEQ ID	FR3 Coordinates	SEQ ID	FR4 Coordinates	SEQ ID	FR4 Coordinates	SEQ ID	Constant Region	SEQ ID
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

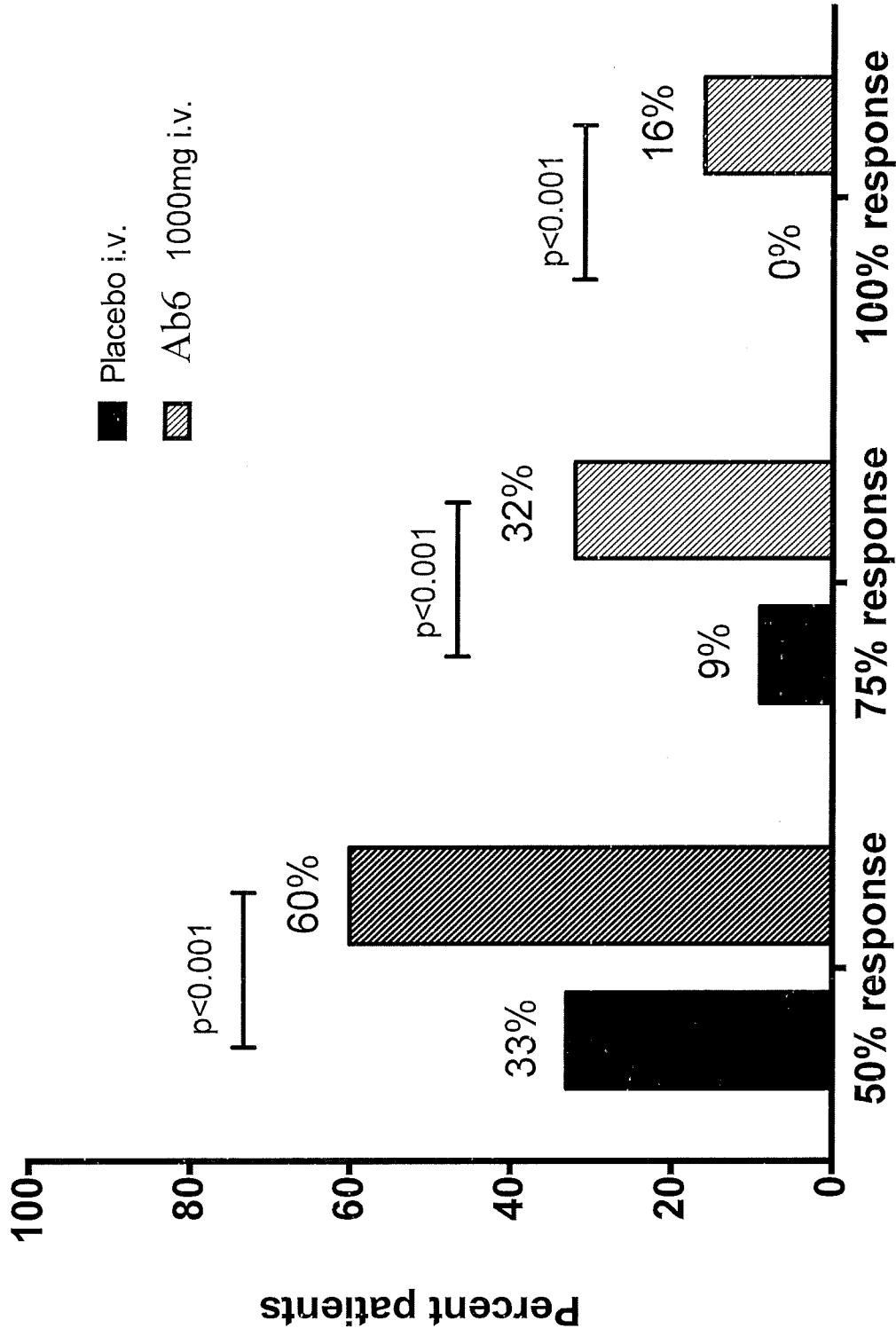
Antibody	Variable Region Coordinates	SEQ ID		SEQ ID		SEQ ID		SEQ ID	
		CDR1 NO: Coordinates	NO: Coordinates	CDR2 NO: Coordinates	NO: Coordinates	CDR3 NO: Coordinates	NO: Coordinates	SEQ ID NO:	
Ab1	1-339	32	67-105	34	151-171	36	268-306	38	
Ab2	1-339	72	67-105	74	151-171	76	268-306	78	
Ab3	1-339	112	67-105	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 1.2  
Light Chain DNA Sequence Features

Antibody	FR1 Coordinates	SEQ ID NO: Coordinates						
Ab1	1-66	33 106-150		35 172-267		37 307-339		39 340-660
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		

# Responders at all three time-points

FIG. 13



# Median % change from baseline: migraine days per month

Median (±IQR) percentage change from baseline in migraine days per month: AB6 versus Placebo

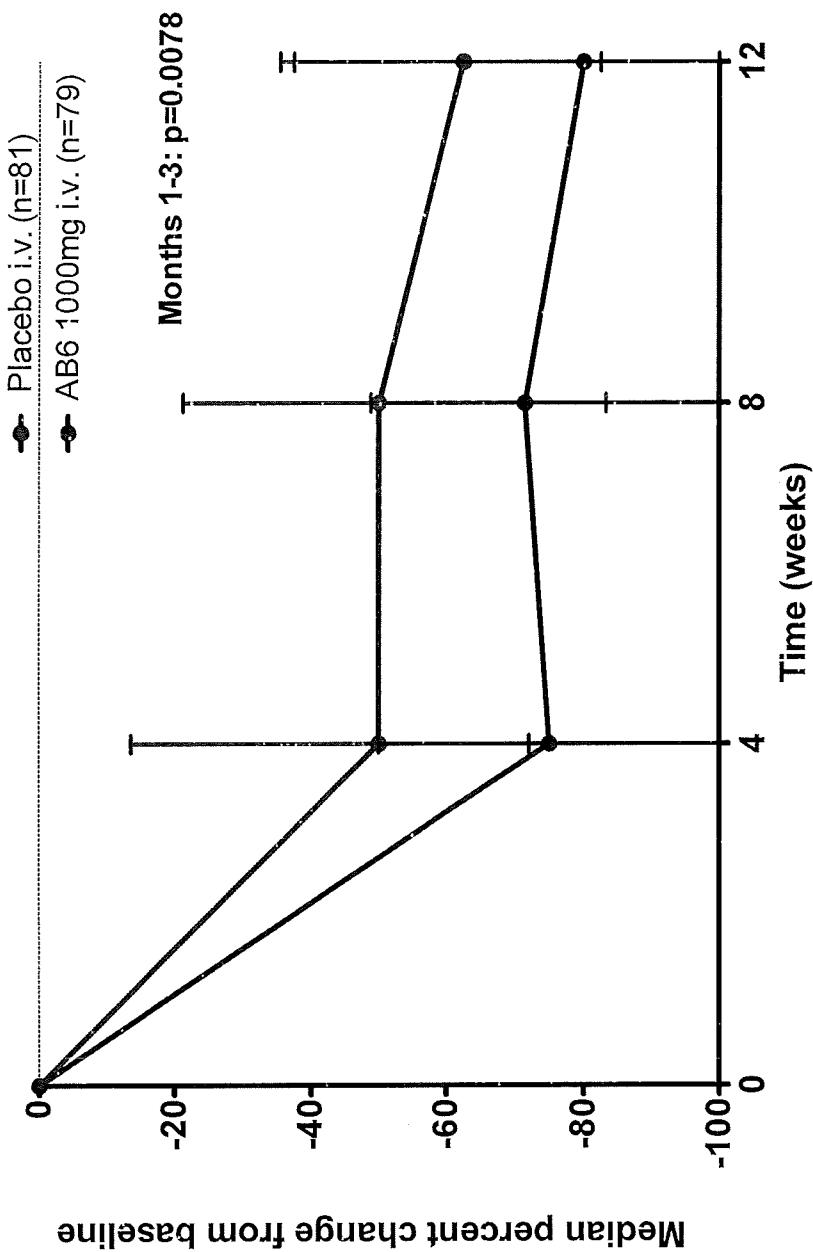
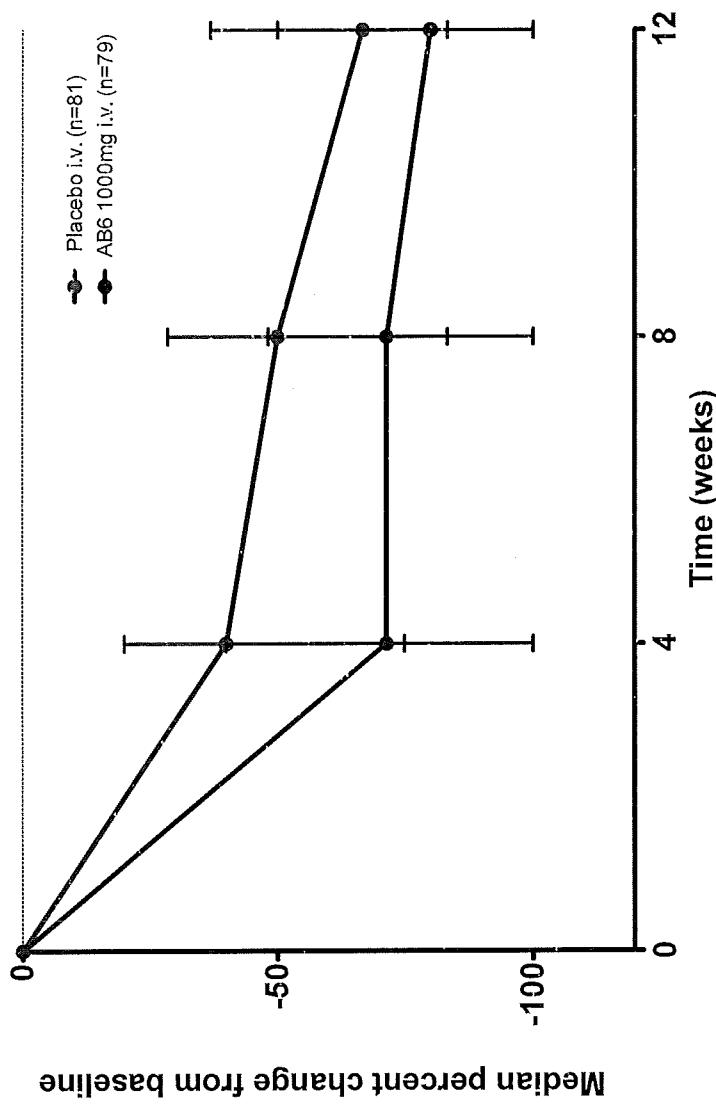


FIG. 15

# Median % change from baseline: migraine episodes per month

Median (±IQR) percentage change from baseline in migraine episodes per month: AB6 versus Placebo



# Median % change from baseline: migraine hours per month

FIG. 16

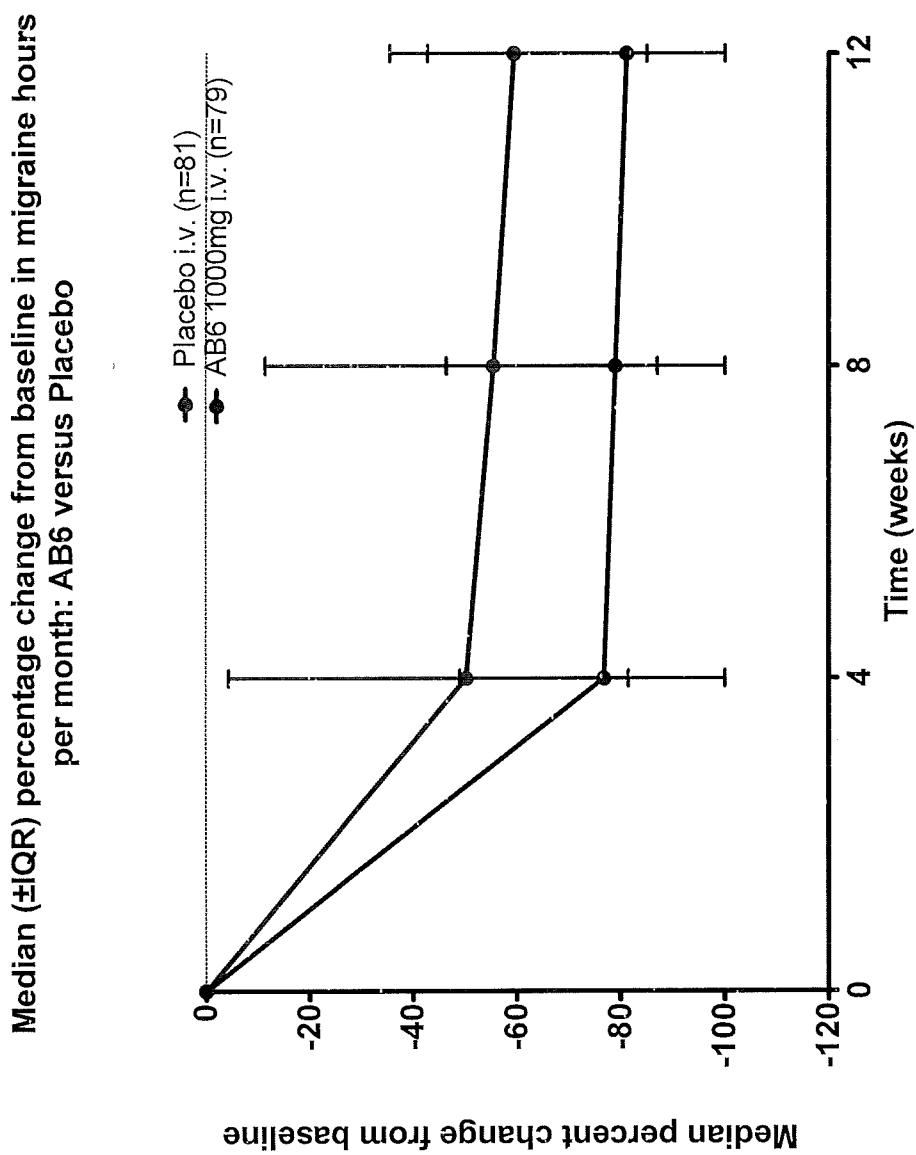
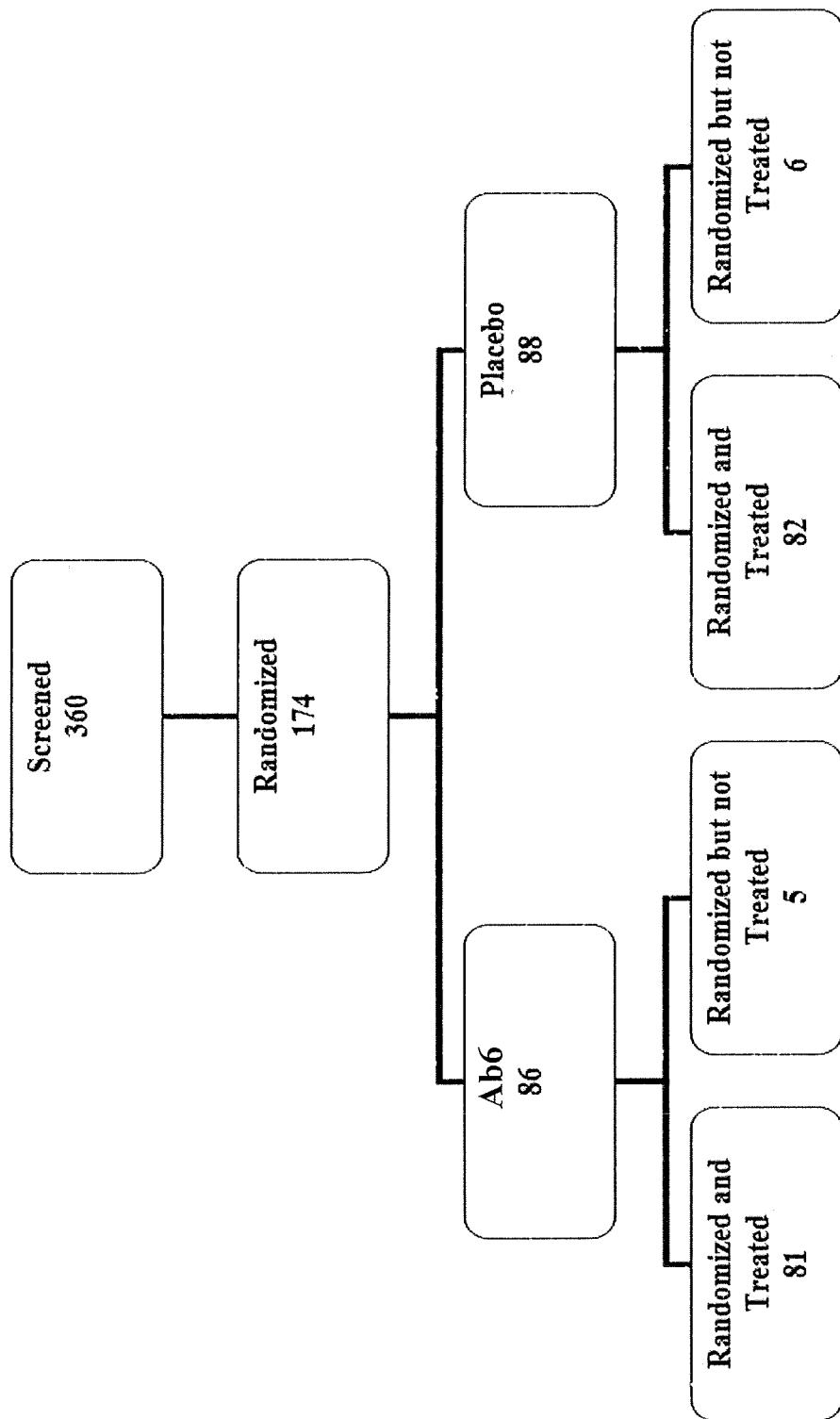


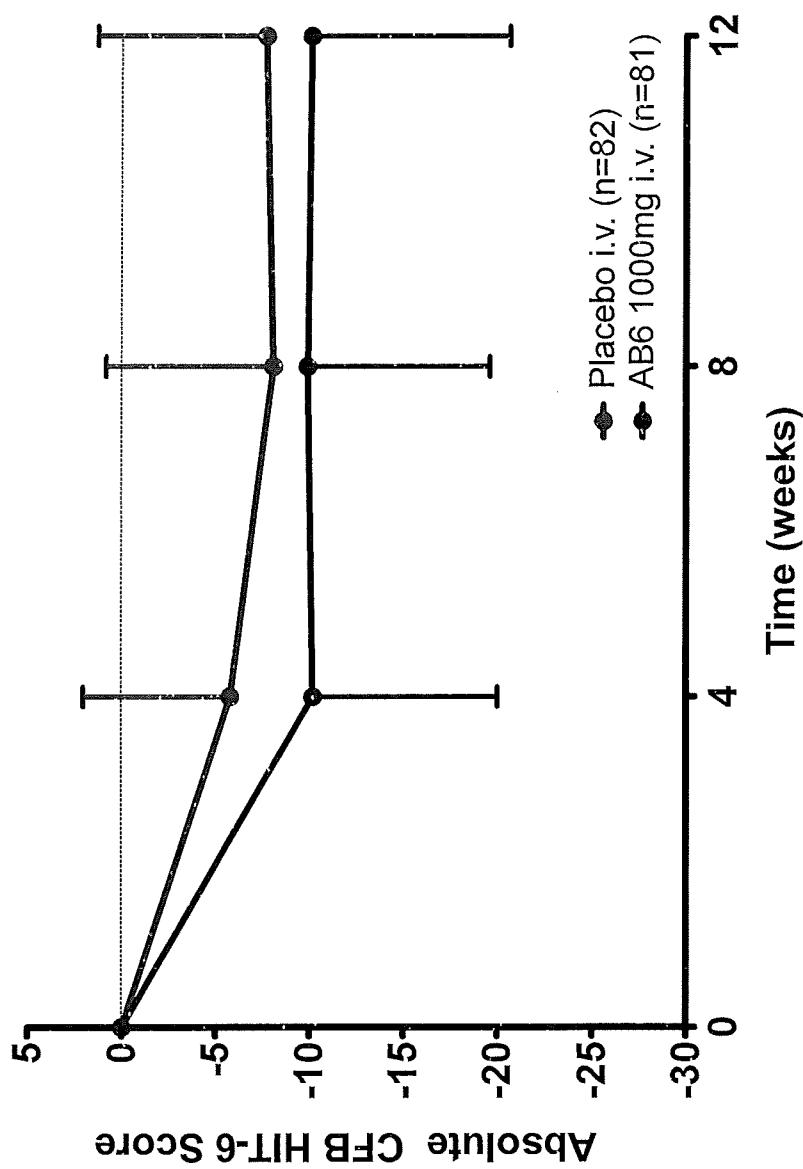
FIG. 17



# Mean Change Baseline HIT-6 score

FIG. 18

Mean (±SD) absolute change from baseline in Headache Impact Test (HIT-6) Score: AB6 vs Placebo



# HIT-6 Responder Analysis

FIG. 19

Percent patients who are some or little/no life impact for headache impact score (HIT-6) versus time:  
AB6 vs Placebo

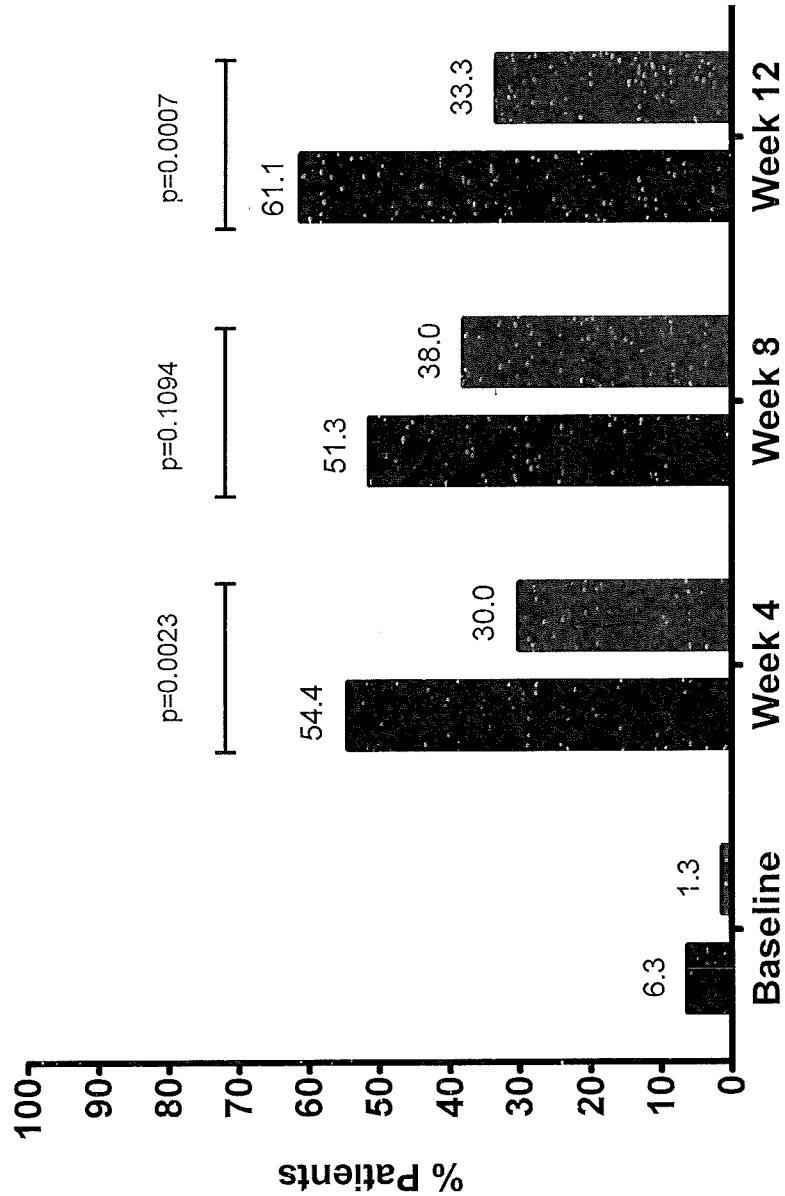


FIG. 20. PK Profile

# Ab6 1000 mg I.V. Mean +/- SD

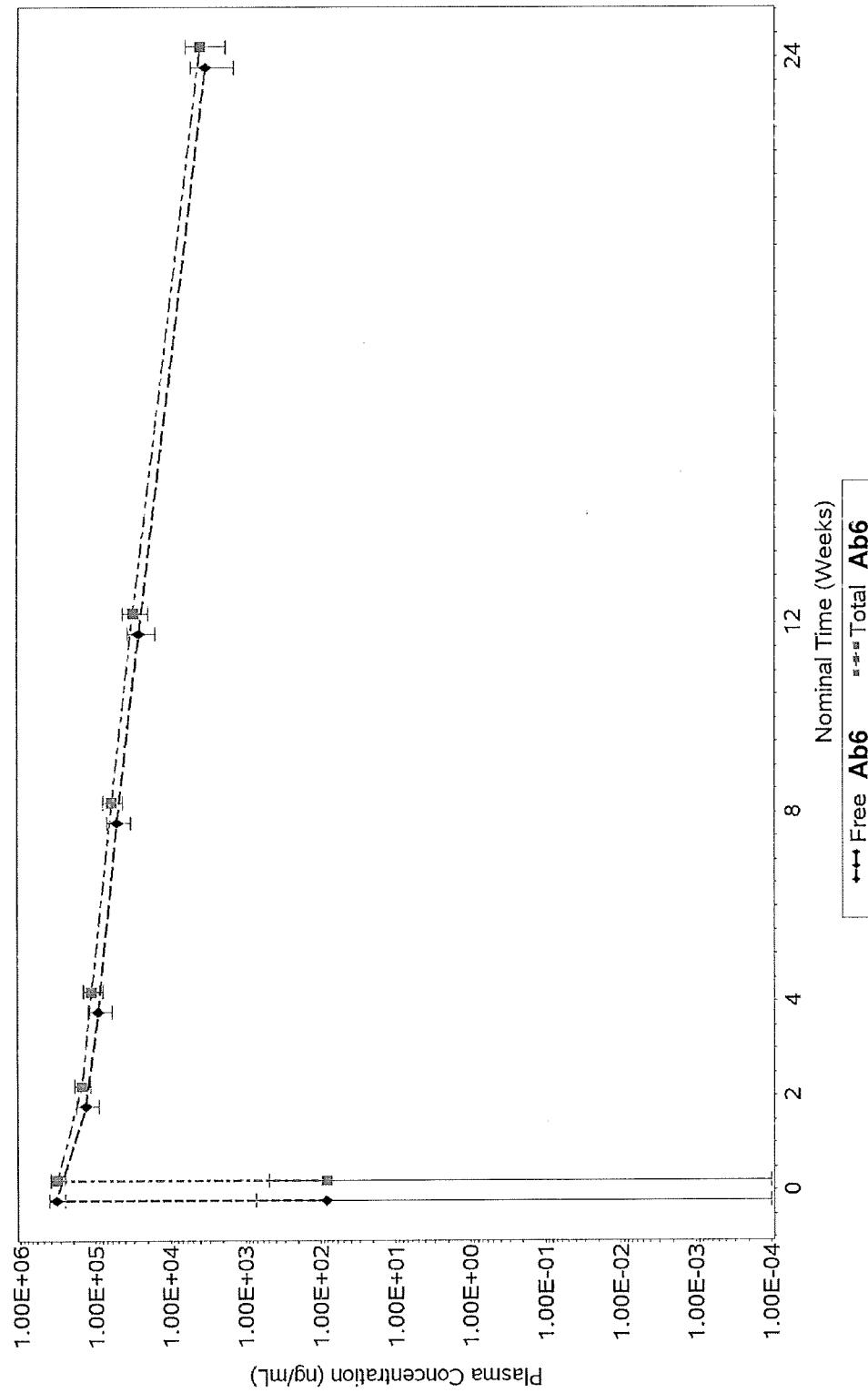


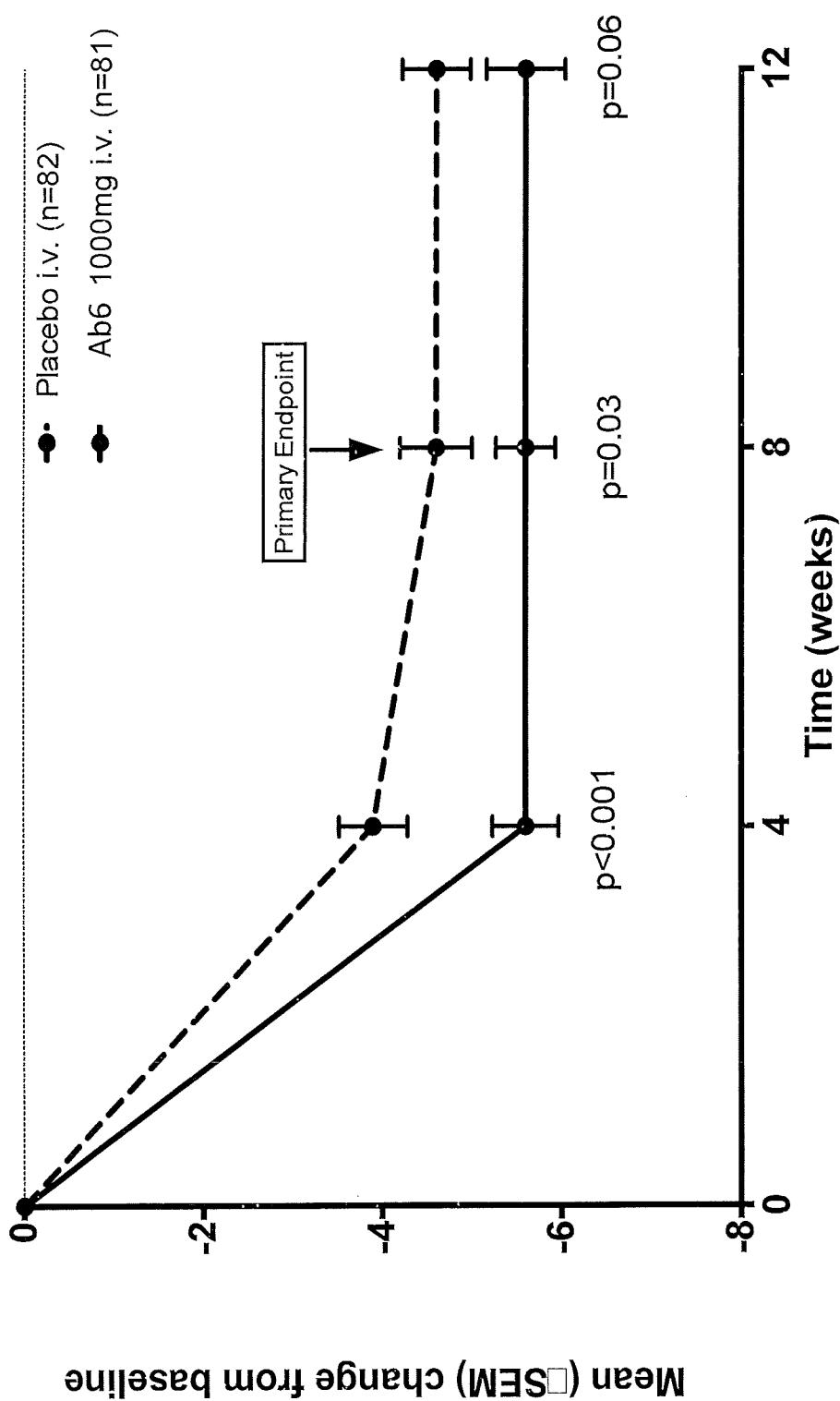
FIG. 21. PK Parameters

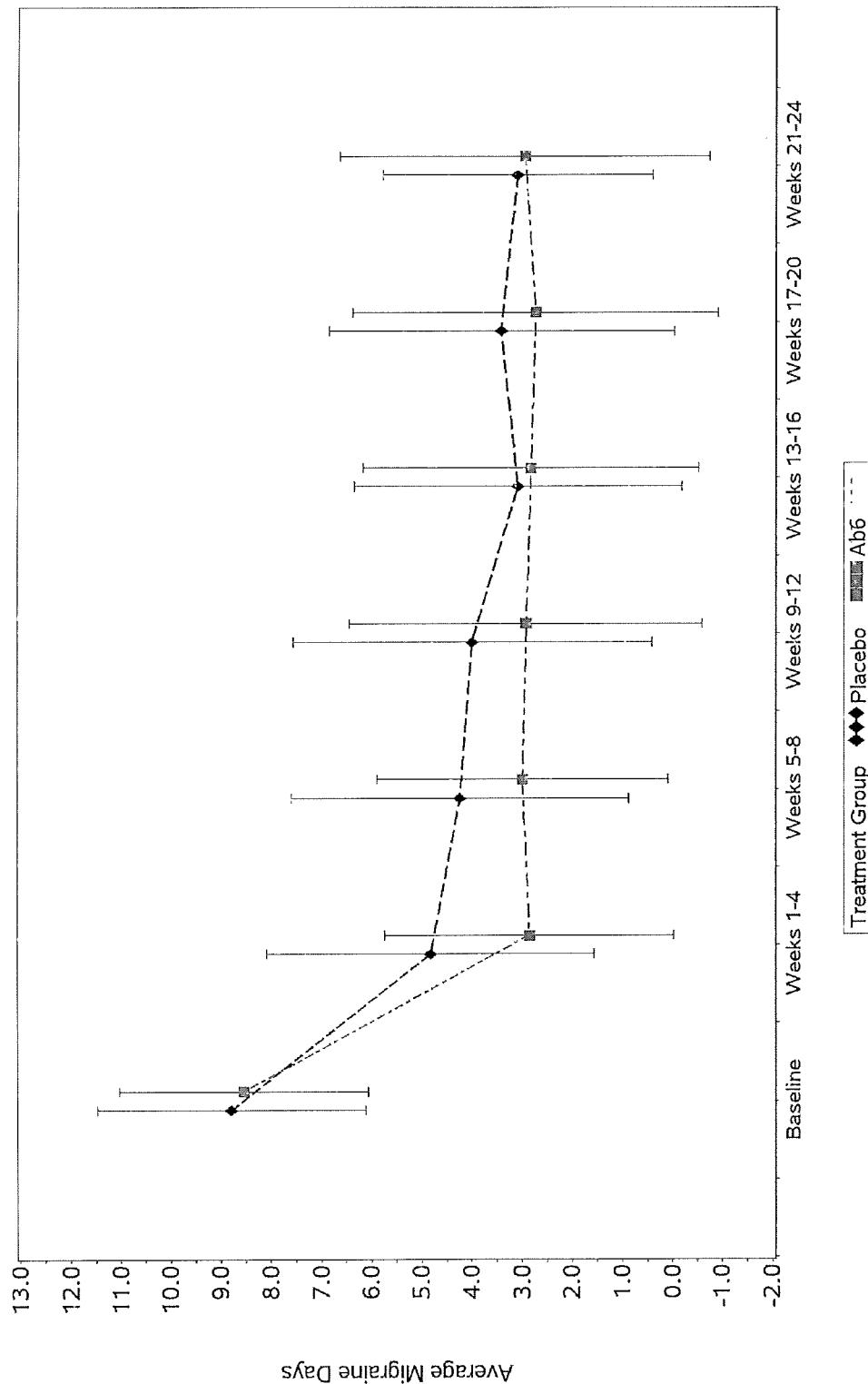
## Plasma Free Ab6\*

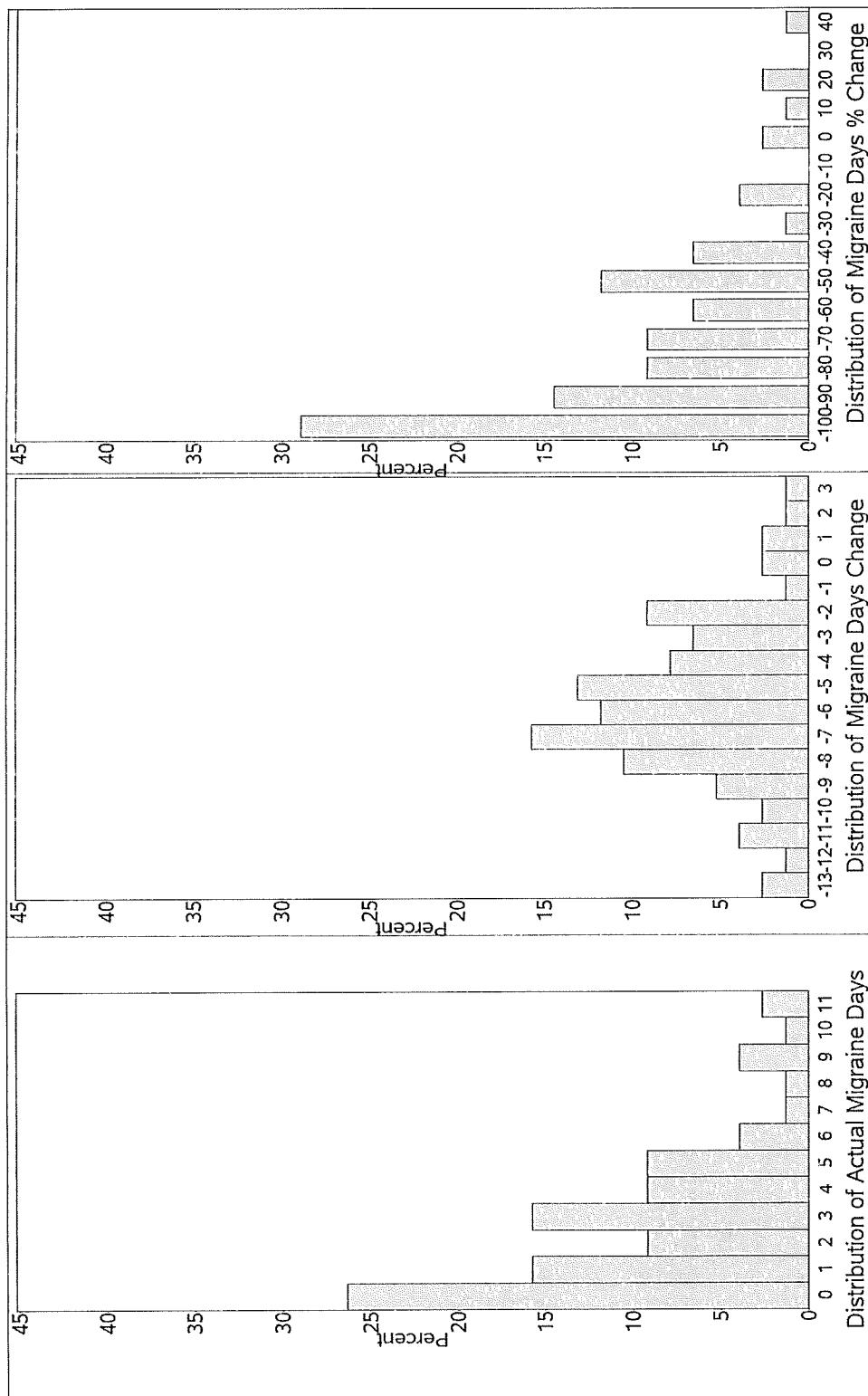
	$C_{max}$ ( $\mu$ g/mL)	$AUC_{0-\infty}$ (mg*hr/mL)	Half-Life (Days)	$V_z$ (L)	CL (mL/hr)
<b>N</b>	81	78	78	78	78
<b>Mean</b>	336	219	31	5.2	5.0
<b>SD</b>	80	64	8	2.1	1.5

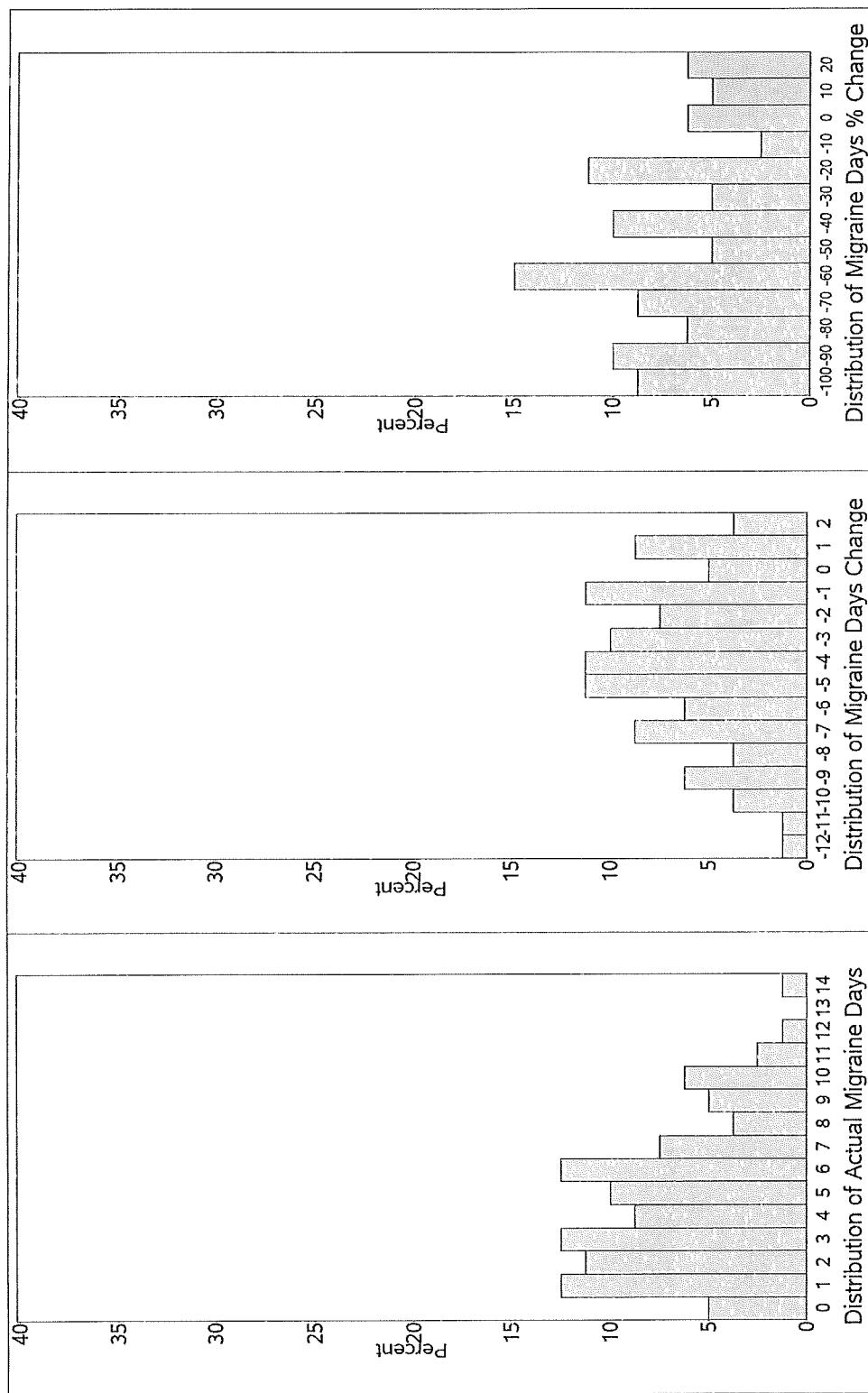
\* - Following 1000 mg Ab6 IV single-dose

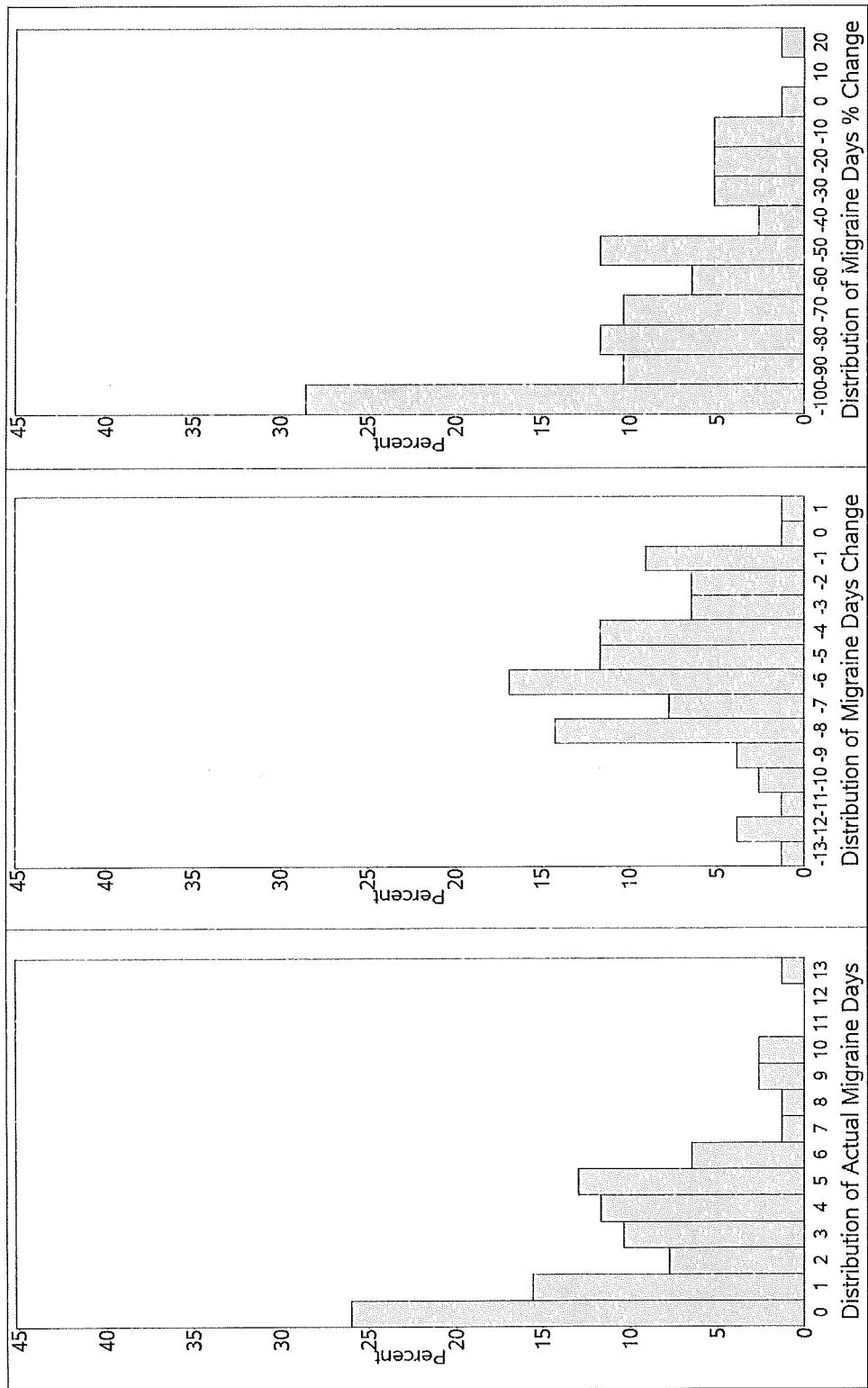
FIG. 22

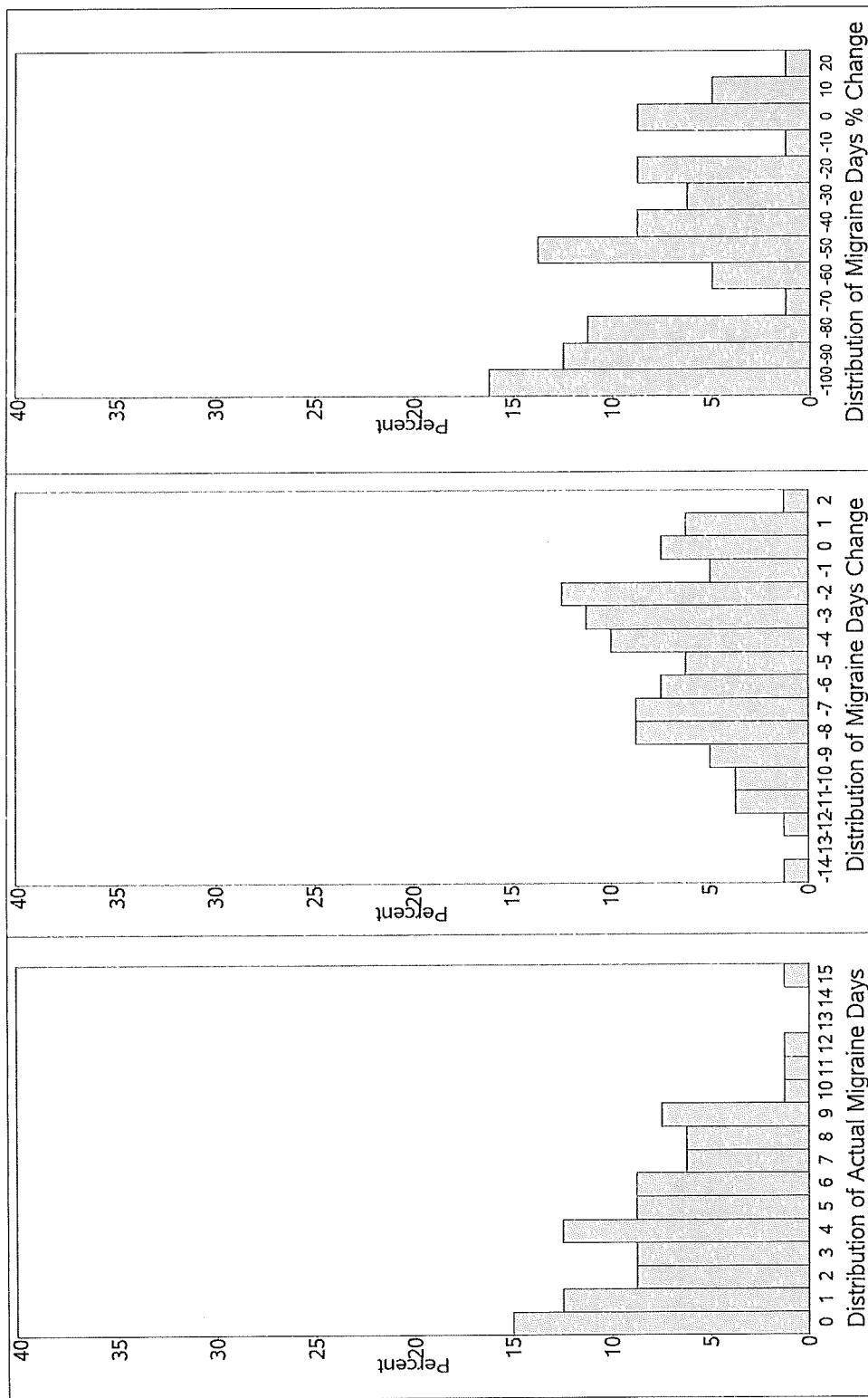


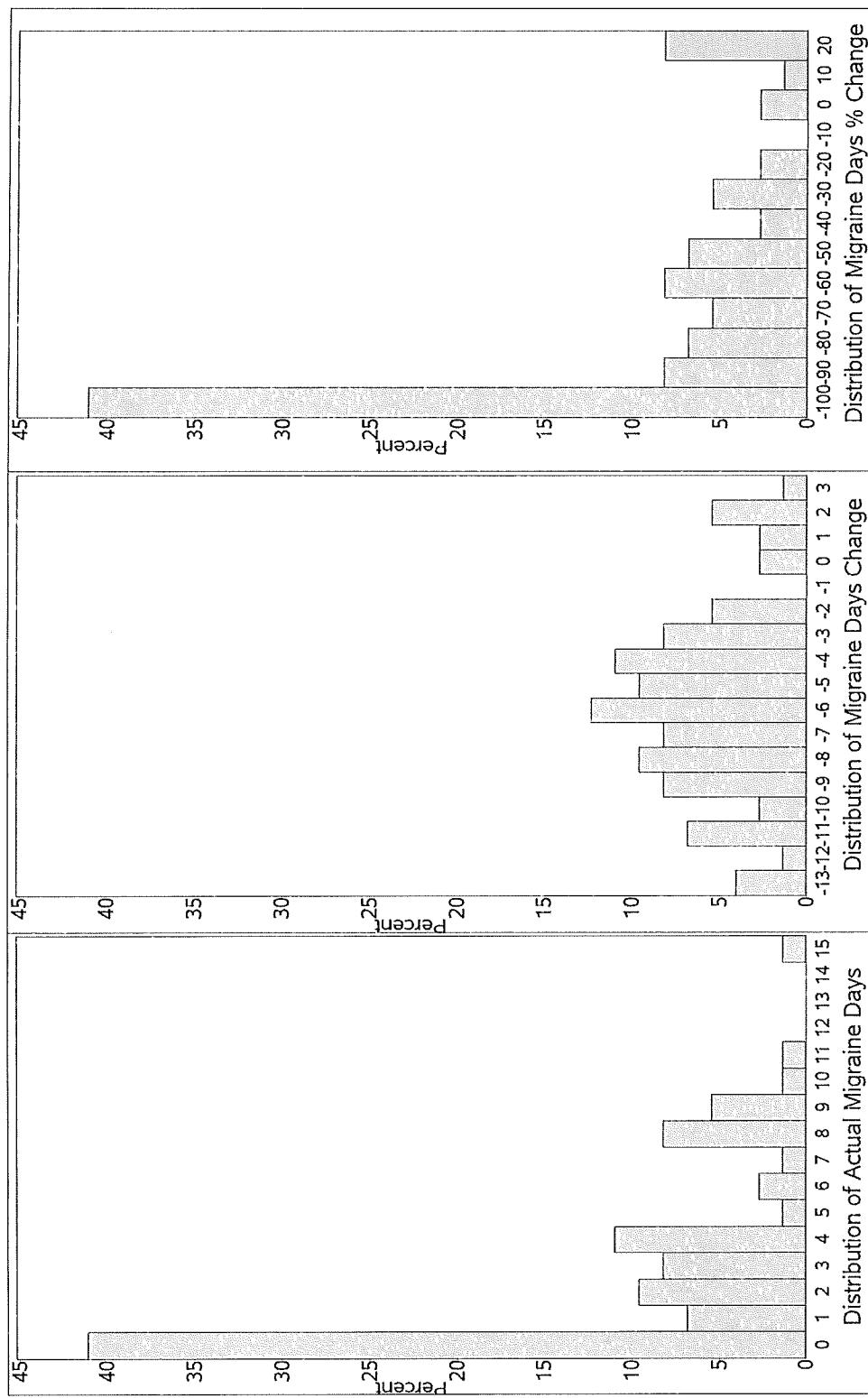
**FIG. 23**

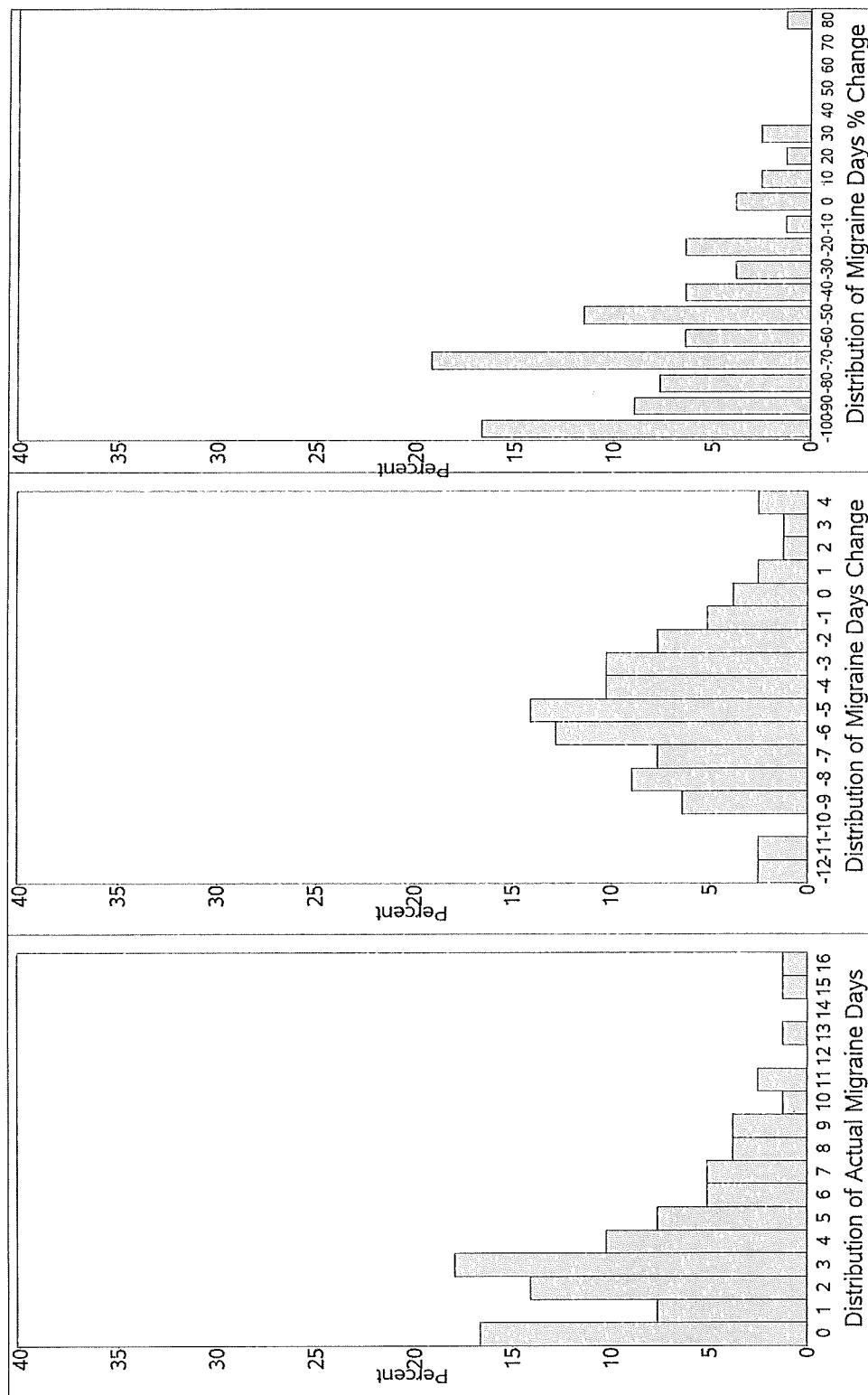
**FIG. 24**

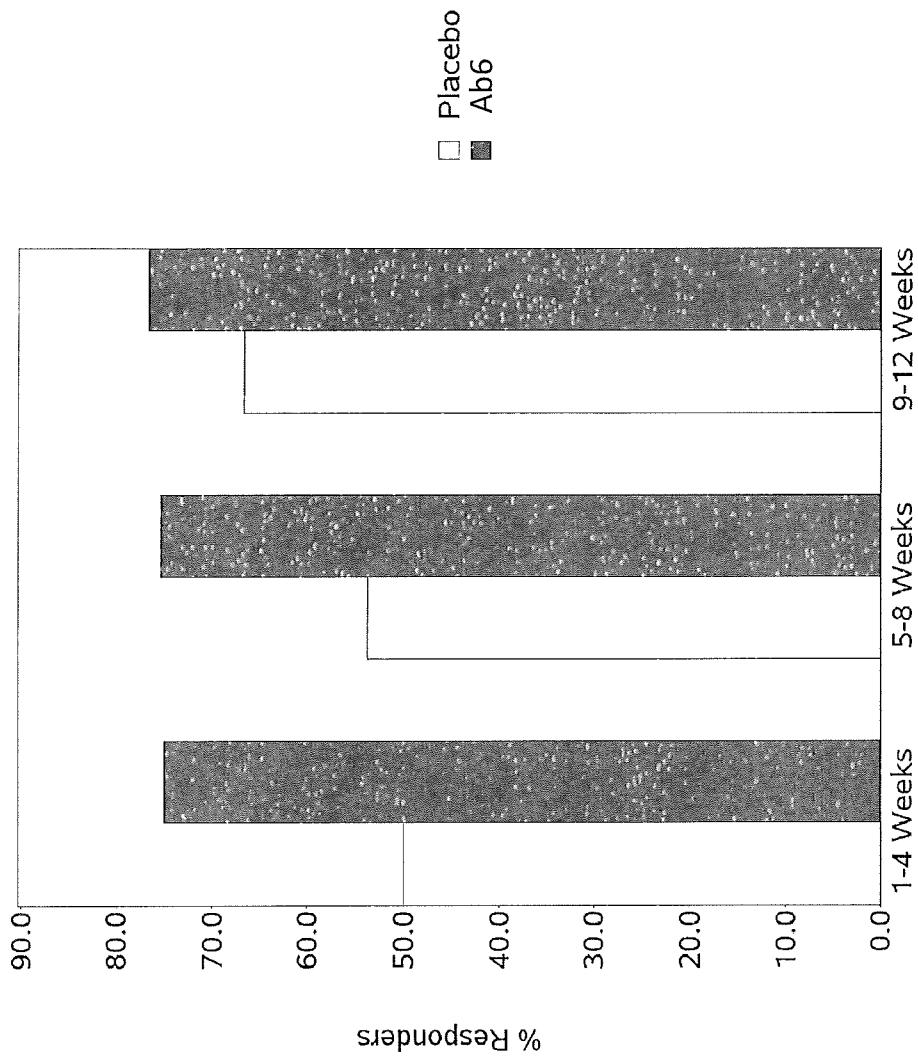
**FIG. 25**

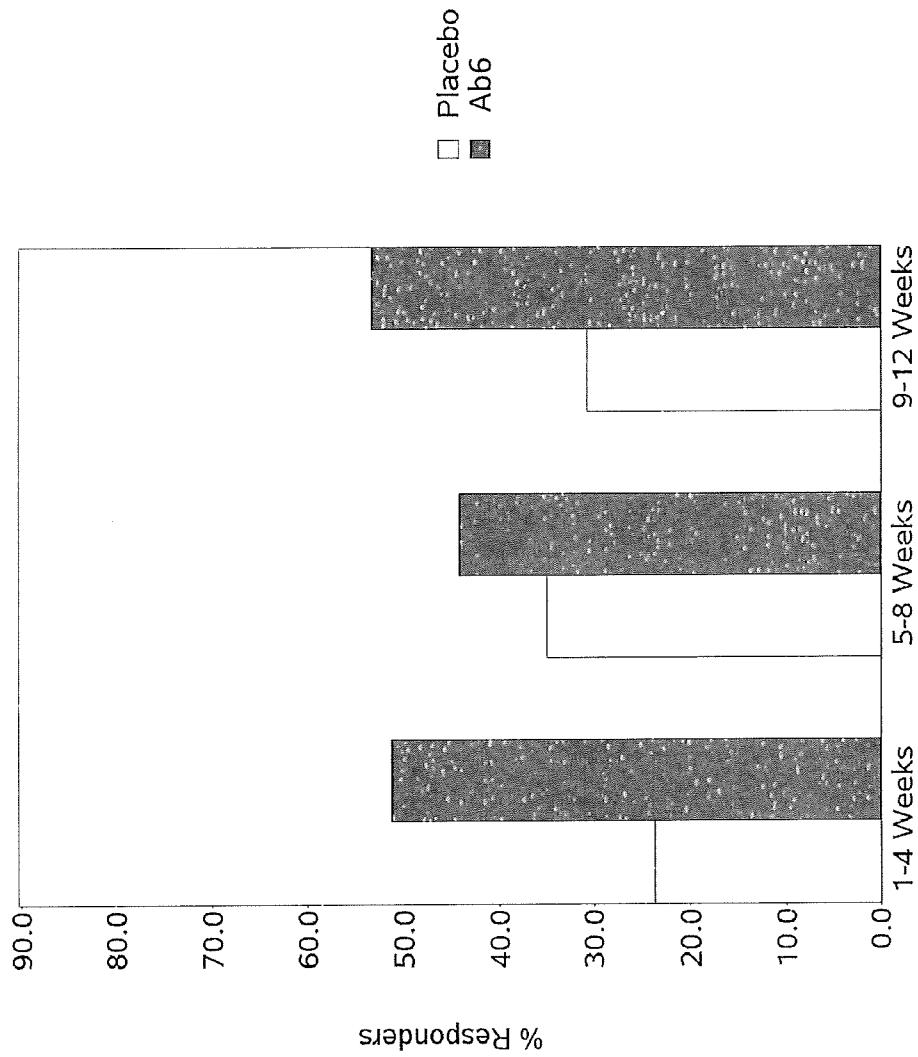
**FIG. 26**

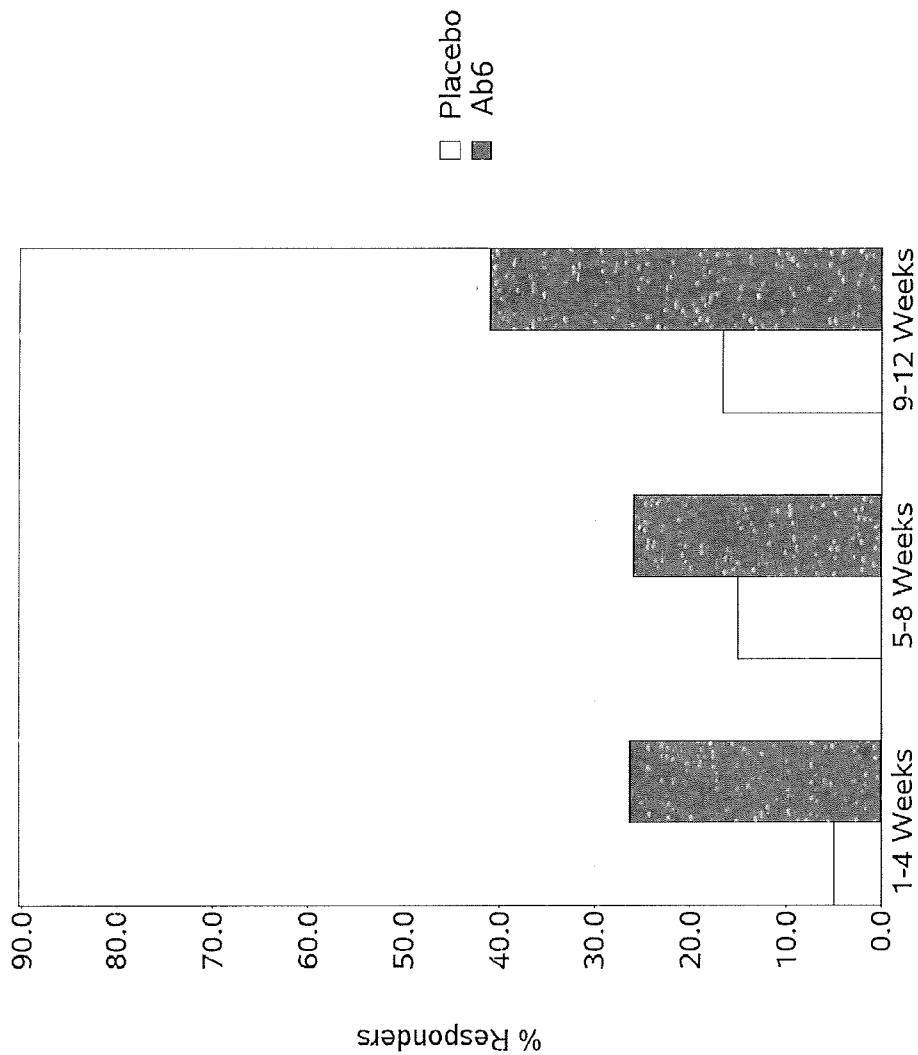
**FIG. 27**

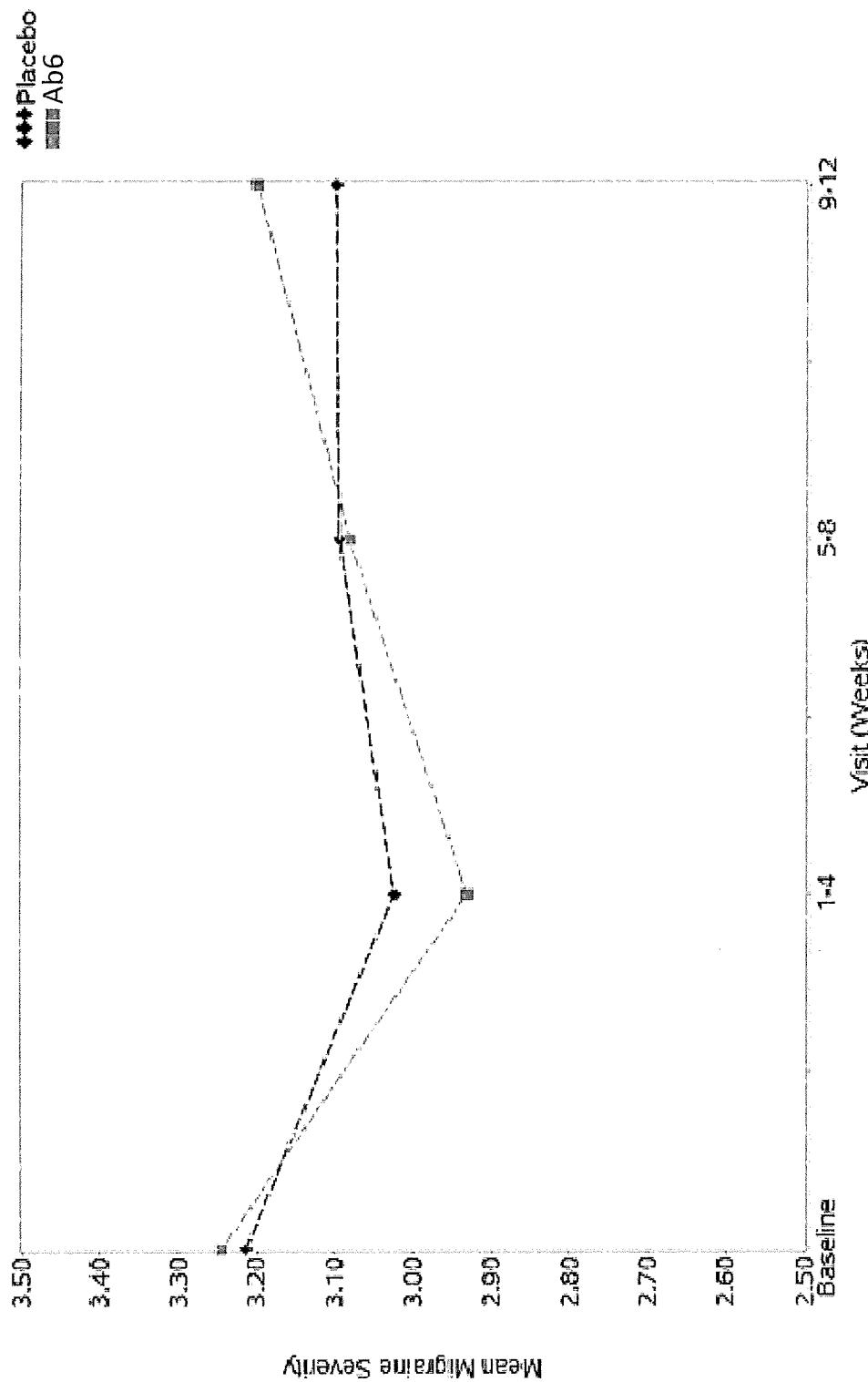
**FIG. 28**

**FIG. 29**

**FIG. 30**

**FIG. 31**

**FIG. 32**

**FIG. 33**

**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)
<b>Migraine Days</b>	-3.9 (3.5)	-5.6 (3.3) <sup>1</sup>	-4.6 (3.6)	-5.6 (3.0) <sup>2</sup>	-4.6 (3.5)	-5.6 (4.0) <sup>3</sup>
<b>Migraine Episodes</b>	-3.0 (2.7)	-3.7 (2.4)	-3.7 (2.9)	-3.8 (2.2)	-3.7 (2.8)	-3.9 (2.6)
<b>Migraine Hours</b>	-33.7 (41.8)	-58.0 (49.1)	-36.1 (45.9)	-54.4 (48.3)	-37.1 (40.0)	-54.6 (60.5)
<b>Average Migraine Severity<sup>4</sup></b>	-0.16 (0.58)	-0.31 (0.58)	-0.10 (0.54)	-0.16 (0.50)	-0.08 (0.54)	-0.11 (0.43)
<b>Headache Frequency</b>	-4.0 (3.8)	-5.6 (3.4)	-5.0 (3.7)	-5.3 (3.5)	-5.1 (3.7)	-5.9 (3.8)
<b>HIT-6 score</b>	-5.8 (7.8)	-10.2 (9.8)	-8.1 (8.9)	-9.9 (9.7)	-7.7 (9.0)	-10.1 (10.6)
<b>MSQ RFP</b>	19.9 (23.8)	29.3 (24.3)	25.2 (24.8)	28.8 (24.7)	22.2 (23.1)	28.5 (24.5)
<b>MSQ RFR</b>	16.3 (23.2)	21.1 (23.9)	20.2 (22.1)	20.9 (23.3)	18.0 (20.5)	21.4 (23.1)
<b>MSQ EF</b>	19.4 (27.6)	25.1 (28.3)	21.2 (25.1)	23.8 (25.8)	21.1 (25.1)	23.1 (26.8)

<sup>1</sup>p<0.001; <sup>2</sup>p=0.03; <sup>3</sup>p=0.06; <sup>4</sup> Severity measured on a 4 point scale with 1=mild and 4=severe

FIG. 35

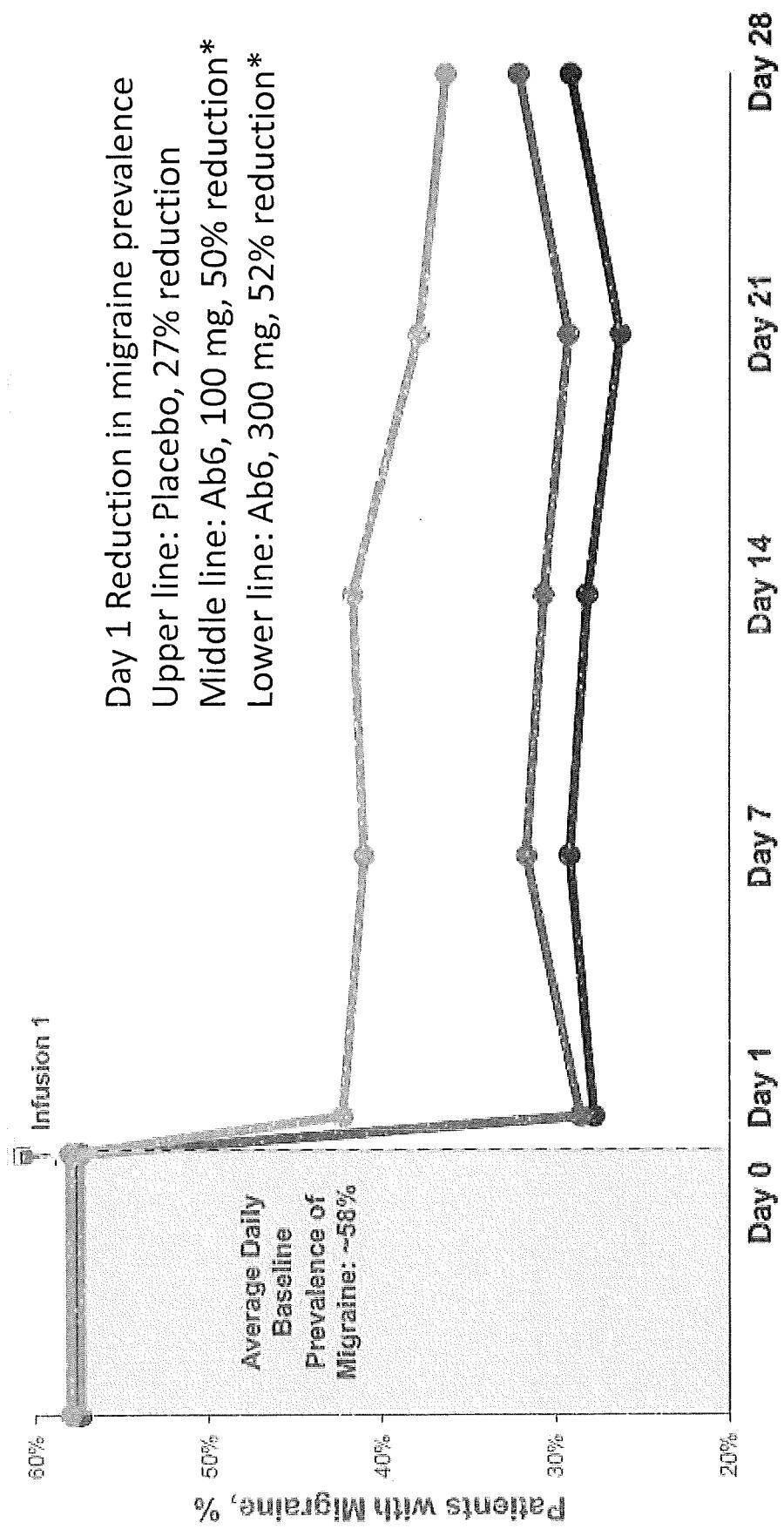


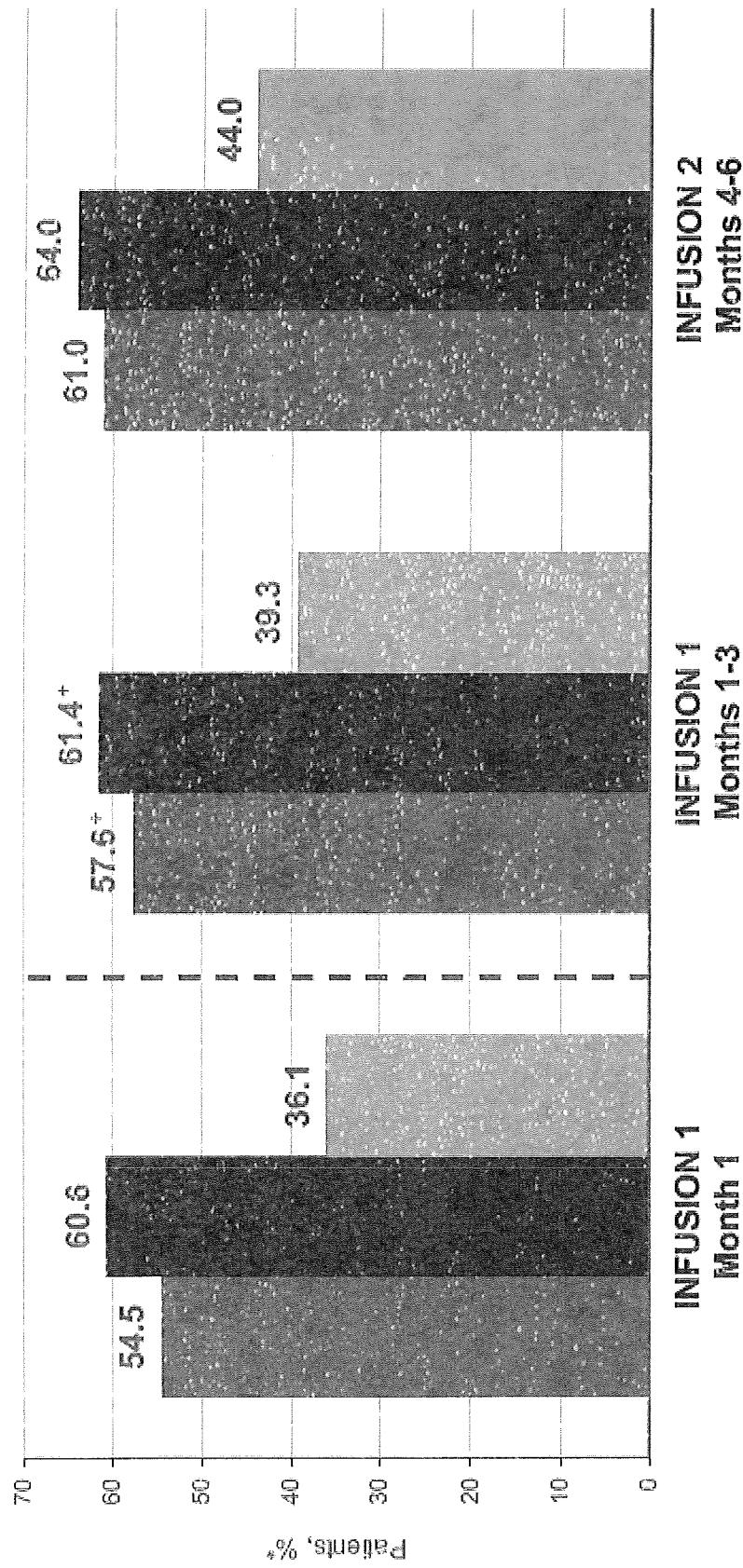
FIG. 36. Chronic migraine  $\geq 50\%$  responder rates

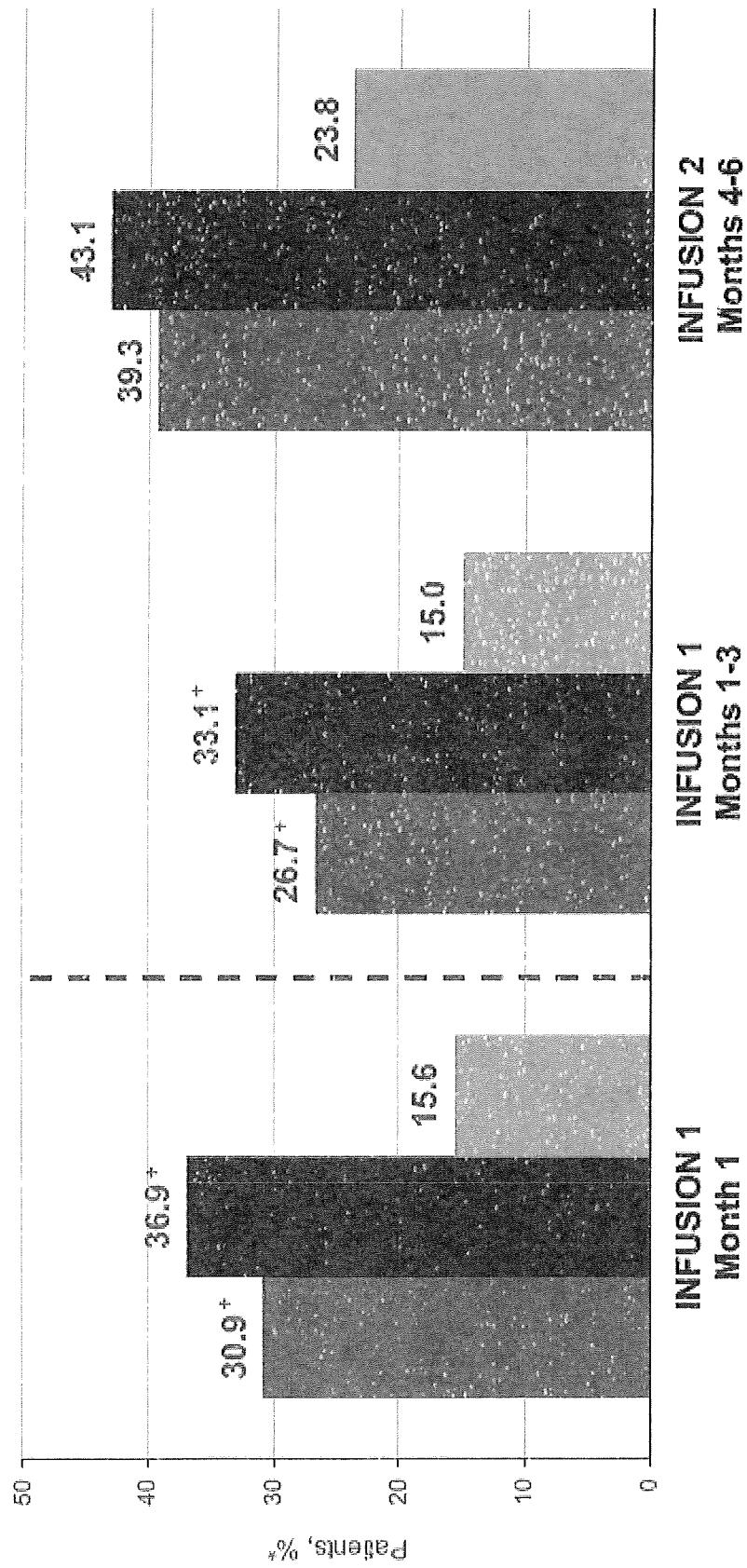
FIG. 37. Chronic migraine  $\geq 75\%$  responder rates

FIG. 38. Chronic migraine 100% responder rates

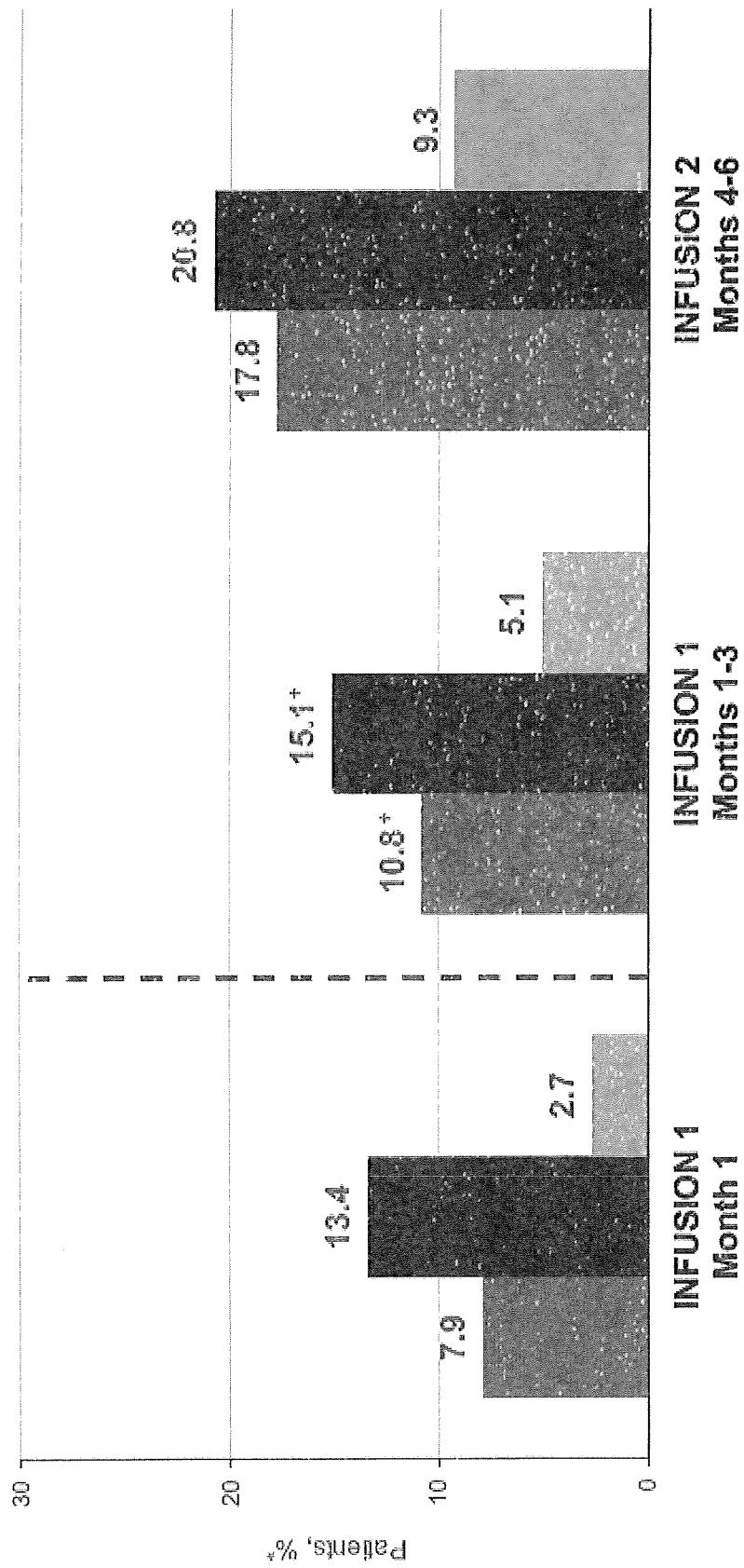


FIG. 39

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 <sup>2</sup> (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)

FIG. 40. Difference from placebo in change from baseline in mean migraine days (MMD) over months 1-3 by baseline subgroup

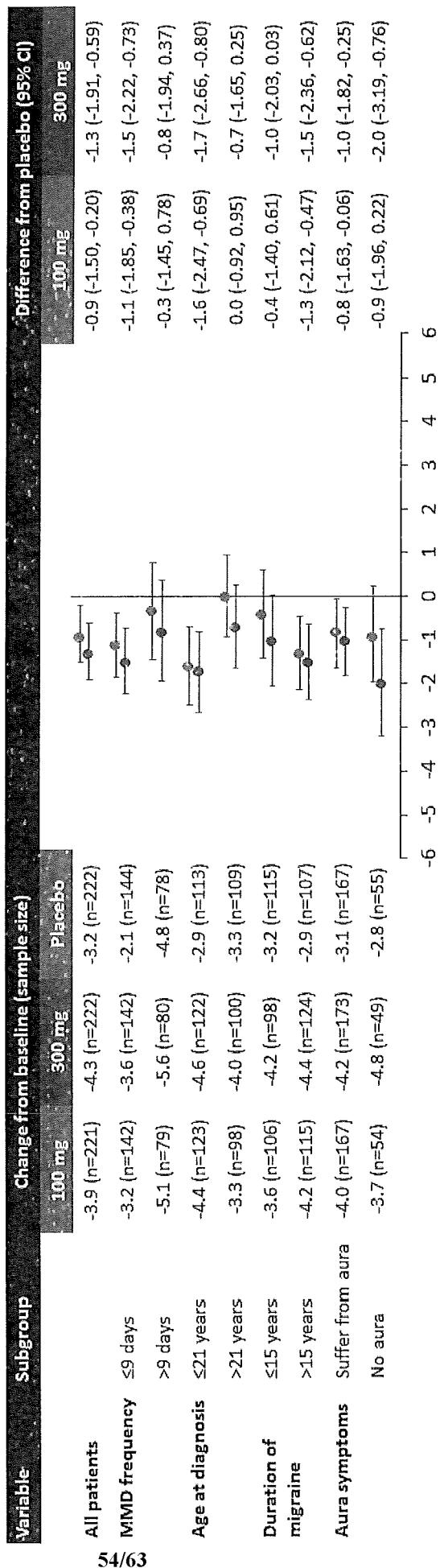


FIG. 41. Difference from placebo in change from baseline in mean migraine days (MMD) over months 1-3 by baseline subgroup

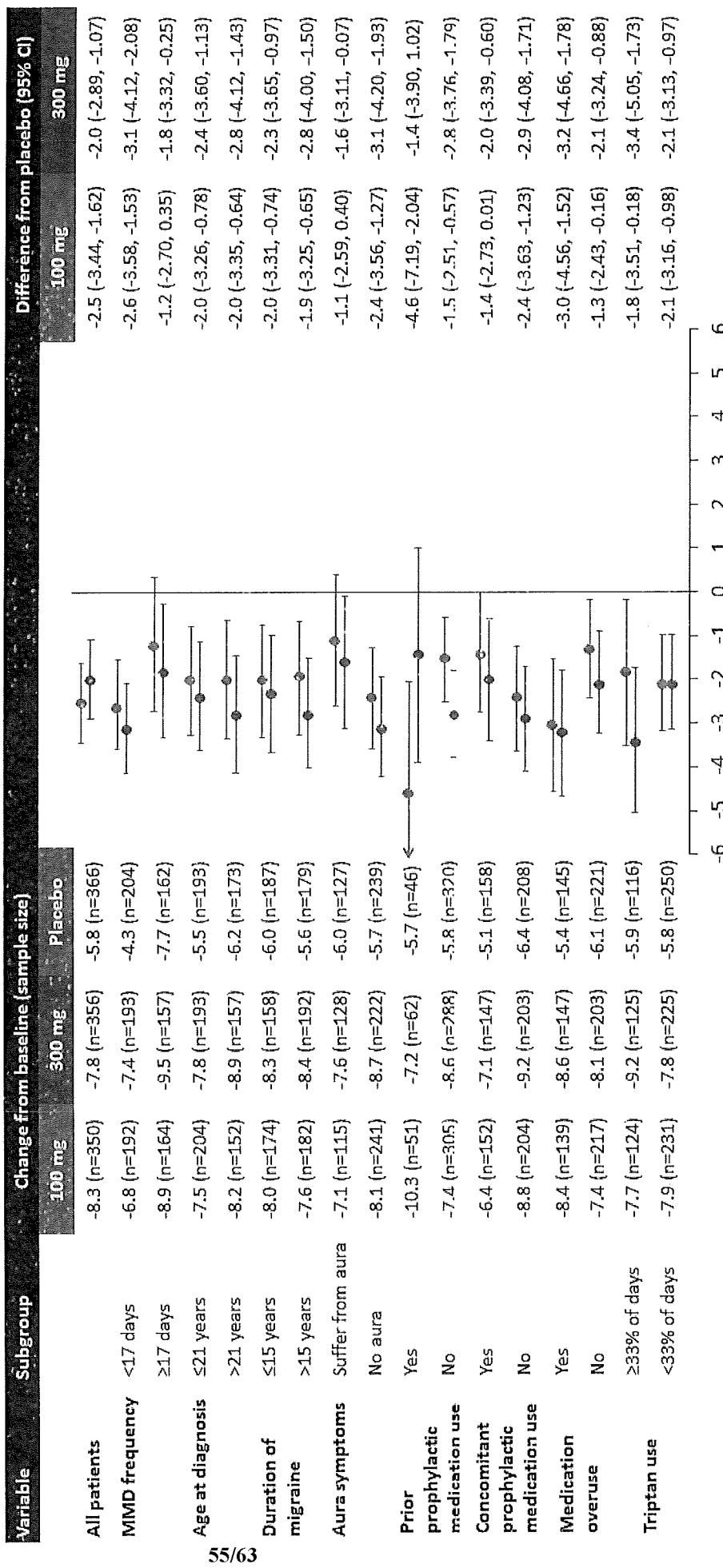


FIG. 42.

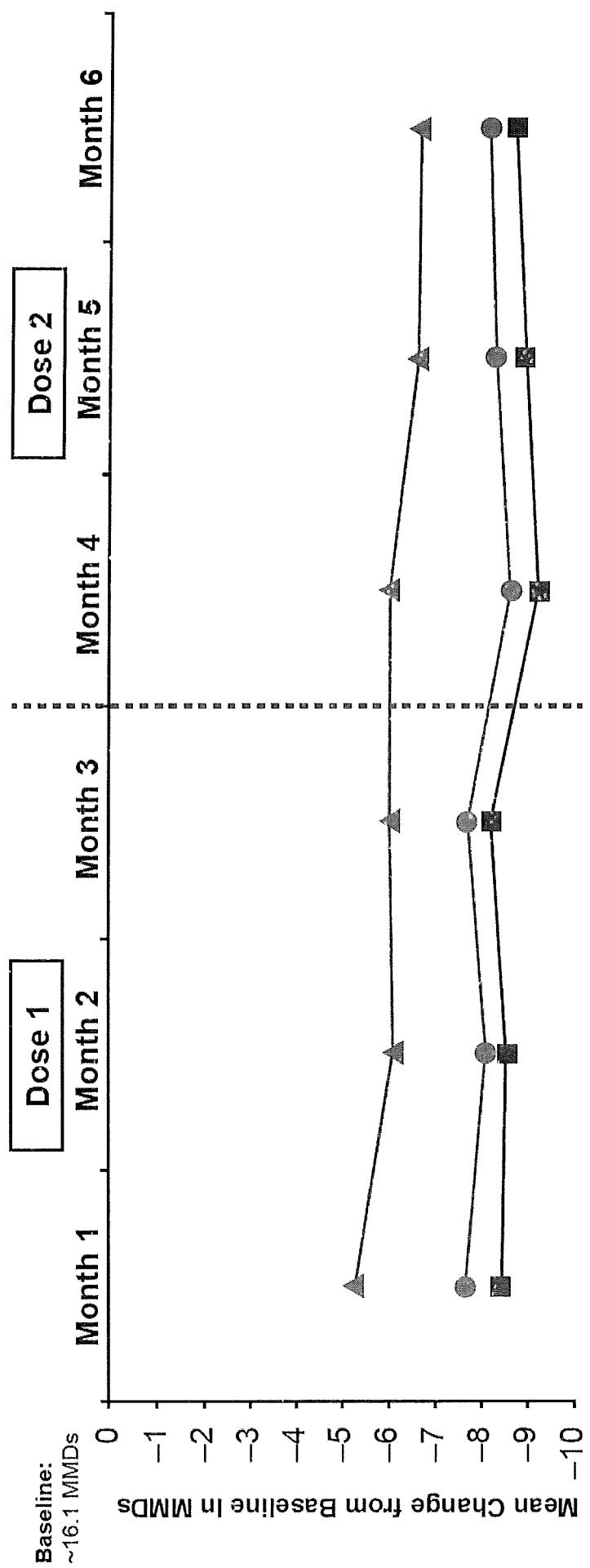


FIG. 43.

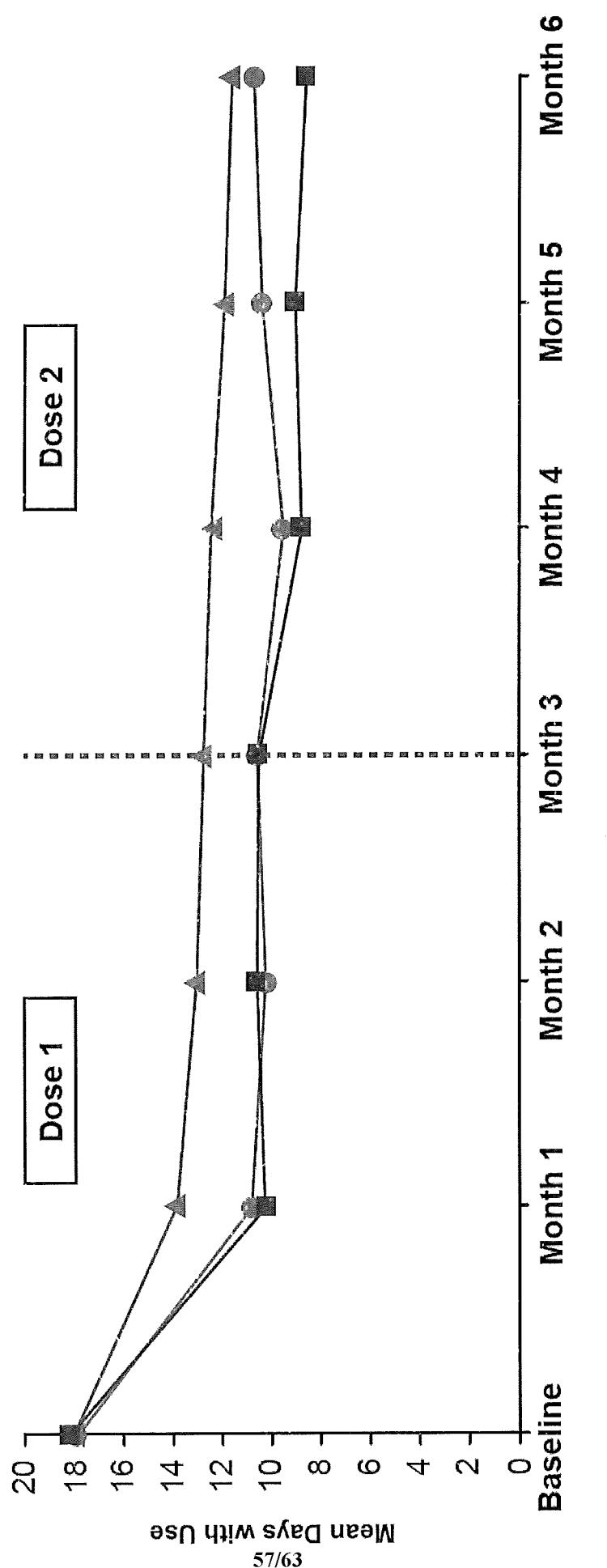


FIG. 44.

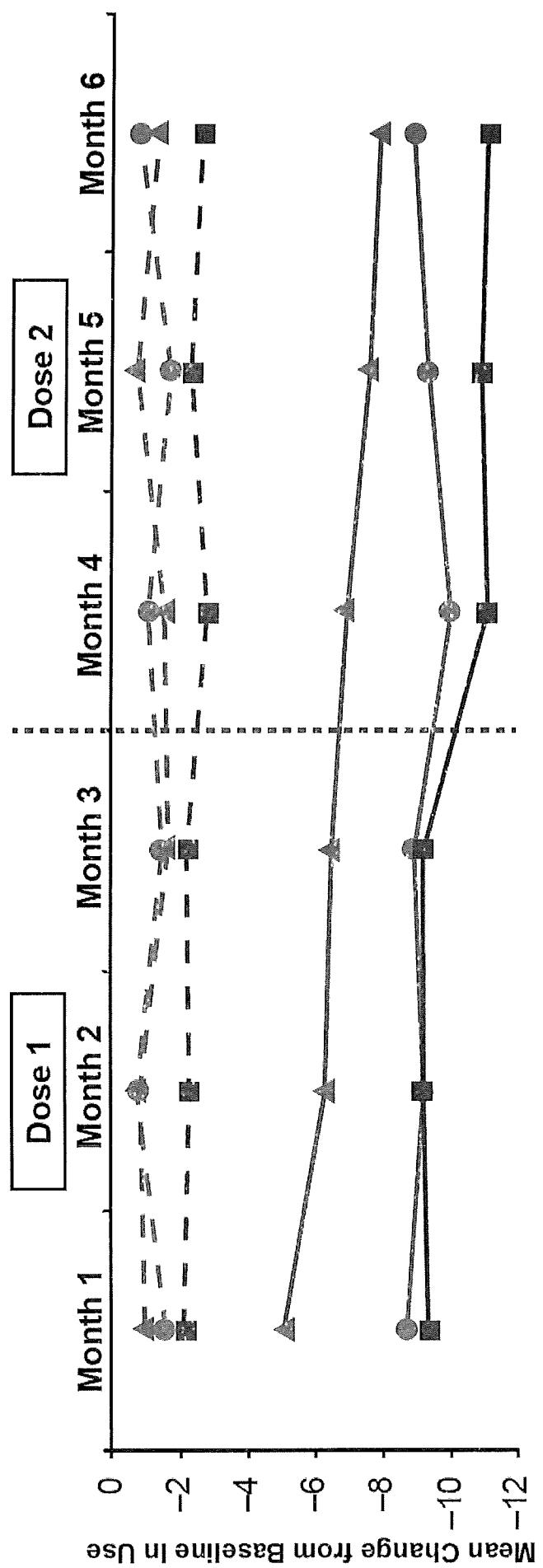
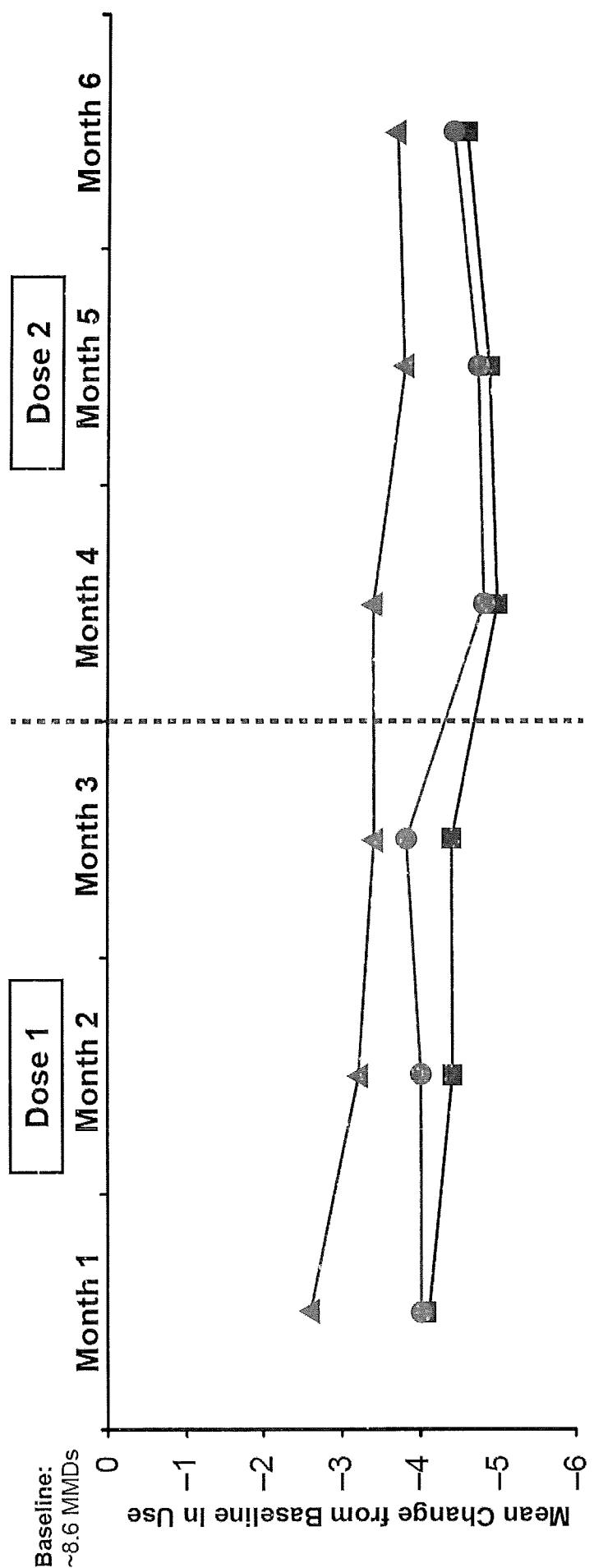


FIG. 45.

	Month 1		Month 6			
	Ab6 100 mg	Ab6 400 mg	Placebo	Ab6 100 mg	Ab6 400 mg	Placebo
<b>Baseline use</b>						
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)
<b>Post-baseline use, mean (SD)</b>						
≥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)
<b>Change from baseline, mean (SD)</b>						
≥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)
<b>Percent change from baseline, mean (SD)</b>						
≥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)

FIG. 46.



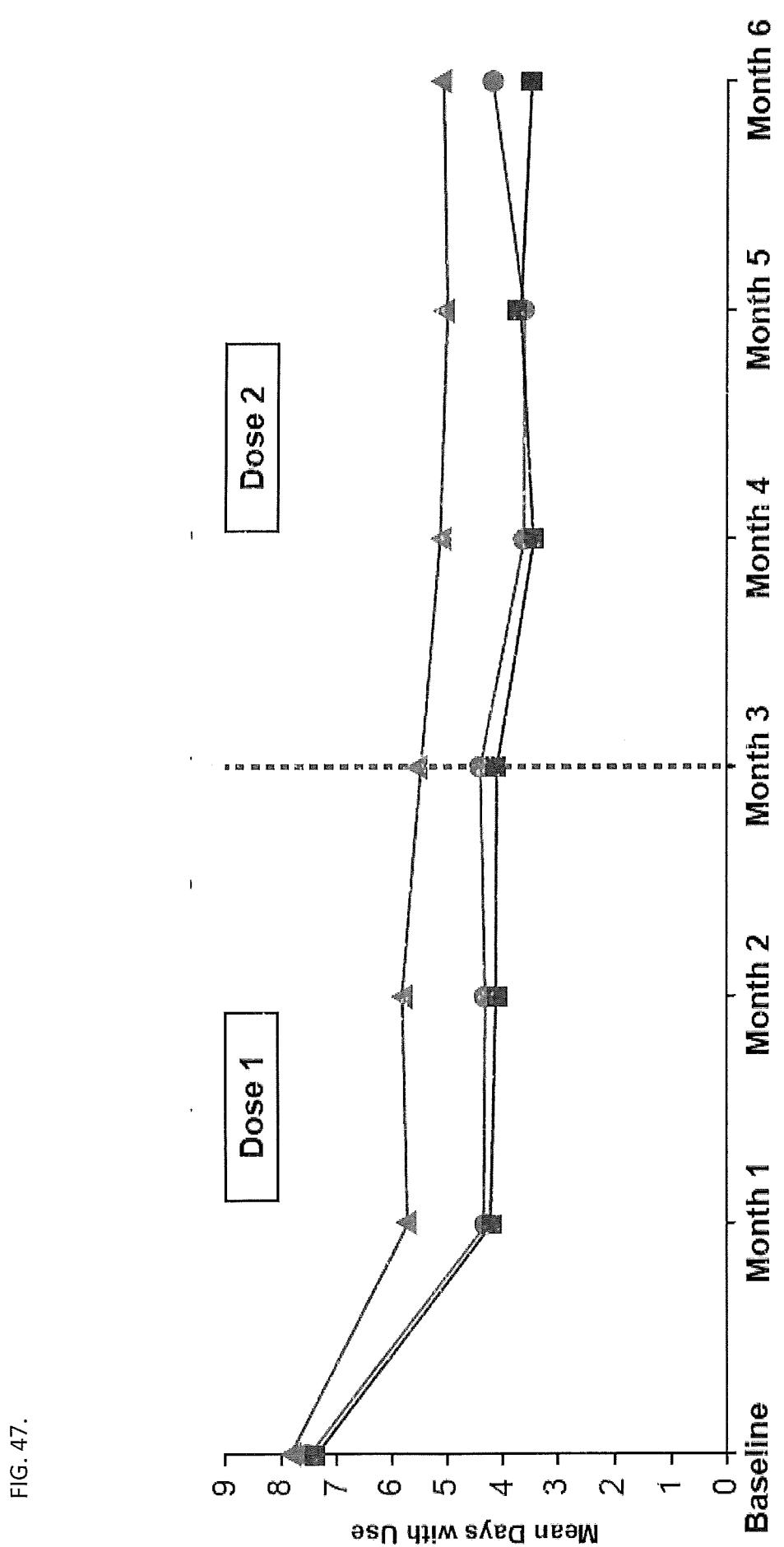


FIG. 48.

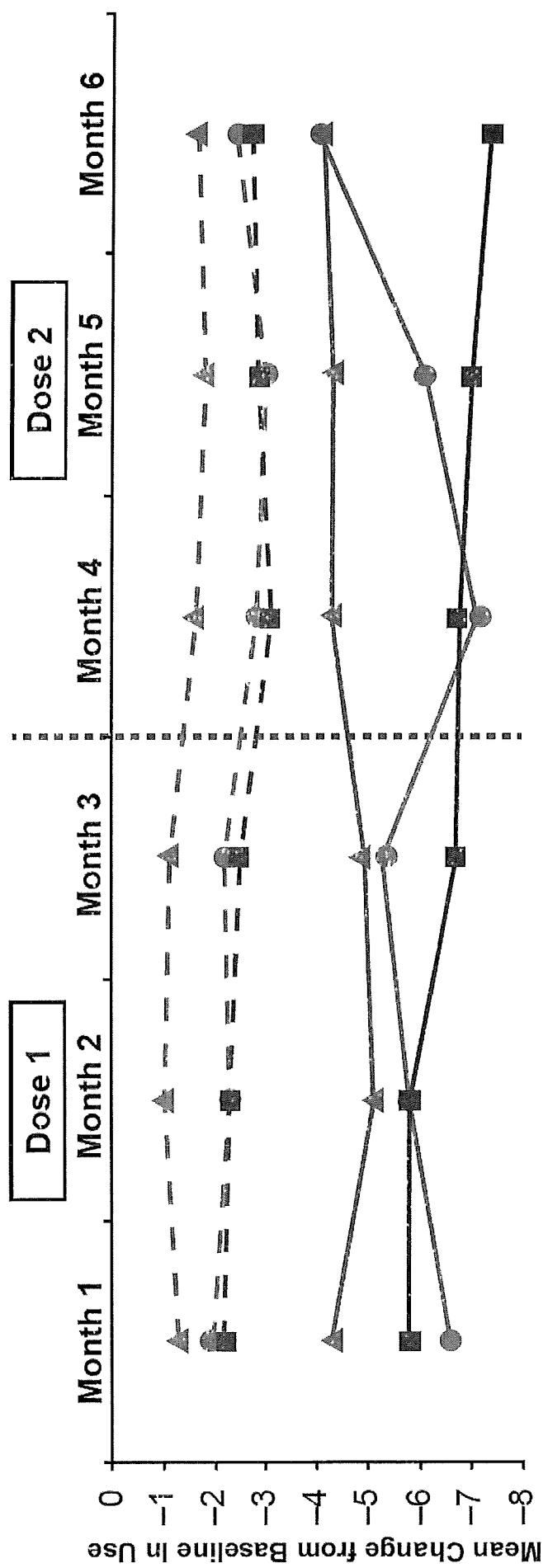


FIG. 49. Summary of Acute Medication Days by Subgroups of Episodic Migraine Patients with Baseline Acute Medication Use

	Month 1			Month 6		
	Ab6 100 mg	Ab6 400 mg	Placebo	Ab6 100 mg	Ab6 400 mg	Placebo
<b>Baseline use</b>						
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)
<b>Post-baseline use, mean (SD)</b>						
≥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)
<b>Change from baseline, mean (SD)</b>						
≥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)
<b>Percent change from baseline, mean (SD)</b>						
≥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)

Figure 1A - Heavy Chain Protein Sequence

Sequence

Name	FR1	CDR1	FR2	CDR2
Ab1	QSLEESGGRLVTPGTPLTLTCTVSGLDLS	SYYM	WVRQAPGKGLEWIG	VIGINDNTYYASWAKG
Ab2	EVQLVESGGGLVQPGGSLRLSCAVSGLDLS	SYYM	WVRQAPGKGLEWVG	VIGINDNTYYASWAKG
Ab3	EVQLVESGGGLVQPGGSLRLSCAVSGLDLS	SYYM	WVRQAPGKGLEWVG	VIGINDNTYYASWAKG
Ab4	QSLEESGGRLVTPGTPLTLCSVSGIDLS	GYYM	WVRQAPGKGLEWIG	VIGINGATYYASWAKG
Ab5	EVQLVESGGGLVQPGGSLRLSCAVSGIDLS	GYYM	WVRQAPGKGLEWVG	VIGINGATYYASWAKG
Ab6	EVQLVESGGGLVQPGGSLRLSCAVSGIDLS	GYYM	WVRQAPGKGLEWVG	VIGINGATYYASWAKG
Ab7	QEQLKESGGRLVTPGTSLLTCTVSGIDLS	NHYM	WVRQAPGKGLEWIG	VVGINGRTYYASWAKG
Ab8	EVQLVESGGGLVQPGGSLRLSCAVSGIDLS	NHYM	WVRQAPGKGLEWVG	VVGINGRTYYASWAKG
Ab9	QSLEESGGRLVTPGTPLTLCTVSGIGLS	SYYM	WVRQSPGRGLEWIG	VIGSDGKTYYATWAKG
Ab10	EVQLVESGGGLVQPGGSLRLSCAVSGIGLS	SYYM	WVRQAPGKGLEWVG	VIGSDGKTYYATWAKG
Ab11	QSLEESGGRLVTPGGSLTLTCTVSGIDVT	NYYM	WVRQAPGKGLEWIG	VIGVNGKRYYASWAKG
Ab12	EVQLVESGGGLVQPGGSLRLSCAVSGIDVT	NYYM	WVRQAPGKGLEWVG	VIGVNGKRYYASWAKG
Ab13	QSVEESGGGLVQPEGSLTLTCTASGFDFS	SNAM	WVRQAPGKGLEWIG	CIYNGDGSTYYASWVNG
Ab14	EVQLVESGGGLVQPGGSLRLSCAVSGIGLS	SYYM	WVRQAPGKGLEWVG	VIGSDGKTYYATWAKG