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# DESCRIPTION

## TECHNICAL FIELD

**[0001]** The disclosure is directed to pharmaceutical products comprising stable liquid pharmaceutical compositions of the IL-17 antibody AIN457 (secukinumab), and processes of making such pharmaceutical products and liquid pharmaceutical compositions.

## BACKGROUND OF THE DISCLOSURE

**[0002]** IL-17A is the central lymphokine of a newly defined subset of inflammatory T cells, the Th17 cells, which are pivotal in several autoimmune and inflammatory processes. IL-17A neutralization is expected to treat the underlying pathophysiology of immune mediated disease, and as a consequence provide relief of symptoms. Secukinumab (AIN457) is a high-affinity fully human monoclonal anti-human antibody that inhibits IL-17A activity, which has emerged as a potential treatment for patients with various autoimmune diseases, e.g., rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, diabetes, asthma, chronic plaque-type psoriasis, and multiple sclerosis. Several Phase II and III studies have shown that secukinumab is superior to placebo in achievement of PASI 75 in treating chronic plaque-type psoriasis (e.g., secukinumab 3×150 mg and 3×75 mg were both superior to placebo in achievement of PASI 75 at Week 12 (81.5% and 57.1%, respectively, vs. 9.1%) in study CAIN457A2220. Secukinumab is currently used in global Phase III studies for the treatment of chronic plaque-type psoriasis, and has again shown superiority over placebo, and newly also over etanercept.

**[0003]** International Patent Application WO2012/059598 provides sucrose-based lyophilized compositions of secukinumab, which are reconstituted with 1 mL water immediately prior to use. However, WO2012/059598 provides no disclosure of a ready-to-use pharmaceutical product or liquid pharmaceutical composition of secukinumab having long-term stability. Indeed, the marginal stability of proteins in liquid compositions often prevents long-term storage at room temperature or refrigerated conditions. In addition, various physical and chemical reactions can occur in solution (aggregation [covalent and noncovalent], deamidation, oxidation, clipping, isomerization, denaturation), leading to an increase in degradation product levels and/or loss of bioactivity. A commercial ready-to-use liquid antibody composition should provide sufficient physical and chemical stability of the antibody during shipping and handling to ensure that the dosage and product safety claims are met when the molecule is administered to a patient. Specifically, an acceptable liquid antibody composition must enhance stability and minimize protein degradation, especially protein aggregation, in order to avoid serious immunogenic reactions. Moreover, the composition must also be of acceptable osmolality and pH value for subcutaneous application and have low viscosity as a prerequisite for manufacturing (compounding, filtration, filling) and syringeability. Balancing these myriad

requirements is difficult, making the production of a commercially viable aqueous biopharmaceutical composition a technical challenge.

**[0004]** Regardless of the technical challenges outlined above, we have now successfully developed novel and beneficial ready-to-use pharmaceutical products and liquid pharmaceutical compositions of the IL-17 antibodies and antigen binding fragments disclosed herein, e.g., secukinumab.

#### BRIEF SUMMARY OF THE DISCLOSURE

**[0005]** The invention provides a pharmaceutical product comprising:

1. a. a container having a headspace, wherein the oxygen content in the headspace is less than 12%, and
2. b. a stable liquid pharmaceutical composition having a pH of 5.2 to 6.2 disposed within said container, said composition comprising:
  1. i. 20 mg/ml to 175 mg/ml secukinumab;
  2. ii. 2.5 to 20 mM L-methionine, and
  3. iii. a non-ionic stabilizer, a surfactant selected from a polysorbate and a poloxamer, and a histidine buffer.

**[0006]** The invention further provides a process for reducing the oxidation of secukinumab, comprising:

1. a. preparing a stable liquid composition having a pH of 5.2 to 6.2 and comprising:
  1. i. 20 mg/ml to 175 mg/ml secukinumab;
  2. ii. 2.5 mM to 20 mM methionine; and
  3. iii. a non-ionic stabilizer, a surfactant selected from a polysorbate and a poloxamer, and a histidine buffer,
2. b. disposing said liquid composition in a container having a headspace; and
3. c. adjusting the oxygen content in the headspace to less than or equal to 12%.

**[0007]** In addition, the invention provides a stable liquid pharmaceutical composition comprising, 25 mg/mL to 150 mg/mL secukinumab, 10 mM to 30 mM histidine pH 5.2-6.2, 180 mM to 300 mM trehalose, 0.01% to 0.04% polysorbate 80, and 2.5 mM to 20 mM methionine.

**[0008]** The disclosure provides pharmaceutical products that include a container (e.g., pen, syringe, vial, autoinjector) having a headspace with less than 12% oxygen (e.g., less than about 10% oxygen, less than about 8% oxygen, less than about 6% oxygen, etc.), and a liquid composition as defined in the appended claims disposed within the container. The liquid

composition is not reconstituted from a lyophilisate, but rather is a ready-to-use liquid composition and broadly includes secukinumab, a buffer, a surfactant, methionine, and a stabilizer, as well as subcombinations thereof. We have determined that the combined use of particular stabilizers with a low oxygen level in the headspace of the container contributes significantly to long-term stability of the liquid pharmaceutical product, and prevents oxidation of the IL-17 antibody (secukinumab) included in the composition. These liquid compositions have excellent properties, e.g.:

after 13 months storage at 25° C, aggregate formation as measured by SEC of ≤ 3.5 % for 2.5 mM methionine, ≤ 3.0 % for 5 mM; and ≤ 2.2 % for 20 mM methionine-containing compositions; and

after 13 months storage at 25° C, degradation products by RP-HPLC (sum of variants before the main peak) of ≤ 39.4 % for 2.5 mM, ≤ 37.8 % for 5.0 mM, and ≤ 34.5 % for 20 mM methionine-containing compositions.

**[0009]** Accordingly, disclosed herein are pharmaceutical products comprising: a container having a headspace, wherein the oxygen content in the headspace is less than 12%, and a liquid pharmaceutical composition having a pH of 5.2 to 6.2 disposed within said container, said composition comprising: 20 mg/ml to 175 mg/ml secukinumab; 2.5 to 20 mM L-methionine, wherein the liquid pharmaceutical composition is not reconstituted from a lyophilisate.

**[0010]** Also disclosed herein are pharmaceutical products comprising: a container having a headspace, wherein the oxygen content in the headspace is less than about 6%; and a liquid pharmaceutical composition disposed within said container, said composition comprising about 25 mg/mL to about 150 mg/mL secukinumab, about 10 mM to about 30 mM histidine pH 5.8, about 200 mM to about 225 mM trehalose, about 0.02% polysorbate 80, and about 2.5 mM to about 20 mM methionine, wherein the liquid pharmaceutical composition is not reconstituted from a lyophilisate.

**[0011]** Also disclosed herein are processes for reducing the oxidation of secukinumab, comprising: preparing a liquid composition having a pH of 5.2 to 6.2 and comprising: about 25 mg/ml to about 150 mg/ml of secukinumab; 2.5mM to 20 mM methionine; disposing said liquid composition in a container having a headspace; and adjusting the oxygen content in the headspace to less than or equal to 12%.

**[0012]** Also disclosed herein are stable liquid pharmaceutical compositions comprising 25 mg/mL to 150 mg/mL of secukinumab, 10 mM to 30 mM buffer (histidine) pH 5.8, about 200 mM to about 225 mM stabilizer (e.g., trehalose), about 0.02% surfactant (e.g., polysorbate 80), and 2.5 mM to 20 mM methionine.

**[0013]** These pharmaceutical products and stable liquid compositions may be used for the

treatment of various IL-17-mediated disorders (e.g., autoimmune disorders, such as psoriasis, ankylosing spondylitis, psoriatic arthritis, and rheumatoid arthritis). Kits containing these pharmaceutical products and stable liquid compositions may be prepared.

**[0014]** Any references in the description to methods of treatment refer to the compounds, pharmaceutical compositions and medicaments of the present invention for use in the method for treatment of the human (or animal) body by therapy.

#### BRIEF DESCRIPTION OF THE DRAWINGS

**[0015]**

**Figure 1A-D** show the impact of different anti-oxidative stabilizers on 150mg/ml secukinumab liquid in syringe stability: parameter estimates for sub-visible particles 1 $\mu$ m by light obscuration (particles/ml) after 8 weeks at 5°C (A) pre-main peak species by RP-HPLC (%) after 8 weeks at 25°C (B) DP-SEC (%) after 8 weeks at 40°C (C) AP-SEC (%) after 8 weeks at 40°C (D).

**Figure 2** shows the effect of L-methionine concentration on 25 mg/ml secukinumab stability at 25°C storage: pre-main peak species by RP- HPLC (%). Grey dashed line: linear fit to 10mM L-methionine/ 5 % headspace oxygen content data; black dashed line: linear fit to 0mM L-methionine/ 5 % headspace oxygen content data.

**Figure 3** shows the effect of L-methionine, trehalose and polysorbate 80 on 150 mg/ml secukinumab liquid in syringe stability stored for 6 months at 25oC: pre-main peak species by RP-HPLC (%).

**Figure 4A and B** show the effect of L-methionine concentration on 150 mg/ml secukinumab liquid in syringe stability stored at 5°C AP-SEC (%) (A) and pre-main peak species by RP-HPLC (%) (B) in the presence of 5 mM and 0 mM L-methionine.

**Figure 5** shows the effect of L-methionine concentration on 150mg/ml secukinumab liquid in syringe stability after 30 months at 5°C and 13 months at 25°C: AP-SEC (%) (A) and pre-main peak species by RP-HPLC (%) (B).

**Figure 6A and B** show the effect of L-methionine concentration on 25 mg/ml secukinumab liquid in vial (10 % headspace oxygen content) stability after 3 months storage at 40°C AP-SEC (%) (A) and sum of impurities by CE-SDS (non-reducing) (%) (B).

**Figure 7** shows the effect of headspace oxygen content on 150 mg/ml secukinumab liquid in Syringe stored at 25°C: AP-SEC (%).

**Figure 8A-D** show the effect of headspace oxygen content and fill volume on AP-SEC (%) in 150 mg/ml secukinumab liquid in syringe after storage at 25°C (A, B) and 5°C (C, D). Fill volume for A & C is 0.5 mL. Fill volume for B & D is 1.0 mL.

**Figure 9** shows the effect of headspace oxygen content and fill volume on 150 mg/ml

secukinumab liquid in syringe stability after 6 months at 5°C and 25°C: purity by RP-HPLC.

**Figure 10** shows the effect of L-methionine concentration and headspace oxygen content on 150 mg/ml secukinumab liquid in syringe stability after 6 months storage at 25°C (A): AP-SEC (%);

**Figure 11** shows the effect of nitrogen purge and L-methionine concentration on 150mg/ml secukinumab liquid in syringe stability: pre-main peak species by RP-HPLC (%).

**Figure 12A and B** show the effect of pH on 150 mg/ml secukinumab liquid in syringe stability after 4 weeks storage at 40°C: scaled estimates/2 (effect of increase in pH by 0.3 units) for stability pre-main peak species by RP-HPLC (% change) (A) and AP-SEC (% change) (B).

**Figure 13A-D** show the effect of pH on 150 mg/ml secukinumab Liquid in Syringe stability after storage at 5°C: Turbidity (NTU) (A), Purity by SEC (%) (B), Acidic variants by CEX (%) (C), AP-SEC (%) (D).

**Figure 14** shows the impact of stabilizer on 150 mg/ml secukinumab liquid in syringe stability after 8 weeks storage at 25°C: parameter estimates for AP-SEC.

**Figure 15** shows the effect of surfactant on 150 mg/ml secukinumab liquid in syringe stability after shaking: Parameter estimates for sub-visible particles  $\geq 1 \mu\text{m}$  by light obscuration (particles per ml).

**Figure 16A-D** shows the effect of buffer type on 150 mg/ml secukinumab liquid in syringe stability: parameter estimates for AP-SEC (%) after freeze-thaw stress (A), AP-SEC (%) after shaking stress (B), pre-main peak species by RP-HPLC (%) after 8 weeks storage at 25°C (C), DP-SEC (%) after shaking stress (D).

## DETAILED DESCRIPTION OF THE DISCLOSURE

**[0016]** The term "comprising" encompasses "including" as well as "consisting," e.g. a composition "comprising" X may consist exclusively of X or may include something additional, e.g., X + Y.

**[0017]** The term "about" in relation to a numerical value x means  $\pm 10\%$  unless the context dictates otherwise.

**[0018]** By "monthly" is meant about every 4 weeks (e.g., every 4 weeks), which is about every 28 days (e.g., every 28 days).

**[0019]** The term "antibody" as referred to herein includes whole antibodies and any antigen-binding fragment or single chains thereof. A naturally occurring "antibody" is a glycoprotein

comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as  $V_H$ ) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as  $V_L$ ) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The  $V_H$  and  $V_L$  regions can be further subdivided into regions of hypervariability, termed hypervariable regions or complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each  $V_H$  and  $V_L$  is composed of three CDRs and four FRs arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (e.g., effector cells) and the first component (C1q) of the classical complement system. In the disclosed methods, regimens, kits, processes, uses and compositions, secukinumab is employed as an antibody to IL-17.

**[0020]** An "isolated antibody", as used herein, refers to an antibody that is substantially free of other antibodies having different antigenic specificities (e.g., an isolated antibody that specifically binds IL-17 is substantially free of antibodies that specifically bind antigens other than IL-17). The term "monoclonal antibody" or "monoclonal antibody composition" as used herein refer to a preparation of antibody molecules of single molecular composition. The term "human antibody," as used herein, is intended to include antibodies having variable regions in which both the framework and CDR regions are derived from sequences of human origin. A "human antibody" need not be produced by a human, human tissue or human cell. The human antibodies of the disclosure may include amino acid residues not encoded by human sequences (e.g., mutations introduced by random or site-specific mutagenesis *in vitro*, by N-nucleotide addition at junctions *in vivo* during recombination of antibody genes, or by somatic mutation *in vivo*).

**[0021]** The term "antigen-binding fragment" of an antibody as used herein, refers to fragments of an antibody that retain the ability to specifically bind to an antigen (e.g., IL-17). It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of binding fragments encompassed within the term "antigen-binding fragment" of an antibody include a Fab fragment, a monovalent fragment consisting of the  $V_L$ ,  $V_H$ , CL and CH1 domains; a F(ab)2 fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consisting of the  $V_H$  and CH1 domains; a Fv fragment consisting of the  $V_L$  and  $V_H$  domains of a single arm of an antibody; a dAb fragment (Ward et al., 1989 *Nature* 341:544-546), which consists of a  $V_H$  domain; and an isolated CDR. Exemplary antigen binding sites include the CDRs of secukinumab as set forth in SEQ ID NOs: 1-6 and 11-13 (**Table 1**), preferably the heavy chain CDR3. Furthermore, although the two domains of the Fv fragment,  $V_L$  and  $V_H$ , are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that

enables them to be made as a single protein chain in which the  $V_L$  and  $V_H$  regions pair to form monovalent molecules (known as single chain Fv (scFv); see, e.g., Bird et al., 1988 *Science* 242:423-426; and Huston et al., 1988 *Proc. Natl. Acad. Sci.* 85:5879-5883). Such single chain antibodies are also intended to be encompassed within the term "antibody". Single chain antibodies and antigen-binding fragments are obtained using conventional techniques known to those of skill in the art.

**[0022]** The term "pharmaceutical product" means a container (e.g., pen, syringe, bag, pump, etc.) having a pharmaceutical composition disposed within said container. By "container" is meant any means for holding a liquid pharmaceutical composition, e.g., a pen, syringe, vial, autoinjector, patch, etc. Each container has a "headspace", i.e., an area within the container that does not contain the liquid pharmaceutical composition. This headspace contains gas, e.g., a mixture of oxygen and other gases normally found in air. The level of oxygen in the headspace may be regulated, e.g., by introducing an inert gas (e.g., nitrogen, argon, etc.) into the headspace in place of oxygen. This may be achieved actively, e.g., by purging, or passively, e.g., by placing a container in a system and removing the oxygen (e.g., by vacuum, etc.). Purging, e.g., using an inert gas, preferably nitrogen, may occur prior to filling of the composition into the container, during filling, or prior and during stopper placement. As used herein, the term "oxygen content in the headspace" refers to the percent oxygen found in the headspace of a given container.

**[0023]** A "stable" composition is one in which the protein therein essentially retains its stability, (e.g., physical, chemical and/or biological activity) upon storage. Various analytical techniques for measuring protein stability are available in the art and are reviewed in Peptide and Protein Drug Delivery, 247-301, Vincent Lee Ed., Marcel Dekker, Inc., New York, N.Y., Pubs. (1991) and Jones, A. *Adv. Drug Delivery Rev.* 10:29-90 (1993). Stability can be measured at a selected temperature for a selected time period. A "stable" liquid antibody composition is a liquid antibody composition with no significant changes observed at a refrigerated temperature (2-8° C) for at least 6 months, 12 months, preferably 2 years, and more preferably 3 years; or at room temperature (23-27°C) for at least 3 months, preferably 6 months, and more preferably 1 year; or at stressed conditions (~40°C) for at least 1 month, preferably 3 months, and more preferably 6 months. Various stability criteria may be used, e.g., no more than 10%, preferably 5%, of antibody monomer is degraded (e.g., as measured by SEC Purity, RP-HPLC Purity, CEX Purity, CE-SDS Purity (non-reducing), etc.). Alternatively, stability may be shown if the solution remains clear to slightly opalescent by visual analysis or by using nephelometry. Alternatively, stability may be shown if concentration, pH and osmolality of the composition have no more than +/-10% variation over a given time period, e.g., at least 3 months, preferably 6 months, and more preferably 1 year. Alternatively, stability may be shown if potency (e.g., as measured by biological activity in an inhibition or CEX assay, etc.) is within 70-130% (e.g., at least 70%, at least 75%, at least 76%, at least 80%, at least 90%, at least 91%, at least 95%), preferably 80-120% of a control over a given time period, e.g., at least 3 months, preferably 6 months, and more preferably 1 year. Alternatively, stability may be shown if no more than 10%, preferably 5% of clipping of the antibody is observed (e.g., as measured by DP-SEC, etc.) over a given time period, e.g., at least 3 months, preferably 6 months, and

more preferably 1 year. Alternatively, stability may be shown if less than 10%, preferably less than 5% aggregates are formed (e.g., as measured by AP-SEC, etc.) over a given time period, e.g., at least 3 months, preferably 6 months, and more preferably 1 year. Alternatively, stability may be shown if, after 13 months storage at 25°C, aggregate formation as measured by SEC is  $\leq$  about 3.5 %,  $\leq$  about 3.0 %; or  $\leq$  about 2.2 %. Alternatively, stability may be shown if, after 13 months storage at 25 °C, degradation product formation (as measured by RP-HPLC (pre-main peak species)) is  $\leq$  about 39.4 %,  $\leq$  about 37.8 %, or  $\leq$  about 34.5 %.

**[0024]** An antibody retains its physical stability in a pharmaceutical composition if it shows no significant increase of aggregation, precipitation and/or denaturation upon visual examination of color and/or clarity (turbidity), or as measured by UV light scattering, size exclusion chromatography (SEC) and dynamic light scattering (DLS). In addition, the protein conformation should not be significantly altered, e.g., as evaluated by fluorescence spectroscopy (determines the protein tertiary structure) or by FTIR spectroscopy (determines the protein secondary structure).

**[0025]** An antibody retains its chemical stability in a pharmaceutical composition if it shows no significant chemical alteration. Chemical stability can be assessed by detecting and quantifying chemically altered forms of the protein. Degradation processes that often alter the protein chemical structure include hydrolysis or clipping (evaluated by methods such as size exclusion chromatography [SEC] and SDS-PAGE), oxidation (evaluated by methods such as by peptide mapping in conjunction with mass spectroscopy or MALDI/TOF/MS), deamidation (evaluated by methods such as cation-exchange chromatography (CEX), capillary isoelectric focusing, peptide mapping, isoaspartic acid measurement), and isomerization (evaluated by measuring the isoaspartic acid content, peptide mapping, etc.).

**[0026]** An antibody retains its biological activity in a pharmaceutical composition, if the biological activity of the protein/antibody at a given time is within a predetermined range of the biological activity exhibited at the time the pharmaceutical composition was prepared. The biological activity of an antibody can be determined, for example, by an antigen binding ELISA assay, potency assay (e.g., evaluating the ability of an IL-17 antibody (e.g., secukinumab) to bind IL-17 and inhibit IL-6 release from chondrocytes), or cysteamine-CEX derivatization.

**[0027]** As used herein, "purity by RP-HPLC" refers to the percentage of main peak in RP-HPLC and can be used to assess the stability of secukinumab. RP-HPLC is used to separate secukinumab and its variants according to their hydrophobicity. Pre-main peak species by RP-HPLC is the percentage sum of the peaks eluting prior to the main peak, which may contain fragmented, isomerized, and oxidized species of the antibody.

**[0028]** As used herein, "purity by CEX" refers to the percentage of main peak in CEX and can be used to assess the stability of secukinumab antibody. CEX is used to evaluate the charge heterogeneity of secukinumab by measuring the percentage of acidic and basic variants.

**[0029]** As used herein, "purity by SEC" refers to the percentage of monomer in SEC and can

be used to assess the stability of secukinumab. SEC is used to separate monomeric secukinumab from aggregates and fragments according to their size under non-denaturing conditions. The sum of peaks eluting prior to the main peak are reported as percentage of aggregation products (AP-SEC), the sum of peaks eluting after the main peak as percentage of degradation products (DP-SEC)

**[0030]** As used herein, "purity by CE-SDS" refers to the percentage of intact antibody in CE-SDS and can be used to assess the stability of secukinumab. CE-SDS is used to separate by- and degradation products from intact secukinumab according to their molecular size under non-reducing conditions. The sum of peaks separated from the main peak is reported as percentage of impurities.

**[0031]** The phrase "liquid pharmaceutical composition" as used herein refers to an aqueous composition that is not reconstituted from a lyophilisate and that contains at least one IL-17 antibody or antigen binding fragment thereof (e.g., secukinumab) and at least one additional excipient (e.g., a buffer). The liquid pharmaceutical composition may include additional excipients (stabilizers, surfactants) and additional active ingredients. This type of formulation is also referred to as a "ready-to-use" formulation.

**[0032]** As used herein, the term "lyophilisate" refers to dried (e.g., freeze dried) pharmaceutical compositions largely devoid of water. Techniques for lyophilisation of antibodies are well known in the art, e.g., see Rey & May (2004) Freeze-Drying/Lyophilization of Pharmaceutical & Biological Products ISBN 0824748689. Lyophilisates are reconstituted to give aqueous compositions - usually for immediate use (e.g., within 1-10 days) - as reconstituted lyophilisates tend to have a limited shelf lives.

**[0033]** The term "high concentration" refers to a composition containing greater than 50 mg/ml antibody or antigen binding fragment thereof. In preferred embodiments, a high concentration liquid composition contains  $\geq$  about 50 mg/ml,  $\geq$  about 75 mg/ml,  $\geq$  about 100 mg/ml,  $\geq$  about 125 mg/ml,  $\geq$  about 150 mg/ml,  $\geq$  about 175 mg/ml,  $\geq$  about 200 mg/ml, or  $\geq$  about 225 mg/ml.

**[0034]** The term "IL-17" refers to IL-17A, formerly known as CTLA8, and includes wild-type IL-17A from various species (e.g., human, mouse, and monkey), polymorphic variants of IL-17A, and functional equivalents of IL-17A. Functional equivalents of IL-17A according to the present disclosure preferably have at least about 65%, 75%, 85%, 95%, 96%, 97%, 98%, or even 99% overall sequence identity with a wild-type IL-17A (e.g., human IL-17A), and substantially retain the ability to induce IL-6 production by human dermal fibroblasts.

**[0035]** The term " $K_D$ " is intended to refer to the dissociation rate of a particular antibody-antigen interaction. The term " $K_D$ ", as used herein, is intended to refer to the dissociation constant, which is obtained from the ratio of  $K_d$  to  $K_a$  (i.e.  $K_d/K_a$ ) and is expressed as a molar concentration (M).  $K_D$  values for antibodies can be determined using methods well established in the art. A method for determining the  $K_D$  of an antibody is by using surface plasmon

resonance, or using a biosensor system such as a Biacore® system. In some embodiments, the IL-17 antibody binds human IL-17 with a  $K_D$  of about 100-250 pM (as measured by Biacore®).

**[0036]** The term "affinity" refers to the strength of interaction between antibody and antigen at single antigenic sites. Within each antigenic site, the variable region of the antibody "arm" interacts through weak non-covalent forces with antigen at numerous sites; the more interactions, the stronger the affinity. Standard assays to evaluate the binding affinity of the antibodies toward IL-17 of various species are known in the art, including for example, ELISAs, western blots and RIAs. The binding kinetics (e.g., binding affinity) of the antibodies also can be assessed by standard assays known in the art, such as by Biacore® analysis.

**[0037]** As used herein, the terms "subject" and "patient" include any human or nonhuman animal. The term "nonhuman animal" includes all vertebrates, e.g., mammals and non-mammals, such as nonhuman primates, sheep, dogs, cats, horses, cows, chickens, amphibians, reptiles, etc.

**[0038]** An antibody that "inhibits" one or more of these IL-17 functional properties (e.g., biochemical, immunochemical, cellular, physiological or other biological activities, or the like) as determined according to methodologies known to the art and described herein, will be understood to relate to a statistically significant decrease in the particular activity relative to that seen in the absence of the antibody (or when a control antibody of irrelevant specificity is present). An antibody that inhibits IL-17 activity affects a statistically significant decrease, e.g., by at least about 10% of the measured parameter, by at least 50%, 80% or 90%, and in certain embodiments of the disclosed methods, uses, processes, kits and compositions, the IL-17 antibody used may inhibit greater than 95%, 98% or 99% of IL-17 functional activity.

**[0039]** "Inhibit IL-6" as used herein refers to the ability of an IL-17 antibody (e.g., secukinumab) to decrease IL-6 production from chondrocytes. The biological activity of the IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab, may be measured based on its capacity to inhibit the IL-17-induced release of IL-6 from an immortalized human chondrocyte cell line, e.g., C-20/A4. In brief, on the first day of the assay, C-20/A4 cells are seeded into 96-well plates, are allowed to attach, and are then incubated overnight in the presence of a fixed, sub-maximal concentration of IL-17 (e.g., at about 20-200 ng/mL, e.g., about 80 ng/mL, in the culture medium) and various concentrations of antibody (e.g., at about 0.01 ug/mL - about 4 ug/mL, e.g., about 0.5  $\mu$ g/mL - about 2 $\mu$ g/mL, in the assay plate). TNFalpha, which facilitates IL-17-induced IL-6 production, is included (e.g., at about 0.01 ng/mL - about 1 ng/mL, e.g., about 0.5 ng/mL, in the culture medium) to increase the dynamic range of the assay. On the second day, the concentration of IL-6 in the cell supernatants is quantified by ELISA. The amount of IL-6 in the cell supernatants is inversely proportional to the activity of the IL-17 antibody present in the sample. The biological activity of an antibody test sample is quantified by comparing its ability to inhibit IL-17-dependent release of IL-6 to that of an antibody reference standard. The samples and standard are normalized on the basis of

protein content. Relative potency is calculated using a parallel line assay according to the European Pharmacopoeia. The final result is expressed as relative potency (in percent) of a sample compared to the reference standard.

**[0040]** The term "derivative", unless otherwise indicated, is used to define amino acid sequence variants, and covalent modifications (e.g., pegylation, deamidation, hydroxylation, phosphorylation, methylation, etc.) of an IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab, according to the present disclosure, e.g., of a specified sequence (e.g., a variable domain). A "functional derivative" includes a molecule having a qualitative biological activity in common with the disclosed IL-17 antibodies or antigen binding fragments thereof. A functional derivative includes fragments and peptide analogs of an IL-17 antibody or antigen binding fragment thereof as disclosed herein. Fragments comprise regions within the sequence of a polypeptide according to the present disclosure, e.g., of a specified sequence. Functional derivatives of the IL-17 antibodies or antigen binding fragments thereof disclosed herein (e.g., functional derivatives of secukinumab) preferably comprise  $V_H$  and/or  $V_L$  domains that have at least about 65%, 75%, 85%, 95%, 96%, 97%, 98%, or even 99% overall sequence identity with the  $V_H$  and/or  $V_L$  sequences of the IL-17 binding molecules disclosed herein (e.g., the  $V_H$  and/or  $V_L$  sequences of **Table 1**), and substantially retain the ability to bind human IL-17 or, e.g., inhibit IL-6 production of IL-17 induced human dermal fibroblasts.

**[0041]** The phrase "substantially identical" means that the relevant amino acid or nucleotide sequence (e.g.,  $V_H$  or  $V_L$  domain) will be identical to or have insubstantial differences (e.g., through conserved amino acid substitutions) in comparison to a particular reference sequence. Insubstantial differences include minor amino acid changes, such as 1 or 2 substitutions in a 5 amino acid sequence of a specified region (e.g.,  $V_H$  or  $V_L$  domain). In the case of antibodies, the second antibody has the same specificity and has at least 50% of the affinity of the same. The sequence identity of a derivative IL-17 antibody (e.g., a derivative of secukinumab, e.g., a secukinumab biosimilar antibody) can be about 90% or greater, e.g., 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or higher relative to the disclosed sequences.

**[0042]** "Identity" with respect to a native polypeptide and its functional derivative is defined herein as the percentage of amino acid residues in the candidate sequence that are identical with the residues of a corresponding native polypeptide, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent identity, and not considering any conservative substitutions as part of the sequence identity. Neither N- or C-terminal extensions nor insertions shall be construed as reducing identity. Methods and computer programs for the alignment are well known. The percent identity can be determined by standard alignment algorithms, for example, the Basic Local Alignment Search Tool (BLAST) described by Altschul et al. ((1990) *J. Mol. Biol.*, 215: 403 410); the algorithm of Needleman et al. ((1970) *J. Mol. Biol.*, 48: 444 453); or the algorithm of Meyers et al. ((1988) *Comput. Appl. Biosci.*, 4: 11 17). A set of parameters may be the Blosum 62 scoring matrix with a gap penalty of 12, a gap extend penalty of 4, and a frameshift gap penalty of 5. The percent identity between two amino acid or nucleotide sequences can also be determined using the algorithm

of E. Meyers and W. Miller ((1989) CABIOS, 4:11-17) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4.

**[0043]** "Amino acid(s)" refer to all naturally occurring L- $\alpha$ -amino acids, e.g., and include D-amino acids. The phrase "amino acid sequence variant" refers to molecules with some differences in their amino acid sequences as compared to the sequences according to the present disclosure. Amino acid sequence variants of a polypeptide according to the present disclosure, e.g., of a specified sequence, still have the ability to bind the human IL-17 or, e.g., inhibit IL-6 production of IL-17 induced human dermal fibroblasts. Amino acid sequence variants include substitutional variants (those that have at least one amino acid residue removed and a different amino acid inserted in its place at the same position in a polypeptide according to the present disclosure), insertional variants (those with one or more amino acids inserted immediately adjacent to an amino acid at a particular position in a polypeptide according to the present disclosure) and deletional variants (those with one or more amino acids removed in a polypeptide according to the present disclosure).

**[0044]** The term "pharmaceutically acceptable" means a nontoxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s).

**[0045]** The term "administering" in relation to a compound, e.g., an IL-17 binding molecule or another agent, is used to refer to delivery of that compound to a patient by any route.

**[0046]** As used herein, a "therapeutically effective amount" refers to an amount of an IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab, that is effective, upon single or multiple dose administration to a patient (such as a human) for treating, preventing, preventing the onset of, curing, delaying, reducing the severity of, ameliorating at least one symptom of a disorder or recurring disorder, or prolonging the survival of the patient beyond that expected in the absence of such treatment. When applied to an individual active ingredient (e.g., an IL-17 antibody, e.g., secukinumab) administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

**[0047]** The term "treatment" or "treat" refer to both prophylactic or preventative treatment as well as curative or disease modifying treatment, including treatment of a patient at risk of contracting the disease or suspected to have contracted the disease as well as patients who are ill or have been diagnosed as suffering from a disease or medical condition, and includes suppression of clinical relapse. The treatment may be administered to a patient having a medical disorder or who ultimately may acquire the disorder, in order to prevent, cure, delay the onset of, reduce the severity of, or ameliorate one or more symptoms of a disorder or recurring disorder, or in order to prolong the survival of a patient beyond that expected in the absence of such treatment.

**[0048]** The phrase "means for administering" is used to indicate any available implement for systemically administering a drug to a patient, including, but not limited to, a pre-filled syringe, a vial and syringe, an injection pen, an autoinjector, an i.v. drip and bag, a pump, a patch pump, etc. With such items, a patient may self-administer the drug (i.e., administer the drug on their own behalf) or a physician may administer the drug. Typically, dosages given in "mg/kg" are administered via an i.v. route, and doses given in "mg" are administered via i.m. or s.c. injections. In some embodiments of the disclosed methods, kits, regimens and uses, the secukinumab is delivered to the patient via the i.v. route. In some embodiments of the disclosed methods, kits, regimens and uses, the secukinumab is delivered to the patient via the s.c. route.

#### **IL-17 Antibodies and Antigen Binding Fragments Thereof**

**[0049]** The disclosed pharmaceutical products, compositions, liquid compositions, regimens, processes, uses, methods and kits contain or utilize secukinumab as an IL-17 antibody.

**[0050]** Secukinumab comprises an immunoglobulin  $V_H$  domain comprising the amino acid sequence set forth as SEQ ID NO: 8 and an immunoglobulin  $V_L$  domain comprising the amino acid sequence set forth as SEQ ID NO: 10.

**[0051]** For ease of reference the amino acid sequences of the hypervariable regions of the secukinumab monoclonal antibody, based on the Kabat definition and as determined by the X-ray analysis and using the approach of Chothia and coworkers, is provided in **Table 1**, below.

**Table 1:** Amino acid sequences of the hypervariable regions of the secukinumab monoclonal antibodies.

Light-Chain		
CDR1'	Kabat	R-A-S-Q-S-V-S-S-S-Y-L-A (SEQ ID NO:4)
	Chothia	R-A-S-Q-S-V-S-S-S-Y-L-A (SEQ ID NO:4)
CDR2'	Kabat	G-A-S-S-R-A-T (SEQ ID NO:5)
	Chothia	G-A-S-S-R-A-T (SEQ ID NO:5)
CDR2'	Kabat	Q-Q-Y-G-S-S-P-C-T (SEQ ID NO:6)
	Chothia	Q-Q-Y-G-S-S-P-C-T (SEQ ID NO:6)
Heavy-Chain		
CDR1	Kabat	N-Y-W-M-N (SEQ ID NO:1)
CDR1-x	Chothia	G-F-T-F-S-N-Y-W-M-N (SEQ ID NO:11)
CDR2	Kabat	A-I-N-Q-D-G-S-E-K-Y-Y-V-G-S-V-K-G (SEQ ID NO:2)
CDR2-x	Chothia	A-I-N-Q-D-G-S-E-K-Y-Y (SEQ ID

Heavy-Chain		
		NO:12)
CDR3	Kabat	D-Y-Y-D-I-L-T-D-Y-Y-I-H-Y-W-Y-F-D-L (SEQ ID NO:3)
CDR3-x	Chothia	C-V-R-D-Y-Y-D-I-L-T-D-Y-Y-I-H-Y-W-Y-F-D-L-W-G (SEQ ID NO:13)

**[0052]** The DNA encoding the VL of secukinumab is set forth in SEQ ID NO:9. The DNA encoding the VH of secukinumab is set forth in SEQ ID NO:7.

**[0053]** Secukinumab comprises the three CDRs of SEQ ID NO:10 and the three CDRs of SEQ ID NO:8. CDRs of SEQ ID NO:8 and SEQ ID NO:10, according to both the Chothia and Kabat definition, may be found in **Table 1**.

**[0054]** Secukinumab comprises the light chain of SEQ ID NO:14 and the heavy chain of SEQ ID NO:15. Secukinumab comprises the three CDRs of SEQ ID NO:14 and the three CDRs of SEQ ID NO:15. CDRs of SEQ ID NO:14 and SEQ ID NO:15, according to both the Chothia and Kabat definition, may be found in **Table 1**.

The heavy chain framework of the secukinumab antibody consists in sequence of FR1 (amino acid 1 to 30 of SEQ ID NO:8), FR2 (amino acid 36 to 49 of SEQ ID NO:8), FR3 (amino acid 67 to 98 of SEQ ID NO:8) and FR4 (amino acid 117 to 127 of SEQ ID NO:8) regions. Taking into consideration the determined hypervariable regions of secukinumab by X-ray analysis, the heavy chain framework consists in sequence of FR1-x (amino acid 1 to 25 of SEQ ID NO:8), FR2-x (amino acid 36 to 49 of SEQ ID NO:8), FR3-x (amino acid 61 to 95 of SEQ ID NO:8) and FR4 (amino acid 119 to 127 of SEQ ID NO:8) regions. In a similar manner, the light chain framework consists, in sequence, of FR1' (amino acid 1 to 23 of SEQ ID NO:10), FR2' (amino acid 36 to 50 of SEQ ID NO: 10), FR3' (amino acid 58 to 89 of SEQ ID NO:10) and FR4' (amino acid 99 to 109 of SEQ ID NO: 10) regions.

**[0055]** The inhibition of the binding of IL-17 to its receptor may be conveniently tested in various assays including such assays as described in WO 2006/013107. By the term "to the same extent" is meant that the reference and the derivative molecules exhibit, on a statistical basis, essentially identical IL-17 inhibitory activity in one of the assays referred to herein (see Example 1 of WO 2006/013107). For example, the IL-17 antibody or antigen binding fragment thereof disclosed herein typically have IC<sub>50</sub>s for the inhibition of human IL-17 on IL-6 production induced by human IL-17 in human dermal fibroblasts which are below about 10 nM, more preferably about 9, 8, 7, 6, 5, 4, 3, 2, or about 1 nM of that of, preferably substantially the same as, the IC<sub>50</sub> of the corresponding reference molecule when assayed as described in Example 1 of WO 2006/013107. Alternatively, the assay used may be an assay of competitive inhibition of binding of IL-17 by soluble IL-17 receptors (e.g. the human IL-17 R/Fc constructs of Example 1 of WO 2006/013107) and the IL-17 antibodies or antigen binding fragments thereof of the disclosure.

**[0056]** Secukinumab binds to an epitope of an IL-17 homodimer having two mature human IL-17 chains, said epitope comprising Leu74, Tyr85, His86, Met87, Asn88, Val124, Thr125, Pro126, Ile127, Val128, His129 on one chain and Tyr43, Tyr44, Arg46, Ala79, Asp80 on the other chain. The residue numbering scheme used to define these epitopes is based on residue one being the first amino acid of the mature protein (i.e., IL-17A lacking the 23 amino acid N-terminal signal peptide and beginning with Glycine). The sequence for immature IL-17A is set forth in the Swiss-Prot entry Q16552. In some embodiments, the IL-17 antibody has a  $K_D$  of about 100-200 pM, e.g., as measured by Biacore<sup>®</sup>. In some embodiments, the IL-17 antibody has an  $IC_{50}$  of about 0.4 nM for *in vitro* neutralization of the biological activity of about 0.67 nM human IL-17A. In some embodiments, the absolute bioavailability of subcutaneously (s.c.) administered IL-17 antibody has a range of about 60 - about 80%, e.g., about 76%. In some embodiments, secukinumab has an elimination half-life of about 4 weeks (e.g., about 23 to about 35 days, about 23 to about 30 days, e.g., about 30 days). In some embodiments, secukinumab has a  $T_{max}$  of about 7-8 days.

**[0057]** Secukinumab is described in Examples 1 and 2 of WO 2006/013107 (US 7,807,155). Secukinumab is a recombinant high-affinity, fully human monoclonal anti-human interleukin-17A (IL-17A, IL-17) antibody of the IgG1/kappa isotype that is currently in clinical trials for the treatment of immune-mediated inflammatory conditions. Secukinumab (see, e.g., WO2006/013107 and WO2007/117749) has a very high affinity for IL-17, i.e., a  $K_D$  of about 100-200 pM (e.g., as measured by Biacore<sup>®</sup>) and an  $IC_{50}$  for *in vitro* neutralization of the biological activity of about 0.67 nM human IL-17A of about 0.4 nM. Thus, secukinumab inhibits antigen at a molar ratio of about 1:1. This high binding affinity makes the secukinumab antibody particularly suitable for therapeutic applications. Furthermore, it has been determined that secukinumab has a very long half-life, i.e., about 4 weeks, which allows for prolonged periods between administration, an exceptional property when treating chronic life-long disorders, such as psoriasis.

#### Pharmaceutical Products Comprising IL-17 Antibodies

**[0058]** The disclosure broadly provides a pharmaceutical product including a container having a headspace with less than 12% oxygen in the headspace, and a liquid composition disposed within the container, wherein said liquid composition comprises secukinumab.

#### Containers

**[0059]** The pharmaceutical products of the disclosure employ primary packaging, i.e., containers, to store, transport, and maintain the disclosed liquid compositions. Pharmaceutically acceptable containers for use as part of the disclosed pharmaceutical products include syringes (e.g., available from Beckton Dickinson, Nuova Ompi, et al.),

stoppered vials, cartridges, autoinjectors, patch pumps and injector pens.

### **Headspace Oxygen**

**[0060]** We have determined that stability of secukinumab in the disclosed liquid composition can be enhanced by including a particular stabilizer (e.g., methionine) while concurrently replacing the oxygen in the container headspace of the pharmaceutical product with an inert gas (e.g., argon, helium, nitrogen), preferably N<sub>2</sub>. Specifically, we have determined that pharmaceutical products having a container that has been purged of oxygen, i.e., having less than about 12% oxygen in the headspace, have improved stability relative to unpurged products, e.g., as measured by SEC and RP-HPLC.

**[0061]** Modification of the oxygen content in the headspace using a purge (e.g., nitrogen purge) may be achieved during the filling stage or during the stoppering stage (or both). A purge (e.g., nitrogen purge) may be achieved by actively introducing the inert gas (e.g., using a needle) or during stoppering.

**[0062]** The oxygen content in the headspace is less than 12% (e.g., less than about 10%, less than about 8%, less than about 6%, etc.). In some embodiments, the oxygen content in the headspace is less than about 6%. The oxygen content in the headspace may be monitored by laser light absorption spectroscopy or fluorescence quenching or gas chromatography. It will be understood that the oxygen content in the headspace of a given container may increase over time, e.g., due to leakage. Thus, as used herein the phrase "the oxygen content in the headspace" refers to the initial level of oxygen in the headspace of a container immediately following closure (e.g., stoppering) of the product.

### **Liquid Compositions**

**[0063]** A liquid composition of the disclosure comprises secukinumab, and at least one additional excipient, e.g., buffer, surfactant, and stabilizer(s), etc. In some embodiments, the liquid composition comprises at least two additional excipients, e.g., a buffer and a stabilizer. In some embodiments, the liquid composition comprises a buffer, at least one stabilizer, and a surfactant.

**[0064]** In general, a pharmaceutical composition will be formulated with excipients that are compatible with the intended route of administration (e.g., oral compositions generally include an inert diluent or an edible carrier). Examples of routes of administration include parenteral (e.g., intravenous), intradermal, subcutaneous, oral (e.g., by mouth or inhalation), transdermal (topical), transmucosal, and rectal. The liquid antibody compositions of this disclosure are suitable for parenteral administration such as intravenous, intramuscular, intraperitoneal, or subcutaneous injection; particularly suitable for subcutaneous injection.

**[0065]** In some embodiments, a liquid composition of the disclosure maintains at least about 86% purity by RP-HPLC upon storage at 2-8°C for 6 months, at least about 76% purity by RP-HPLC upon storage at 25°C/60% RH for 6 months (preferably at least about 76%), and/or at least about 60% purity by RP-HPLC upon storage at 30°C/75% RH for 6 months. In some embodiments, a liquid composition of the disclosure maintains at least about 84% purity by RP-HPLC upon storage at 2-8°C for 24 months.

**[0066]** In some embodiments, a liquid composition of the disclosure maintains at least about 77% purity by CEX upon storage at 2-8°C for 6 months, at least about 62% purity by CEX upon storage at 25°C/60% RH for 6 months, and/or at least about 50% purity by CEX upon storage at 30°C/75% RH for 6 months. In some embodiments, a liquid composition of the disclosure maintains at least about 73% purity by CEX upon storage at 2-8°C for 24 months.

**[0067]** In some embodiments, a liquid composition of the disclosure maintains at least about 98% purity by SEC upon storage at 2-8°C for 6 months, at least about 96% purity by SEC upon storage at 25°C/60% RH for 6 months, and/or at least about 94% purity by SEC upon storage at 30°C/75% RH for 6 months. In some embodiments, a liquid composition of the disclosure maintains at least about 97% purity by SEC upon storage at 2-8°C for 24 months.

**[0068]** In some embodiments, a liquid composition of the disclosure maintains at least about 97% purity by CE-SDS (non-reducing conditions) upon storage at 2-8°C for 6 months, at least about 95% purity by CE-SDS (non-reducing conditions) upon storage at 25°C/60% RH for 6 months, and/or at least about 94% (preferably at least about 92%) purity by CE-SDS (non-reducing conditions) upon storage at 30°C/75% RH for 6 months. In some embodiments, a liquid composition of the disclosure maintains at least about 97% purity by CE-SDS (non-reducing conditions) upon storage at 2-8°C for 24 months.

**[0069]** In some embodiments, a liquid composition of the disclosure maintains less than about 0.57% impurity by SDS-PAGE (reducing conditions) upon storage at 2-8°C for 6 months, less than about 1.1% impurity by SDS-PAGE (reducing conditions) upon storage at 25°C/60% RH for 6 months, and/or less than about 1.9% impurity by SDS-PAGE (reducing conditions) upon storage at 30°C/75% RH for 6 months. In some embodiments, a liquid composition of the disclosure maintains less than about 0.91% impurity by SDS-PAGE (reducing conditions) upon storage at 2-8°C for 24 months.

**[0070]** In some embodiments, a liquid composition of the disclosure maintains at least about 88% relative biological activity by inhibition of IL-6 release from C-20/A4 chondrocytes upon storage at 2-8°C for 24 months, at least about 94% relative biological activity by inhibition of IL-6 release from chondrocytes upon storage at 25°C/60% RH for 6 months, and/or at least about 85% relative biological activity by inhibition of IL-6 release from chondrocytes upon storage at 30°C/75% RH for 6 months.

#### ***Antibody Concentration***

**[0071]** The IL-17 antibody secukinumab used in the disclosed liquid compositions is described *supra*. We have determined that, at least within the range of about 25 mg/ml to about 150 mg/ml, the concentration of antibody did not have a significant effect on composition stability. Therefore, in some embodiments, the antibody in the liquid composition is present at concentration of at least 25 mg/ml (e.g., about 25 mg/ml to about 150 mg/ml). In some embodiments, the concentration of the antibody in the liquid composition is a high concentration of at least about 25 mg/mL, at least about 50 mg/ml, at least about 75 mg/ml, at least about 100 mg/mL, or at least about 150 mg/ml. In some embodiments, the concentration of the antibody in the liquid composition is a high concentration of about 25 mg/mL - about 150 mg/mL. In one embodiment, the concentration of secukinumab in the liquid composition is about 25 mg/ml. In one embodiment, the concentration of secukinumab in the liquid composition is about 150 mg/ml.

#### ***Buffers and pH***

**[0072]** Suitable buffering agents for use with the disclosed liquid compositions include, but are not limited to, a gluconate buffer, histidine buffer, a citrate buffer, a phosphate [e.g., sodium or potassium] buffer, a succinate [e.g., sodium] buffer, an acetate buffer, a Tris buffer, glycine, arginine and combinations thereof. We have determined that there was no beneficial impact of succinate or acetate buffer on the stability of liquid compositions of secukinumab. Citrate buffer was assessed as beneficial in the compositions with regard to degradation products by SEC, CEX-acidic and aggregation products by RP HPLC. Overall, histidine buffer showed advantages in aggregation and degradation products by SEC, CEX acidic and RP-B. Thus, histidine buffer is a preferred buffer for the disclosed stable liquid compositions of secukinumab.

**[0073]** A histidine buffer (e.g., at a concentration of about 5 mM to about 50 mM, e.g., about 20 mM to about 50 mM, about 5 mM, about 10 mM, about 15 mM, about 20 mM, about 25 mM, about 30 mM, about 35 mM, about 40 mM, about 45 mM, about 50 mM) is particularly useful. In one embodiment, the stable liquid composition comprises about 20 mM to about 50 mM histidine buffer. The pH of the liquid composition is in the range 5.2-6.2 (e.g., 5.2 to about 5.8, e.g., 5.2, about 5.3, about 5.4, about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, about 6, 6.2). We have determined that with increasing the pH from 5.2 to 5.8, a positive trend in stability was observed (SEC-AP, DLS, SEC-DP, ALP-DP, CEX basic, RP-HPLC). Overall testing indicated that the ideal composition pH of the disclosed liquid compositions is 5.8. Thus, in one embodiment, the pH of the stable liquid antibody composition is about 5.8.

#### ***Surfactants***

**[0074]** Suitable surfactants for use with the disclosed liquid compositions include, but are not

limited to, non-ionic surfactants, ionic surfactants, zwitterionic surfactants and combinations thereof. Typical surfactants for use with the invention include, but are not limited to, sorbitan fatty acid esters (e.g., sorbitan monocaprylate, sorbitan monolaurate, sorbitan monopalmitate), sorbitan trioleate, glycerine fatty acid esters (e.g., glycerine monocaprylate, glycerine monomyristate, glycerine monostearate), polyglycerine fatty acid esters (e.g., decaglyceryl monostearate, decaglyceryl distearate, decaglyceryl monolinoleate), polyoxyethylene sorbitan fatty acid esters (e.g., polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan trioleate, polyoxyethylene sorbitan tristearate), polyoxyethylene sorbitol fatty acid esters (e.g., polyoxyethylene sorbitol tetrastearate, polyoxyethylene sorbitol tetraoleate), polyoxyethylene glycerine fatty acid esters (e.g., polyoxyethylene glyceryl monostearate), polyethylene glycol fatty acid esters (e.g., polyethylene glycol distearate), polyoxyethylene alkyl ethers (e.g., polyoxyethylene lauryl ether), polyoxyethylene polyoxypropylene alkyl ethers (e.g., polyoxyethylene polyoxypropylene glycol, polyoxyethylene polyoxypropylene propyl ether, polyoxyethylene polyoxypropylene cetyl ether), polyoxyethylene alkylphenyl ethers (e.g., polyoxyethylene nonylphenyl ether), polyoxyethylene hydrogenated castor oils (e.g. polyoxyethylene castor oil, polyoxyethylene hydrogenated castor oil), polyoxyethylene beeswax derivatives (e.g., polyoxyethylene sorbitol beeswax), polyoxyethylene lanolin derivatives (e.g., polyoxyethylene lanolin), and polyoxyethylene fatty acid amides (e.g., polyoxyethylene stearic acid amide); C10-C18 alkyl sulfates (e.g., sodium cetyl sulfate, sodium lauryl sulfate, sodium oleyl sulfate), polyoxyethylene C10-C18 alkyl ether sulfate with an average of 2 to 4 moles of ethylene oxide units added (e.g., sodium polyoxyethylene lauryl sulfate), and C1-C18 alkyl sulfosuccinate ester salts (e.g., sodium lauryl sulfosuccinate ester); and natural surfactants such as lecithin, glycerophospholipid, sphingophospholipids (e.g., sphingomyelin), and sucrose esters of C12-C18 fatty acids. A composition may include one or more of these surfactants. Preferred surfactants are poloxamer (e.g., poloxamer 188) or polyoxyethylene sorbitan fatty acid esters, e.g. polysorbate 20, 40, 60 or 80. Polysorbate 80 (Tween 80) (e.g., at a concentration of about 0.01% - about 0.1% (w/v), e.g., about 0.01% to about 0.04% (w/v), e.g., about 0.01%, about 0.02%, about 0.04%, about 0.06%, about 0.08%, about 0.1%) is particularly useful. In one embodiment, the stable liquid composition comprises about 0.02% (w/v) polysorbate 80. In one embodiment, the stable liquid composition comprises about 0.02% (w/v) polysorbate 20.

**[0075]** We have determined that there is a significant increase in turbidity, as well as an increase in the amount of visible particles, in liquid compositions lacking a surfactant. However, no advantage of Poloxamer 188 was detected compared to Polysorbate 20 and 80, except for an increase in ALP-DP and RP. Polysorbate 20 and 80 showed comparable efficiency in preventing an increase in turbidity, subvisible and visible particles. Thus, polysorbate 20 and 80 are preferred surfactants for use in the disclosed stable liquid compositions.

### ***Stabilizers***

**[0076]** Stabilizers assist in preventing oxidation and aggregation of proteins in pharmaceutical

compositions, particularly liquid pharmaceutical compositions, which have a shorter shelf life due to tendency of proteins to oxidize and/or aggregate while in aqueous solutions. Various analytical methods may be used to assess the stability of a given composition, e.g., RP-HPLC may be used to assay the level of oxidation products (pre-main peaks) in the liquid compositions disclosed herein, while SEC may be used to assay the level of aggregation in the liquid compositions disclosed herein.

**[0077]** Suitable stabilizers for use in the disclosed liquid compositions include ionic and non-ionic stabilizers (and combinations thereof), e.g., sugars, glycine, sodium chloride, arginine, EDTA, sodium ascorbate, cysteine, sodium bisulfate, sodium citrate, methionine, and benzyl alcohol. In some embodiments, the liquid pharmaceutical composition will contain at least one stabilizer from group 1 (e.g., sugars [e.g., trehalose, mannitol], amino acids [e.g., glycine, arginine], and sodium chloride). In some embodiments, the liquid pharmaceutical composition will contain at least one stabilizer from group 2 (EDTA, sodium ascorbate, cysteine, sodium bisulfate, sodium citrate, methionine, and benzyl alcohol). Group 2 stabilizers tend to have anti-oxidant properties, which may reduce oxidation of residues in the IL-17 antibodies. In preferred embodiments, a liquid pharmaceutical composition will contain two stabilizers - one from group 1 and one from group 2.

**[0078]** For a group 1 stabilizer, non-ionic stabilizers are preferred. Suitable non-ionic stabilizers include monosaccharides, disaccharides and trisaccharides, e.g., trehalose, raffinose, maltose, sorbitol or mannitol. The sugar may be a sugar alcohol or an amino sugar. The concentration of the group 1 stabilizer may be about 175 mM to about 350 mM, e.g., about 200 mM to about 300 mM, e.g., about 250 mM to about 270 mM, e.g., about 180 to about 300 mM, about 200 mM to about 225 mM, about 175 mM, about 180 mM, about 185 mM, about 190 mM, about 195 mM, about 200 mM, about 225 mM, about 250 mM, about 270 mM, 275 mM, about 300 mM. Mannitol at a concentration of about 200 mM to about 300 mM (e.g., about 250 mM to about 270 mM), trehalose at a concentration of about 180 mM to about 300 mM, e.g., about 200 mM to about 225 mM, sodium chloride at a concentration of about 130 mM to about 150 mM, arginine at a concentration of about 160 mM, glycine at a concentration of about 270 mM are particularly useful.

**[0079]** We have determined that glycine as stabilizer (group 1) was slightly advantageous regarding SEC-AP and DLS, but an increase in almost all degradation products was observed. NaCl as stabilizer (group 1) led to an increase in degradation and aggregation products by SEC and CEX basic variants. Trehalose and mannitol acted as comparable beneficial stabilizer, confirmed with almost all analytics, but mannitol showed a slightly inferior effect (SEC-AP, DLS), plus lower aqueous solubility compared to Trehalose. Thus, trehalose is the preferred stabilizer group 1 due to positive effects on degradation products. In one embodiment, the liquid composition comprises about 200 mM to about 225 mM trehalose. In one embodiment, the liquid composition comprises about 200 mM trehalose. In one embodiment, the liquid composition comprises about 225 mM trehalose.

**[0080]** We have determined that there is a significant impact of the group 2 on the stability of

liquid compositions of secukinumab. Our experiments showed that the use of no group 2 stabilizer was inferior (SEC-AP, DLS, turbidity, RP-B), compared to the compositions containing a group 2 stabilizer. Tetrasodium EDTA and cysteine showed an increase in aggregation and degradation product in the respective analytical methods. The addition of cysteine as group 2 stabilizer resulted in turbid compositions after freeze-thaw stress and precipitation within 4 weeks at 40°C storage. However, we determined that methionine is advantageous in all compositions regarding the analytics. Therefore, for a group 2 stabilizer, methionine, which also has anti-oxidant properties, is preferred. The concentration of the group 2 stabilizer (e.g., methionine) may be 2.5 to 20 mM (e.g., 2.5 mM, about 5 mM, about 10 mM or 20 mM). In preferred embodiments, a liquid pharmaceutical composition will contain at least one stabilizer from group 1 and methionine. In some embodiments, the disclosed liquid compositions include about 5 mM methionine.

#### ***Other Excipients***

**[0081]** The liquid antibody compositions of the disclosure may include further excipients, e.g., additional buffers, salts (e.g., sodium chloride, sodium succinate, sodium sulfate, potassium chloride, magnesium chloride, magnesium sulfate, and calcium chloride), additional stabilizing agents, tonicity modifier (e.g., salts and amino acids [e.g., proline, alanine, L-arginine, asparagine, L-aspartic acid, glycine, serine, lysine, and histidine]), glycerol, albumin, alcohols, preservatives, additional surfactants, anti-oxidants, etc. A thorough discussion of such additional pharmaceutical ingredients is available in Gennaro (2000) Remington: The Science and Practice of Pharmacy. 20th edition, ISBN: 0683306472.

#### ***Additional Active Agents***

**[0082]** The pharmaceutical products and stable liquid compositions of the disclosure may contain, in addition to secukinumab one or more other active agents (e.g., psoriasis agents, psoriatic arthritis agents, ankylosing spondylitis agents, rheumatoid arthritis agents). Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with secukinumab or to minimize side effects caused by secukinumab.

**[0083]** Examples of psoriasis agents that may be co-formulated with secukinumab include cyclosporine, methotrexate, mycophenolate mofetil, mycophenolic acid, sulfasalazine, 6-thioguanine, fumarates (e.g., dimethylfumarate and fumaric acid esters), azathioprine, corticosteroids, leflunomide, tacrolimus, T-cell blockers (such as Amevive® (alefacept) and Raptiva® (efalizumab), tumor necrosis factor-alpha (TNF-alpha) blockers (such as Enbrel® (etanercept), Humira® (adalimumab), Remicade® (infliximab) and Simponi® (golimumab)) and interleukin 12/23 blockers (such as Stelara® (ustekinumab), tasocitinib, and briakinumab).

**[0084]** Additional psoriasis agents that may be co-formulated with secukinumab for the treatment of psoriasis include apremilast, mometasome, voclosporin, ketokonazole, Neuroskin Forte, recombinant human interleukin-10, voclosporin, MK-3222, tofacitinib, VX-765, MED-1545, fluphenazine decanoate, acetomuinophn, bimosiamose cream, doxycycline, vancomycin, AbCm168, Vitamin D3, RO5310074, fludarabine Calcipotriol and hydrocortisone (LEO 80190), Focetria (Monovalent MF59-Adjuvanted vaccine, tgAAC94 gene therapy vector, Capsaicin, Psirelax, ABT-874 (anti IL-12), IDEC-114, MEDI-522, LE29102, BMS 587101, CD 2027, CRx-191, 8-methoxysoralen or 5- methoxysoralen, Bicillin L-A, LY2525623, INCB018424, LY2439821, CEP-701, CC-10004, certolizumab (CZP), GW786034 (pazopanib), doxycycline Curcuminoids C3 Complex, NYC 0462, RG3421, hOKT3gamma 1(Ala-Ala), BT061, teplizumab, Chondroitin sulphate, CNTO 1275, monoclonal antibody to IL-12p40 and IL-23 p40 subunits, BMS-582949, MK0873, MEDI-507, M518101, ABT-874, AMG 827, AN2728, AMG714, AMG 139, PTH (1-34), U0267 Foam, CNTO 1275, QRX-101, CNTO 1959, LEO 22811, Imiquimod, CTLA4Ig, Alga Dunaliella Bardawil, pioglitazone, pimecrolimus, ranibizumab, Zidovudine CDP870 (Certolizumab pegol), Onercept (r-hTBP-1), ACT-128800, 4,4-dimethyl-benziso-2H-selenazine, CRx-191, CRx-197, doxercalciferol, LAS 41004, WBI-1001, tacrolimus, RAD001, rapamycin, rosiglitazone, pioglitazone, ABT-874, Aminopterin, AN2728, CD2027, ACT-128800, mometasone furoate, CT 327, clobetasol + LCD, BTT1023, E6201, topical vitamin B12, IP10.C8, BFH772, LEO 22811, Fluphenazine, MM-093, Clobex, SCH 527123, CF101, SRT2104, BIRT2584, CC10004, Tetrathiomolybdate, CP-690,550, U0267, ASP015K, VB-201, Acitretin (also called U0279), RWJ-445380, Clobetasol propionate, botulinum toxin type A, alefacept, erlotinib, BCT194, Roflumilast, CNTO 1275, halobetasol, ILV-094, CTA018 cream, COL-121, MEDI-507, AEB071.

**[0085]** Additional psoriasis agents that may be co-formulated with secukinumab include IL-6 antagonists, CD20 antagonists, CTLA4 antagonists, IL-17 antagonists, IL-8 antagonists, IL-21 antagonists, IL-22 antagonists, VGEF antagonists, CXCL antagonists, MMP antagonists, defensin antagonists, IL-1beta antagonists, and IL-23 antagonists (e.g., receptor decoys, antagonistic antibodies, etc.). Preferred psoriasis agents that may be co-formulated with secukinumab are DMARDs (e.g., MTX and cyclosporine), IL-12/-23 antagonists (e.g., ustekinumab), CTLA-4 antagonists (e.g., CTLA4-Ig), and TNF-alpha antagonists.

**[0086]** Broadly speaking, rheumatoid arthritis agents, psoriatic arthritis agents, and ankylosing spondylitis agents that may be co-formulated with secukinumab may be, *inter alia*, an immunosuppressive agent, a DMARD, a pain-control drug, a steroid, a non-steroidal antiinflammatory drug (NSAID), a cytokine antagonist, a bone anabolic, a bone anti-resorptive, and combinations thereof. Representative agents include cyclosporin, retinoids, corticosteroids, propionic acid derivative, acetic acid derivative, enolic acid derivatives, fenamic acid derivatives, Cox-2 inhibitors, lumiracoxib, ibuprophen, cholin magnesium salicylate, fenoprofen, salsalate, difunisal, tolmetin, ketoprofen, flurbiprofen, oxaprozin, indomethacin, sulindac, etodolac, ketorolac, nabumetone, naproxen, valdecoxib, etoricoxib, MK0966; rofecoxib, acetominophen, Celecoxib, Diclofenac, tramadol, piroxicam, meloxicam, tenoxicam, droxicam, lornoxicam, isoxicam, mefanamic acid, meclofenamic acid, flufenamic acid, tolfenamic, valdecoxib, parecoxib, etodolac, indomethacin, aspirin, ibuprophen, firocoxib,

methotrexate (MTX), antimalarial drugs (e.g., hydroxychloroquine and chloroquine), sulfasalazine, Leflunomide, azathioprine, cyclosporin, gold salts, minocycline, cyclophosphamide, D-penicillamine, minocycline, auranofin, tacrolimus, myocrisin, chlorambucil, TNF alpha antagonists (e.g., TNF alpha antagonists or TNF alpha receptor antagonists), e.g., ADALIMUMAB (Humira<sup>®</sup>), ETANERCEPT (Enbrel<sup>®</sup>), INFILIXIMAB (Remicade<sup>®</sup>; TA-650), CERTOLIZUMAB PEGOL (Cimzia<sup>®</sup>; CDP870), GOLIMUMAB (Simpom<sup>®</sup>; CNT0148), ANAKINRA (Kineret<sup>®</sup>), RITUXIMAB (Rituxan<sup>®</sup>; MabThera<sup>®</sup>), ABATACEPT (Orencia<sup>®</sup>), TOCILIZUMAB (RoActemra /Actemra<sup>®</sup>), integrin antagonists (TYSABRI<sup>®</sup> (natalizumab)), IL-1 antagonists (ACZ885 (Ilaris)), Anakinra (Kineret<sup>®</sup>)), CD4 antagonists, IL-23 antagonists, IL-20 antagonists, IL-6 antagonists, BLyS antagonists (e.g., Atacicept, Benlysta<sup>®</sup>/LymphoStat-B<sup>®</sup> (belimumab)), p38 Inhibitors, CD20 antagonists (Ocrelizumab, Ofatumumab (Arzerra<sup>®</sup>)), interferon gamma antagonists (Fontolizumab), prednisolone, Prednisone, dexamethasone, cortisol, cortisone, hydrocortisone, methylprednisolone, betamethasone, triamcinolone, beclometasone, fludrocortisone, deoxycorticosterone, aldosterone, SB-681323, Rob 803, AZD5672, AD 452, SMP 114, HZT-501, CP-195,543, Doxycycline, vancomycin, CRx-102, AMG108, pioglitazone, SBI-087, SCIO-469, Cura-100, Oncoxin + Viusid, TwHF, PF-04171327, AZD5672, Methoxsalen, ARRY-438162, Vitamin D - ergocalciferol, Milnacipran, Paclitaxel, GW406381, rosiglitazone, SC12267 (4SC-101); LY2439821, BTT-1023, ERB-041, ERB-041, KB003, CF101, ADL5859, MP-435, ILV-094, GSK706769, GW856553, ASK8007, MOR103, HE3286, CP-690,550 (tasocitinib), REGN88 (SAR153191), TRU-015, BMS-582949, SBI-087, LY2127399, E-551S-551, H-551, GSK3152314A, RWJ-445380, Tacrolimus (Prograf<sup>®</sup>), RAD001, rapamune, rapamycin, fostamatinib, Fentanyl, XOMA 052, CNT0 136, JNJ 38518168, Imatinib, ATN-103, ISIS 104838, folic acid, folate, TNFa kinoid, MM-093, type II collagen, VX-509, AMG 827 70, masitinib (AB1010), LY2127399, cyclosporine, SB-681323, MK0663, NNC 0151-0000-0000, ATN-103, CCX 354-C, CAM3001, LX3305, Cetrorelix, MDX-1342, TMI-005, MK0873, CDP870, Tranilast, CF101, mycophenolic acid (and esters thereof), VX-702, GLPG0259, SB-681323, BG9924, ART621, LX3305, T-614, Fostamatinib disodium (R935788), CCI-779, ARRY-371797, CDP6038, AMG719, BMS-582949, GW856553, rosiglitazone, CH-4051, CE-224,535, GSK1827771, GW274150, BG9924, PLX3397, TAK-783, INCB028050, LY2127399, LY3009104, R788, Curcumin (Longvida<sup>™</sup>), Rosuvastatin, PRO283698, AMG 714, MTRX1011A, Maraviroc, MEDI-522, MK0663, STA 5326 mesylate, CE-224,535, AMG108, BG00012 (BG-12; Biogen), ramipril, VX-702, CRx-102, LY2189102, SBI-087, SB-681323, CDP870, Milnacipran, PD 0360324, PH-797804, AK106-001616, PG-760564, PLA-695, MK0812, ALD518, Cobiprostone, somatropin, tgAAC94 gene therapy vector, MK0359, GW856553, esomeprazole, everolimus, trastuzumab, bone anabolics and bone anti-resorptives (e.g., PTH, bisphosphonates (e.g., zoledronic acid), JAK1 and JAK2 inhibitors, pan JAK inhibitors, e.g., tetracyclic pyridone 6 (P6), 325, PF-956980, sclerostin antagonists (e.g., disclosed in WO09047356, WO2000/32773, WO2006102070, US20080227138, US20100028335, US 20030229041, WO2005003158, WO2009039175 WO2009079471, WO03106657, WO2006119062, WO08115732, WO2005/014650, WO2005/003158, WO2006/119107, WO2008/061013, WO2008/133722, WO2008/115732, US7592429,

US7879322, US7744874 [preferred anti-sclerostin antibodies and antigen-binding portions thereof for use in the disclosed methods, pharmaceutical compositions, kits and uses are found in WO09047356 (equivalent to US7879322), WO06119107 (equivalent to US7872106 and US 7592429) and WO08115732 (equivalent to US7744874)], denosumab, IL-6 antagonists, CD20 antagonists, CTLA4 antagonists, IL-8 antagonists, IL-21 antagonists, IL-22 antagonist, integrin antagonists (Tysabri® (natalizumab)), VEGF antagonists, CXCL antagonists, MMP antagonists, defensin antagonists, IL-1 antagonists (including IL-1 beta antagonists), and IL-23 antagonists (e.g., receptor decoys, antagonistic antibodies, etc.). Preferred rheumatoid arthritis agents that may be co-formulated with secukinumab are DMARDs, such as methotrexate, and TNF alpha antagonists. Preferred ankylosing spondylitis agents that may be co-formulated with secukinumab are NSAIDs, DMARDs, such as sulfasalazine, and TNF alpha antagonists. Preferred psoriatic arthritis agents that may be co-formulated with secukinumab are DMARDs, such as cyclosporine, CTLA-4 blockers (e.g., CLTA4-Ig), alefacept, and TNF alpha antagonists.

**[0087]** A skilled artisan will be able to discern the appropriate dosages of the above agents for co-composition with secukinumab.

**[0088]** Disclosed herein are stable liquid pharmaceutical compositions comprising 20 mg/ml to 175 mg/ml (e.g., about 25 mg/ml to about 150 mg/ml) of secukinumab, about 10 mM to about 30 mM buffer (Histidine) pH 5.2 - about 6.0, about 200 mM to about 225 mM stabilizer (e.g., trehalose), about 0.02% surfactant (e.g., polysorbate 80), and 2.5 mM to 20 mM methionine.

**[0089]** In some embodiments, the concentration of methionine in the liquid pharmaceutical composition of the disclosed pharmaceutical is 2.5 mM, about 5 mM, about 10 mM or 20 mM, preferably about 5 mM. In some embodiments, the pH of the liquid pharmaceutical composition is about 5.8. In some embodiments, the concentration of secukinumab of the disclosed composition is about 25 mg/ml or about 150 mg/ml. The liquid pharmaceutical composition comprises a histidine buffer. Also disclosed herein is a liquid pharmaceutical composition comprising a buffer selected from the group consisting of a histidine buffer, a citrate buffer, an acetate buffer, and a succinate buffer. In some embodiments, the liquid pharmaceutical composition employs a histidine buffer at a concentration of about 20mM. The liquid pharmaceutical composition comprises a surfactant selected from a polysorbate and a poloxamer. In some embodiments, the liquid pharmaceutical composition further comprises a surfactant selected from polysorbate 80, polysorbate 20, and poloxamer 188. In some embodiments, the liquid pharmaceutical composition comprises polysorbate 80 at a concentration of about 0.01% (w/v) to about 0.04% (w/v), preferably at about 0.02% (w/v). In some embodiments, the liquid pharmaceutical composition comprises polysorbate 20 at a concentration of about 0.02% (w/v). In some embodiments, the liquid pharmaceutical composition comprises a stabilizer selected from the group consisting of mannitol, sodium chloride, trehalose, arginine HCL, and glycine. In some embodiments, the liquid pharmaceutical composition comprises trehalose at a concentration of about 180 mM to about 300 mM, preferably at about 200 mM or about 225 mM.

**[0090]** Disclosed herein are pharmaceutical products comprising: a container having a headspace, wherein the oxygen content in the headspace is less than 12%, and a liquid pharmaceutical composition having a pH of 5.2 to 6.2 disposed within said container, said composition comprising: 20 mg/ml to 175 mg/ml (e.g., about 25 mg/ml to about 150 mg/ml) secukinumab; 2.5 to 20 mM L-methionine, wherein the liquid pharmaceutical composition is not reconstituted from a lyophilisate.

**[0091]** In some embodiments, the concentration of methionine in the liquid pharmaceutical composition of the disclosed pharmaceutical is 2.5 mM, about 5 mM, about 10 mM or 20 mM, preferably about 5 mM. In some embodiments, the oxygen content in the headspace of the disclosed pharmaceutical product is less than about 10%, e.g., less than about 8%, preferably less than about 6%. In some embodiments, the liquid pharmaceutical composition of the disclosed pharmaceutical product has a pH of about 5.8. In some embodiments, the concentration of secukinumab of the disclosed pharmaceutical product is about 25 mg/ml or about 150 mg/ml. The liquid pharmaceutical composition of the disclosed pharmaceutical product further comprises a histidine buffer. Also disclosed herein is a liquid pharmaceutical composition of the disclosed pharmaceutical product further comprising a buffer selected from the group consisting of a histidine buffer, a citrate buffer, an acetate buffer, and a succinate buffer. In some embodiments, the liquid pharmaceutical composition of the disclosed pharmaceutical product employs a buffer at a concentration of about 10 mM to about 30 mM. In some embodiments, the liquid pharmaceutical composition of the disclosed pharmaceutical product employs a histidine buffer at a concentration of about 20 mM. The liquid pharmaceutical composition of the disclosed pharmaceutical product further comprises a surfactant selected from a polysorbate and a poloxamer. In some embodiments, the liquid pharmaceutical composition of the disclosed pharmaceutical product further comprises a surfactant selected from polysorbate 80, polysorbate 20, and poloxamer 188. In some embodiments, the liquid pharmaceutical composition of the disclosed pharmaceutical product further comprises polysorbate 80 at a concentration of about 0.01% (w/v) to about 0.04% (w/v), preferably at about 0.02% (w/v). In some embodiments, the liquid pharmaceutical composition of the disclosed pharmaceutical product further comprises polysorbate 20 at a concentration of about 0.02% (w/v). In some embodiments, the liquid pharmaceutical composition of the disclosed pharmaceutical product further comprises a stabilizer selected from the group consisting of mannitol, sodium chloride, trehalose, arginine HCL, and glycine. In some embodiments, the liquid pharmaceutical composition of the disclosed pharmaceutical product further comprises trehalose at a concentration of about 180 mM to about 300 mM, preferably at about 200 mM or about 225 mM. In some embodiments, the container of the disclosed pharmaceutical product is a cartridge, syringe, pen or vial.

**[0092]** Disclosed herein are pharmaceutical products comprising: a container having a headspace, wherein the oxygen content in the headspace is less than about 6%; and a liquid pharmaceutical composition disposed within said container, said composition comprising 20 mg/ml to 175 mg/ml (e.g., about 25 mg/ml to about 150 mg/ml) secukinumab, 10 mM to 30 mM histidine pH 5.8, about 200 mM to about 225 mM trehalose, about 0.02% polysorbate 80, and 2.5 mM to 20 mM methionine, wherein the liquid pharmaceutical composition is not

reconstituted from a lyophilisate.

**[0093]** In some embodiments, the pharmaceutical product comprises about 25 mg/ml secukinumab and about 225 mM trehalose. In some embodiments, the pharmaceutical product comprises about 150 mg/ml secukinumab and about 200 mM trehalose. In some embodiments, the container of the disclosed pharmaceutical product is a cartridge, syringe, pen or vial.

**[0094]** In some embodiments, the pharmaceutical product has a sufficient amount of secukinumab to allow delivery of at least about 75 mg - about 300 mg secukinumab per unit dose. In some embodiments, the pharmaceutical product has a sufficient amount of secukinumab to allow delivery of at least about 10 mg/kg per unit dose. In some embodiments, the pharmaceutical product is formulated at a dosage to allow intravenous delivery of about 10 mg/kg secukinumab per unit dose. In some embodiments, the pharmaceutical product is formulated at a dosage to allow subcutaneous delivery of about 75 mg - about 300 mg secukinumab per unit dose.

### **Processes of Making Liquid Compositions and Pharmaceutical Products**

**[0095]** Also described herein are processes of making the pharmaceutical products and liquid compositions of the disclosure. These processes help reduce oxidation of the disclosed IL-17 antibodies. In brief, a liquid composition is prepared by combining the desired excipients (e.g., group 1 stabilizer (e.g., trehalose), group 2 stabilizer (methionine), surfactant (e.g., PS80), buffer (e.g., histidine)) with secukinumab to the desired concentrations (e.g., about 25 to about 150 mg/ml secukinumab, about 20 mM histidine pH 5.8, about 200 mM to about 225 mM trehalose, about 0.02% polysorbate 80, and 2.5 mM to 20 mM methionine) and pH (e.g., about pH 5.8). This liquid composition is then disposed in the container of choice (e.g., vial, syringe, cartridge [e.g., for use with an autoinjector]). The oxygen content in the headspace is adjusted to the desired level (e.g., less than 12%, less than 10%, less than about 8%, less than about 6%, etc.), which may occur prior to filling of the container with the liquid composition, during filling of the container with the liquid composition, or during stoppering/sealing of the container.

**[0096]** Disclosed herein are processes for reducing the oxidation of secukinumab, comprising: preparing a liquid composition having a pH of 5.2 to 6.2 and comprising: 20 mg/ml to 175 mg/ml (e.g., about 25 mg/ml to about 150 mg/ml) secukinumab; and 2.5mM to 20 mM methionine; disposing said liquid composition in a container having a headspace; and adjusting the oxygen content in the headspace to less than or equal to 12%.

**[0097]** In some embodiments of the disclosed processes, adjusting step c) is performed by purging the headspace using an inert gas. In some embodiments of the disclosed processes, the inert gas is nitrogen or argon. In some embodiments of the disclosed processes, the concentration of methionine in the liquid composition is 2.5 mM, about 5 mM, about 10 mM or 20 mM, preferably about 5 mM. In some embodiments of the disclosed processes, the oxygen

content in the headspace is adjusted to less than about 10%, e.g., less than about 8%, preferably less than about 6%. In some embodiments of the disclosed processes, the liquid composition has a pH of about 5.8. In some embodiments of the disclosed processes, the concentration of secukinumab in the liquid composition is about 25 mg/ml or about 150 mg/ml. In some embodiments of the disclosed processes, the container is a cartridge, syringe, pen or vial.

### Methods of Using Pharmaceutical Products and Liquid Compositions

**[0098]** The disclosed pharmaceutical products and liquid compositions will be used for the treatment of patients, e.g., having autoimmune diseases (e.g., psoriasis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, etc.). The appropriate dosage of secukinumab will, of course, vary depending upon, for example, the host, the mode of administration and the nature and severity of the condition being treated, and on the nature of prior treatments that the patient has undergone. Ultimately, the attending health care provider will decide the amount of the IL-17 antibody with which to treat each individual patient. In some embodiments, the attending health care provider may administer low doses of the IL-17 antibody and observe the patient's response. In other embodiments, the initial dose(s) of IL-17 antibody administered to a patient are high, and then are titrated downward until signs of relapse occur. Larger doses of the IL-17 antibody may be administered until the optimal therapeutic effect is obtained for the patient, and the dosage is not generally increased further.

**[0099]** The timing of dosing is generally measured from the day of the first dose of the active compound (e.g., secukinumab), which is also known as "baseline". However, different health care providers use different naming conventions, as shown in **Table 2**, below.

**Table 2** - Common naming conventions for dosing regimens. Bolded items refer to the naming convention used herein.

Week	0/1	1/ 2	2/3	3/4	4/5	5/6	6/7	7/8	8/9	Etc.
1st day	0/1	7/ 8	14/15	21/22	28/29	35/36	42/43	49/50	56/57	Etc.

**[0100]** Notably, week zero may be referred to as week 1 by some health care providers, while day zero may be referred to as day one by some health care providers. Thus, it is possible that different physicians will designate, e.g., a dose as being given during week 3 / on day 21, during week 3 / on day 22, during week 4 / on day 21, during week 4 / on day 22, while referring to the same dosing schedule. For consistency, the first week of dosing will be referred to herein as week 0, while the first day of dosing will be referred to as day 1. However, it will be understood by a skilled artisan that this naming convention is simply used for consistency and should not be construed as limiting, i.e., weekly dosing is the provision of a weekly dose of secukinumab, regardless of whether the physician refers to a particular week as "week 1" or "week 2". As an example of naming using the convention designated herein, five doses of

secukinumab administered weekly may be provided during week 0 (e.g., on about day 1), during week 1 (e.g., on about day 8), during week 2 (e.g., on about day 15), during week 3 (e.g., on about day 22), and during week 4 (e.g., on about day 29). It will be understood that a dose need not be provided at an exact time point, e.g., a dose due approximately on day 29 could be provided, e.g., on day 24 to day 34, e.g., day 30, as long as it is provided in the appropriate week.

**[0101]** In some embodiments, the disclosed methods and uses employ an initial (sometimes called "induction") regimen that lasts 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 weeks. In some embodiments, the initial regimen uses dosing during weeks 0, 1, 2, and 3. In other embodiments, the initial regimen uses dosing during weeks 0, 1, 2, 3, 4, 8 and 12. In some embodiments, the initial regimen comprises administering several (e.g., 1, 2, 3, 4, 5, 6, 7, preferably 4 or 5) doses of about 150 mg - 300 mg, e.g., about four or five doses of 150 mg or 300 mg (preferably five doses of about 150 mg - about 300 mg) of secukinumab. In further embodiments, initial doses are delivered weekly, bi-weekly, every other week, or monthly [every 4 weeks], preferably weekly. In some embodiments, 150 mg or 300 mg of secukinumab is administered by subcutaneous injection, with initial dosing at weeks 0, 1, 2 and 3.

**[0102]** For a maintenance regimen, a dose may be provided every month (also called "monthly" dosing) (i.e., every 4 weeks, i.e., about every 28 days), every two months (i.e., every 8 weeks, i.e., about every 56 days), or every three months (i.e., every 12 weeks, i.e., about every 84 days). In some embodiments, the maintenance regimen begins following week 12. In some embodiments, the maintenance regimen begins following week 3. A first dose of a maintenance regimen will be administered on a date usually measured from the final dose of the induction regimen. Thus, as an example, if the final dose of the induction regimen is provided during week 12, then the first dose as part of a monthly [every 4 weeks] maintenance regimen will be delivered during week 16, the first dose as part of an every two month maintenance regimen will be delivered during week 20, the first dose as part of an every three month maintenance regimen will be delivered during week 24, etc. In some embodiments, the maintenance regimen comprises administering a dose of secukinumab weekly, every two weeks, monthly [every 4 weeks], every other month, quarterly, bi yearly, or yearly. In some embodiments, the maintenance regimen employs monthly dosing (every 4 weeks). In some embodiments, the first dose of the maintenance regimen is delivered during week 4 or during 16. In some embodiments, the maintenance regimen comprises administering a dose of about 150 mg - 300 mg, e.g., about 150 mg or about 300 mg of secukinumab.

**[0103]** Delivery of secukinumab during a loading regimen, induction regimen and/or maintenance regimen may be via a subcutaneous route, e.g., delivery of dosages of about 75 mg - about 300 mg (e.g., about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg), via an intravenous route, e.g., delivery of dosages of about 1 mg/kg, - about 50 mg/kg (e.g., about 1 mg/kg, about 3 mg/kg, about 10 mg/kg, about 30 mg/kg, about 40 mg/kg, about 50 mg/kg, etc.) or any other route of administration (e.g., intramuscular, i.m.). In preferred embodiments, the dose of secukinumab is delivered s.c.

**[0104]** In preferred embodiments the patient is administered a dose of about 150 mg - about 300 mg (e.g., about 150 mg or about 300 mg) of secukinumab by subcutaneous injection, with initial dosing at weeks 0, 1, 2 and 3, followed by monthly maintenance dosing, starting at week 4. In this regimen, dosing occurs during each of weeks 0, 1, 2, 3, 4, 8, 12, 16, 20, etc. A 300 mg dose may be given as two subcutaneous injections of 150 mg.

**[0105]** Disclosed herein are methods of treating an autoimmune disease (e.g., psoriasis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis), comprising administering to a patient in need thereof a dose of about 150 mg - about 300 mg (e.g., about 150 mg or about 300 mg) of secukinumab by subcutaneous injection, with initial dosing at weeks 0, 1, 2 and 3, followed by monthly maintenance dosing, starting at week 4, wherein secukinumab is provided as part of a pharmaceutical composition comprising: 20 mg/ml to 175 mg/ml (e.g., about 25 mg/ml to about 150 mg/ml) secukinumab; a buffer having a pH of 5.2 to 6.2; and 2.5 to 20 mM methionine, wherein the liquid pharmaceutical composition is not reconstituted from a lyophilisate.

**[0106]** Disclosed herein is the use of secukinumab for the manufacture of a medicament for the treatment of an autoimmune disease (e.g., psoriasis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis) in a patient, wherein the medicament is formulated to comprise containers, each container having headspace with an oxygen content of less than 12% (e.g., less than about 10%, less than about 8%, less than about 7%, less than about 6%, etc.) and a liquid pharmaceutical composition disposed within said container, said composition comprising: 20 mg/ml to 175 mg/ml (e.g., about 25 mg/ml to about 150 mg/ml) secukinumab; a buffer having a pH of 5.2 to 6.2; and 2.5 to 20 mM methionine, wherein the liquid pharmaceutical composition is not reconstituted from a lyophilisate

#### **Kits Comprising Pharmaceutical Products and Liquid Compositions**

**[0107]** Kits for treating various autoimmune diseases (e.g., psoriasis) may be prepared. Such kits broadly include at least one of the disclosed pharmaceutical products or liquid compositions and instructions for use. The instructions will disclose appropriate techniques for the provision of the stable liquid composition to the patient as part of a dosing regimen. These kits may also contain additional agents (described *supra*) for treating autoimmune diseases, e.g., psoriasis, for delivery in combination with (i.e., simultaneously or sequentially [before or after]) the enclosed liquid composition.

**[0108]** Kits may be used for the treatment of a patient having an autoimmune disease (e.g., psoriasis), said kits comprising: a) a container having a headspace, wherein the oxygen content in the headspace is less than 12% (e.g., less than about 10%, less than about 8%, less than about 7%, less than about 6%, etc.), b) a liquid pharmaceutical composition disposed within said container, said composition comprising: i) about 20 mg/ml to about 175 mg/ml (e.g., about 25 mg/ml to about 150 mg/ml) secukinumab; ii) a buffer having a pH of 5.2 to 6.2; and iii)

2.5 to 20 mM methionine, wherein the liquid pharmaceutical composition is not reconstituted from a lyophilisate; and c) instructions for administering the liquid pharmaceutical composition to the patient. In some embodiments, the container is a pen, pre-filled syringe, autoinjector or vial.

## General

**[0109]** The details of one or more embodiments of the disclosure are set forth in the accompanying description above. Other features, objects, and advantages of the disclosure will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms include plural referents unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. The following Examples are presented in order to more fully illustrate the preferred embodiments of the disclosure.

## EXAMPLES:

**[0110]** It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications and changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the amended claims.

**[0111]** These examples describe the development of stable liquid compositions of secukinumab. The data shows that the composition pH and the choice of group 2 stabilizer had a large effect on the stability of the liquid composition. The data also shows an impact of headspace oxygen content as influencing the stability of the liquid composition. The antibody concentration, choice of surfactant, choice of group 1 stabilizer and choice of buffer system had a smaller influence on stability. Therefore, when considering the variables having greater influence on stability, the disclosed pharmaceutical products comprise a container (e.g., PFS or vial) having a headspace, wherein the oxygen content in the headspace is less than about 12%, and a liquid pharmaceutical composition disposed within said container, said composition having a pH of about 5.2 to about 6.2 and comprising secukinumab in a concentration of about 20 mg/mL to 175 mg/mL and about 2.5 to about 20 mM L-methionine. When considering the variables having both large and small impacts on stability, the disclosed pharmaceutical products comprise a container (e.g., PFS or vial) having a headspace, wherein the oxygen content in the headspace is less than about 12%, and a liquid pharmaceutical composition disposed within said container, said composition having a pH of about 5.2 to about 6.2 and comprising secukinumab; a buffer; a surfactant, a stabilizer, and about 2.5 to about 20 mM L-methionine.

**[0112]** Based on the data disclosed below, preferred liquid compositions comprise about 25 mg/mL - about 165 mg/mL secukinumab, about 185 mM - about 225 mM trehalose, about 0.01 % - about 0.03 % polysorbate 80, about 2.5 mM - about 20 mM L-methionine and about 10-30 mM histidine buffer (e.g., about 20 mM histidine buffer) at pH about 5.8.

**[0113]** A preferred liquid composition I comprises about 150 mg/mL secukinumab, about 200 mM trehalose, about 0.02 % polysorbate 80, about 5 mM L-methionine, and about 20 mM histidine buffer at pH about 5.8. A preferred pharmaceutical product I comprises the aforementioned liquid composition I disposed in a pre-filled syringe (PFS).

**[0114]** Another preferred liquid composition II comprises about 25 mg/mL secukinumab, about 225 mM trehalose, about 0.02 % polysorbate 80, about 5 mM L-methionine, and about 20 mM histidine buffer at pH about 5.8. A preferred pharmaceutical product II comprises the aforementioned liquid composition II disposed in a vial.

**Table 3:** Abbreviations used in Examples

Abbreviation	Definition
CE-SDS	Capillary Electrophoresis (Sodium Dodecyl Sulfate)
CEX	Cation Exchange Chromatography
Cys-CEX	Cystamine Cation Exchange Chromatography
DLS	Dynamic Light Scattering
DoE	Design of Experiment
HPLC	High Performance Liquid Chromatography
LLS	Laser Light Scattering
RH	Relative humidity
RP-HPLC	Reverse phase-High Performance Liquid Chromatography
SDS-PAGE	Sodium Dodecyl Sulfate-Polyacrylamide Gel Electrophoresis
SEC	Size Exclusion Chromatography
AP-SEC	Aggregation Products by SEC
DP-SEC	Degradation Products by SEC

**Table 4:** Analytics used in Examples.

Analytical Assay
UV: Assay of protein by UV absorption
SEC: Purity by SEC, AP-SEC, DP-SEC
SDS-PAGE: purity by SDS-PAGE (non-reducing), purity by SDS-PAGE (reducing), impurities by SDS-PAGE (reducing)
CE-SDS: Purity by CE-SDS (non-reducing), Impurities by CE-SDS (non-reducing)
LLS: average molecular weight by LLS
DLS: polydispersity by DLS, hydrodynamic radius by DLS

Analytical Assay
Turbidity
Sub-visible particles by light obscuration
Visible particles
RP-HPLC: purity by RP-HPLC, and pre-main peak species by RP-HPLC
CEX: purity by CEX, acidic variants by CEX, basic variants by CEX
Color
activity by Cys-CEX
Free SH-groups (Ellmans test)
biological activity

## 1.1 Part I - Detailed Analysis of variables with greater influence on secukinumab liquid state stability (headspace oxygen, pH and L-methionine)

### 1.1.1 Example 1: L-Methionine

**[0115]** The effect of several anti-oxidative stabilizers on secukinumab stability was characterized using a broad set of analytical techniques.

**[0116]** In early studies, a range of anti-oxidative stabilizers, comprising tetra sodium EDTA sodium ascorbate, cysteine, sodium bisulfite and sodium citrate were evaluated. Although none of these adequately stabilized the molecule, a small stabilizing effect on aggregation products by SEC of tetra sodium EDTA and sodium citrate as compared to the compositions containing no anti-oxidative stabilizers has been seen (data not shown).

**[0117]** In further studies, the stabilizers cysteine, tetra sodium EDTA and L-methionine were evaluated at a concentration of 10 mM and compared to no stabilizer using secukinumab concentration of 150 mg/mL with a DoE approach. The compositions were filled in PFS and placed on a 2 months stability study at long-term (5°C), accelerated (25°C) and stressed (40°C) conditions and were evaluated with regards to physical stability (AP-SEC, DLS, turbidity, visible and sub-visible particles by light obscuration), chemical stability (purity by CEX, purity by RP-HPLC, color) and indicators of biological activity (activity by Cys-CEX, free SH-groups). In addition, freeze-thaw (5 cycles of -20 °C to room temperature) and shaking stress (150 rpm for one week) was applied to compositions filled in 2 mL vials.

**[0118]** L-methionine was found to be the best group 2 stabilizer for secukinumab. This was demonstrated by higher purity levels as measured by purity by CEX and purity by RP-HPLC and lower turbidity levels and visible particles counts. A significantly better stability was shown

in the presence of L-methionine as compared to a composition without stabilizer. Compositions with L-methionine had lower levels of AP-SEC, more consistent DLS data, lower turbidity and lower amounts of pre-main peak species by RP-HPLC after 8 weeks of stability at accelerated conditions of 25 °C and 40 °C. EDTA was disadvantageous due to increases in AP-SEC, DLS, basic variants by CEX and pre-main peak species by RP-HPLC. Cysteine lead to increases in almost all aggregation and degradation products as indicated by various analytic methods.

**[0119]** **Figure 1** lists selected quality attributes after storage under different conditions. Only L-methionine was observed to have a consistently stabilizing effect on secukinumab. The stabilizing effect was especially observed on pre-main peak species by RP-HPLC (**Figure 1 B**) and AP-SEC (**Figure 1 D**). Further effects were also observed in turbidity and hydrodynamic radius by DLS. The effect of different L-methionine concentrations on secukinumab quality attributes was evaluated in subsequent studies.

**[0120]** **Figure 2** displays the change in pre-main peak species by RP-HPLC during storage at 25 °C at a secukinumab concentration of 25 mg/mL and a trehalose concentration of 225 mM and a polysorbate 80 concentration of 0.02 % in histidine buffer pH 5.8 in the presence and absence of L-methionine. Compositions were filled into 2 mL vials and stored for up to 3 months under stressed conditions. The black dashed line represents a linear fit to the values obtained for the composition containing 0 mM L-methionine, the grey dashed line represents a linear fit to the values obtained for the composition containing 10 mM L-methionine. Clearly, reduced degradation kinetics were observed in the presence of L-methionine.

**[0121]** A concentration dependent effect was also observed for compositions containing 150 mg/mL secukinumab. A study was conducted with compositions containing trehalose at concentrations between 200 mM and 300 mM, polysorbate 80 between 0.01 % and 0.04 % as well as L-methionine from 0 mM to 10 mM. Compositions were filled into 1mL PFS and stored for up to three months at long-term, accelerated and stressed conditions. Secukinumab physical (AP-SEC, DLS, sub-visible particles by light obscuration and visible particles, turbidity) and chemical (purity by CEX, purity by RP-HPLC, color) stability as well as biological activity were monitored

**[0122]** **Figure 3** displays the pre-main peak species by RP-HPLC after 6 months storage at 25 °C. Whereas the effect of trehalose and polysorbate 80 on degradation was negligible, clearly reduced degradation levels were observed in the presence of L-methionine. This effect was more pronounced comparing secukinumab stability with and without L-methionine, but also concentration dependence in the range of 2.5 - 10 mM L-methionine was observed.

**[0123]** The same stabilizing effect of L-methionine was observed after long-term storage (up to 30 months) in compositions containing 150 mg/mL secukinumab, 200 mM trehalose, 0.02% polysorbate 80 in a histidine buffer pH 5.8 filled into 1 mL PFS. **Figure 4** displays AP-SEC (A) and pre-main peak species by RP-HPLC (B) during up to 30 months of storage at 5 °C. The black dashed line represents a linear fit to the values obtained for the composition containing 5 mM L-methionine, the grey dashed line represents a linear fit to the values obtained for the

composition containing 0 mM L-methionine. Clearly, reduced degradation kinetics were observed in the presence of L-methionine.

**[0124]** The concentration dependence was further confirmed in a study that evaluated the impact of L-methionine concentration (0 - 20 mM) on secukinumab stability (150 mg/mL, trehalose 200 mM, polysorbate 80 0.02 %, histidine buffer pH 5.8). The different compositions were filled into PFS and stored at long-term and accelerated conditions for 13 months and 30 months (5 °C only). Secukinumab stability was assessed by a set of selected analytical techniques that was observed to be stability-indicating in previous screens (purity by RP-HPLC, purity by SEC, turbidity). No clear trend could be concluded from turbidity measurements. However, AP- SEC and pre-main peak species by RP-HPLC showed a clear dependence on the L-methionine concentration. This effect was small at real-time storage conditions, but distinct differences were observed at 25 °C (**Figure 5**).

**[0125]** After 13 months storage at 25°C storage, the levels of aggregates by SEC in the composition without L-methionine increased by 4.5 % from a starting level of < 1 % at t0. With the addition of L-methionine in the composition, this increase in aggregate formation was reduced to 3.5 % for 2.5 mM, 3.0 % for 5 mM and 2.2 % for 20 mM L-methionine. At 5 °C, the difference between the composition without L-methionine and the composition with 20 mM L-methionine was only 0.3 %. The pre-main peak species by RP-HPLC increased from 9.1 % to 42.7 % during 13 months storage at 25°C in the sample containing 0 mM L-methionine. This increase in pre-main peak species by RP-HPLC was reduced to 39.4 % for 2.5 mM, 37.8 % for 5.0 mM and 34.5 % for 20 mM L-methionine containing samples. In summary, reduced levels of AP-SEC and pre-main peak species by RP-HPLC were observed in the presence of L-methionine during storage at 5°C and 25°C in PFS. Differences were observed to be more distinct after storage at 25°C, but were also detectable after 5°C storage.

**[0126]** Already at a level of 2.5 mM L-methionine, degradation rates were distinctly reduced as compared to compositions without L-methionine. This was also confirmed in a further study comparing secukinumab stability in the presence of 0, 2.5 and 5.0 mM L-methionine. No difference was observed between the composition containing 2.5 mM and 5.0 mM L-methionine in purity by RP-HPLC, purity by SEC as well as turbidity after 24 months storage at the intended storage condition.

**[0127]** Addition of L-methionine to liquid antibody compositions in vials also decreased AP-SEC and impurities by CE-SDS (non-reducing) (**Figure 6**). Interestingly, reduced L-methionine concentration dependence was observed for liquid antibody compositions in vials having 25 mg/mL secukinumab (**Figure 6**), suggesting that a lower concentration of L-methionine is sufficient to maintain the integrity and stability of antibody in compositions having lower antibody concentration.

**[0128]** Based on the combined data from the above experiments, a methionine concentration of at least 2.5 mM (preferably about 5 mM) is ideal for liquid compositions of secukinumab, and is superior to other group 2 stabilizers.

## 1.1.2 Example 2: Headspace oxygen content

### 1.1.2.1 Primary Packaging - PFS:

**[0129]** The effect of headspace oxygen content on secukinumab stability was evaluated at a concentration of 150 mg/mL secukinumab and in a composition with 200 mM trehalose, 5 mM L-methionine, 0.02 % polysorbate 80 in a histidine buffer pH 5.8. Compositions were filled into 1 mL PFS from various PFS suppliers. The headspace oxygen content was measured to be either between 13 % and 15 % (0.5 mL fill volume) or between 3-4 % (0.5 mL fill volume)/ 7-8 % (1.0 mL fill volume), respectively. The samples were stored for up to six months at long-term, accelerated and stressed conditions. Selected compositions were stored for up to 24 months under long-term conditions. Secukinumab stability was monitored by purity by SEC, purity by RP-HPLC, purity by CEX, purity by CE-SDS (non-reducing), turbidity, color, free SH-groups, biological activity, sub-visible by light obscuration and visible particles.

**[0130]** An impact of headspace oxygen content was observed on pre- main peak species by RP-HPLC and AP-SEC at long-term, accelerated and stressed conditions. **Figure 7** displays AP-SEC during up to 9 months storage at 25 °C. Clearly, PFS with a headspace oxygen content between 13-15 % showed increased aggregation at 25 °C. However, there was little absolute difference in aggregate level relative to headspace oxygen content at 2-8°C storage conditions (6 months data) (data not shown).

**[0131]** The impact of different headspace oxygen content levels ranging from 6% to 21% (i.e. not purged) on secukinumab quality attributes (turbidity, purity by SEC, purity by RP-HPLC, purity by CE-SDS (non-reducing), free SH groups, biological activity, sub-visible particles by light obscuration, visible particles, color) was further evaluated during storage at 5°C for 12 months as well as under accelerated conditions (25°C) for 6 months and under stressed conditions (40°C) for 3 months. The study was performed at 150 mg/mL secukinumab and in a composition with 200 mM trehalose, 5 mM L-methionine, 0.02 % polysorbate 80 in a histidine buffer pH 5.8. Samples were filled into PFS and purged with certified oxygen mixtures to yield the targeted headspace oxygen content.

**[0132]** Over storage time no change was observed in turbidity; no distinct effect of headspace oxygen content on sub-visible particles by light obscuration, color and free SH-groups was observed and differences between the different headspace oxygen content samples were within the scatter of the method. The methionine concentration did not relevantly change during storage at 5 °C or 25 °C and was observed to be 4.9 mM (initial value 4.9 - 5.0 mM) after 12 months at 5 °C regardless of the headspace oxygen content.

**[0133]** In contrast to our earlier findings, which showed a relatively large impact of headspace oxygen content on aggregation products by SEC, in this experiment only small changes were

observed during storage up to 12 months at the intended storage condition (5°C), even in the non-purged reference sample. No relevant differences in purity and aggregates by SEC were observed between samples with different oxygen levels in the headspace for the different stability points tested (up to 12 months storage at 2-8 °C and up to 6 months storage at 25 °C) (**Figure 8**). In contrast, we did note an increase in main purity by RP-HPLC with increasing headspace oxygen content. This was observed at 5°C (after 12 months of storage) (data not shown) and at 25°C (after 6 months of storage) (**Figure 9**). No new peaks appeared.

#### 1.1.2.2 Primary Packaging - Vials:

**[0134]** Compositions were filled into 2 mL vials and stored for 12 months at refrigerated conditions and up to 3 months under accelerated and stressed conditions. **Tables 5-7** summarize the change in pre-main peak species by RP-HPLC and SEC-AP during storage at 5°C, 25°C and 40°C at a secukinumab concentration of 25 mg/mL and a trehalose concentration of 225 mM and a polysorbate 80 concentration of 0.02 % in histidine buffer pH 5.8 in the presence and absence of 5mM L-methionine.

**Table 5:** RP-HPLC and SEC results for 25 mg/ml secukinumab liquid in vial after 6 and 12-months storage at 5°C. Composition 25 mg/ml secukinumab, 225mM trehalose, 5mM L-methionine, 0.02% PS80.

Headspace oxygen content	Pre-main peak species by RP-HPLC (%)			AP- SEC (%)		
	T0	6 M	12 M	T0	6 M	12 M
5 %	-	-	4.5	-	-	0.81
10 %	8.2	3.4	6.1	0.84	0.78	0.86
20 %	-	4.2	7.1	-	0.79	0.91

**Table 6:** RP-HPLC and SEC results for 25 mg/ml secukinumab liquid in vial after 3 months storage at 25°C and 40°C. Composition 25 mg/ml secukinumab, 225mM trehalose, 5mM L-methionine, 0.02% PS80.

Headspace oxygen content	Pre-main peak species by RP-HPLC (%)			AP-SEC (%)		
		25°C	40°C		25°C	40°C
	T0	3 M	3M	T0	3M	3M
5 %	-	17.9	40.6	-	1.10	1.80
10 %	8.0	18.4	43.1	0.84	1.00	2.00
20 %	-	20.6	46.2	-	0.93	2.50

**Table 7:** RP-HPLC and SEC results for 25 mg/ml secukinumab liquid in vial after 6 and 12-months storage at 5°C. Composition 25 mg/ml secukinumab, 225mM trehalose, 0mM L-methionine, 0.02% PS80.

Headspace oxygen content	Pre-main peak species by RP-HPLC (%)			AP-SEC (%)		
	T0	6 M	12 M	T0	6 M	12 M
5 %	8.3	3.8	6.1	0.84	0.82	0.91

**Table 8:** RP-HPLC and SEC results for 25mg/ml secukinumab liquid in vial after 3 months storage at 25°C and 40°C. Composition 25 mg/ml secukinumab, 225mM trehalose, 0mM L-methionine, 0.02% PS80.

Headspace oxygen content	Pre-main peak species by RP-HPLC (%)			AP-SEC (%)		
		25°C	40°C		25°C	40°C
	T0	3 M	3M	T0	3M	3M
Headspace oxygen content	Pre-main peak species by RP-HPLC (%)			AP-SEC (%)		
5 %	-	20.9	44.6	-	1.10	2.60
10 %	8.3	21.4	46.7	0.84	1.10	2.90
20 %	-	25.5	50.9	-	1.30	3.50

**[0135]** An impact of headspace oxygen content on 25 mg/ml secukinumab liquid in vial stability is seen by pre-main peak species by RP-HPLC after 12 months at 5°C (4.5% at 5% headspace oxygen content vs. 7.1% at 20% headspace oxygen content, see **Table 5**), after 3 months at 25°C (17.9% at 5% headspace oxygen content vs. 20.6 % at 20% oxygen, see **Table 6**) and after 3 months at 40°C (40.6% at 5% headspace oxygen content vs. 46.2% at 20 % headspace oxygen content, see **Table 6**). The same trend is deductible for AP-SEC after 3 months at 40°C (1.8% at 5% headspace oxygen content vs. 2.5% at 20% headspace oxygen content, see **Table 6**). Moreover, L-methionine concentration has a further impact when combined with lower headspace oxygen content. For example, comparing pre-main peak species by RP-HPLC in the compositions containing 5% oxygen headspace content data after 12 months storage at 5°C, 6.1% (**Table 7**) were found for the composition containing no L-methionine as compared to 4.5% (**Table 5**) for the composition with 5mM L-Methionine. The same difference is seen for pre-main peak species by RP-HPLC after 3 months at 25°C (5% -20% oxygen: 20.9-25.5% in absence of L-methionine (**Table 8**) vs. 17.9-25.5% in presence of 5mM L-methionine (**Table 6**)), and after 3 months at 40°C (5% -20% oxygen: 44.6-50.9% in absence of L-methionine (**Table 8**) vs.40.6-46.2% in presence of 5mM L-methionine (**Table 6**)).

**[0136]** Based on the above experiments, a nitrogen purge to decrease the headspace oxygen content to less than about 12% is viewed as beneficial in enhancing the stability of the liquid composition in both PFS and vials (as assessed by pre-main peak species by RP-HPLC).

### 1.1.3 Example 3: Interaction of L-Methionine concentration and headspace oxygen content

**[0137]** A further study evaluated the interaction between the L-methionine concentration and the headspace oxygen content. Compositions containing L-methionine in a range of 2.5 - 7.5 mM and headspace oxygen content between 3 and 9 % were prepared. Compositions were filled into PFS and stored under long-term and accelerated conditions for 6 months. Relevant secukinumab quality attributes (purity by SEC, purity by RP-HPLC; purity by CEX, free SH-groups, biological activity, sub-visible and visible particles by light obscuration, turbidity and color of the solution) were monitored after 3 and 6 months storage. **Figure 10** displays purity by AP-SEC after 6 months storage at 25°C as a function of L-methionine and headspace oxygen content. No interaction was observed in the tested range when analyzed using purity by AP-SEC.

**[0138]** In another study, the effect of reduced headspace oxygen content and L-methionine concentration was evaluated at secukinumab concentration of 150 mg/mL. The compositions comprised 270 mM mannitol, 0.04 % polysorbate 80 and different L-methionine concentrations ranging from 0.15 % to 2 %. Compositions were filled into 2 mL glass vials, either purged with nitrogen or not and stored at long-term, accelerated and stressed conditions for up to 6 months.

**[0139]** **Figure 11** depicts pre-main peak species by RP-HPLC after up to 36 months storage in compositions containing 0.15 % (10 mM), 1 % (67 mM) or 2 % (134 mM) L-methionine and either a nitrogen or air headspace. As observed before, pre-main peak species by RP-HPLC were at a lower level in compositions containing higher amounts of L-methionine. The same composition showed lower levels of pre-main peak species by RP-HPLC when the headspace was purged with nitrogen.

**[0140]** Based on the combined data from various experiments using both vials and PFS as primary packaging, a headspace oxygen content of less than about 12% in combination with an L-methionine concentration of at least about 2.5 mM is ideal for liquid compositions of secukinumab.

#### 1.1.4 Example 4: pH

**[0141]** The effect of pH on secukinumab stability was initially evaluated at a concentration of 10 mg/ml in 100 mM citric acid / sodium phosphate buffer containing 90 mM sodium chloride in a pH range between 4.0 and 7.5. Samples were stored for 3 weeks at 5°C and 40°C. In parallel, secukinumab stability after five freeze thaw cycles from ≤ -60°C to room temperature was monitored.

**[0142]** The optimal pH for secukinumab varied depending on the degradation pathway analyzed. Aggregation and proteolysis determined by purity by SEC, purity by SDS-PAGE (reducing) and the average molecular weight by LLS were minimal at pH 5.7 to 6.2, whereas

optimal pH for purity by CEX was pH 5.3. Active secukinumab contains one free Cysteine residue on each light chain, thus, 2 Mol thiol groups / Mol secukinumab are expected. Since a reduced level of free SH-groups correlates with loss of biological activity in secukinumab, the free SH-groups were quantified using a method based on Ellman's reagent. Only at pH 4.3, a slightly lower value of 1.94 Mol/Mol was observed. The secukinumab freeze thaw resistance monitored by purity by SEC and the average molecular weight by LLS was maximum at pH 5.3 to 5.7. A pH 5.8 was selected for further formulating secukinumab.

**[0143]** Further studies on the effect of pH on secukinumab stability were conducted in PFS using a DoE approach. The effect of pH in the range of 5.2 - 5.8 was evaluated at a secukinumab concentration of 150 mg/mL. Compositions were placed on a 2 months stability study at long-term (5°C), accelerated (25°C) and stressed (40°C) conditions and were evaluated with regards to physical stability (AP-SEC, DLS, turbidity, visible particles and sub-visible particles by light obscuration), chemical stability (purity by CEX, purity by RP-HPLC, color) and indicators of biological activity (activity by Cys-CEX, free SH-groups). In addition, freeze-thaw (5 cycles of - 20°C to room temperature) and shaking stress (150 rpm for one week) was applied to compositions filled in 2 mL vials. pH-values in the investigated range were found to significantly impact secukinumab stability (AP-SEC, DP-SEC, DLS, basic variants by CEX, purity by RP-HPLC). Results from earlier studies were confirmed with regard to pH 5.8 as ideal (AP-SEC, DP-SEC and pre-main peak species by RP-HPLC) (**Figure 12**).

**[0144]** The effect of pH was further evaluated in compositions containing secukinumab at a concentration of 150 mg/mL, trehalose 200 mM, L-methionine in a range of 2.5 - 7.5 mM and headspace oxygen content between 3 and 9 %. The pH of the histidine buffer was varied between 5.4 and 6.2. Compositions were filled into PFS and stored under long-term and accelerated conditions for 6 months. Relevant secukinumab quality attributes (purity by SEC, purity by RP-HPLC; purity by CEX, free SH-groups, biological activity, sub-visible particles by light obscuration, visible particles, turbidity and color of the solution,) were monitored after 3 and 6 months storage. **Figure 13** depicts the effect of pH on secukinumab quality attributes after storage at 5 °C. Increased turbidity, AP- SEC and acidic variants by CEX as well as decreased purity by SEC were observed at higher pH values, further confirming observations from the initial screen.

**[0145]** Based on the combined data from various experiments, a pH range from about 5.2 to about 6.2 is ideal for liquid compositions of secukinumab.

## **1.2 Part 2 - Detailed Analysis of Excipients with smaller influence on secukinumab liquid state stability (stabilizer, surfactant and buffer)**

### **1.2.1 Example 5: The Choice of stabilizer has little influence on stability**

**[0146]** Initial composition development for the liquid dosage form focused on the evaluation of different stabilizers with regards to secukinumab soluble and insoluble aggregate formation (AP-SEC, purity by SDS-PAGE, light scattering techniques), chemical stability (purity by RP-HPLC, purity by CEX, color) and biological activity (activity by Cys-CEX, free SH-groups, biological activity) during storage at long-term storage condition as well as accelerated and stressed conditions.

**[0147]** Stabilizers were divided into three different classes: Group I comprised non-ionic (mannitol, trehalose dihydrate) and ionic (sodium chloride and arginine hydrochloride) stabilizers. All group 1 stabilizers provided benefit over no stabilizer. However, non-ionic stabilizers (trehalose and mannitol) were observed to better stabilize the molecule as observed by lower aggregate levels and higher activity by Cys-CEX.

**[0148]** Based on the conclusions from the initial composition development studies, further studies were conducted in PFS using a DoE approach. The effect of stabilizer group I (glycine, mannitol, trehalose dihydrate, sodium chloride) was evaluated. The compositions were filled in pre-filled syringes and placed on a 2 months stability study at long-term, accelerated and stressed conditions and were evaluated with regards to physical stability (AP-SEC, DLS, turbidity, visible and sub-visible particles by light obscuration), chemical stability (purity by CEX, purity by RP-HPLC, color) and indicators of biological activity (activity by Cys-CEX, free SH-groups). In addition, freeze-thaw (5 cycles of -20 °C to room temperature) and shaking stress (150 rpm for one week) was applied to compositions filled in 2 mL vials. With regards to stabilizer class I, observations from earlier screens were confirmed: 1) all group 1 stabilizers provided benefit over no stabilizer; and 2) non-ionic stabilizers were found to be better stabilizers for secukinumab protein (Figure 14). This was especially prominent in purity by SEC, purity by RP-HPLC and polydispersity by DLS. Comparing different non-ionic stabilizers, no relevant effect was observed.

**[0149]** Next, we identified the ideal concentration of the stabilizer class I (trehalose dihydrate, 200-300 mM). Samples were filled in PFS and stored for up to three months at long-term, accelerated and stressed conditions. Secukinumab physical (AP-SEC, DLS, sub-visible particles by light obscuration, visible particles, turbidity) and chemical (purity by CEX, purity by RP-HPLC, color) stability as well as biological activity were monitored. No relevant difference in secukinumab quality attributes was observed with varying trehalose concentrations (Figure 3).

### 1.2.2 Example 6: The choice of surfactant has little influence on stability

**[0150]** Initial composition development for the 150 mg/ml liquid composition focused on the evaluation of different excipients (e.g., stabilizers and surfactants) with regards to secukinumab soluble and insoluble aggregate formation (AP-SEC, purity by SDS-PAGE, light scattering techniques), chemical stability (purity by RP-HPLC, purity by CEX, color) and biological activity (activity by Cys-CEX, free SH-groups, biological activity) during storage at long-term storage condition as well as accelerated and stressed conditions. Excipients were divided into three

different classes: Group III comprised the surfactants polysorbate 20 and 80. No difference was observed between polysorbate 20 and 80 at a concentration of 0.04 % as compared to no surfactant during quiescent storage.

**[0151]** Based on the conclusions from the initial composition development studies, further studies were conducted in PFS using a DoE approach. The effect of surfactant (polysorbate 20, polysorbate 80, Poloxamer 188, none) was evaluated. The compositions were filled in PFS and placed on a 2 months stability study at long-term, accelerated and stressed conditions and were evaluated with regards to physical stability (AP-SEC, DLS, turbidity, visible and sub-visible particles by light obscuration), chemical stability (purity by CEX, purity by RP-HPLC, color) and indicators of biological activity (activity by Cys-CEX, free SH-groups). In addition, freeze-thaw (5 cycles of -20 °C to room temperature) and shaking stress (150 rpm for one week) was applied to compositions filled in 2 mL vials. The presence of a surfactant was beneficial as observed by lower turbidity levels and visible and sub-visible particles by light obscuration counts. However, there was only a weak impact of the surfactant type (**Figure 15**).

**[0152]** We next identified the ideal concentration of the surfactant group III (polysorbate 80 0.01-0.04 (w/v) %). Samples were filled in PFS and stored for up to three months at long-term, accelerated and stressed conditions. Secukinumab physical (AP- SEC, DLS, sub-visible particles by light obscuration, visible particles, turbidity) and chemical (purity by CEX, purity by RP-HPLC, color) stability as well as biological activity were monitored. No distinct effect of polysorbate 80 concentrations on secukinumab quality attributes was observed during quiescent storage (**Figure 3**) as well as after 1 week of shaking at 150 rpm. Polydispersity by DLS and sub-visible particles by light obscuration were slightly increased at higher surfactant concentrations; therefore the concentration of polysorbate 80 was defined as 0.02 %, in order to keep a safety margin for the lowest evaluated concentration.

### **1.2.3 Example 5: The choice of buffer has little influence on stability**

**[0153]** The effect of buffer species (citrate, histidine, succinate, acetate) was evaluated in PFS using a DOE-approach. The compositions were filled in PFS and placed on a 2 months stability study at long-term, accelerated and stressed conditions and were evaluated with regards to physical stability (AP-SEC, DLS, turbidity, visible and sub-visible particles by light obscuration), chemical stability (purity by CEX, purity by RP-HPLC, color) and indicators of biological activity (activity by CysCEX, free SH-groups). In addition, freeze-thaw (5 cycles of - 20 °C to room temperature) and shaking stress (150 rpm for one week) was applied to compositions filled in 2 mL vials. No relevant impact of the buffer type was observed. **Figure 16** shows selected quality attributes.

### **1.2.4 Example 6: Antibody-concentration in the range tested has little influence on stability**

**[0154]** The effect of secukinumab concentration on liquid composition quality attributes was evaluated in a range of 124.5 - 175.5 mg/mL. Compositions also contained 200 mM trehalose, 5 mM L-methionine and 0.02 % polysorbate 80 in a histidine buffer pH 5.8. Compositions were filled into PFS and stored under long-term and accelerated conditions for 6 months. Relevant secukinumab quality attributes (purity by SEC, purity by RP-HPLC; purity by CEX, free SH-groups, biological activity, sub-visible particles by light obscuration, visible particles, turbidity and color of the solution) were monitored after 3 and 6 months storage. No relevant impact of secukinumab concentration on liquid composition quality attributes was observed within the range of 25 mg/ml to 150 mg/ml (data not shown).

### 1.3 Part 3 - Properties of a Preferred Final Market Composition

**[0155]** A preferred pharmaceutical product of secukinumab comprises a liquid composition of 150 mg/ml secukinumab in 20 mM histidine buffer, pH 5.8, 200 mM trehalose, 0.02% polysorbate 80 and 5 mM L-methionine, which is provided in PFS. At initial fill and finish, the headspace in the PFS has an oxygen content of less than 12%. These pharmaceutical products have excellent shelf life and overall stability.

**[0156]** Stability testing of various batches of the secukinumab drug product (150 mg/ml secukinumab, 200 mM trehalose dihydrate, 20 mM L-histidine/L-histidine hydrochloride monohydrate, 5 mM L-methionine, 0.02% polysorbate 80 (% w/v), pH 5.8) in PFS was performed. Results of testing under long term storage conditions (2-8°C) up to 24 months of storage, under accelerated storage conditions (25°C) up to 6 months storage, and under temperature stressed conditions (30°C) up to 6 months of storage months are shown in Tables 9-11, below. Based on the stability data presented, up to 24 months real time data for secukinumab 150 mg / 1 ml Liquid in pre-filled syringe (PFS) and up to 36 months stability data generated during development (bulk-syringe), a shelf life of 24 months is proposed for secukinumab 150 mg / 1 ml liquid in PFS commercial product when stored at long term conditions of 5°C ± 3°C, protected from light and preventing from freezing.

**Table 9** Purity by SEC, CEX and RP-HPLC. \*This higher value is related to the appearance of a small peak just before the main peak. As this new peak is integrated separately from the main peak, the sum of variants before main peak becomes higher.

		Purity by SEC			Purity by CEX			Purity by RP-HPLC	
		Purity/ Monomer [%]	AP-SEC [%]	DP-SEC [%]	Main variant [%]	Sum of basic variants [%]	Sum of acidic variants [%]	Main variant [%]	Sum of pre-main peak species [%]
<b>Storage conditions</b>									
	Initial analysis	99.1	0.90	<0.10	78.2	11.3	10.5	88.7	2.2
-20°C	1.5 months	99.0	0.92	<0.10	77.5	11.8	10.6	89.4	1.8
5°C ± 3°C	1.5 months	99.0	0.96	<0.10	77.2	12.0	10.7	89.4	1.9
	3 months	98.7	1.0	0.20	77.5	12.1	10.3	88.7	1.9
	6 months	98.8	1.1	<0.10	77.5	11.5	10.9	86.5	4.1*
	9 months	98.7	1.2	0.10	76.7	12.4	10.8	88.2	2.1
	12 months	98.5	1.3	0.16	76.4	12.6	10.9	88.6	3.0
	18 months	98.2	1.3	0.43	73.8	14.7	11.5	84.8	6.8*
	24 months	97.9	1.4	0.56	76.5	11.5	11.9	87.3	4.3
25°C / 60%RH	1.5 months	98.6	1.2	0.14	72.3	14.6	12.7	87.9	3.8
	3 months	97.5	1.6	0.83	68.6	15.9	15.4	81.1	9.9
	6 months	96.2	2.0	1.7	62.8	16.2	21.0	76.1	15.3
30°C / 75%RH	1.5 months	97.6	1.5	0.90	67.9	16.4	15.5	86.7	5.1
	3 months	96.5	2.0	1.4	60.9	17.2	21.8	77.1	14.0
	6 months	94.1	3.0	2.8	50.6	17.4	31.9	60.3	22.0

Table 10 Purity by CE-SDS (non-reducing) and Impurities by SDS-PAGE (reducing).

Storage conditions		Purity by CE-SDS (non-reducing)	Impurity by SDS-PAGE (reducing)
		Purity/Monomer [%]	Sum of impurities [%]
	Initial analysis	97.5	0.60
- 20°C	1.5 months	97.3	0.92
5°C ± 3°C	1.5 months	97.2	0.91
	3 months	97.4	0.63
	6 months	97.4	0.57
	9 months	97.5	0.66
	12 months	97.4	0.58
	18 months	97.1	0.63
	24 months	97.2	0.61
25°C / 60%RH	1.5 months	97.1	1.3
	3 months	96.7	0.86
	6 months	95.3	1.1
30°C / 75%RH	1.5 months	96.8	1.1
	3 months	95.6	1.3
	6 months	94.0	1.9

**Table 11** Potency and quantity. \*samples were tested > 30 days after pull date, this deviation has no impact on potency assay results.

Storage conditions		Inhibition of IL-16 from C-20/A4 chondrocytes [%]	Assay of protein by UV absorption
		Potency [%]	Quantity [mg / mL]
	Initial analysis	107	147.9
- 20°C	1.5 months	107	149.6
5°C ± 3°C	1.5 months	92	149.4
	3 months	92*	149.5
	6 months	102*	149.6
	9 months	103	149.5
	12 months	90*	149.0
	18 months	88	147.9
	24 months	98	149.4
25°C/60%RH	1.5 months	100	149.4

Storage conditions	Inhibition of IL-16 from C-20/A4 chondrocytes [%]		Assay of protein by UV absorption
	Potency [%]	Quantity [mg / mL]	
	3 months	107*	149.7
	6 months	94*	149.6
30°C / 75%RH	1.5 months	90	149.1
	3 months	119*	149.3
	6 months	85*	149.4

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**Patentkrav****1. Farmaceutisk produkt omfattende:**

- a. en beholder med et hovedrum, hvor oxygenindholdet i hovedrummet er mindre end 12%, og
- 5 b. en stabil flydende farmaceutisk sammensætning med en pH på 5,2 til 6,2 anbragt i nævnte beholder, hvilken sammensætning omfatter:
  - i. 20 mg/ml til 175 mg/ml secukinumab;
  - ii. 2,5 til 20 mM L-methionin og
  - iii. en ikke-ionisk stabilisator, et overfladeaktivt middel valgt fra et
- 10 polysorbat og en poloxamer og en histidinbuffer.

**2. Det farmaceutiske produkt ifølge krav 1, hvor koncentrationen af methionin er 2,5 mM, 5 mM, 10 mM eller 20 mM.**

15 **3. Det farmaceutiske produkt ifølge et hvilket som helst af de ovennævnte krav, hvor oxygenindholdet i hovedrummet er mindre end 10%, mindre end 8% eller mindre end 6%.**

20 **4. Det farmaceutiske produkt ifølge et hvilket som helst af de ovennævnte krav, hvor den flydende farmaceutiske sammensætning har en pH på 5,8.**

**5. Det farmaceutiske produkt ifølge et hvilket som helst af de ovennævnte krav, hvor koncentrationen af secukinumab er 150 mg/ml.**

25 **6. Farmaceutisk produkt ifølge krav 1, omfattende**

- a. en beholder med et hovedrum, hvor oxygenindholdet i hovedrummet er mindre end 6%; og
- 30 b. en stabil flydende farmaceutisk sammensætning anbragt i beholderen, hvilken sammensætning omfatter 25 mg/ml til 150 mg/ml secukinumab, 10 mM til 30 mM histidin pH 5,2-6,2, 180 mM til 300 mM trehalose, 0,01% til 0,040% polysorbat 80 og 2,5 mM til 20 mM methionin.

**7.** Det farmaceutiske produkt ifølge krav 6, omfattende 150 mg/ml secukinumab og 200 mM trehalose.

**8.** Fremgangsmåde til at reducere oxidationen af secukinumab, omfattende:

5        a. fremstilling af en stabil flydende sammensætning med en pH på 5,2 til 6,2 og omfattende:

- i. 20 mg/ml til 175 mg/ml secukinumab;
- ii. 2,5 mM til 20 mM methionin; og
- iii. en ikke-ionisk stabilisator, et overfladeaktivt middel valgt fra et

10      polysorbat og en poloxamer og en histidinbuffer,

- b. anbringelse af nævnte flydende sammensætning i en beholder med et hovedrum; og
- c. justering af oxygenindholdet i hovedrummet til mindre end eller lig med 12%.

15

**9.** Fremgangsmåden ifølge krav 8, hvor justering af trin c) udføres ved at rense hovedrummet under anvendelse af en inert gas.

**10.** Fremgangsmåden ifølge krav 9, hvor den inerte gas er nitrogen eller argon.

20

**11.** Fremgangsmåden ifølge krav 8 eller krav 9, hvor koncentrationen af methionin er 2,5 mM, 5 mM, 10 mM eller 20 mM.

25      **12.** Fremgangsmåden ifølge krav 8 eller krav 9, hvor oxygenindholdet i hovedrummet er justeret til mindre end 10%, mindre end 8% eller mindre end 6%.

**13.** Fremgangsmåden ifølge krav 8 eller krav 9, hvor den flydende sammensætning har en pH på 5,8.

30

**14.** Fremgangsmåden ifølge krav 8 eller krav 9, hvor koncentrationen af secukinumab er 150 mg/ml.

35      **15.** Stabil flydende farmaceutisk sammensætning omfattende 25 mg/ml til 150 mg/ml secukinumab, 10 mM til 30 mM histidin pH 5,2-6,2, 180 mM til

300 mM trehalose, 0,01% til 0,04% polysorbat 80 og 2,50 mM og 20 mM methionin.

**16.** Den flydende farmaceutiske sammensætning ifølge krav 15, omfattende  
5 25 mg/ml til 150 mg/ml secukinumab, 10 mM til 30 mM histidin pH 5,8, 200 mM  
til 225 mM trehalose, 0,02% polysorbat 80 og 2,5 mM methionin til 20 mM  
methionin.

**17.** Den farmaceutiske sammensætning ifølge krav 15 eller krav 16, omfattende  
10 150 mg/ml secukinumab, 20 mM histidin pH 5,8, 200 mM trehalose, 0,02%  
polysorbat 80 og 5 mM L-methionin.

**18.** Det farmaceutiske produkt ifølge et hvilket som helst af kravene 1-7, hvor  
beholderen er valgt fra gruppen bestående af en patron, en sprøjte, en pen, en  
15 fyldt sprøjte, en autoinjektor og et hætteglas.

## DRAWINGS

Fig. 1

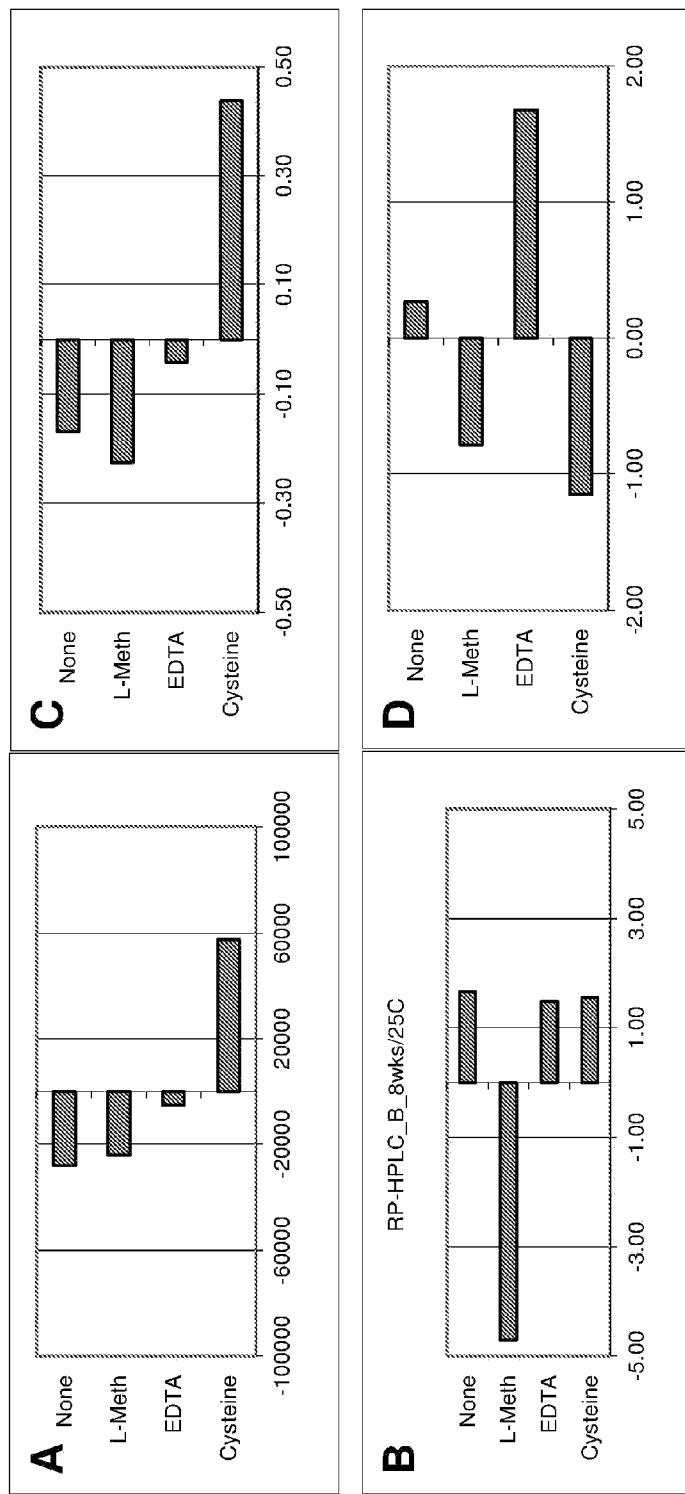


Fig. 2

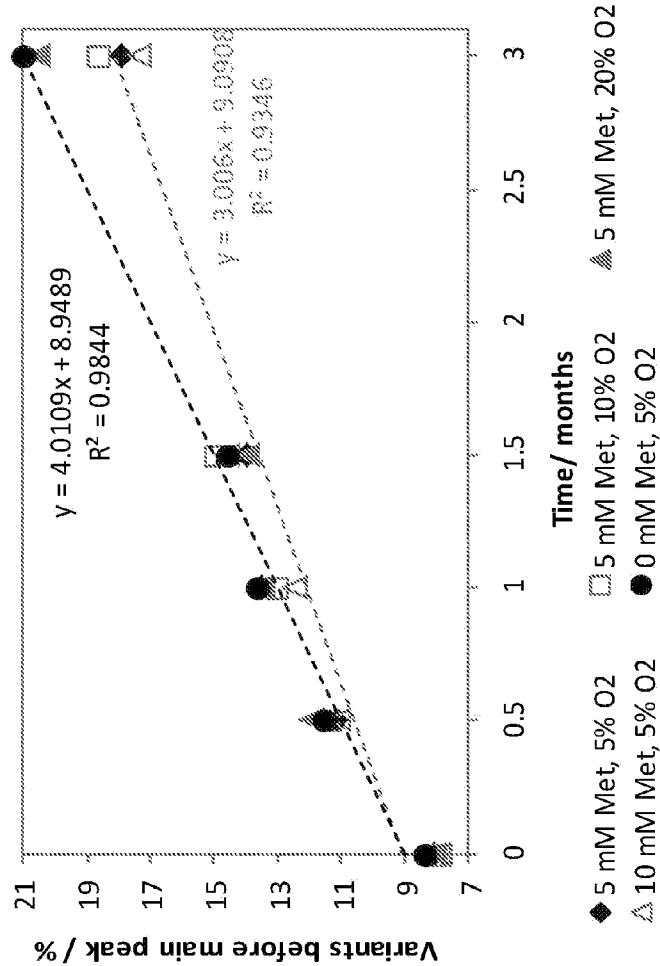


Fig. 3

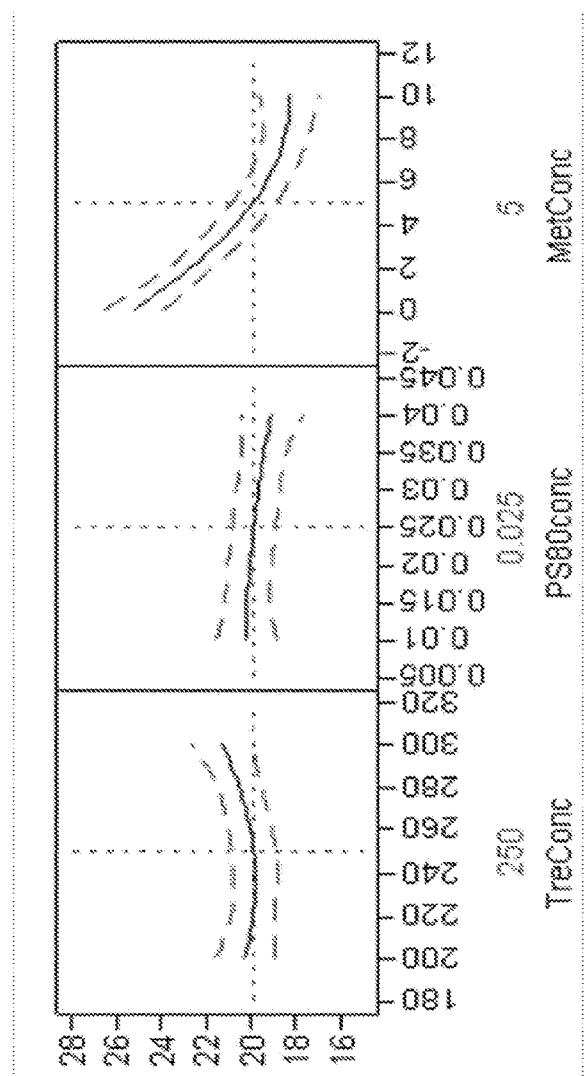


Fig. 4

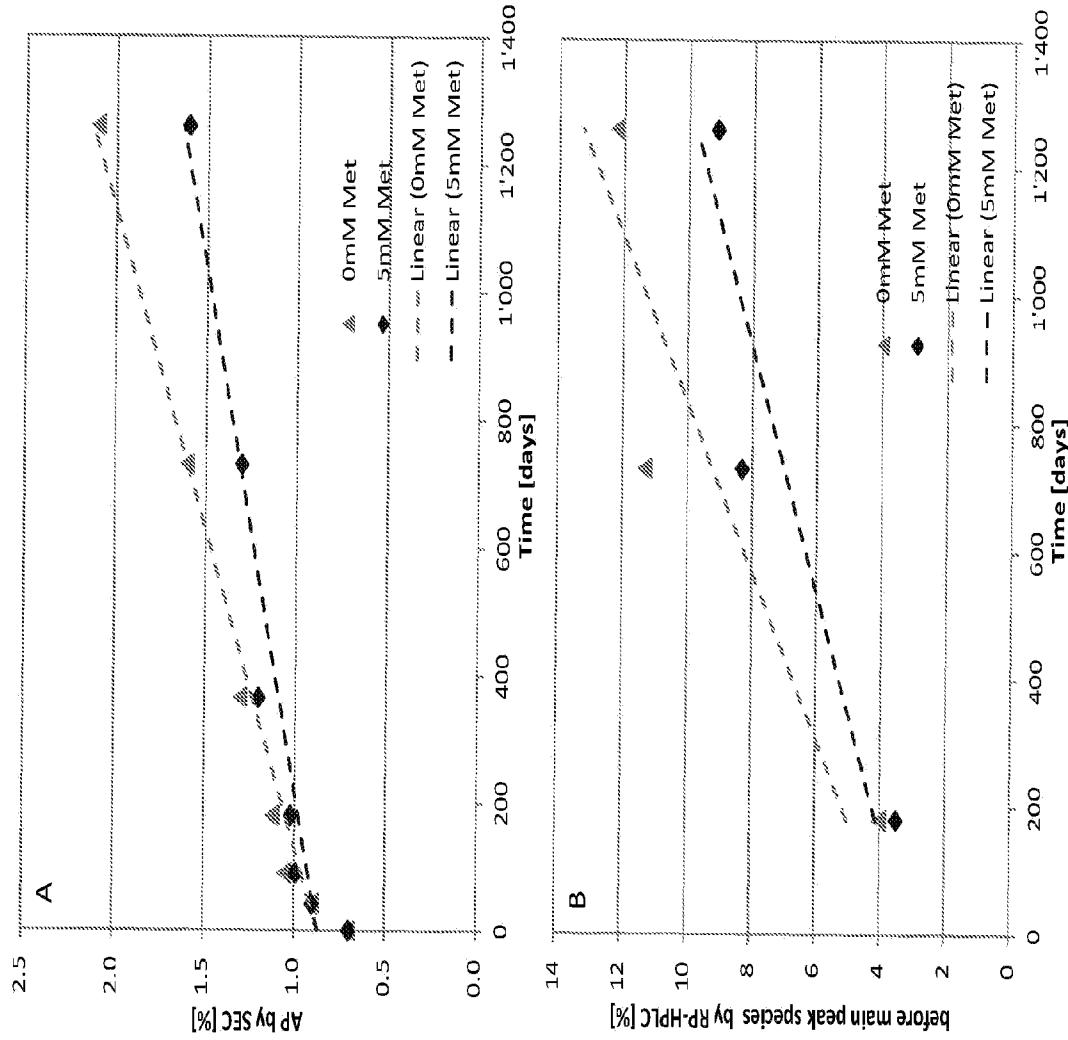


Fig. 5

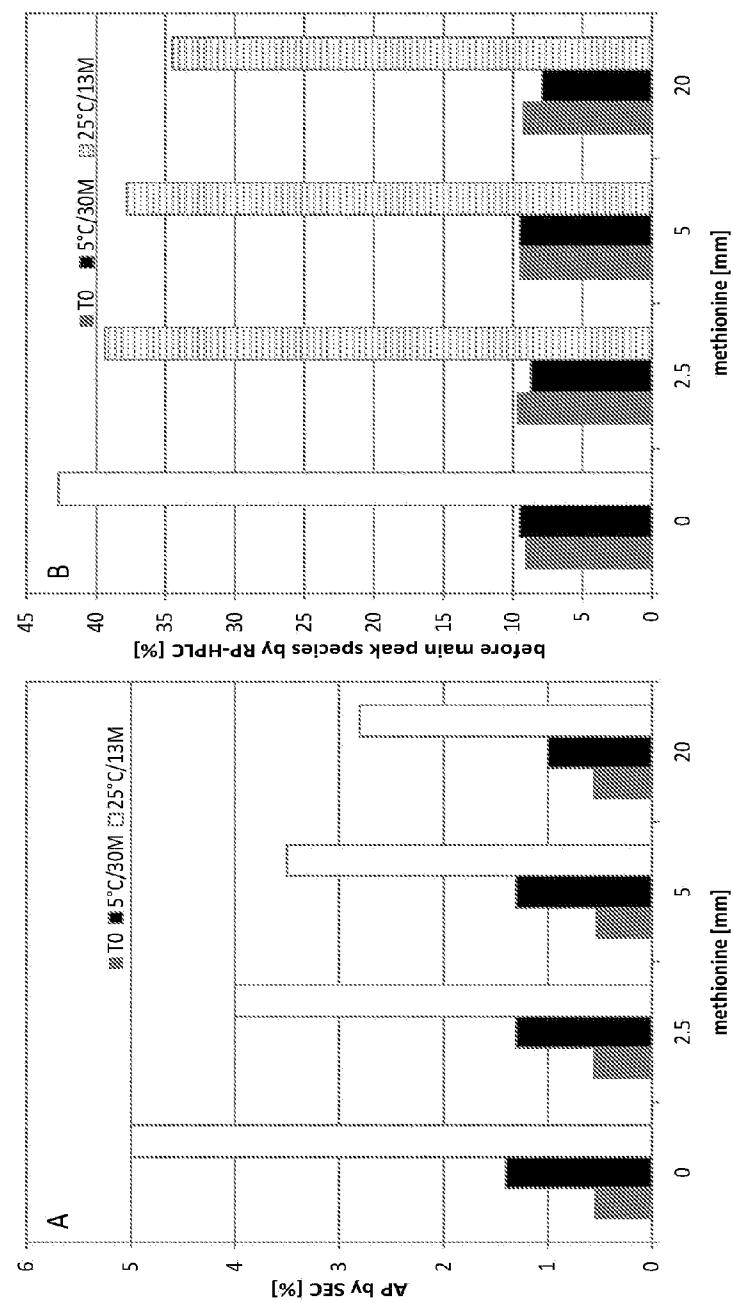


Fig. 6

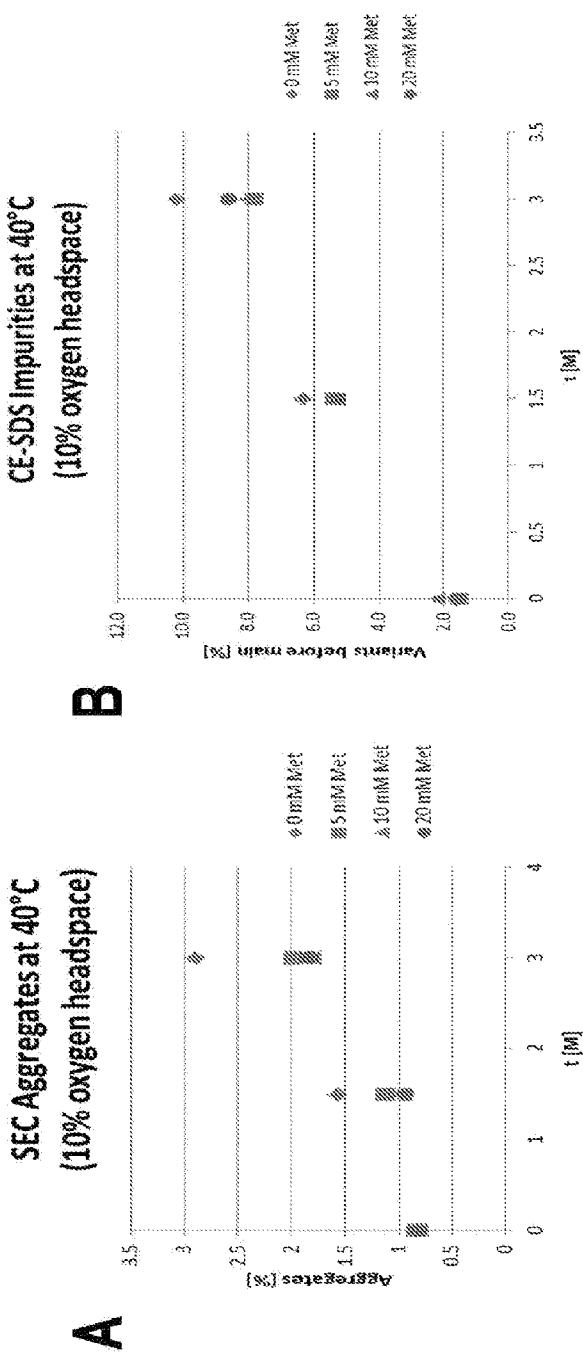


Fig. 7

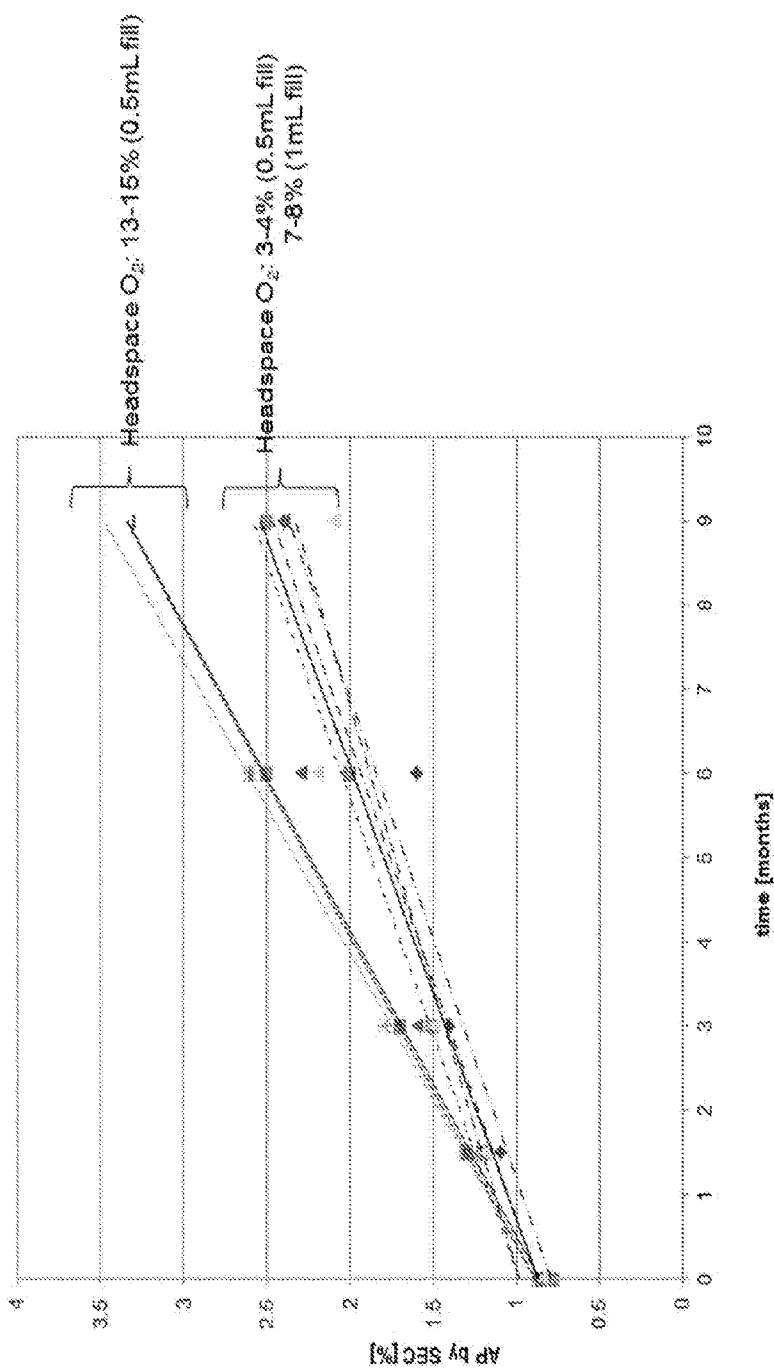


Fig. 8

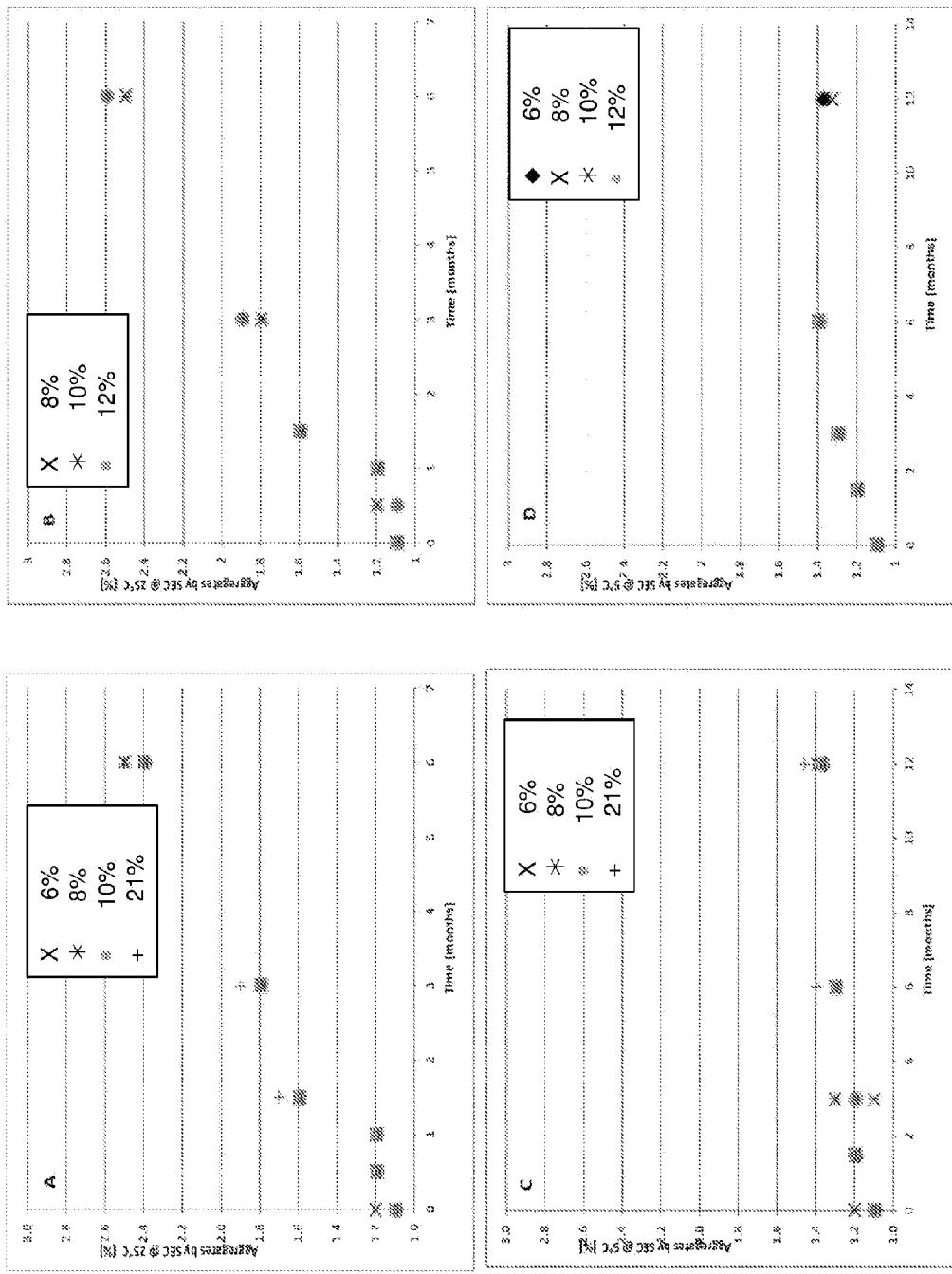
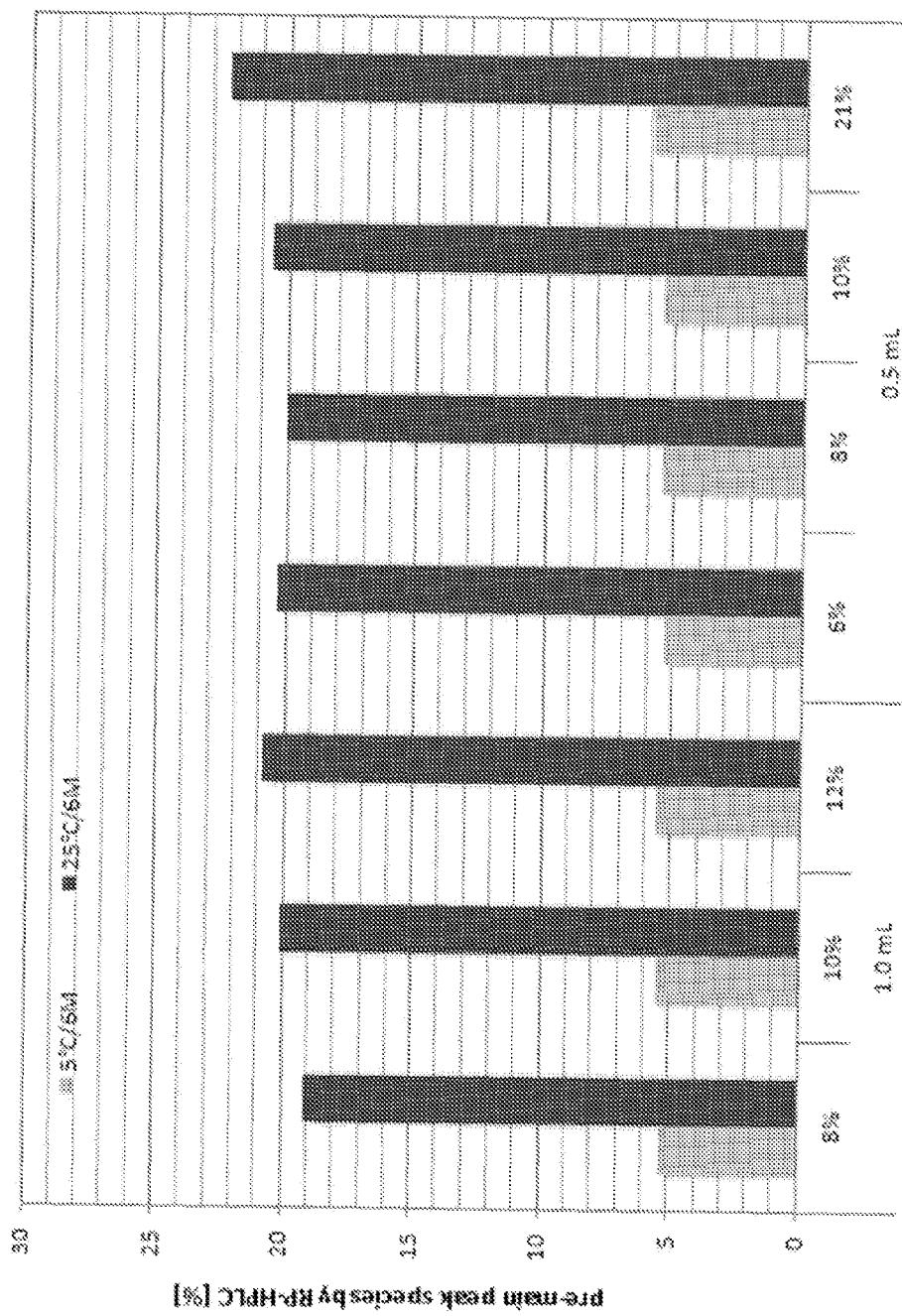


Fig. 9



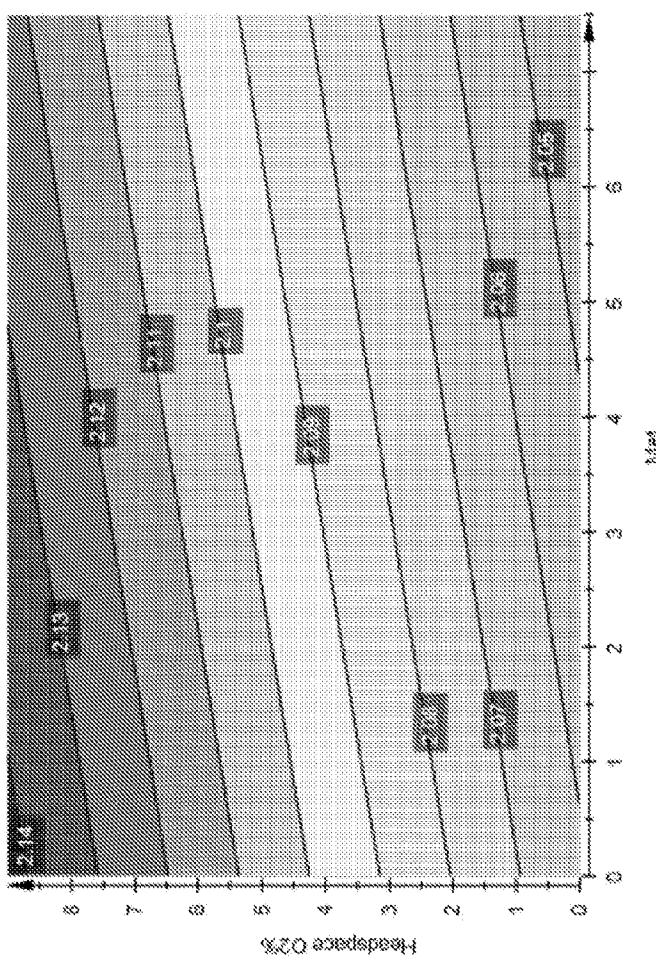


Fig. 10

Fig. 1

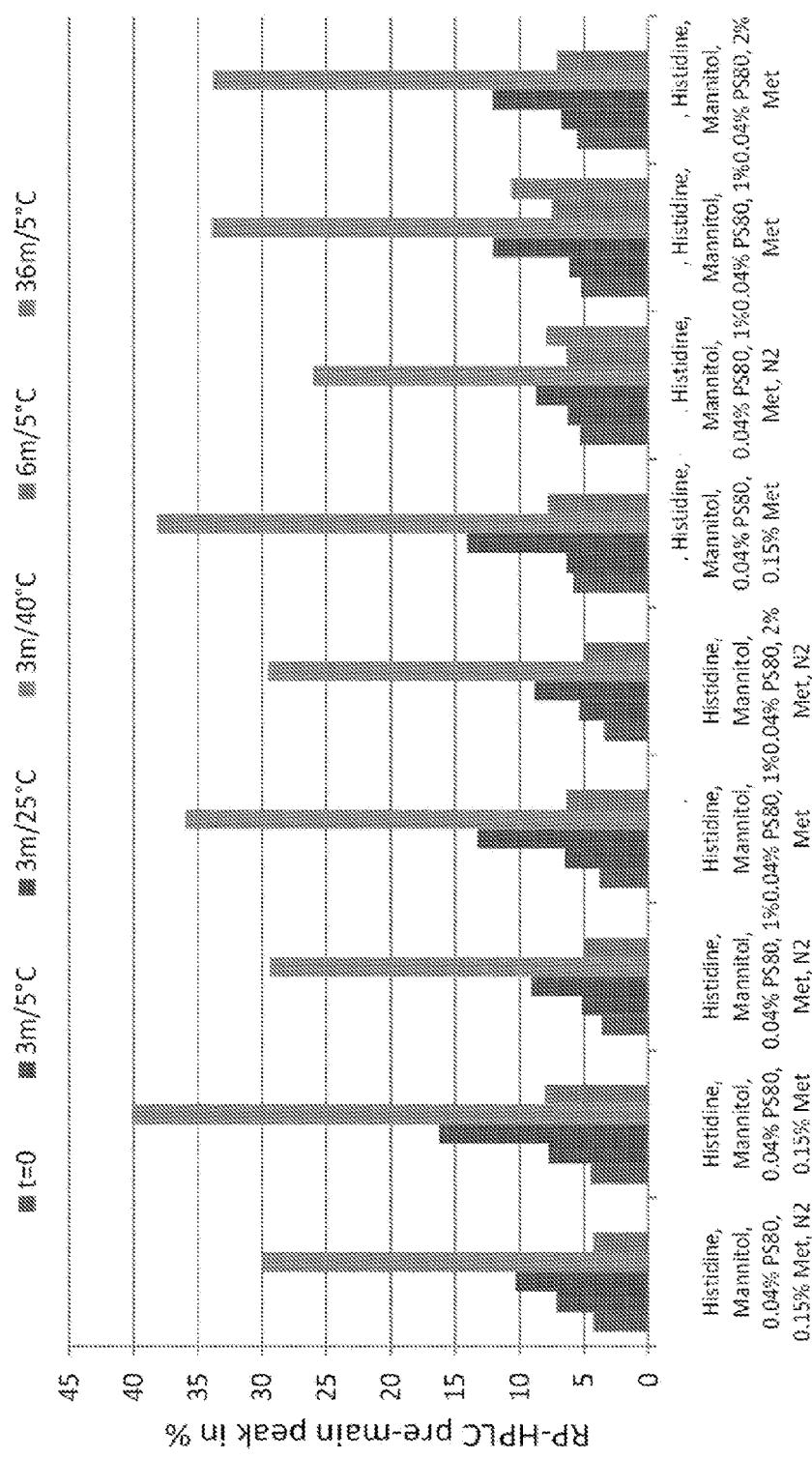


Fig. 12

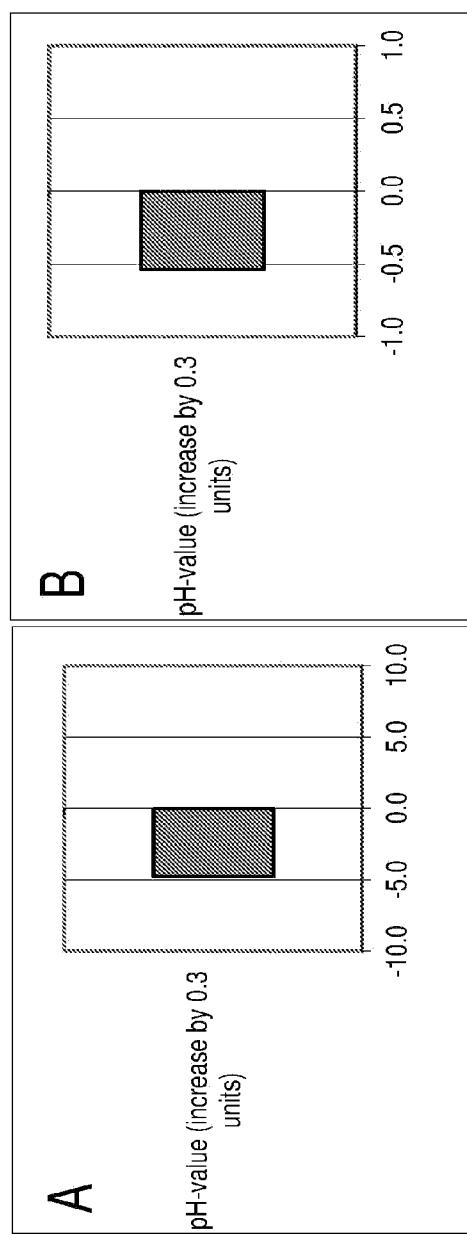
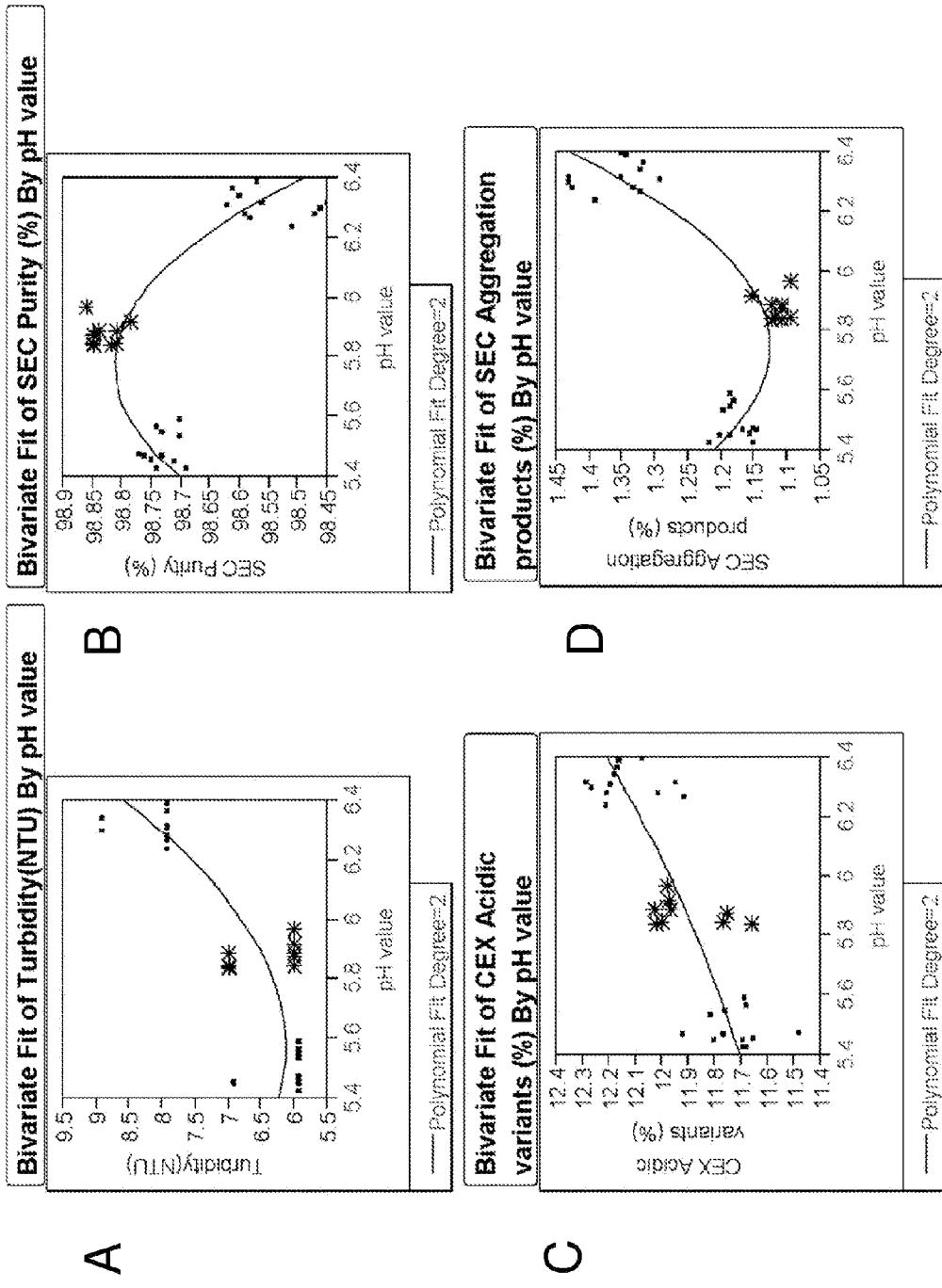


Fig. 13



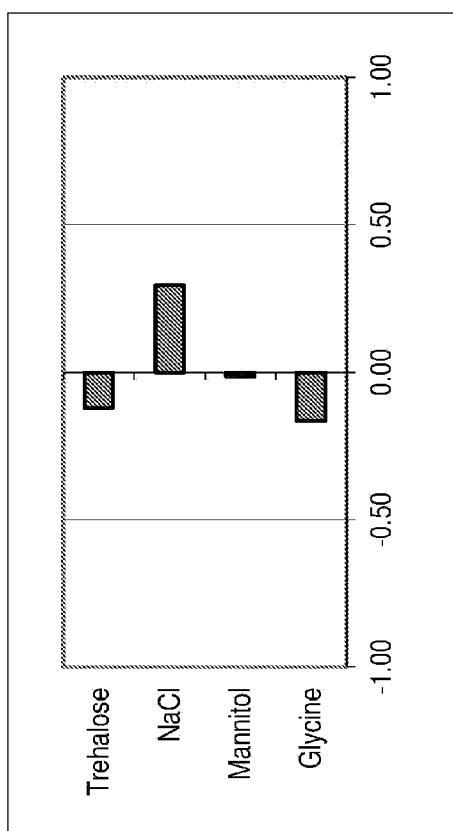


Fig. 14

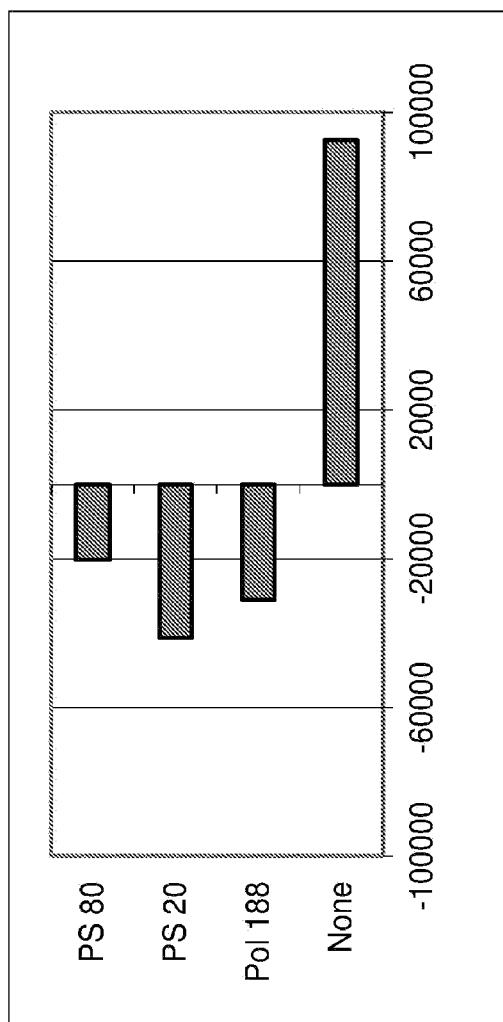
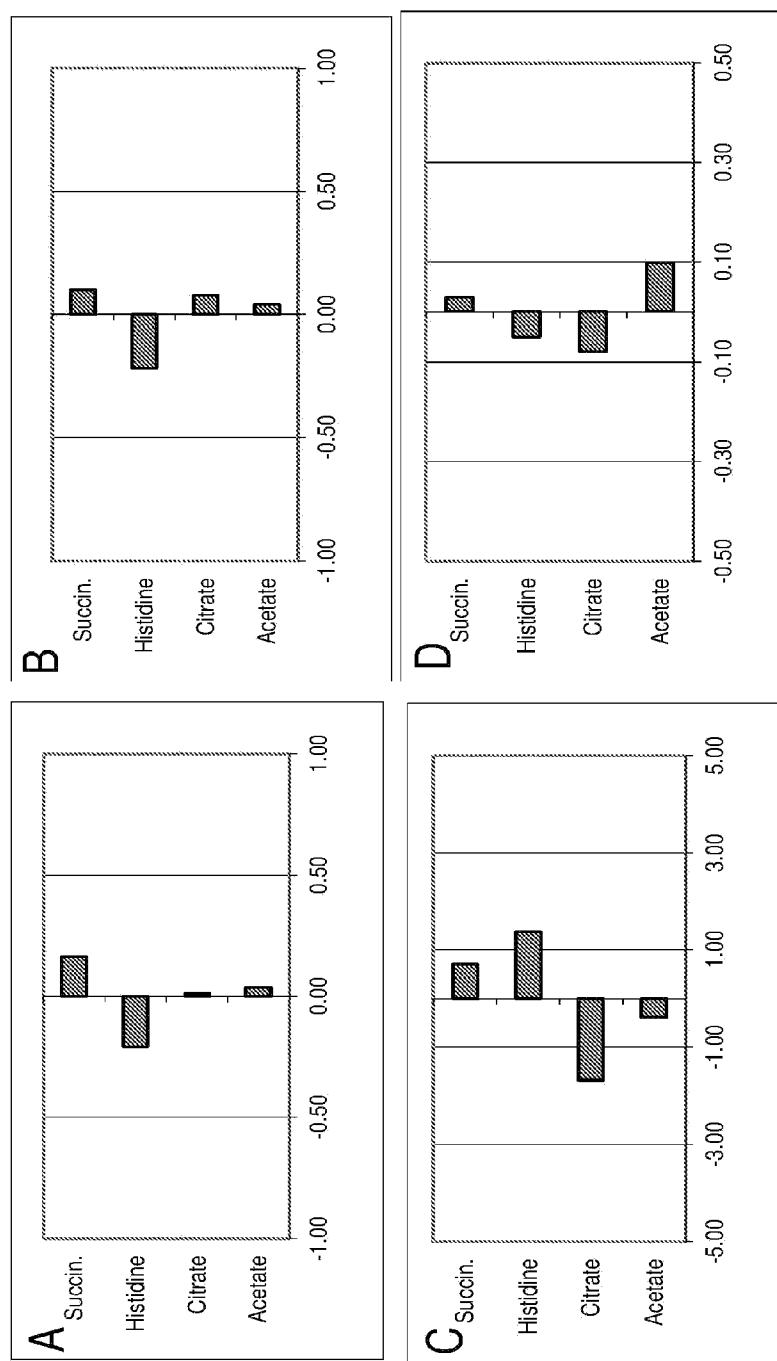


Fig. 15

Fig. 16



SEKVENSLISTE

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