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earlier application (Rule 4.17(iii))

(54) Title: PSORIASIS DISEASE MODIFICATION FOLLOWING LONG-TERM TREATMENT WITH AN IL-17 ANTAGONIST

(57) Abstract: The present disclosure relates to methods for modifying the psoriasis disease course in particular patients having chronic plaque-type psoriasis and inhibiting the progression to psoriatic arthritis (PsA) in these patients, using IL-17 antagonists, e.g., secukinumab. Also disclosed herein are uses of IL-17 antagonists, e.g., IL-17 antibodies, such as secukinumab, for use in modifying the psoriasis disease course in particular patients having chronic plaque-type psoriasis and inhibiting the progression to PsA in these patients, as well as medicaments, dosing regimens, pharmaceutical formulations, dosage forms, and kits for use in the disclosed uses and methods.



PSORIASIS DISEASE MODIFICATION FOLLOWING LONG-TERM TREATMENT WITH AN IL-17 ANTAGONIST

RELATED APPLICATIONS

The instant application claims priority to US Provisional Patent application No. 62/466,556, filed March 3, 2017, which is incorporated by reference herein in its entirety.

TECHNICAL FIELD

The present disclosure relates to methods of modifying the psoriasis disease course in patients having chronic plaque-type psoriasis and inhibiting the progression to psoriatic arthritis (PsA) and other psoriasis-related comorbidities, e.g., cardiovascular disease and diabetes, in these patients, using IL-17 antagonists, e.g., secukinumab.

BACKGROUND OF THE DISCLOSURE

Plaque psoriasis is a chronic, systemic, relapsing disease characterized by thick, red and scaly plaques of the skin that can cover the majority of the body. (Agency EM. Guideline on clinical investigation of medicinal products indicated for treatment of psoriasis. London 2004). Psoriasis has a detrimental impact on patients' functional, psychological, and social well-being. More than 90% of plaque psoriasis patients have chronic disease. (Nast Aet al. S3 - Guidelines on the treatment of psoriasis vulgaris (English version). Update. J Dtsch Dermatol Ges. 2012;10 Suppl 2:S1-95).

There is currently no cure for psoriasis and moderate to severe chronic psoriasis requires long term treatment. Treatment can lead psoriasis into remission, however many factors can lead to a worsening or flare, such as infection (such as common cold), psychological stress, skin trauma (cuts, bumps), certain medications (e.g., beta blockers for hypertension) and others. Without treatment, spontaneous remissions are very rare, particularly when the disease is chronic and severe. (Hartman R, Kimball A. Clinical Presentation of Psoriasis and Psoriatic Arthritis. In: Richard W, Menter, A., editor. Handbook of Psoriasis and Psoriatic Arthritis Switzerland: Springer International Publishing; 2016. p. 17-25). When psoriasis treatment is stopped, skin lesions typically recur quickly, usually in the same anatomical locations and growing to the size

and severity they were before therapy. (they revert to their “baseline” severity) (Clark (2011) J Invest Dermatol. 131(2): 283–285). This is because even when skin is cleared and appears healed by a treatment, the inflammation and histological changes in skin persist, albeit invisible. In addition, the ever present underlying inflammation is not “static,” it gradually worsens over time, making psoriasis a progressive disease. For a disease for which no cure currently exists, disease modification or changing the natural course to a less severe state is the best possible outcome.

Psoriasis is unfortunately not just a skin disease, it is a systemic inflammatory condition that impacts other organs. Consequently, patients can develop psoriatic arthritis, cardiovascular disease, metabolic syndrome (diabetes mellitus, obesity) and other conditions. Patients with more severe psoriasis are at a particularly high risk to develop these conditions. Therefore, psoriasis patients need to be treated as a whole, not just for their skin. Modifying the course of psoriasis beyond the skin, by preventing or delaying the onset of some of the most debilitating comorbidities is the best a treatment can do for the patients, without being able to cure the disease - the ultimate goal.

SUMMARY OF THE DISCLOSURE

Secukinumab is the first IL-17A inhibitor approved for the treatment of psoriasis in patients requiring systemic treatment. We have now discovered that extended treatment of particular chronic plaque-type psoriasis patients with IL-17 antagonists, such as secukinumab, modifies the psoriasis disease course in these patients. The observed clinical outcome is a change in the natural course of the disease to a milder state, i.e., inducing minimal, or no, disease activity. Furthermore, such long-term treatment is expected to inhibit the progression to psoriatic arthritis (PsA) in these patients. Accordingly, disclosed herein are methods of modifying the psoriasis disease course in a patient having chronic plaque-type psoriasis, comprising administering a therapeutically effective amount of an IL-17 antagonist (e.g., secukinumab) to a patient in need thereof.

Additionally disclosed herein are methods of, and IL-17 antagonists (e.g., secukinumab) for use in, slowing psoriasis disease progression in a patient having chronic plaque-type psoriasis, decreasing the severity of psoriasis flares in a patient having chronic plaque-type psoriasis, decreasing the frequency of psoriasis flares in a patient having chronic plaque-type

psoriasis, preventing psoriasis flares in a patient having chronic plaque-type psoriasis, changing the natural course of the psoriasis disease to a milder state in a patient having chronic plaque-type psoriasis, preventing progression from psoriasis to psoriatic arthritis (PsA) in a patient having chronic plaque-type psoriasis, and/or decreasing the risk that a patient having chronic plaque-type psoriasis will develop PsA and other psoriasis-related comorbidities, e.g., cardiovascular complications, comprising administering an IL-17 antibody or antigen-binding fragment thereof to a patient in need thereof.

In some embodiments of the disclosed uses, methods and kits, the IL-17 antagonist is an IL-17 antibody or antigen-binding fragment thereof. In some embodiments of the disclosed uses, methods and kits, the IL-17 antibody or antigen-binding fragment thereof is selected from the group consisting of: a) an IL-17 antibody or antigen-binding fragment thereof that binds to an epitope of human IL-17 comprising Leu74, Tyr85, His86, Met87, Asn88, Val124, Thr125, Pro126, Ile127, Val128, His129; b) an IL-17 antibody or antigen-binding fragment thereof that binds to an epitope of human IL-17 comprising Tyr43, Tyr44, Arg46, Ala79, Asp80; c) an IL-17 antibody or antigen-binding fragment thereof that binds to an epitope of an IL-17 homodimer having two mature human IL-17 protein 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; d) an IL-17 antibody or antigen-binding fragment thereof that binds to an epitope of an IL-17 homodimer having two mature human IL-17 protein 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, wherein the IL-17 antibody or antigen-binding fragment thereof has a K_D of about 100-200 pM, and wherein the IL-17 antibody or antigen-binding fragment thereof has an *in vivo* half-life of about 23 to about 35 days; and e) an IL-17 antibody or antigen-binding fragment thereof comprising: i) an immunoglobulin heavy chain variable domain (V_H) comprising the amino acid sequence set forth as SEQ ID NO:8; ii) an immunoglobulin light chain variable domain (V_L) comprising the amino acid sequence set forth as SEQ ID NO:10; iii) 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; iv) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3; v) an immunoglobulin V_L domain comprising the

hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; vi) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13; vii) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; viii) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; ix) an immunoglobulin light chain comprising the amino acid sequence set forth as SEQ ID NO:14; x) an immunoglobulin heavy chain comprising the amino acid sequence set forth as SEQ ID NO:15; or xi) an immunoglobulin light chain comprising the amino acid sequence set forth as SEQ ID NO:14 and an immunoglobulin heavy chain comprising the amino acid sequence set forth as SEQ ID NO:15. In some embodiments of the disclosed uses, methods and kits, the IL-17 antibody or antigen-binding fragment thereof is a human or humanized antibody. In some embodiments of the disclosed uses, methods and kits, the IL-17 antibody or antigen-binding fragment thereof is secukinumab.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1. CAIN457A2302E1 study design. PASI 75 responders at Week 52 of ERASURE and FIXTURE continued to randomized withdrawal period; PASI, Psoriasis Area and Severity Score.

Figure 2. Proportion of patients maintaining at least 50% of their PASI improvement for at least 1 year and 2 years after the last dose of secukinumab 300mg and 150mg (given at 48 weeks) in the CAIN457A2302E1 extension study.

Figure 3. Mean absolute PASI score in patients maintaining at least 50% of the PASI improvement for at least 1 year after the last dose of secukinumab 300 mg (given at 48 weeks) from CAIN457A2302E1 study. Also shown is the mean baseline PASI score at first dose of secukinumab in the core CAIN457A2302/2303 trial and the mean PASI score following the last dose of secukinumab at the end of the core CAIN457A2302/2303 trial and during the CAIN457A2302E1 extension study.

Figure 4. Mean absolute PASI score in patients maintaining at least 50% of the PASI improvement for at least 2 year after the last dose of secukinumab 300 mg (given at 48 weeks) from CAIN457A2302E1 study. Also shown is the mean baseline PASI score at first dose of secukinumab in the core CAIN457A2302/2303 trial and the mean PASI score following the last dose of secukinumab at the end of the core CAIN457A2302 trial and during the CAIN457A2302E1 extension study.

Figure 5. CAIN457A2223 study design. EOT, End of Treatment; EoS, End of Study; PASI, Psoriasis Area and Severity Index; IGA mod 2011, 2011 modified investigator's global assessment.

Figure 6. Representative nonlesional and lesional skin biopsies showing marked improvement (histological disease reversal; Score +3) from baseline following 12 weeks of secukinumab 300 mg treatment in CAIN457A2223 study.

Figure 7. Heat map of changes in psoriasis transcriptome genes following secukinumab treatment. Secukinumab induces rapid and progressive changes in lesional plaque skin gene expression signatures through 1 year of treatment. BL, Fold change (FC) of differentially expressed genes in LS vs NL skin at baseline = "psoriasis transcriptome"; Wkn = FC in LS at Week n vs. LS at baseline; Heat map shows hierarchical clustering of 1595 baseline psoriasis transcriptome genes (fold difference in LS vs. NL skin at baseline $> +/1$ 1.5, adjusted $p < 0.5$) that show statistically significant changes (adjusted $p < 0.5$) in expression with secukinumab in LS at weeks 12 and 52.

DETAILED DESCRIPTION OF THE DISCLOSURE

As used herein, IL-17 refers to interleukin-17A (IL-17A).

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.

The term "about" in relation to a numerical value x means, for example, $\pm 10\%$. When used in front of a numerical range or list of numbers, the term "about" applies to each number in the series, e.g., the phrase "about 1-5" should be interpreted as "about 1 – about 5", or, e.g., the phrase "about 1, 2, 3, 4" should be interpreted as "about 1, about 2, about 3, about 4, etc."

The word “substantially” does not exclude “completely,” e.g., a composition which is “substantially free” from Y may be completely free from Y. Where necessary, the word “substantially” may be omitted from the definition of the disclosure.

The term "antibody" as referred to herein includes naturally-occurring and whole antibodies. 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. Exemplary antibodies include secukinumab (**Table 1**), antibody XAB4 (US Patent No. 9,193,788), and ixekizumab (U.S. Patent No. 7,838,638), the disclosures of which are incorporated by reference herein in their entirety.

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 portion" 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 fragments include the CDRs of secukinumab as set

forth in SEQ ID NOs: 1-6 and 11-13 (**Table 2**), 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 portions are obtained using conventional techniques known to those of skill in the art.

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*). In some embodiments of the disclosed processes and compositions, the IL-17 antibody is a human antibody, an isolated antibody, and/or a monoclonal antibody.

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.

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

preferred 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 or antigen-binding fragment thereof, e.g., secukinumab, binds human IL-17 with a K_D of about 100-250 pM.

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.

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 and compositions, the IL-17 antibody used may inhibit greater than 95%, 98% or 99% of IL-17 functional activity.

"Inhibit IL-6" as used herein refers to the ability of an IL-17 antibody or antigen-binding fragment thereof (e.g., secukinumab) to decrease IL-6 production from primary human dermal fibroblasts. The production of IL-6 in primary human (dermal) fibroblasts is dependent on IL-17 (Hwang et al., (2004) *Arthritis Res Ther*; 6:R120-128). In short, human dermal fibroblasts are stimulated with recombinant IL-17 in the presence of various concentrations of an IL-17 binding molecule or human IL-17 receptor with Fc part. The chimeric anti-CD25 antibody Simulect® (basiliximab) may be conveniently used as a negative control. Supernatant is taken after 16 h stimulation and assayed for IL-6 by ELISA. An IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab, typically has an IC_{50} for inhibition of IL-6 production (in the presence 1 nM human IL-17) of about 50 nM or less (e.g., from about 0.01 to about 50 nM) when tested as above, i.e., said inhibitory activity being measured on IL-6 production induced by

hu-IL-17 in human dermal fibroblasts. In some embodiments of the disclosed methods and compositions, IL-17 antibodies or antigen-binding fragments thereof, e.g., secukinumab, and functional derivatives thereof have an IC₅₀ for inhibition of IL-6 production as defined above of about 20 nM or less, more preferably of about 10 nM or less, more preferably of about 5 nM or less, more preferably of about 2 nM or less, more preferably of about 1 nM or less.

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. A functional derivative includes fragments and peptide analogs of an IL-17 antibody 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 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 antibodies and antigen-binding fragments thereof 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.

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. Sequences substantially identical (e.g., at least about 85% sequence identity) to the sequences disclosed herein are also part of this application. In some embodiments, 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.

"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.

"Amino acid(s)" refer to all naturally occurring L- α -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 an antibody 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).

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

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.

As used herein, a “therapeutically effective amount” refers to an amount of an IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 antibody or antigen-binding fragment thereof) that is effective, upon single or multiple dose administration to a patient (such as a human) for treating, preventing, preventing the onset of, curing (if applicable), 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 antagonist, 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.

The term “treatment” or “treat” is herein defined as the application or administration of an IL-17 antibody according to the disclosure, for example, secukinumab or ixekizumab, or a pharmaceutical composition comprising said anti-IL-17 antibody, to a subject or to an isolated tissue or cell line from a subject, where the subject has a particular disease (e.g., psoriasis), a symptom associated with the disease (e.g., psoriasis), or a predisposition towards development of the disease (e.g., psoriasis), where the purpose is to cure (if applicable), delay the onset of, reduce the severity of, alleviate, ameliorate one or more symptoms of the disease, improve the disease, reduce or improve any associated symptoms of the disease or the predisposition toward the development of the disease. The term “treatment” or “treat” includes treating a patient suspected to have the disease as well as patients who are ill or who have been diagnosed as suffering from the disease or medical condition, and includes suppression of clinical relapse.

In some embodiments, the patient is administered the IL-17 antagonist (e.g., IL-17 antibody, like secukinumab) monthly (e.g., following an initial weekly induction regimen during week 0, 1, 2, 3 and 4), which extends to at least 48 weeks. In some embodiments, the patient is administered the IL-17 antagonist (e.g., IL-17 antibody, like secukinumab) monthly (e.g., following an initial weekly induction regimen during week 0, 1, 2, 3 and 4), which extends to at least 100 weeks, at least 152 weeks, at least 204 weeks, at least 5 years, or at least 10 years. In some embodiments, following long-term treatment (i.e., administration of the IL-17 antagonist (e.g., IL-17 antibody, like secukinumab) for at least 48 weeks), treatment is withdrawn. As used herein, the phrases “withdrawing treatment”, “treatment withdrawal” and “withdrawal of

treatment” and the like refer to discontinuing administration of a given drug, e.g., an IL-17 antagonist (e.g., an IL-17 antibody, e.g., secukinumab). In some embodiments of the disclosure, the IL-17 antibody is administered during week 0, 1, 2, 3, and 4, and then monthly thereafter, wherein the monthly dosing extends to at least 48 weeks, at least 100 weeks, at least 152 weeks, at least 204 weeks, at least 5 years, or at least 10 years before withdrawal of treatment. The final administration of the IL-17 antibody (e.g., secukinumab) delivered prior to withdrawal of treatment is referred to as the “the last dose.” As used herein the phrase “monthly dosing extends to at least X” means that the last dose before withdrawal of treatment is delivered at time point X.

As used herein, the phrase “chronic” is used to mean plaque-type psoriasis in which the first psoriasis plaque appeared (debuted) over 12 months (>12 months) prior to the start of treatment with the IL-17 antagonist (e.g., secukinumab). In some embodiments of the disclosed kits, uses and methods, the patient has had chronic plaque-type psoriasis for at least 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 15 years, 20 years, or more.

As used herein, the phrase “has not been previously treated with phototherapy for psoriasis” refers to a psoriasis patient who has not been previously treated with narrow band-UVB (nb-UVB) for psoriasis. In some embodiments of the disclosed methods, regimens, uses, kits, and pharmaceutical compositions, the patient has not been previously treated with phototherapy for psoriasis. As used herein, the phrase “has been previously treated with phototherapy for psoriasis” refers to a psoriasis patient who has been previously treated with narrow band-UVB (nb-UVB) for psoriasis. In some embodiments of the disclosed methods, regimens, uses, kits, and pharmaceutical compositions, the patient has been previously treated with a systemic treatment for psoriasis.

As used herein, the phrases “has not been previously treated with a systemic treatment for psoriasis” and “naïve” refer to a psoriasis patient who has not been previously treated with a systemic agent, e.g., methotrexate, cyclosporine, a biological (e.g., ustekinumab, infliximab, TNF alpha inhibitors, etc.), etc., for psoriasis. Systemic agents (i.e., agents given orally, by injection, etc.) differ from local agents (e.g., topicals and phototherapy) in that systemic agents have a systemic (body-wide) effect when delivered to a patient. In some embodiments of the

disclosed methods, regimens, uses, kits, and pharmaceutical compositions, the patient has not been previously treated with a systemic treatment for psoriasis.

As used herein, the phrase “has been previously treated with a systemic treatment for psoriasis” is used to mean a patient that has previously undergone psoriasis treatment using a systemic agent. Such patients include those previously treated with a biological agent (i.e., a drug produced by a living organism, e.g., antibodies, receptor decoys, etc.), such as ustekinumab, a TNF alpha inhibitor (e.g., etanercept, adalimumab, remicade), an IL-17 antagonist (e.g., brodalumab, ixekizumab), etc., and those previously treated with non-biologics, such as methotrexate or cyclosporine. In some embodiments of the disclosed methods, regimens, uses, kits, and pharmaceutical compositions, the patient has been previously treated with phototherapy for psoriasis.

In some embodiments, the patient has been previously treated with a systemic agent for psoriasis (e.g., methotrexate, cyclosporine), but the patient has **not** been previously treated with a systemic biological agent for psoriasis (e.g., ustekinumab, ixekizumab, brodalumab, TNF alpha inhibitors (etanercept, adalimumab, remicade, etc.), secukinumab, etc.). In this case, the patient is referred to as “biological-naïve.” In preferred embodiments, the patient is biological-naïve.

As used herein, the term “TNF failure” refers to a patient who had an inadequate response to a TNF alpha antagonist (e.g., etanercept, adalimumab, remicade, etc.) or a patient who was intolerant to prior treatment with a TNF alpha antagonist. A patient who has been treated with a TNF antagonist, but who did not achieve a treatment goal (e.g., PASI 50 or PASI 75, in the case of a patient having psoriasis), is referred to as having had an inadequate response to a TNF alpha antagonist. A patient who responded adequately to prior treatment with a TNF alpha antagonist (i.e., the patient did achieve a treatment goal), but who discontinued due to a side effect, is referred to as being intolerant to prior treatment with a TNF alpha antagonist. TNF failures are also sometimes referred to as “TNF-IR” patients. In some embodiments, prior to administering the IL-17 antagonist, the patient is a TNF failure.

As used herein, “selecting” and “selected” in reference to a patient is used to mean that a particular patient is specifically chosen from a larger group of patients on the basis of (due to) the particular patient having a predetermined criteria. Similarly, “selectively treating” refers to providing treatment to a patient having a particular disease, where that patient is specifically chosen from a larger group of patients on the basis of the particular patient having a

predetermined criterion. Similarly, “selectively administering” refers to administering a drug to a patient that is specifically chosen from a larger group of patients on the basis of (due to) the particular patient having a predetermined criterion. By selecting, selectively treating and selectively administering, it is meant that a patient is delivered a personalized therapy based on the patient’s personal history (e.g., prior therapeutic interventions, e.g., prior treatment with biologics), biology (e.g., particular genetic markers), and/or manifestation (e.g., not fulfilling particular diagnostic criteria), rather than being delivered a standard treatment regimen based solely on the patient’s membership in a larger group. Selecting, in reference to a method of treatment as used herein, does not refer to fortuitous treatment of a patient having a particular criterion, but rather refers to the deliberate choice to administer treatment to a patient based on the patient having a particular criterion. Thus, selective treatment/administration differs from standard treatment/administration, which delivers a particular drug to all patients having a particular disease, regardless of their personal history, manifestations of disease, and/or biology. In some embodiments, the patient having chronic plaque-type psoriasis (e.g., moderate to severe chronic plaque-type psoriasis) is selected for treatment based on the patient being a TNF-failure, the patient having achieved PASI 75 following treatment (e.g., with administration extending to at least 48 weeks) with the IL-17 antibody or antigen-binding fragment thereof (e.g., secukinumab), the patient being biological-naïve, the patient being TNF-naïve, the patient having a low baseline PASI score (e.g., a baseline PASI score of ≤ 39 , ≤ 26 , < 25 , ≤ 23 , ≤ 22 , ≤ 21.4 , ≤ 21 , ≤ 20 , ≤ 19 , ≤ 15 , ≤ 10), and any combination thereof.

The following definitions are used according to Committee for medicinal products for human use (CHMP), European Medicines Agency for the Evaluation of Medicines for Human Use. (2004) Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis. CHMP/EWP/2454/02 corr document. London, UK:

- Treatment response (responder): Patients achieving $\geq 75\%$ improvement (reduction) in Psoriasis Area and Severity Index (PASI) score compared to baseline (also referred to as PASI 75) are defined as treatment responders.
- Partial response (partial responder): Patients achieving a $\geq 50\%$ improvement from baseline PASI score (also referred to as PASI 50) but less than 75% (also referred to as PASI 75) are defined as partial responders.

- Non response (non-responder): Patients achieving a PASI reduction of < 50% from baseline PASI score are defined as non-responders.
- Relapse (relapser): If patients loose >50% of the PASI gain achieved during the previous time in the study, patients will be regarded as having a “relapse”.
- Rebound (rebounder): Worsening of the value at baseline PASI (or new pustular, erythrodermic or more inflammatory psoriasis occurring within 8 weeks of stopping therapy), e.g., a PASI of > 125% of the value at baseline PASI.

In the PASI scoring system, the head, trunk, upper limbs and lower limbs are assessed separately for erythema, thickening (plaque elevation, induration), and scaling (desquamation) as defined in **Table 1**. The average degree of severity of each sign in each of the four body regions is assigned a score of 0 to 4. The area covered by lesions on each body region is estimated as a percentage of the total area of that particular body region. Because the head and neck, upper limbs, trunk and lower limbs correspond to approximately 10%, 20%, 30% and 40% of the body surface area, respectively, the PASI score is calculated using the formula:

$$\text{PASI} = 0.1(\text{EH}+\text{IH}+\text{DH})\text{AH} + 0.2(\text{EU}+\text{IU}+\text{DU})\text{AU} + 0.3(\text{ET}+\text{IT}+\text{DT})\text{AT} + 0.4(\text{EL}+\text{IL}+\text{DL})\text{AL}$$

Body Region	Erythema (E)	Thickening (I) (plaque levation, induration)	Scaling (D) (desquamation)	Area score (A) (based on true area %)*
Head and neck (H)	0 = none	0 = none	0 = none	0 = 0%
	1 = slight	1 = slight	1 = slight	1 = 1 – 9%
	2 = moderate	2 = moderate	2 = moderate	2 = 10 – 29%
	3 = severe	3 = severe	3 = severe	3 = 30 – 49%
	4 = very severe	4 = very severe	4 = very severe	4 = 50 – 69%
				5 = 70 – 89%
				6 = 90 – 100%
Upper limbs (U)	0 = none	0 = none	0 = none	0 = 0%
	1 = slight	1 = slight	1 = slight	1 = 1 – 9%
	2 = moderate	2 = moderate	2 = moderate	2 = 10 – 29%
	3 = severe	3 = severe	3 = severe	3 = 30 – 49%
	4 = very severe	4 = very severe	4 = very severe	4 = 50 – 69%
				5 = 70 – 89%
				6 = 90 – 100%
Trunk, axillae	0 = none	0 = none	0 = none	0 = 0%
	1 = slight	1 = slight	1 = slight	1 = 1 – 9%

Body Region	Erythema (E)	Thickening (I) (plaque levation, induration)	Scaling (D) (desquamation)	Area score (A) (based on true area %)*
and groin (T)	2 = moderate	2 = moderate	2 = moderate	2 = 10 – 29%
	3 = severe	3 = severe	3 = severe	3 = 30 – 49%
	4 = very severe	4 = very severe	4 = very severe	4 = 50 – 69%
				5 = 70 – 89%
				6 = 90 – 100%
Lower limbs and buttocks (L)	0 = none	0 = none	0 = none	0 = 0%
	1 = slight	1 = slight	1 = slight	1 = 1 – 9%
	2 = moderate	2 = moderate	2 = moderate	2 = 10 – 29%
	3 = severe	3 = severe	3 = severe	3 = 30 – 49%
	4 = very severe	4 = very severe	4 = very severe	4 = 50 – 69%
				5 = 70 – 89%
				6 = 90 – 100%

Table 1 – The PASI Scoring System

PASI scores can range from a lower value of 0, corresponding to no signs of psoriasis, up to a theoretic maximum of 72.0. PASI scores are specific to a tenth of a point, e.g., 9.0, 10.1, 14.2, 17.3, etc. Further information on PASI scoring is available in Henseler T, Schmitt-Rau K (2008) *Int. J. Dermatol.*; 47: 1019 – 1023. In a preferred example, patients are assessed using the PASI scoring system (physician assessed or patient assessed, preferably physician assessed). In some embodiments of the disclosed methods, kits, and uses, the patient achieves at least a 50% reduction of the Psoriasis Area and Severity Index Score (PASI 50) at week 12 of treatment. In some embodiments of the disclosed methods, kits, and uses, the patient achieves at least a 75% reduction of the Psoriasis Area and Severity Index Score (PASI 75) at week 12 of treatment. In some embodiments of the disclosed methods, kits, and uses, the patient achieves at least a 90% reduction of the Psoriasis Area and Severity Index Score (PASI 90) at week 12 of treatment. In some embodiments of the disclosed methods, kits, and uses, the patient achieves 100% reduction of the Psoriasis Area and Severity Index Score (PASI 100) at week 12 of treatment.

We have determined that, for patients switching from 300 mg secukinumab to placebo, those patients not relapsing for a minimum of 1 year after the last dose of secukinumab had baseline PASI scores of 12-38.7, and those patients not relapsing for a minimum of 2 years after the last dose of secukinumab had baseline PASI scores of 12-25.4. Thus, in some embodiments,

the patient has a baseline PASI score of ≤ 39 or ≤ 26 . In some embodiments, the patient has a baseline PASI score of ≤ 39 and the patient maintains at least 50% of the PASI improvement achieved between baseline and week 52 for at least 1 year after the last dose of the IL-17 antibody or antigen-binding fragment thereof. In some embodiments, the patient has a baseline PASI score of ≤ 26 and the patient maintains at least 50% of the PASI improvement achieved between baseline and week 52 for at least 2 years after the last dose of the IL-17 antibody or antigen-binding fragment thereof. In some embodiments, the patient has a baseline PASI score of ≤ 25 , ≤ 24 , ≤ 23 , ≤ 22 , ≤ 21.4 , ≤ 21 , ≤ 20 , ≤ 19 , ≤ 15 , or ≤ 12 . The term “baseline” refers to an initial score, e.g., PASI score. As used herein “PASI improvement” refers to the difference between a baseline score, e.g., PASI score, and a score, e.g., PASI score, at a later time point. For example, if a patient has a baseline PASI score of 12 and a PASI score of 2 at week 52, the PASI improvement is 10. If that patient maintains a PASI score of ≤ 7 ((50% of 10) + 2), he/she has maintained at least 50% of this PASI improvement. If that patient maintains a PASI score of ≤ 3 ((90% of 10) + 2) he/she has maintained at least 90% of this PASI improvement. A loss of over 50% PASI improvement is considered a relapse.

Psoriasis patient's response to treatment may be measured by other available scoring system, e.g., physician's assessed efficacy measures, such as visual assessment of index lesions, body surface measurement (BSA), clinical signs score: Total Severity Sign score (TSS), Physician's global assessment of improvement (PGA) or other global score (e.g., Investigators global assessment of improvement (IGA)); or patient's assessed efficacy measures, such as symptom improvement (pruritis, soreness), Patient's assessment of global improvement, Patient's assessment of PASI (self-administered PASI –SAPASI), or HRQL scales for dermatology (general scales, such as DLQI, DQOLS and specific psoriasis scales, such as PDI, PLSI)).

The plaque (also called “plaque-type”) psoriasis disease course begins with small skin plaques $\sim 1/8$ of an inch wide, typically in the same areas on opposite sides of the body. They grow slowly and develop into thick, dry plaques. If the plaque is scratched or scraped, bleeding spots the sizes of pinheads appear underneath. This is known as the Auspitz sign. Some patches become annular, with a clear center and scaly raised borders. Eventually, separate patches join together to form larger areas. In some cases, the patches cover wide areas of the back or chest, termed geographic plaques. As used herein, the phrase “slowing psoriasis disease progression”

means decelerating the advancement rate of the disease course of plaque-type psoriasis. In some embodiments of the disclosure, treatment with the IL-17 antagonist (e.g., secukinumab) slows psoriasis disease progression.

Long term treatment of patients having chronic plaque-type psoriasis using an IL-17 antagonist (e.g., IL-17 antibody, like secukinumab) changes the underlying cellular pathology of psoriasis, e.g., by reducing tissue resident memory T-cells in the skin, reducing subset effector T-cells producing interleukin -17 (IL-17) and/or interleukin -22 (IL-22) in the skin, reducing regulatory T cells in the skin, and reducing dermal dendritic cell-T cell aggregates in the skin (e.g., reducing cell-mediated immunity in the skin, reducing T-cell-mediated immune response in the skin), etc. The phrase “modifying the psoriasis disease course” refers to changing the underlying cellular pathology of psoriasis which leads to change in the course of the disease (clinical presentation). We have determined that patients whose psoriasis disease course has been modified are capable of maintaining low PASI levels (e.g., ≤ 11.2 [e.g., ranging from 0.3 to 11.2], ≤ 7.2 [ranging from 0.3 to 7.2], ≤ 5.0 , ≤ 4.0 , ≤ 3.3 , ≤ 3.0 , ≤ 1 , etc.) after the last dose of the IL-17 antagonist (e.g., IL-17 antibody, like secukinumab). In some embodiments, the patient is capable of maintaining a PASI score of ≤ 11.2 for at least six months or at least one year after the last dose of the IL-17 antibody or antigen-binding fragment thereof. In some embodiments, the patient is capable of maintaining a PASI score of ≤ 7.2 for at least 6 months, at least one year, or at least two years after the last dose of the IL-17 antibody or antigen-binding fragment thereof. In some embodiments of the disclosure, the patient is capable of maintaining at least 50% of the PASI improvement (preferably at least 90% of the PASI improvement) achieved between baseline and treatment withdrawal (e.g., the last dose being given at week 48, week 100, week 204, 3 years, 5 years, 7 years, 10 years, 12 years, 15 year) after the last dose of the IL-17 antibody or antigen-binding fragment thereof. In some embodiments of the disclosure, the patient is capable of maintaining at least 50% of the PASI improvement (preferably at least 75% of the PASI improvement) achieved between baseline and treatment withdrawal (e.g., the last dose being given at week 48, week 100, week 204, 3 years, 5 years, 7 years, 10 years, 12 years, 15 year) after the last dose of the IL-17 antibody or antigen-binding fragment thereof. In some embodiments of the disclosure, the patient is capable of maintaining at least 50% of the PASI improvement (preferably at least 90% of the PASI improvement) achieved between baseline and treatment withdrawal (e.g., the last dose being given at week 48, week 100, week 204, 3 years, 5

years, 7 years, 10 years, 12 years, 15 year) for at least 6 months, at least 1 year, or at least 2 years (preferably at least 2 years) after the last dose of the IL-17 antibody or antigen-binding fragment thereof.

As used herein, the phrase “psoriasis flare” comprises the manifestation of plaque-type psoriasis, including plaques, irritated patches of skin, redness (e.g., particularly on elbows, knees, trunk and scalp), changes and/or disfiguration in nails, dandruff, and any combination thereof. Typically, a psoriasis flare includes the formation of psoriasis plaques. In some embodiments of the disclosure, treatment with the IL-17 antagonist (e.g., secukinumab) prevents psoriasis flares, decreases the severity of psoriasis flares, and/or decreases the frequency of psoriasis flares.

As used herein, the phrase “decreasing the severity of psoriasis flares” and the like means reducing the intensity of a psoriasis flare, e.g., reducing the percentage of skin affected by psoriasis, reducing the intensity of a particular flare component (e.g., reducing the number, size, thickness, etc. of plaques, reducing the extent of skin irritation, reducing scaling, reducing erythema, reducing changes and/or disfigurations in nails, reducing dandruff, etc.), and/or reducing the amount of time a flare (or component thereof) persists. The severity of a flare may be measured using various tools, e.g., the body surface area (BSA) test, the investigator’s global assessment (IGA, IGA mod 2011), physicians global assessment (PGA), the psoriasis area and severity index (PASI), and patient reported outcomes, e.g., the Dermatology life quality index (DLQI) and the Work productivity and activity impairment questionnaire: psoriasis (WPAI:PSO).

As used herein, the phrase “decreasing the frequency of psoriasis flares” and the like means reducing the incidence of psoriasis flares, e.g., reducing the incidence of plaques and/or other psoriasis flare components (e.g., plaques, skin irritation, scaling, erythema, changes in nails, dandruff, etc.). By decreasing the frequency of psoriasis flares, a patient will experience fewer psoriasis relapses. The incidence of flares may be assessed by monitoring a patient over time to determine if the prevalence of flares decreases.

As used herein, the phrase “preventing psoriasis flares” means eliminating future psoriasis flares and/or flare components.

Numerous psoriasis patients eventually progress to PsA. Extended long-term treatment (e.g., at least 48 weeks) with an IL-17 antagonist (e.g., an IL-17 antibody, like secukinumab) is expected to decrease the likelihood that patients treated long-term with that IL-17 antagonist will

develop PsA, cardiovascular disease, metabolic syndrome (diabetes mellitus, obesity), and other conditions. As used herein, the phrase “decreasing the likelihood that a psoriasis patient will develop psoriatic arthritis” refers to a reduction in the probability that a psoriasis patient will develop psoriatic arthritis. As used herein, the phrase “delaying the onset of psoriatic arthritis in a psoriasis patient” refers to postponing development of the signs and symptoms, and/or structural damage associated with PsA in a psoriasis patient. As used herein, the phrase “preventing progression from psoriasis to psoriatic arthritis in a psoriasis patient” refers to inhibiting the development of PsA in a psoriasis patient.

As used herein “mild psoriasis” is defined as psoriasis disease in which body surface area (BSA) ≤ 10 and psoriasis area and severity index (PASI) < 10 and dermatology life quality index (DLQI) ≤ 10 . As used herein, “moderate to severe psoriasis” is defined as psoriasis disease in which (BSA > 10 or PASI > 10) and DLQI > 10 . *See* Mrowietz et al. (2011) Arch Dermatol Res. 303(1):1-10. In some embodiments of the disclosed methods, uses and kits, the patient has mild psoriasis. In some embodiments of the disclosed methods, uses and kits, the patient has moderate to severe psoriasis. In some embodiments of the disclosed methods, uses and kits, long-term treatment with the IL-17 antagonist (e.g., IL-17 antibody, such as secukinumab) patient converts from having moderate to severe psoriasis to having mild psoriasis due to a modification of the psoriasis disease course.

In a preferred embodiment, the methods and uses disclosed herein provide treatment of moderate to severe chronic plaque-type psoriasis in adult patients who are candidates for systemic therapy (or phototherapy). In some embodiments, that adult patient has a BSA $\geq 5\%$, preferably a BSA $\geq 3\%$.

IL-17 Antagonists

The various disclosed processes, kits, uses and methods utilize an IL-17 antagonist, e.g., IL-17 binding molecule (e.g., soluble IL-17 receptor, IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 receptor antibody or antigen-binding fragment thereof). In some embodiments, the IL-17 antagonist is an IL-17 binding molecule, preferably an IL-17 antibody or antigen-binding fragment thereof.

In one embodiment, the IL-17 antibody or antigen-binding fragment thereof comprises at least one immunoglobulin heavy chain variable domain (V_H) comprising hypervariable regions

CDR1, CDR2 and CDR3, said CDR1 having the amino acid sequence SEQ ID NO:1, said CDR2 having the amino acid sequence SEQ ID NO:2, and said CDR3 having the amino acid sequence SEQ ID NO:3. In one embodiment, the IL-17 antibody or antigen-binding fragment thereof comprises at least one immunoglobulin light chain variable domain (V_L) comprising hypervariable regions CDR1', CDR2' and CDR3', said CDR1' having the amino acid sequence SEQ ID NO:4, said CDR2' having the amino acid sequence SEQ ID NO:5 and said CDR3' having the amino acid sequence SEQ ID NO:6. In one embodiment, the IL-17 antibody or antigen-binding fragment thereof comprises at least one immunoglobulin heavy chain variable domain (V_H) comprising hypervariable regions CDR1-x, CDR2-x and CDR3-x, said CDR1-x having the amino acid sequence SEQ ID NO:11, said CDR2-x having the amino acid sequence SEQ ID NO:12, and said CDR3-x having the amino acid sequence SEQ ID NO:13.

In one embodiment, the IL-17 antibody or antigen-binding fragment thereof comprises at least one immunoglobulin V_H domain and at least one immunoglobulin V_L domain, wherein: a) the immunoglobulin V_H domain comprises (e.g., in sequence): i) hypervariable regions CDR1, CDR2 and CDR3, said CDR1 having the amino acid sequence SEQ ID NO:1, said CDR2 having the amino acid sequence SEQ ID NO:2, and said CDR3 having the amino acid sequence SEQ ID NO:3; or ii) hypervariable regions CDR1-x, CDR2-x and CDR3-x, said CDR1-x having the amino acid sequence SEQ ID NO:11, said CDR2-x having the amino acid sequence SEQ ID NO:12, and said CDR3-x having the amino acid sequence SEQ ID NO:13; and b) the immunoglobulin V_L domain comprises (e.g., in sequence) hypervariable regions CDR1', CDR2' and CDR3', said CDR1' having the amino acid sequence SEQ ID NO:4, said CDR2' having the amino acid sequence SEQ ID NO:5, and said CDR3' having the amino acid sequence SEQ ID NO:6.

In one embodiment, the IL-17 antibody or antigen-binding fragment thereof comprises: a) an immunoglobulin heavy chain variable domain (V_H) comprising the amino acid sequence set forth as SEQ ID NO:8; b) an immunoglobulin light chain variable domain (V_L) comprising the amino acid sequence set forth as SEQ ID NO:10; c) 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; d) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3; e) an immunoglobulin V_L domain comprising the hypervariable regions set forth as

SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; f) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13; g) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; or h) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6.

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 2**, below.

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 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)

Table 2: Amino acid sequences of the hypervariable regions of secukinumab.

In preferred embodiments, the constant region domains also comprise suitable human constant region domains, for instance as described in "Sequences of Proteins of Immunological Interest", Kabat E.A. et al, US Department of Health and Human Services, Public Health Service, National Institute of Health. The DNA encoding the VL of secukinumab is set forth in SEQ ID NO:9. The DNA encoding the V_H of secukinumab is set forth in SEQ ID NO:7.

In some embodiments, the IL-17 antibody or antigen-binding fragment thereof (e.g., secukinumab) comprises the three CDRs of SEQ ID NO:10. In other embodiments, the IL-17 antibody or antigen-binding fragment thereof comprises the three CDRs of SEQ ID NO:8. In other embodiments, the IL-17 antibody or antigen-binding fragment thereof 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 may be found in **Table 2**. The free cysteine in the light chain (CysL97) may be seen in SEQ ID NO:6.

In some embodiments, IL-17 antibody or antigen-binding fragment thereof comprises the light chain of SEQ ID NO:14. In other embodiments, the IL-17 antibody or antigen-binding fragment thereof comprises the heavy chain of SEQ ID NO:15. In other embodiments, the IL-17 antibody or antigen-binding fragment thereof comprises the light chain of SEQ ID NO:14 and the heavy domain of SEQ ID NO:15. In some embodiments, the IL-17 antibody or antigen-binding fragment thereof comprises the three CDRs of SEQ ID NO:14. In other embodiments, IL-17 antibody or antigen-binding fragment thereof comprises the three CDRs of SEQ ID NO:15. In other embodiments, the IL-17 antibody or antigen-binding fragment thereof

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 may be found in **Table 2**.

Hypervariable regions may be associated with any kind of framework regions, though preferably are of human origin. Suitable framework regions are described in Kabat E.A. et al, *ibid*. The preferred heavy chain framework is a human heavy chain framework, for instance that of the secukinumab antibody. It consists in sequence, e.g. 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, another preferred 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.

In one embodiment, the IL-17 antibody or antigen-binding fragment thereof (e.g., secukinumab) is selected from a human IL-17 antibody that comprises at least: a) an immunoglobulin heavy chain or fragment thereof which comprises a variable domain comprising, in sequence, the hypervariable regions CDR1, CDR2 and CDR3 and the constant part or fragment thereof of a human heavy chain; said CDR1 having the amino acid sequence SEQ ID NO:1, said CDR2 having the amino acid sequence SEQ ID NO:2, and said CDR3 having the amino acid sequence SEQ ID NO:3; and b) an immunoglobulin light chain or fragment thereof which comprises a variable domain comprising, in sequence, the hypervariable regions CDR1', CDR2', and CDR3' and the constant part or fragment thereof of a human light chain, said CDR1' having the amino acid sequence SEQ ID NO:4, said CDR2' having the amino acid sequence SEQ ID NO:5, and said CDR3' having the amino acid sequence SEQ ID NO:6.

In one embodiment, the IL-17 antibody or antigen-binding fragment thereof is selected from a single chain antibody or antigen-binding fragment thereof that comprises an antigen-binding site comprising: a) a first domain comprising, in sequence, the hypervariable regions CDR1, CDR2 and CDR3, said CDR1 having the amino acid sequence SEQ ID NO:1, said CDR2 having the amino acid sequence SEQ ID NO:2, and said CDR3 having the amino acid sequence

SEQ ID NO:3; and b) a second domain comprising, in sequence, the hypervariable regions CDR1', CDR2' and CDR3', said CDR1' having the amino acid sequence SEQ ID NO:4, said CDR2' having the amino acid sequence SEQ ID NO:5, and said CDR3' having the amino acid sequence SEQ ID NO:6; and c) a peptide linker which is bound either to the N-terminal extremity of the first domain and to the C-terminal extremity of the second domain or to the C-terminal extremity of the first domain and to the N-terminal extremity of the second domain.

Alternatively, an IL-17 antibody or antigen-binding fragment thereof as used in the disclosed methods may comprise a derivative of the IL-17 antibodies set forth herein by sequence (e.g., a pegylated version of secukinumab). Alternatively, the V_H or V_L domain of an IL-17 antibody or antigen-binding fragment thereof used in the disclosed methods may have V_H or V_L domains that are substantially identical to the V_H or V_L domains set forth herein (e.g., those set forth in SEQ ID NO:8 and 10). A human IL-17 antibody disclosed herein may comprise a heavy chain that is substantially identical to that set forth as SEQ ID NO:15 and/or a light chain that is substantially identical to that set forth as SEQ ID NO:14. A human IL-17 antibody disclosed herein may comprise a heavy chain that comprises SEQ ID NO:15 and a light chain that comprises SEQ ID NO:14. A human IL-17 antibody disclosed herein may comprise: a) a heavy chain which comprises a variable domain having an amino acid sequence substantially identical to that shown in SEQ ID NO:8 and the constant part of a human heavy chain; and b) a light chain which comprises a variable domain having an amino acid sequence substantially identical to that shown in SEQ ID NO:10 and the constant part of a human light chain.

Alternatively, an IL-17 antibody or antigen-binding fragment thereof used in the disclosed methods may be an amino acid sequence variant of the reference IL-17 antibodies set forth herein, as long as it contains CysL97. The disclosure also includes IL-17 antibodies or antigen-binding fragments thereof (e.g., secukinumab) in which one or more of the amino acid residues of the V_H or V_L domain of secukinumab (but not CysL97), typically only a few (e.g., 1-10), are changed; for instance by mutation, e.g., site directed mutagenesis of the corresponding DNA sequences. In all such cases of derivative and variants, the IL-17 antibody or antigen-binding fragment thereof is capable of inhibiting the activity of about 1 nM (= 30 ng/ml) human IL-17 at a concentration of about 50 nM or less, about 20 nM or less, about 10 nM or less, about 5 nM or less, about 2 nM or less, or more preferably of about 1 nM or less of said molecule by 50%, said inhibitory activity being measured on IL-6 production induced by hu-IL-17 in human

dermal fibroblasts as described in Example 1 of WO 2006/013107.

In some embodiments, the IL-17 antibodies or antigen-binding fragments thereof, e.g., secukinumab, bind to an epitope of mature human IL-17 comprising Leu74, Tyr85, His86, Met87, Asn88, Val124, Thr125, Pro126, Ile127, Val128, His129. In some embodiments, the IL-17 antibody, e.g., secukinumab, binds to an epitope of mature human IL-17 comprising Tyr43, Tyr44, Arg46, Ala79, Asp80. In some embodiments, the IL-17 antibody, e.g., 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 determined by a Biacore® assay). 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 (SC) administered IL-17 antibody has a range of about 60 – about 80%, e.g., about 76%. In some embodiments, the IL-17 antibody, such as 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, the IL-17 antibody (such as secukinumab) has a T_{max} of about 7-8 days.

Particularly preferred IL-17 antibodies or antigen-binding fragments thereof used in the disclosed methods are human antibodies, especially secukinumab as described in Examples 1 and 2 of WO 2006/013107. 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 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.

Other preferred IL-17 antibodies for use in the disclosed methods, kits and regimens are those set forth in US Patent Nos: 8,057,794; 8,003,099; 8,110,191; and 7,838,638 and US Published Patent Application Nos: 20120034656 and 20110027290, which are incorporated by reference herein in their entirety.

Methods of Treatment and Uses of IL-17 Antagonists for Chronic Plaque-Type Psoriasis

The disclosed IL-17 antagonists, e.g., IL-17 binding molecules (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g., IL-17 receptor antibody or antigen-binding fragment thereof), may be used *in vitro*, *ex vivo*, or incorporated into pharmaceutical compositions and administered *in vivo* to treat chronic plaque-type psoriasis patients (e.g., human patients).

The IL-17 antagonists, e.g., IL-17 binding molecules (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g., IL-17 antibody or antigen-binding fragment thereof), may be used as a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. Such a composition may contain, in addition to an IL-17 antagonist, carriers, various diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The characteristics of the carrier will depend on the route of administration. The pharmaceutical compositions for use in the disclosed methods may also contain additional therapeutic agents for treatment of the particular targeted disorder. For example, a pharmaceutical composition may also include anti-inflammatory agents. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with the IL-17 binding molecules, or to minimize side effects caused by the IL-17 antagonists, e.g., IL-17 binding molecules (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g., IL-17 antibody or antigen-binding fragment thereof).

Pharmaceutical compositions for use in the disclosed methods may be manufactured in conventional manner. In one embodiment, the pharmaceutical composition is provided in lyophilized form. For immediate administration it is dissolved in a suitable aqueous carrier, for example sterile water for injection or sterile buffered physiological saline. If it is considered

desirable to make up a solution of larger volume for administration by infusion rather than a bolus injection, may be advantageous to incorporate human serum albumin or the patient's own heparinized blood into the saline at the time of formulation. The presence of an excess of such physiologically inert protein prevents loss of antibody by adsorption onto the walls of the container and tubing used with the infusion solution. If albumin is used, a suitable concentration is from 0.5 to 4.5% by weight of the saline solution. Other formulations comprise liquid or lyophilized formulation.

Antibodies, e.g., antibodies to IL-17, are typically formulated either in aqueous form ready for parenteral administration or as lyophilisates for reconstitution with a suitable diluent prior to administration. In some embodiments of the disclosed methods and uses, the IL-17 antagonist, e.g., IL-17 antibody, e.g., secukinumab, is formulated as a lyophilisate. Suitable lyophilisate formulations can be reconstituted in a small liquid volume (e.g., 2ml or less, e.g., 1 ml) to allow subcutaneous administration and can provide solutions with low levels of antibody aggregation. The use of antibodies as the active ingredient of pharmaceuticals is now widespread, including the products HERCEPTIN™ (trastuzumab), RITUXAN™ (rituximab), SYNAGIS™ (palivizumab), etc. Techniques for purification of antibodies to a pharmaceutical grade are well known in the art. When a therapeutically effective amount of an IL-17 antagonist, e.g., IL-17 binding molecules (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g., IL-17 antibody or antigen-binding fragment thereof) is administered by intravenous, cutaneous or subcutaneous injection, the IL-17 antagonist will be in the form of a pyrogen-free, parenterally acceptable solution. A pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection may contain, in addition to the IL-17 antagonist, an isotonic vehicle such as sodium chloride, Ringer's solution, dextrose, dextrose and sodium chloride, lactated Ringer's solution, or other vehicle as known in the art.

The appropriate dosage will vary depending upon, for example, the particular IL-17 antagonists, e.g., IL-17 binding molecules (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g., IL-17 antibody or antigen-binding fragment thereof) to be employed, 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-

IL-17 antagonist with which to treat each individual patient. In some embodiments, the attending health care provider may administer low doses of the IL-17 antagonist and observe the patient's response. In other embodiments, the initial dose(s) of IL-17 antagonist administered to a patient are high, and then are titrated downward until signs of relapse occur. Larger doses of the IL-17 antagonist may be administered until the optimal therapeutic effect is obtained for the patient, and the dosage is not generally increased further.

In practicing some of the methods of treatment or uses of the present disclosure, a therapeutically effective amount of an IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 antibody or antigen-binding fragment thereof) is administered to a patient, e.g., a mammal (e.g., a human). While it is understood that the disclosed methods provide for treatment of chronic plaque-type psoriasis patients using an IL-17 antagonist (e.g., secukinumab), this does not preclude that, if the patient is to be ultimately treated with an IL-17 antagonist, such IL-17 antagonist therapy is necessarily a monotherapy. Indeed, if a patient is selected for treatment with an IL-17 antagonist, then the IL-17 antagonist (e.g., secukinumab) may be administered in accordance with the methods of the disclosure either alone or in combination with other agents and therapies for treating chronic plaque-type psoriasis patients, e.g., in combination with at least one additional psoriasis agent. When coadministered with one or more additional psoriasis agent(s), an IL-17 antagonist may be administered either simultaneously with the other agent, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering the IL-17 antagonist in combination with other agents and the appropriate dosages for co-delivery.

Various therapies may be beneficially combined with the disclosed IL-17 antibodies, such as secukinumab, during treatment of chronic plaque psoriasis and the other disorders disclosed herein. Such therapies include topicals (over the counter, non-steroidal compounds, and steroidal compound), phototherapy and systemic treatment (e.g., with biologicals or chemical entities).

Non-limiting examples of topical psoriasis agents for use with the disclosed IL-17 antibodies, such as secukinumab, include salicylic acid, coal tar, Dovonex® (calcipotriene), Taclonex® (calcipotriene and betamethasone dipropionate), Tazorec® (tazarotene), pimecrolimus, tacrolimus, Vectical® (calcitriol), Zithranol-RR® (anthralin) and topical steroids

(e.g., corticosteroids).

Examples of phototherapy for use with the disclosed IL-17 antibodies, such as secukinumab, include treatment with psoralen + UVA (PUVA) or treatment with UVB (with or without tar).

Examples of psoriasis agents used in systemic treatment for use with the disclosed IL-17 antibodies, such as secukinumab, include retinoids such as Acitretin (e.g., Soriatane®), cyclosporine, methotrexate, hydroxyurea (e.g., Hydrea®), isotretinoin, 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.

Additional psoriasis agents for use in combination with the disclosed IL-17 antibodies, such as secukinumab, during treatment of psoriasis include apremilast, mometasone, voclosporin, ketokonazol, Neuroskin Forte, recombinant human interleukin-10, voclosporin, MK-3222, tofacitinib, VX-765, MED-I545, fluphenazine decanoate, acetaminophen, bimosiamose cream, doxycycline, vancomycin, AbGn168, Vitamin D3, RO5310074, fludarabine, Calcipotriol and hydrocortisone (LEO 80190), LE80185 (Taclonex® Scalp topical suspension/Xamiol® gel), Focetria (Monovalent MF59-Adjuvanted vaccine, tgAAC94 gene therapy vector, Apremilast, Capsaicin, Psirelax, ABT-874 (anti IL-12), IDEC-114, MEDI-522, INCB018424 phosphate cream, LE29102, BMS 587101, CD 2027, CRx-191, 8-methoxypsoralen or 5-methoxypsoralen, Bicillin L-A, LY2525623, INCB018424, LY2439821, CEP-701, CC-10004, certolizumab (CZP), GW786034 (pazopanib), doxycycline Curcuminoids C3 Complex, NYC 0462, RG3421, hOKT3gamma1(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, AMG 714, AMG 139, PTH (1-34), U0267 Foam, CNTO 1275, QRX-101, CNTO 1959, LEO 22811, Imiquimod, CTLA4Ig, Alga Dunaliella Bardawil, AS101 Cream, pioglitazone, pimecrolimus, ranibizumab, Zidovudine CDP870 (Certolizumab pegol), Onercept (r-hTBP-1), ACT-128800, 4,4-dimethyl-benziso-2H-selenazine, CRx-191, CRx-197, doxercalciferol, LEO 19123 Cream (calcipotriol plus LEO

80122), 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, INCB018424 Phosphate Cream, Xamiol gel, 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, Psoralait, Clobetasol propionate, botulinum toxin type A, alefacept, erlotinib, BCT194, Ultravate Ointment, Roflumilast, CNTO 1275, halobetasol, ILV-094, CTA018 cream, COL-121, MEDI-507, AEB071. Additional agents for use in combination with secukinumab during treatment of psoriasis include IL-6 antagonists, CD20 antagonists, CTLA4 antagonists, IL-17 antagonists, IL-8 antagonists, IL-21 antagonists, IL-22 antagonist, VEGF antagonists, CXCL antagonists, MMP antagonists, defensin antagonists, IL-1beta antagonists, and IL-23 antagonists (e.g., receptor decoys, antagonistic antibodies, etc.). A skilled artisan will be able to discern the appropriate dosages of the above agents for co-delivery with the disclosed IL-17 antibodies, such as secukinumab.

An IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 receptor antibody or antigen-binding fragment thereof) is conveniently administered parenterally, e.g., intravenously (e.g., into the antecubital or other peripheral vein), intramuscularly, or subcutaneously. The duration of intravenous (IV) therapy using a pharmaceutical composition of the present disclosure will vary, depending on the severity of the disease being treated and the condition and personal response of each individual patient. Also contemplated is subcutaneous (SC) therapy using a pharmaceutical composition of the present disclosure. The health care provider will decide on the appropriate duration of IV or SC therapy and the timing of administration of the therapy, using the pharmaceutical composition of the present disclosure.

Preferred dosing and treatment regimens (including both induction and maintenance regimens) for treating chronic plaque-type psoriasis are provided in PCT Application No. PCT/US2011/064307 and PCT/IB2014/063902, which are incorporated by reference herein in their entirety.

The IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 receptor antibody or antigen-binding fragment thereof) may be administered to the patient

intravenously (IV), e.g., at about 10 mg/kg every other week during week 0, 2, and 4 and thereafter administered to the patient subcutaneously (SC), e.g., at about 75 mg – about 300 mg (e.g., about 150 mg, about 300 mg) monthly, beginning during week 8. In this manner, the patient may be dosed IV with about 10 mg/kg during week 0, 2, 4, and then the patient is dosed SC with about 150 mg – about 300 mg (e.g., about 150 mg, about 300 mg) of the IL-17 antagonist (e.g., secukinumab) during week 8, 12, 16, 20, etc.

The IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 receptor antibody or antigen-binding fragment thereof) may be administered to the patient SC, e.g., at about 150 mg – about 300 mg (e.g., about 150 mg, about 300 mg) weekly during weeks 0, 1, 2, and 3, and thereafter administered to the patient SC, e.g., at about 150 mg – about 300 mg (e.g., about 150 mg, about 300 mg) monthly, beginning during week 4. In this manner, the patient is dosed SC with about 150 mg – about 300 mg (e.g., about 150 mg, about 300 mg) of the IL-17 antagonist (e.g., secukinumab) during weeks 0, 1, 2, 3, 4, 8, 12, 16, 20, etc.

Alternatively, the IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 receptor antibody or antigen-binding fragment thereof) may be administered to the patient without a loading regimen, e.g., the antagonist may be administered to the patient SC at about 150 mg – about 300 mg (e.g., about 150 mg, about 300 mg) every 4 weeks (monthly). In this manner, the patient is dosed SC with about 150 mg – about 300 mg (e.g., about 75 mg, about 150 mg, about 300 mg) of the IL-17 antagonist (e.g., secukinumab) during weeks 0, 4, 8, 12, 16, 20, etc.

It will be understood that dose escalation may be required for certain patients, e.g., patients that display inadequate response to treatment with the IL-17 antagonists, e.g., IL-17 binding molecules (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g., IL-17 receptor antibody or antigen-binding fragment thereof). Thus, SC dosages of secukinumab may be greater than about 150 mg to about 300 mg SC, e.g., about 175 mg, about 200 mg, about 250 mg, about 350 mg, about 400 mg, about 450 mg, etc.; similarly, IV dosages may be greater than about 10 mg/kg, e.g., about 11 mg/kg, 12 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, etc. It will also be understood that dose reduction may also be required for certain patients, e.g., patients that display adverse events

or an adverse response to treatment with the IL-17 antagonist (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab). Thus, dosages of the IL-17 antagonist (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab), may be less than about 150 mg to about 300 mg SC, e.g., about 80 mg, about 100 mg, about 125 mg, about 175 mg, about 200 mg, 250 mg, etc.; similarly, IV dosages may be less than about 10 mg/kg, e.g., about 9 mg/kg, 8 mg/kg, 5 mg/kg, 4 mg/kg, 3 mg/kg, 2 mg/kg, 1 mg/kg, etc. In some embodiments, the IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 receptor antibody or antigen-binding fragment thereof) may be administered to the patient at an initial dose of 150 mg or 300 mg delivered SC, and the dose is then escalated to about 450 mg if needed, as determined by a physician.

In some embodiment of the disclosed methods, uses and kits, after induction phase (typically the first 16 weeks of treatment, but extendable until week 24 depending on the type of drug and dose regimen used) and during maintenance therapy, treatment can be continued unchanged if reduction in PASI is $\geq 75\%$. The treatment regimen can be modified (e.g., increased dose [e.g., from 150 mg to 300 mg, or from 300 mg to 400 mg or 450 mg] or frequency [e.g., from every 4 weeks to every 3 weeks or every 2 weeks]) if improvement of PASI is $< 50\%$. In a situation where the therapeutic response improved $\geq 50\%$ but $< 75\%$, as assessed by PASI, therapy can be modified if the DLQI is > 5 but can be continued if the DLQI is ≤ 5 . See Mrowietz et al. (2011) Arch Dermatol Res. 303(1):1-10.

The timing of dosing is generally measured from the day of the first dose of of the IL-17 antibody (e.g., secukinumab) (which is also known as “baseline”). However, health care providers often use different naming conventions to identify dosing schedules, as shown in

Table 3.

Week	0/1	1/2	2/3	3/4	4/5	5/6	6/7	7/8	8/9	9/10	10/11	etc
1 st day of week	0/1	7/8	14/15	21/22	28/29	35/36	42/43	49/50	56/57	63/64	70/71	etc.

Table 3: Common naming conventions for dosing regimens. Bolded items refer to the naming convention used herein.

Notably, “week zero” may be referred to as “week one” 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 convenience and should not be construed as limiting, i.e., weekly dosing is the provision of a weekly dose of the IL-17 antibody regardless of whether the physician refers to a particular week as “week 1” or “week 2”. Moreover, in a preferred dosing regimen, the antibody is administered during week 0, 1, 2, 3, 4 8, 12, 16, 20, etc. Some providers may refer to this regimen as weekly for five weeks and then monthly (or every 4 weeks) thereafter, beginning during week 8, while others may refer to this regimen as weekly for four weeks and then monthly (or every 4 weeks) thereafter, beginning during week 4. Thus, it will be appreciated by a skilled artisan that administering a patient an injection at weeks 0, 1, 2 and 3, followed by once monthly dosing starting at week 4 is the same as: 1) administering the patient an injection at weeks 0, 1, 2, 3, and 4, followed by once monthly dosing starting at week 8; 2) administering the patient an injection at weeks 0, 1, 2, 3 and 4 followed by dosing every 4 weeks; and 3) administering the patient an injection at weeks 0, 1, 2, 3 and 4 followed by monthly administration.

Disclosed herein are methods of, and IL-17 antagonists for use in, slowing psoriasis disease progression in a patient having chronic plaque-type psoriasis, decreasing the severity of psoriasis flares in a patient having chronic plaque-type psoriasis, decreasing the frequency of psoriasis flares in a patient having chronic plaque-type psoriasis, preventing psoriasis flares in a patient having chronic plaque-type psoriasis, and/or changing the natural course of the psoriasis disease to a milder state in a patient having chronic plaque-type psoriasis, comprising administering the patient a dose of about 150 mg - about 300 mg of an IL-17 antibody or antigen-binding fragment thereof by subcutaneous injection at weeks 0, 1, 2, 3, and 4, followed by once monthly dosing extending to at least 48 weeks, wherein the patient is capable of

maintaining at least 50% (preferably at least 75%, more preferably at least 90%) of the PASI improvement achieved between baseline and week 52 for at least 6 months (preferably at least 1 year, more preferably at least 2 years) after the last dose of the IL-17 antibody or antigen-binding fragment thereof, and further wherein the IL-17 antibody or antigen-binding fragment thereof binds to an epitope of an IL-17 homodimer having two mature human IL-17 protein 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, wherein the IL-17 antibody or antigen-binding fragment thereof has a K_D of about 100-200 pM.

Additionally disclosed herein are methods of, and IL-17 antagonists for use in, modifying the psoriasis disease course in a patient having chronic plaque-type psoriasis, comprising: a) administering the patient a dose of about 150 mg - about 300 mg of an IL-17 antibody or antigen-binding fragment thereof by subcutaneous injection at weeks 0, 1, 2, 3, and 4, followed by once monthly dosing extending to at least 48 weeks, and b) thereafter, withdrawing treatment of the IL-17 antibody or antigen-binding fragment thereof, wherein the patient maintains at least 50% (preferably at least 75%, more preferably at least 90%) of the PASI improvement achieved between baseline and week 52 for at least 6 months (preferably at least 1 year, more preferably at least 2 years) after the last dose of the IL-17 antibody or antigen-binding fragment thereof, wherein the IL-17 antibody or antigen-binding fragment thereof binds to an epitope of an IL-17 homodimer having two mature human IL-17 protein 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, wherein the IL-17 antibody or antigen-binding fragment thereof has a K_D of about 100-200 pM, and wherein the IL-17 antibody or antigen-binding fragment thereof has an *in vivo* half-life of about 4 weeks.

Additionally disclosed herein are methods of, and IL-17 antagonists for use in, modifying the psoriasis disease course in a patient having chronic plaque-type psoriasis, comprising administering the patient a dose of about 150 mg - about 300 mg of an IL-17 antibody or antigen-binding fragment thereof by subcutaneous injection at weeks 0, 1, 2, 3, and 4, followed by once monthly dosing extending to at least 48 weeks, wherein the patient is capable of maintaining at least 50% (preferably at least 75%, more preferably at least 90%) of the PASI improvement achieved between baseline and week 52 for at least 6 months (preferably at least 1 year, more preferably at least 2 years) after the last dose of the IL-17 antibody or antigen-binding

fragment thereof, wherein the IL-17 antibody or antigen-binding fragment thereof binds to an epitope of an IL-17 homodimer having two mature human IL-17 protein 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, wherein the IL-17 antibody or antigen-binding fragment thereof has a K_D of about 100-200 pM, and wherein the IL-17 antibody or antigen-binding fragment thereof has an *in vivo* half-life of about 4 weeks.

Additionally disclosed herein are methods of, and IL-17 antagonists for use in, decreasing the likelihood that a psoriasis patient will develop psoriatic arthritis, delaying the onset of psoriatic arthritis in a psoriasis patient, and preventing progression from psoriasis to psoriatic arthritis in a psoriasis patient, comprising administering the patient a dose of about 150 mg - about 300 mg of an IL-17 antibody or antigen-binding fragment thereof by subcutaneous injection at weeks 0, 1, 2, 3, and 4, followed by once monthly dosing extending to at least 48 weeks, wherein the patient is capable of maintaining at least 50% (preferably at least 75%, more preferably at least 90%) of the PASI improvement achieved between baseline and week 52 for at least 6 months (preferably at least 1 year, more preferably at least 2 years) after the last dose of the IL-17 antibody or antigen-binding fragment thereof.

In some embodiments of the disclosed uses, methods, and kits, the patient has moderate to severe plaque-type psoriasis. In some embodiments of the disclosed uses, methods, and kits, the patient has mild plaque-type psoriasis.

In some embodiments of the disclosed uses, methods, and kits, the patient has not been previously treated with a systemic treatment for psoriasis. In some embodiments of the disclosed uses, methods, and kits, the patient is biological-naïve.

In some embodiments of the disclosed uses, methods, and kits, the patient has been previously treated with a systemic treatment for psoriasis. In some embodiments of the disclosed uses, methods, and kits, the systemic treatment comprises a biological agent. In some embodiments of the disclosed uses, methods, and kits, the systemic treatment comprises a biological agent that is a TNF alpha antagonist. In some embodiments of the disclosed uses, methods, and kits, the patient is a TNF failure.

In some embodiments of the disclosed uses, methods, and kits, the patient has been previously treated with phototherapy for psoriasis. In some embodiments of the disclosed uses, methods, and kits, the patient has not been previously treated with phototherapy for psoriasis.

In some embodiments of the disclosed uses, methods, and kits, the patient is administered a dose of about 150 mg – about 300 mg of the IL-17 antibody or antigen-binding fragment thereof (e.g., secukinumab) by subcutaneous (SC) injection at weeks 0, 1, 2, 3, and 4, followed by once monthly dosing. In some embodiments of the disclosed uses, methods, and kits, the once monthly dosing extends to at least 48 weeks, at least 100 weeks, at least 152 weeks, at least 204 weeks, at least 3 years, at least 5 years, or at least 10 years. In some embodiments of the disclosed uses, methods, and kits, the dose of the IL-17 antibody or antigen-binding fragment thereof (e.g., secukinumab) is about 300 mg. In some embodiments of the disclosed uses, methods, and kits, the dose of the IL-17 antibody or antigen-binding fragment thereof (e.g., secukinumab) is about 150 mg.

In some embodiments of the disclosed uses, methods, and kits, the patient has had chronic plaque-type psoriasis for at least 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 15 years, 20 years, or more.

In some embodiments of the disclosed uses, methods, and kits, prior to withdrawal of treatment with the IL-17 antibody or antigen-binding fragment thereof (e.g., secukinumab), the patient has achieved at least PASI 75.

In some embodiments of the disclosed uses, methods, and kits, the patient has a baseline PASI score of ≤ 39 or ≤ 26 . In some embodiments of the disclosed uses, methods, and kits, the patient has a baseline PASI score of ≤ 25 , ≤ 23 , ≤ 22 , ≤ 21.4 , ≤ 21 , ≤ 20 , ≤ 19 , ≤ 15 . In some embodiments of the disclosed uses, methods, and kits, the patient has a baseline PASI score of ≤ 39 and the patient maintains at least 50% of the PASI improvement achieved between baseline and week 52 for at least 1 year after the last dose of the IL-17 antibody or antigen-binding fragment thereof. In some embodiments of the disclosed uses, methods, and kits, the patient has a baseline PASI score of ≤ 26 and the patient maintains at least 50% of the PASI improvement achieved between baseline and week 52 for at least 2 years after the last dose of the IL-17 antibody or antigen-binding fragment thereof.

In some embodiments of the disclosed uses, methods, and kits, the patient is capable of maintaining a PASI score of ≤ 7.2 for at least 6 months, at least one year, or at least two years after the last dose of the IL-17 antibody or antigen-binding fragment thereof (e.g., secukinumab). In some embodiments of the disclosed uses, methods, and kits, the patient is capable of maintaining a PASI score of ≤ 11.2 for at least 6 months or at least one year after the last dose of

the IL-17 antibody or antigen-binding fragment thereof (e.g., secukinumab). In some embodiments of the disclosed uses, methods, and kits, the patient is capable of maintaining at least 90% of the PASI improvement achieved between baseline and week 52 for at least 6 months, at least one year, or at least two years after the last dose of the IL-17 antibody or antigen-binding fragment thereof.

In some embodiments of the disclosed uses, methods, and kits, the patient is capable of maintaining at least 75% of the PASI improvement achieved between baseline and week 52 for at least 6 months, at least one year, or at least two years after the last dose of the IL-17 antibody or antigen-binding fragment thereof. In some embodiments of the disclosed uses, methods, and kits, the patient is capable of maintaining at least 50% of the PASI improvement achieved between baseline and week 52 for at least 6 months, at least one year, or at least two years after the last dose of the IL-17 antibody or antigen-binding fragment thereof.

In some embodiments of the disclosed uses, methods, and kits, the IL-17 antibody or antigen-binding fragment thereof comprises: i) an immunoglobulin heavy chain variable domain (V_H) comprising the amino acid sequence set forth as SEQ ID NO:8; ii) an immunoglobulin light chain variable domain (V_L) comprising the amino acid sequence set forth as SEQ ID NO:10; iii) 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; iv) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3; v) an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; vi) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13; vii) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; viii) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; ix) an immunoglobulin light chain comprising the amino acid sequence set forth as SEQ ID NO:14; x) an immunoglobulin heavy chain comprising the amino acid sequence set forth as SEQ ID NO:15; or xi) an immunoglobulin light chain comprising the

amino acid sequence set forth as SEQ ID NO:14 and an immunoglobulin heavy chain comprising the amino acid sequence set forth as SEQ ID NO:15.

In some embodiments of the disclosed uses, methods, and kits, the IL-17 antibody or antigen-binding fragment thereof is a monoclonal antibody. In some embodiments, the IL-17 antibody or antigen-binding fragment thereof is a human or humanized antibody. In some embodiments, the IL-17 antibody or antigen-binding fragment thereof is a human antibody. In some embodiments, the IL-17 antibody or antigen-binding fragment thereof is a human antibody of the IgG₁ subtype. In some embodiments, the IL-17 antibody or antigen-binding fragment thereof is secukinumab.

In some embodiments of the disclosed uses, methods, and kits, at least 60%, at least 67%, at least 70%, at least 71%, at least 77%, or at least 81% of patients (e.g., adult patients) treated according to the disclosed methods achieve PASI 75 at week 12. In some embodiments, at least 50%, at least 51%, at least 62%, or at least 65% of patients (e.g., adult patients) patients treated according to the disclosed methods a response of 0 or 1 on the modified investigator's global assessment (IGA) at week 12.

In some embodiments of the disclosed uses, methods, and kits, at least 35%, at least 39%, at least 41%, at least 54%, or at least 59% of patients (e.g., adult patients) treated according to the disclosed methods achieve PASI 90 at week 12. In some embodiments, at least 10%, at least 12%, at least 14%, at least 24%, or at least 28% of patients (e.g., adult patients) treated according to the disclosed methods achieve PASI 90 at week 12. In some embodiments, the disclosed methods are used to treat a population of patients having moderate to severe chronic plaque psoriasis, and at least 60%, at least 67%, at least 70%, at least 71%, at least 77%, or at least 81%, of said patients achieve at least PASI 75 response at week 12 of the treatment. In some embodiments, the disclosed methods are used to treat a population of patients having moderate to severe chronic plaque psoriasis, and at least 50%, at least 51%, at least 62%, or at least 65% of said patients achieve a response of 0 or 1 on the modified investigator's global assessment (IGA) at week 12 of the treatment. In some embodiments, the disclosed methods are used to treat a population of patients having moderate to severe chronic plaque psoriasis, and at least 35%, at least 39%, at least 41%, at least 54%, or at least 59% of said patients achieve at least PASI 90 response at week 12 of the treatment. In some embodiments, the disclosed methods are used to treat a population of patients having moderate to severe chronic plaque psoriasis, and at least

10%, at least 12%, at least 14%, at least 24%, or at least 28% of said patients achieve PASI 100 response at week 12 of the treatment.

Kits

The disclosure also encompasses kits for treating particular chronic plaque-type psoriasis patients. Such kits comprise an IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 antibody or antigen-binding fragment thereof) (e.g., in liquid or lyophilized form) or a pharmaceutical composition comprising the IL-17 antagonist (described *supra*). Additionally, such kits may comprise means for administering the IL-17 antagonist (e.g., an auto-injector, a syringe and vial, a prefilled syringe, a prefilled pen) and instructions for use. These kits may contain additional therapeutic psoriasis agents (described *supra*) for treating chronic plaque-type psoriasis, e.g., for delivery in combination with the enclosed IL-17 antagonist, e.g., IL-17 binding molecule, e.g., IL-17 antibody, e.g., secukinumab. Such kits may also comprise instructions for administration of the IL-17 antagonist (e.g., IL-17 antibody, e.g., secukinumab) to treat the chronic plaque-type psoriasis patient. Such instructions may provide the dose (e.g., 10 mg/kg, 75 mg, 150 mg, 300 mg), route of administration (e.g., IV, SC), and dosing regimen (e.g., every other week during weeks 0, 2, and 4, and thereafter monthly, beginning during week 8; weekly during week 0, 1, 2, and 3 and thereafter monthly (every 4 weeks), beginning during week 4; etc.) for use with the enclosed IL-17 antagonist, e.g., IL-17 binding molecule, e.g., IL-17 antibody, e.g., secukinumab.

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 auto-injector, an IV drip and bag, a pump, etc. With such items, a patient may self-administer the drug (i.e., administer the drug without the assistance of a physician) or a medical practitioner may administer the drug.

Disclosed herein are kits for use in modifying the psoriasis disease course in a patient having chronic plaque-type psoriasis, comprising an IL-17 antagonist (e.g., IL-17 binding molecule, e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab). In some embodiments, the kit further comprises means for administering the IL-17 antagonist to the patient. In some embodiments, the kit further comprises instructions for administration of the IL-

IL-17 antagonist, wherein the instructions indicate that the IL-17 antagonist (e.g., IL-17 binding molecule, e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) is to be administered to the patient SC at about 150 mg – about 300 mg (e.g., about 150 mg, or about 300 mg) weekly during weeks 0, 1, 2, and 3, and thereafter SC at about 150 mg – about 300 mg (e.g., about 150 mg, about 300 mg) monthly (every 4 weeks), beginning during week 4. In some embodiments, the instructions will provide for dose escalation (e.g., from a dose of about 150 mg or about 300 mg to a higher dose of about 450 mg as needed, to be determined by a physician).

General

In preferred embodiments of the disclosed methods, treatments, medicaments, regimens, uses, pharmaceutical compositions, and kits, the IL-17 antagonist is an IL-17 binding molecule. In preferred embodiments, the IL-17 binding molecule is an IL-17 antibody or antigen-binding fragment thereof. In more preferred embodiments, the IL-17 antibody or antigen-binding fragment thereof is selected from the group consisting of: a) an IL-17 antibody or antigen-binding fragment thereof that binds to an epitope of human IL-17 comprising Leu74, Tyr85, His86, Met87, Asn88, Val124, Thr125, Pro126, Ile127, Val128, His129; b) an IL-17 antibody or antigen-binding fragment thereof that binds to an epitope of human IL-17 comprising Tyr43, Tyr44, Arg46, Ala79, Asp80; c) an IL-17 antibody or antigen-binding fragment thereof that binds to an epitope of an IL-17 homodimer having two mature human IL-17 protein 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; d) an IL-17 antibody or antigen-binding fragment thereof that binds to an epitope of an IL-17 homodimer having two mature human IL-17 protein 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, wherein the IL-17 binding molecule has a K_D of about 100-200 pM, and wherein the IL-17 binding molecule has an *in vivo* half-life of about 23 to about 35 days; and e) an IL-17 antibody or antigen-binding fragment thereof comprising: i) an immunoglobulin heavy chain variable domain (V_H) comprising the amino acid sequence set forth as SEQ ID NO:8; ii) an immunoglobulin light chain variable domain (V_L) comprising the amino acid sequence set forth as SEQ ID NO:10; iii) 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; iv) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3; v) an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; vi) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13; vii) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; viii) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; ix) an immunoglobulin light chain comprising the amino acid sequence set forth as SEQ ID NO:14; x) an immunoglobulin heavy chain comprising the amino acid sequence set forth as SEQ ID NO:15; or xi) an immunoglobulin light chain comprising the amino acid sequence set forth as SEQ ID NO:14 and an immunoglobulin heavy chain comprising the amino acid sequence set forth as SEQ ID NO:15.

In more preferred embodiments, the IL-17 antibody or antigen-binding fragment thereof is a monoclonal antibody. In more preferred embodiments, the IL-17 antibody or antigen-binding fragment thereof is a human or humanized antibody, preferably a human antibody. In more preferred embodiments, the IL-17 antibody or antigen-binding fragment thereof is a human antibody of the IgG₁ isotype. In most preferred embodiments, the antibody or antigen-binding fragment thereof is secukinumab.

The details of one or more embodiments of the disclosure are set forth in the accompanying description above. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, the preferred methods and materials are now described. 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. All patents and publications cited in this specification are incorporated by

reference. The following Examples are presented in order to more fully illustrate the preferred embodiments of the disclosure. These examples should in no way be construed as limiting the scope of the disclosed patient matter, as defined by the appended claims.

EXAMPLES

Example 1. CAIN457A2302E1 Study Design

The clinical study is an extension of pivotal phase 3 studies ERASURE (CAN457A2302) and FIXTURE (CAN457A2303) described in Langley et al. (2014) N Engl J Med 371:326-38.

As shown in **Figure 1**, after 52 weeks of treatment with secukinumab (last dose given at week 48) in two pivotal randomized, double-blind, phase III trials ERASURE and FIXTURE, PASI 75 responders were randomly assigned to either continue with secukinumab treatment or treatment was withdrawn and the patient was switched to placebo, in a double-blinded fashion. 120 patients and 100 patients after being treated for 52 weeks with secukinumab 300mg and 150mg respectively, were switched to placebo. Patients attended site visits every 4 weeks and if the patient lost 50% of the PASI improvement achieved between baseline and week 52, the patient would be switched to active treatment with 150 mg or 300 mg secukinumab given weekly until week 4 and then every 4 weeks. Total duration of treatment withdrawal period in the extension study was 2 years. Thereafter, all patients were unblinded and put on secukinumab treatment.

For inclusion criteria, patients entering the original study were required to have had moderate to severe psoriasis for least 6 months since the diagnosis, PASI ≥ 12 , BSA $\geq 10\%$ and their disease must have been inadequately controlled with prior psoriasis treatments. During the extension study, patients were not allowed to use concomitant psoriasis treatment (systemic, topical or UV) in order to avoid confounding of efficacy results.

Example 2. Baseline Characteristics of Patients in CAIN457A2302E1 Extension Trial

Before starting secukinumab treatment in the extension trials, patients who later had treatment withdrawn had a mean BSA $\sim 30\%$ and mean PASI ~ 23 . Baseline characteristics were well-balanced across the two groups (secukinumab 300mg --> placebo and secukinumab 150mg --> placebo), as shown below in **Table 4**.

Baseline characteristics	secukinumab 300 mg --> placebo (N=120)	secukinumab 150 mg --> placebo (N=100)
Age, years (Mean $\pm$ SD)	45.4 $\pm$ 13.6	46.3 $\pm$ 13.6
Gender (males) n (%)	77 (64.2)	67 (67.0)
Caucasian, n (%)	85 (70.8)	73 (73.0)
BMI, kg/m ² (Mean $\pm$ SD)	28.31 $\pm$ 5.89	27.93 $\pm$ 6.15
PASI score (mean $\pm$ SD)	22.77 $\pm$ 9.98	22.83 $\pm$ 10.16
BSA, % (mean $\pm$ SD)	30.65 $\pm$ 16.36	31.02 $\pm$ 18.31
Time since psoriasis diagnosis, years (mean $\pm$ SD)	16.43 $\pm$ 12.63	17.56 $\pm$ 12.53

Table 4: Baseline characteristics of patients in CAIN457A2302E1 extension trial

Example 3. Long term skin assessment of patients withdrawn from treatment

3.1: Proportion of patients not relapsing after treatment withdrawal in CAIN457A2302E1:

Long after patients were washed out from previous secukinumab treatment (data not shown), the percentage of patients that did not relapse was remarkably high. As shown in **Figure 2**, 21% and 10% of patients did not relapse for at least 1 year and 2 years (respectively) after the last dose of secukinumab 300 mg. As shown in **Figure 2**, there is a correlation (“dose response”) between the dose of previous secukinumab treatment and the proportion of patients not relapsing after secukinumab was discontinued. Since these patients originally had chronic moderate to severe psoriasis, relapse would have been expected to occur quickly after treatment withdrawal, but this was surprisingly not the case.

3.2: Long term PASI assessment in CAIN457A2302E1:

Average PASI score of patients that did not relapse after secukinumab wash out remained low despite these patients no longer receiving active treatment. As it can be seen in **Figure 3** and **Figure 4**, these patients displayed an average PASI score of 2.7 at the end of year 1 (**Figure 3**) an average PASI score of 1.7 at the end of year 2 (**Figure 4**). Patients switching from 300mg to placebo and not relapsing for 2 years had PASI scores in those 2 years of between 0.3 and 7.2.

Patients switching from 300mg to placebo and not relapsing for 1 year had PASI scores in that 1 year of between 0.3 and 11.2.

To conclude, the expected course of chronic moderate to severe psoriasis is that once treatment is withdrawn, psoriasis plaques will quickly reappear and psoriasis will revert to its baseline severity. However, in the double-blind CAIN457A2302E1 study, long after secukinumab was withdrawn, a high proportion of patients did not revert to baseline severity, staying relapse free and maintaining low PASI scores for up to 2 years. Thus, secukinumab treatment for at least 52 weeks (last dose given at week 48) appears to have modified the course of moderate-to-severe psoriasis, potentially converting it to mild psoriasis, despite intervening late in the course of these patients' disease.

Example 4. Baseline Characteristics Predictive of Modifying the Psoriasis Disease Course

Cox regression model assessing time to relapse showed that baseline PASI and time since psoriasis diagnosis in the CAIN457A2302E1 trial appears to influence time to relapse, and hence could be used to identify and select patients amenable to disease course modification, i.e., patients capable of maintaining at least 50% of the PASI improvement achieved between baseline and week 52 for at least 6 months after the last dose of secukinumab. Specifically, patients that did not relapse for at least one 1 year following treatment withdrawal had baseline PASI 12-38.7; those that did not relapse for at least one 2 years following treatment withdrawal had baseline PASI 12-25.4. We believe this is because patients with lower baseline PASI have less inflammation, allowing modification of their chronic moderate-to-severe psoriasis on a molecular and clinical level, leading to longer relapse-free time, and potentially even prevention of relapse, following treatment withdrawal.

Example 5. Histological and Gene Expression Reversal Following Secukinumab 300 mg Treatment

Mechanistic study CAIN457A2223 (design in **Figure 5**), has shown, based on skin biopsies taken at baseline and during the treatment, that, after secukinumab treatment, there is histological disease reversal (**Figure 6**) and reversal of the majority of gene expression abnormalities in lesional psoriatic skin (**Figure 7**). Following treatment, lesional psoriatic skin (taken in the areas

of psoriatic plaques) looked remarkably like non-lesional skin (skin not affected by plaques) (**Figure 6**). This further supports the CAIN457A2302E1 extension results presented above, suggesting that certain patients can experience modification of their chronic moderate-to-severe psoriasis on a molecular and clinical level, leading to longer relapse-free time, and potentially even prevention of relapse, following treatment withdrawal.

Example 6. Long Term Secukinumab Treatment and Impact on Comorbidities, Such as Psoriatic Arthritis (PsA)

Based on the above results, which suggest that certain patients can experience modification of their psoriasis disease state following long-term secukinumab treatment, we investigate secukinumab psoriasis studies for patients who did not have concomitant PsA at baseline in order to determine if these patients will eventually develop PsA. Patients from several studies are examined:

- patients in long term extension studies for moderate to severe psoriasis (CAIN457A2302E1 and CAIN457A2304E1) treated over, e.g., 5 years;
- patients in long term study of moderate to severe psoriasis and significant nail psoriasis (CAIN457A2313), a population “enriched” for nail psoriasis, which is associated with an increased risk of PsA.

It is expected, that, based on the ability of long-term secukinumab treatment to modify the psoriasis disease course via extended antagonism of the IL-17A cytokine, the incidence of new-onset PsA in patients receiving secukinumab in all populations mentioned above will be lower than what would be generally expected in moderate to severe psoriasis patients. Similarly, long-term secukinumab treatment is also expected to reduce the incidence of onset or delay onset of other psoriasis-related comorbidities, e.g., diabetes and cardiovascular disease, via extended antagonism of the IL-17A cytokine.

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WHAT IS CLAIMED IS:

1. A method of modifying the psoriasis disease course in a patient having chronic plaque-type psoriasis, comprising:
 - a) administering the patient a dose of about 150 mg - about 300 mg of an IL-17 antibody or antigen-binding fragment thereof by subcutaneous injection at weeks 0, 1, 2, 3, and 4, followed by once monthly dosing extending to at least 48 weeks, and
 - b) thereafter, withdrawing treatment of the IL-17 antibody or antigen-binding fragment thereof, wherein the patient maintains at least 50% of the PASI improvement achieved between baseline and week 52 for at least 6 months after the last dose of the IL-17 antibody, wherein the IL-17 antibody or antigen-binding fragment thereof binds to an epitope of an IL-17 homodimer having two mature human IL-17 protein 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, wherein the IL-17 antibody or antigen-binding fragment thereof has a K_D of about 100-200 pM, and wherein the IL-17 antibody or antigen-binding fragment thereof has an *in vivo* half-life of about 4 weeks.
2. The method according to claim 1, wherein the patient maintains at least 90% of the PASI improvement achieved between baseline and week 52 for at least 6 months, at least one year, or at least two years after the last dose of the IL-17 antibody or antigen-binding fragment thereof.
3. The method according to claim 1, wherein the patient maintains a PASI score of ≤ 7.2 for at least 6 months, at least one year, or at least two years after the last dose of the IL-17 antibody or antigen-binding fragment thereof.
4. The method according to claim 1, wherein the patient maintains a PASI score of ≤ 11.2 for at least 6 months or at least one year after the last dose of the IL-17 antibody or antigen-binding fragment thereof.

5. The method according to claim 1, wherein, prior to treatment with the IL-17 antibody or antigen-binding fragment thereof, the patient has a baseline PASI score of ≤ 39 and the patient maintains at least 50% of the PASI improvement achieved between baseline and week 52 for at least 1 year after the last dose of the IL-17 antibody or antigen-binding fragment thereof or the patient has a baseline PASI score of ≤ 26 and the patient maintains at least 50% of the PASI improvement achieved between baseline and week 52 for at least 2 years after the last dose of the IL-17 antibody or antigen-binding fragment thereof.
6. The method according to claim 1, wherein, prior to withdrawal of treatment with the IL-17 antibody or antigen-binding fragment thereof, the patient has achieved at least PASI 75.
7. A method of modifying the psoriasis disease course in a patient having chronic plaque-type psoriasis, comprising administering the patient a dose of about 150 mg - about 300 mg of an IL-17 antibody or antigen-binding fragment thereof by subcutaneous injection at weeks 0, 1, 2, 3, and 4, followed by once monthly dosing extending to at least 48 weeks, wherein the patient is capable of maintaining at least 50% of the PASI improvement achieved between baseline and week 52 for at least 6 months after the last dose of the IL-17 antibody or antigen-binding fragment thereof, wherein the IL-17 antibody or antigen-binding fragment thereof binds to an epitope of an IL-17 homodimer having two mature human IL-17 protein 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, wherein the IL-17 antibody or antigen-binding fragment thereof has a K_D of about 100-200 pM, and wherein the IL-17 antibody or antigen-binding fragment thereof has an *in vivo* half-life of about 4 weeks
8. The method according to claim 7, wherein the patient is capable of maintaining at least 90% of the PASI improvement achieved between baseline and week 52 for at least 6 months, at least one year, or at least two years after the last dose of the IL-17 antibody or antigen-binding fragment thereof.

9. The method according to claim 7, wherein the patient is capable of maintaining a PASI score of ≤ 7.2 for at least six months, at least one year, or at least two years after the last dose of the IL-17 antibody or antigen-binding fragment thereof.

10. The method according to claim 7, wherein the patient is capable of maintaining a PASI score of ≤ 11.2 for at least 6 months or at least one year after the last dose of the IL-17 antibody or antigen-binding fragment thereof.

11. The method according to claim 7, wherein, prior to treatment with the IL-17 antibody or antigen-binding fragment thereof, the patient has a baseline PASI score of ≤ 39 and the patient maintains at least 50% of the PASI improvement achieved between baseline and week 52 for at least 1 year after the last dose of the IL-17 antibody or the patient has a baseline PASI score of ≤ 26 and the patient maintains at least 50% of the PASI improvement achieved between baseline and week 52 for at least 2 years after the last dose of the IL-17 antibody or antigen-binding fragment thereof.

12. The method according to claim 7, wherein, prior to withdrawal of treatment with the IL-17 antibody or antigen-binding fragment thereof, the patient has achieved at least PASI 75.

13. The method according to any of the above claims, wherein, prior to treatment with the IL-17 antibody or antigen binding fragment thereof, the patient has had psoriasis for more than 1 year, at least 2 years, at least 5 years, at least 7 years, at least 10 years, at least 12 years, at least 15 years, or at least 20 years.

14. The method according to any of the above claims, wherein the dose of the IL-17 antibody or antigen-binding fragment thereof is about 150 mg.

15. The method according to any of claims 1-13, wherein the dose of the IL-17 antibody or antigen-binding fragment thereof is about 300 mg.

16. The method according to any of the above claims, wherein the IL-17 antibody or antigen-binding fragment thereof comprises:

- i) an immunoglobulin heavy chain variable domain (V_H) comprising the amino acid sequence set forth as SEQ ID NO:8;
- ii) an immunoglobulin light chain variable domain (V_L) comprising the amino acid sequence set forth as SEQ ID NO:10;
- iii) 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;
- iv) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3;
- v) an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6;
- vi) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13;
- vii) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6;
- viii) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6;
- ix) an immunoglobulin light chain comprising the amino acid sequence set forth as SEQ ID NO:14;
- x) an immunoglobulin heavy chain comprising the amino acid sequence set forth as SEQ ID NO:15; or
- xi) an immunoglobulin light chain comprising the amino acid sequence set forth as SEQ ID NO:14 and an immunoglobulin heavy chain comprising the amino acid sequence set forth as SEQ ID NO:15.

17. The method according to claim 16, wherein the IL-17 antibody or antigen-binding fragment thereof is a human or humanized antibody.
18. The method according to claim 17, wherein the IL-17 antibody or antigen-binding fragment thereof is secukinumab.
19. A method decreasing the likelihood that a patient having chronic plaque-type psoriasis will develop psoriatic arthritis, comprising administering the patient a dose of about 150 mg - about 300 mg of secukinumab by subcutaneous injection at weeks 0, 1, 2, 3, and 4, followed by once monthly dosing extending to at least 52 weeks, wherein the patient is capable of maintaining at least 50% of the PASI improvement achieved between baseline and week 52 for at least 6 months after the last dose of the secukinumab.
20. The method according to claim 19, wherein the patient is capable of maintaining at least 90% of the PASI improvement achieved between baseline and week 52 for at least 6 months, at least one year, or at least two years after the last dose of the secukinumab.
21. The method according to claim 19, wherein the patient is capable of maintaining a PASI score of ≤ 7.2 for at least six months, at least one year, or at least two years after the last dose of the secukinumab.
22. The method according to claim 19, wherein the patient is capable of maintaining a PASI score of ≤ 11.2 for at least 6 months or at least one year after the last dose of the secukinumab.
23. The method according to claim 19, wherein, prior to treatment with secukinumab, the patient has a baseline PASI score of ≤ 39 and the patient maintains at least 50% of the PASI improvement achieved between baseline and week 52 for at least 1 year after the last dose of secukinumab or the patient has a baseline PASI score of ≤ 26 and the patient maintains at least 50% of the PASI improvement achieved between baseline and week 52 for at least 2 years after the last dose of secukinumab.

24. The method according to claim 19, wherein, prior to treatment with secukinumab, the patient has had psoriasis for at least 2 years, at least 5 years, at least 7 years, at least 10 years, at least 12 years, at least 15 years, or at least 20 years.
25. The method according to claim 19, wherein the secukinumab dose is about 150 mg.
26. The method according to claim 19, wherein the secukinumab dose is about 300 mg.
27. The method according to any of the above claims, wherein the once monthly dosing extends to at least at least 48 weeks, at least 100 weeks, at least 152 weeks, at least 204 weeks, at least 5 years, or at least 10 years.
28. The method according to any of the above claims, wherein the patient has moderate to severe plaque-type psoriasis.
29. The method according to any of the above claims, wherein the patient has mild plaque-type psoriasis.
30. The method according to any of the above claims, wherein the patient has been previously treated with a systemic treatment for psoriasis.
31. The method according to claim 30, wherein the systemic treatment comprises a biological agent.
32. The method according to claim 31, wherein the biological agent is a TNF alpha antagonist.
33. The method according to claim 32, wherein the patient is a TNF failure.
34. The method according to any of claims 1-29, wherein the patient has not been previously treated with a systemic treatment for psoriasis.

35. The method according to claim 34, wherein the patient is biological-naïve.
36. The method according to any of the above claims, wherein the patient has been previously treated with phototherapy for psoriasis.
37. The method according to any of claims 1-35, wherein the patient has not been previously treated with phototherapy for psoriasis.

Fig. 1

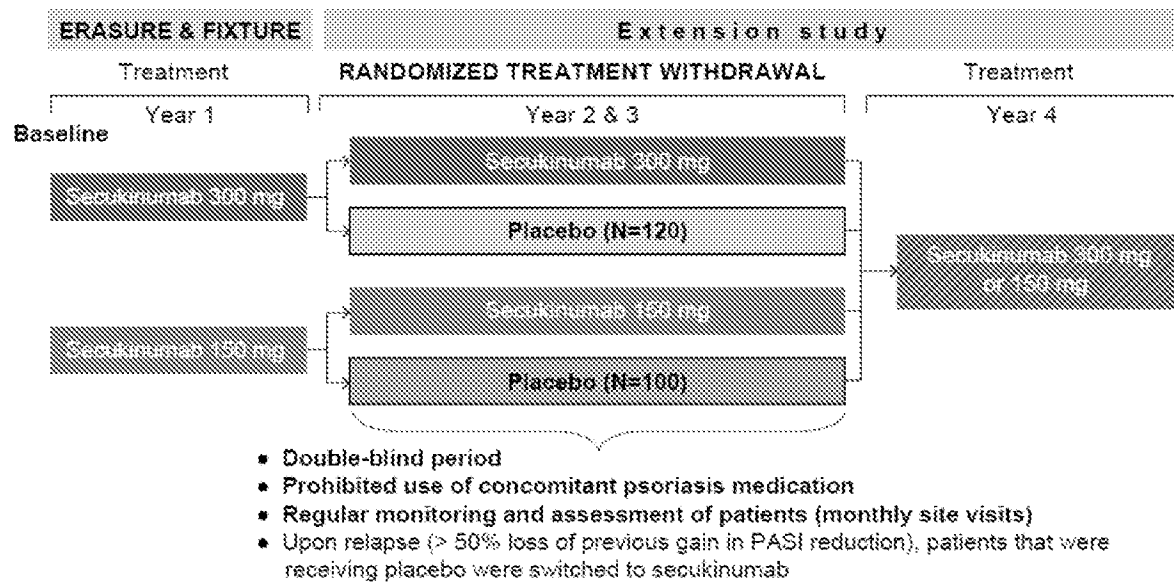


Fig. 2

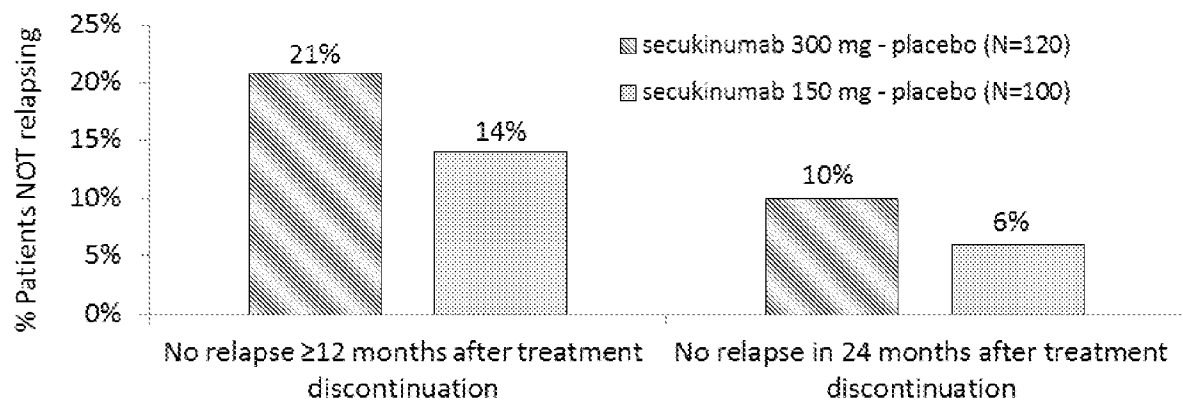


Fig. 3

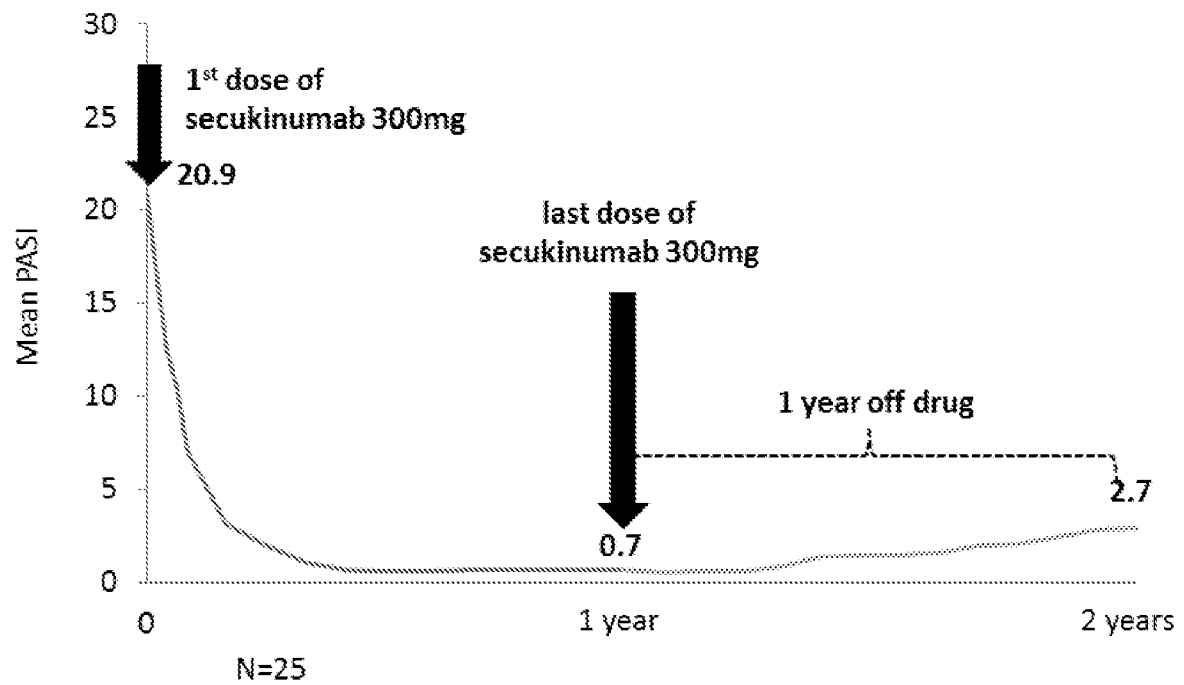


Fig. 4

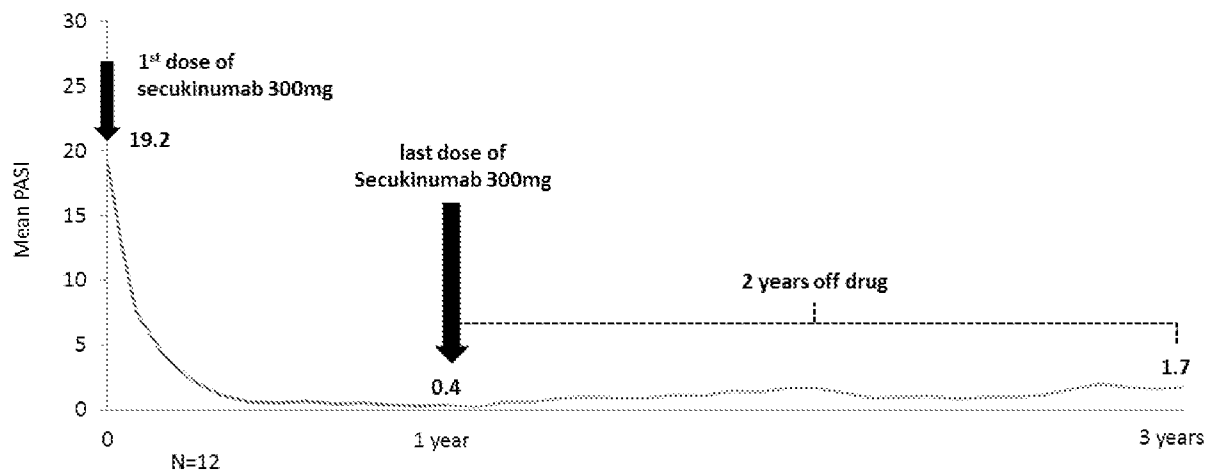


Fig. 5

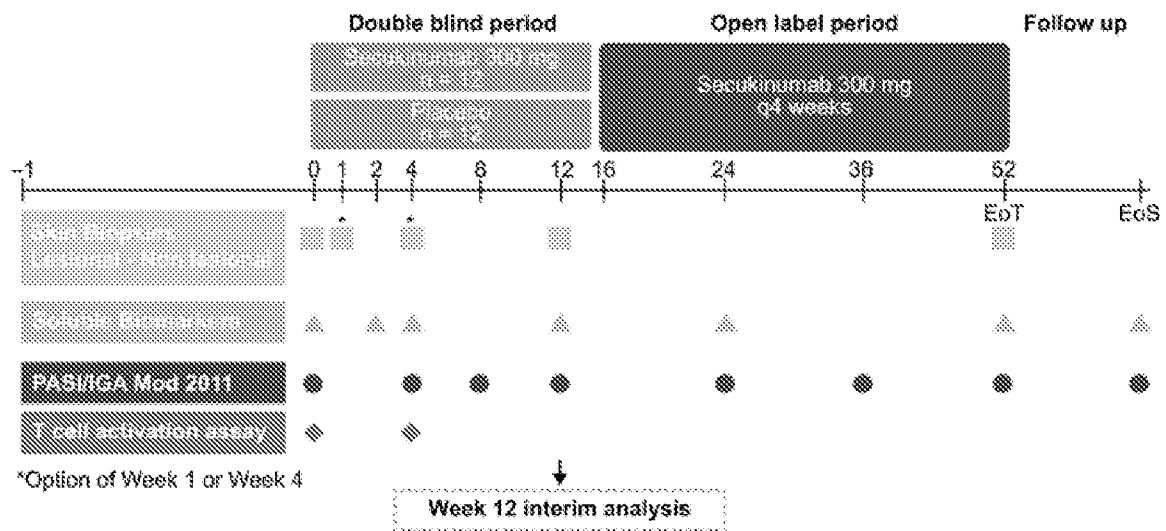


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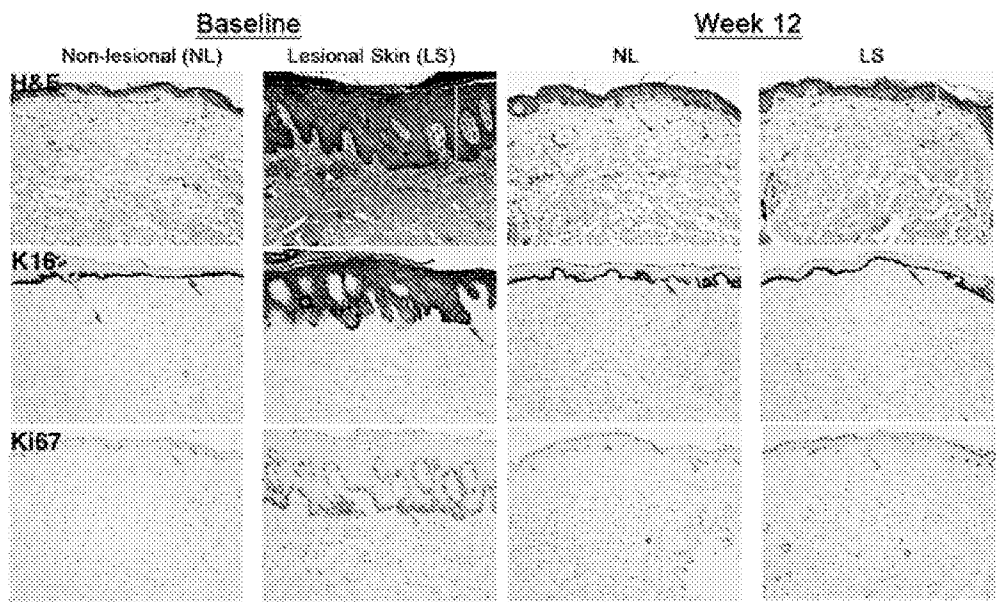
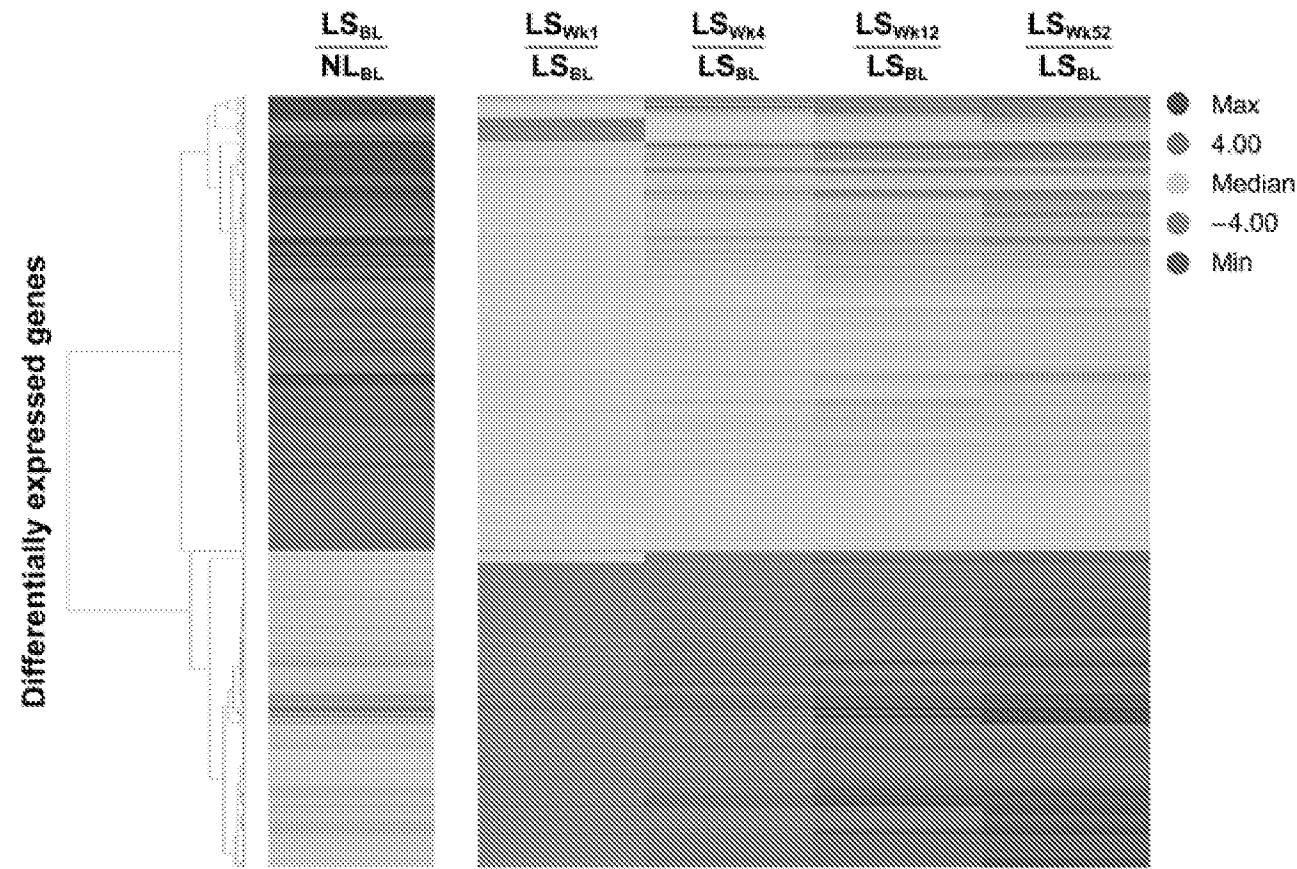


Fig. 7



INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2018/051343

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K39/395 C07K16/24 A61P17/06
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C07K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, Sequence Search, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RICHARD G. LANGLEY ET AL: "Secukinumab in Plaque Psoriasis - Results of Two Phase 3 Trials", NEW ENGLAND JOURNAL OF MEDICINE, THE - NEJM -, vol. 371, no. 4, 24 July 2014 (2014-07-24) , pages 326-338, XP055414280, US ISSN: 0028-4793, DOI: 10.1056/NEJMoa1314258 cited in the application pages 326,328	1-18, 27-37
Y	WO 2012/045848 A1 (NOVARTIS AG [CH]; GUETTNER ACHIM [CH]; MACHACEK MATTHIAS [CH]; PAPAVALAS) 12 April 2012 (2012-04-12) claim 1 ----- -/--	1-18, 27-37



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

17 July 2018

Date of mailing of the international search report

25/07/2018

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Fax: (+31-70) 340-3016

Authorized officer

Scheffzyk, Irmgard

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2018/051343

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DIAMANT THAÇI ET AL: "Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial", JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY., vol. 73, no. 3, 1 September 2015 (2015-09-01), pages 400-409, XP055387207, US ISSN: 0190-9622, DOI: 10.1016/j.jaad.2015.05.013 page 402; table 1 -----	1-18, 27-37

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2018/051343

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-18(completely); 27-37(partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-18(completely); 27-37(partially)

A method of modifying the psoriasis disease course in a patient having chronic plaque type psoriasis

2. claims: 19-26(completely); 27-37(partially)

A method of decreasing the likelihood that a patient having chronic plaque-type psoriasis will develop psoriatic arthritis

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2018/051343

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2012045848	A1	12-04-2012	
		AU 2011311482 A1	04-04-2013
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		PT 2625199 T	28-02-2018
		RU 2013120957 A	20-11-2014
		SG 188979 A1	31-05-2013
		SI 2625199 T1	30-03-2018
		TW 201216984 A	01-05-2012
		TW 201630625 A	01-09-2016
		US 2013202610 A1	08-08-2013
		US 2017304439 A1	26-10-2017
		WO 2012045848 A1	12-04-2012
