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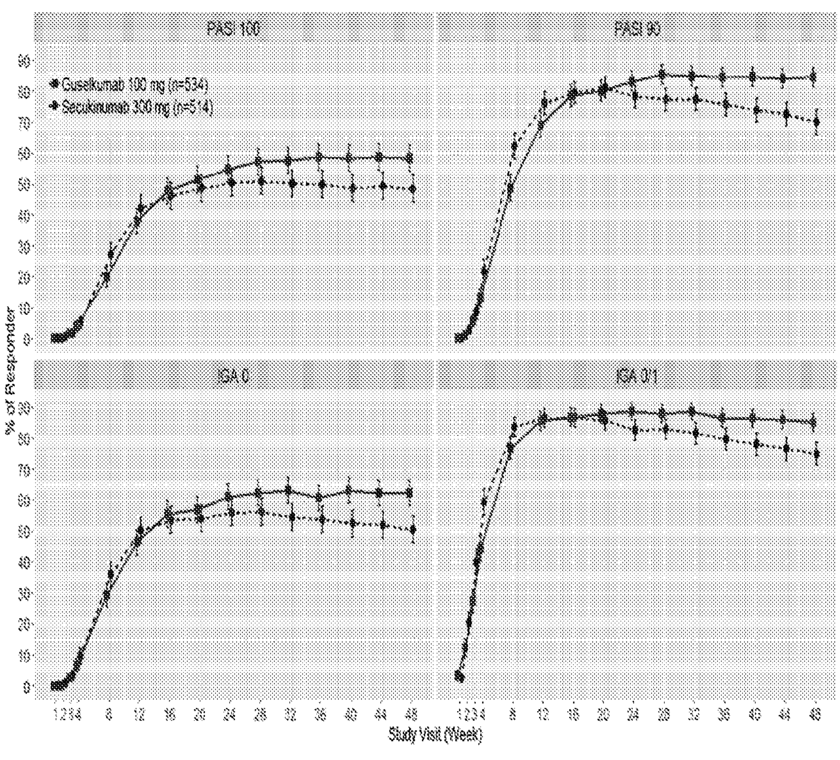
(54) Titre : PROCEDE SUR ET EFFICACE DE TRAITEMENT DU PSORIASIS AVEC UN ANTICORPS SPECIFIQUE ANTI-IL-23
(54) Title: SAFE AND EFFECTIVE METHOD OF TREATING PSORIASIS WITH ANTI-IL-23 SPECIFIC ANTIBODY

FIG. 1



(57) Abrégé/Abstract:
A method of treating psoriasis in a patient by administering an IL-23 specific antibody, e.g., guselkumab, in a clinically proven safe and clinically proven effective amount and the patient achieves PASI90, PASI100 or IGA 0 or 1 score as measured 16, 24, 32, 40 and 48 weeks after initial treatment and the patient achieves higher efficacy than a patient treated with the secukinumab antibody.

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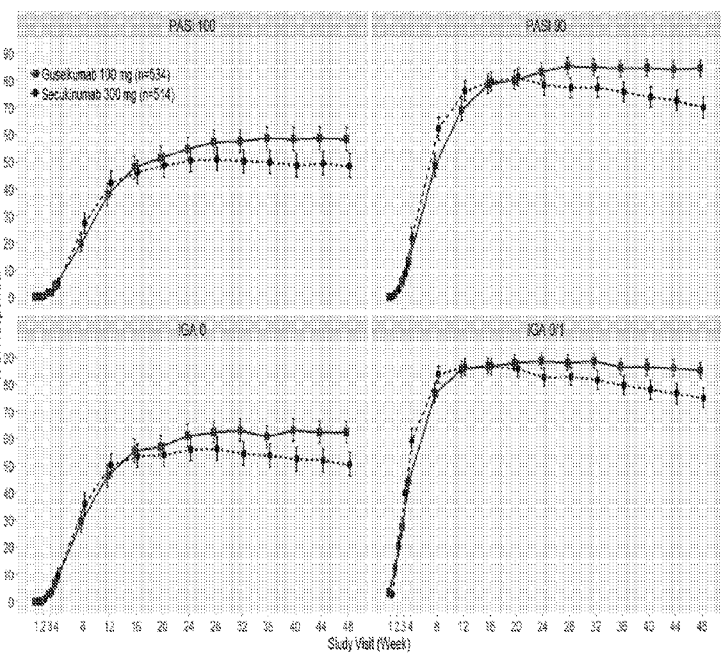
(54) Title: SAFE AND EFFECTIVE METHOD OF TREATING PSORIASIS WITH ANTI-IL-23 SPECIFIC ANTIBODY

FIG. 1



(57) **Abstract:** A method of treating psoriasis in a patient by administering an IL-23 specific antibody, e.g., guselkumab, in a clinically proven safe and clinically proven effective amount and the patient achieves PASI90, PASI100 or IGA 0 or 1 score as measured 16, 24, 32, 40 and 48 weeks after initial treatment and the patient achieves higher efficacy than a patient treated with the secukinumab antibody.

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SAFE AND EFFECTIVE METHOD OF TREATING PSORIASIS WITH ANTI-IL-23 SPECIFIC ANTIBODY

REFERENCE TO SEQUENCE LISTING SUBMITTED ELECTRONICALLY

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on 19 November 2019, is named PCTSEQUENCELISTING.txt and is 80,004 bytes in size.

FIELD OF THE INVENTION

The present invention concerns methods for treating psoriasis with an antibody that binds the human IL-23 protein. In particular, it relates to a method of administering an anti-IL-23 specific antibody and specific pharmaceutical compositions of an antibody, e.g., guselkumab, which is safe and effective for patients suffering from psoriasis.

BACKGROUND OF THE INVENTION

Interleukin (IL)-12 is a secreted heterodimeric cytokine comprised of 2 disulfide-linked glycosylated protein subunits, designated p35 and p40 for their approximate molecular weights. IL-12 is produced primarily by antigen-presenting cells and drives cell-mediated immunity by binding to a two-chain receptor complex that is expressed on the surface of T cells or natural killer (NK) cells. The IL-12 receptor beta-1 (IL-12Rβ1) chain binds to the p40 subunit of IL-12, providing the primary interaction between IL-12 and its receptor. However, it is IL-12p35 ligation of the second receptor chain, IL-12Rβ2, that confers intracellular signaling (e.g. STAT4 phosphorylation) and activation of the receptor-bearing cell (Presky et al, 1996). IL-12 signaling concurrent with antigen presentation is thought to invoke T cell differentiation towards the T helper 1 (Th1) phenotype, characterized by interferon gamma (IFNγ) production (Trinchieri, 2003). Th1 cells are believed to promote immunity to some intracellular pathogens, generate complement-fixing antibody isotypes, and contribute to tumor immunosurveillance. Thus, IL-12 is thought to be a significant component to host defense immune mechanisms.

It was discovered that the p40 protein subunit of IL-12 can also associate with a separate protein subunit, designated p19, to form a novel cytokine, IL-23 (Oppman et al, 2000). IL-23 also signals through a two-chain receptor complex. Since the p40 subunit is shared between IL-12 and IL-23, it follows that the IL-12Rβ1 chain is also shared between IL-12 and IL-23. However, it is the IL-23p19 ligation of the second component of the IL-23 receptor complex, IL-23R, that confers IL-23 specific intracellular signaling (e.g., STAT3 phosphorylation) and subsequent IL-17 production by T cells (Parham et al, 2002; Aggarwal et al. 2003). Recent studies have demonstrated that the biological functions of IL-23 are distinct from those of IL-12, despite the structural similarity between the two cytokines (Langrish et al, 2005).

Abnormal regulation of IL-12 and Th1 cell populations has been associated with many immune-mediated diseases since neutralization of IL-12 by antibodies is effective in treating animal models of psoriasis, multiple sclerosis (MS), rheumatoid arthritis, inflammatory bowel disease, insulin-dependent (type 1) diabetes mellitus, and uveitis (Leonard et al, 1995; Hong et al, 1999; Malfait et al, 1998; Davidson et al, 1998). However, since these studies targeted the shared p40 subunit, both IL-12 and IL-23 were neutralized *in vivo*. Therefore, it was unclear whether IL-12 or IL-23 was mediating disease, or if both cytokines needed to be inhibited to achieve disease suppression. Recent studies have confirmed through IL-23p19 deficient mice or specific antibody neutralization of IL-23 that IL-23 inhibition can provide equivalent benefit as anti-IL-12p40 strategies (Cua et al, 2003, Murphy et al, 2003, Benson et al 2004). Therefore, there is increasing evidence for the specific role of IL-23 in immune-mediated disease. Neutralization of IL-23 without inhibition of IL-12 pathways could then provide effective therapy of immune-mediated disease with limited impact on important host defense immune mechanism. This would represent a significant improvement over current therapeutic options.

Psoriasis is a common, chronic immune-mediated skin disorder with significant co-morbidities, such as psoriatic arthritis (PsA), depression, cardiovascular disease, hypertension, obesity, diabetes, metabolic syndrome, and Crohn's disease. Plaque psoriasis is the most common form of the disease and manifests in well demarcated erythematous lesions topped with white silver scales. Plaques are pruritic, painful, often disfiguring and disabling, and a significant proportion of psoriatic patients have plaques on hands/nails face, feet and genitalia. As such, psoriasis negatively impacts health-related quality of life (HRQoL) to a significant extent, including imposing physical and psychosocial burdens that extend beyond the physical dermatological symptoms and interfere with everyday activities. For example, psoriasis negatively impacts familial, spousal, social, and work relationships, and is associated with a higher incidence of depression and increased suicidal tendencies.

Histologic characterization of psoriasis lesions reveals a thickened epidermis resulting from aberrant keratinocyte proliferation and differentiation as well as dermal infiltration and co-localization of CD3+ T lymphocytes and dendritic cells. While the etiology of psoriasis is not well defined, gene and protein analysis have shown that IL-12, IL-23 and their downstream molecules are over-expressed in psoriatic lesions, and some may correlate with psoriasis disease severity. Some therapies used in the treatment of psoriasis modulate IL-12 and IL-23 levels, which is speculated to contribute to their efficacy. Th1 and Th17 cells can produce effector cytokines that induce the production of vasodilators, chemoattractants and expression of adhesion molecules on endothelial cells which in turn, promote monocyte and neutrophil recruitment, T cell infiltration, neovascularization and keratinocyte activation and hyperplasia. Activated keratinocytes can produce chemoattractant factors that promote neutrophil, monocyte, T cell, and dendritic cell trafficking, thus establishing a cycle of inflammation and keratinocyte hyperproliferation.

Elucidation of the pathogenesis of psoriasis has led to effective biologic treatments targeting tumor necrosis factor-alpha (TNF-α), both interleukin (IL)-12 and IL-23 and, most recently, IL-17 as well as IL-23 alone (including in Phase 1 and 2 clinical trials using guselkumab). Guselkumab (also known as CNTO 1959) is a fully human IgG1 lambda monoclonal antibody that binds to the p19 subunit of IL-23 and inhibits the intracellular and downstream signaling of IL-23, required for terminal differentiation of T helper (Th)17 cells.

SUMMARY OF THE INVENTION

In a first aspect, the invention concerns a method of treating psoriasis in a patient comprising subcutaneously administering an anti-IL-23 specific antibody (also referred to as IL-23p19 antibody), e.g., guselkumab, to the patient, wherein the anti-IL-23 specific antibody is administered at an initial dose, a dose 4 weeks thereafter, and at a dosing interval of once every 8 weeks thereafter, e,g., a dose at 0, 4, 8, 16, 24, 32, 40 and 48 weeks.

In the method of treating psoriasis in a patient, the patient treated with the antibody to IL-23 demonstrates greater efficacy in a psoriasis clinical endpoint than efficacy in the psoriasis clinical endpoint achieved by a patient treated with the antibody secukinumab (marketed as Cosentyx® by Novartis). The psoriasis clinical endpoint may be PASI90, PASI100, IGA 0 and/or IGA 1 and is measured 24, 28, 32, 36, 40, 44 and/or 48 weeks after initial treatment, preferably, 48 weeks after initial treatment.

In the method of the invention, the antibody to IL-23 is administered in an initial dose, 4 weeks after the initial dose and every 8 weeks after the dose at 4 weeks and the secukinumab antibody is administered in an initial dose, 1 week after the initial dose, 2 weeks after the initial dose, 3 weeks after the initial dose, 4 weeks after the initial dose and every 4 weeks after the dose at 4 weeks. In an embodiment of the method, the antibody to IL-23 is administered at a dose of 100 mg and the antibody to IL-23 is safe and effective treating psoriasis at an area of a patient selected from the group consisting of scalp, nails, hands and feet.

In another embodiment of the method, the antibody to IL-23 is effective to reduce a symptom of psoriasis in the patient, induce clinical response, induce or maintain clinical remission, inhibit disease progression, or inhibit a disease complication in the patient and the patient is treated for moderate to severe psoriasis.

In a further embodiment of the invention, the method further comprises the step of discontinuing treatment of a patient previously treated with at least one dose of secukinumab and deciding to treat the patient with guselkumab. In an additional embodiment, the method further comprises the step of measuring the psoriasis clinical endpoint PASI90, PASI100, IGA 0 and/or IGA 1 at 24, 28, 32, 36, 40, 44 and/or 48 weeks after initial treatment and discontinuing treatment of a patient previously treated with at least one dose of secukinumab and treating the patient with guselkumab.

In another aspect, the composition used in the method of the invention comprises a pharmaceutical composition comprising: an anti-IL-23 specific antibody in an amount from about 1.0 µg/ml to about 1000 mg/ml, specifically at 50 mg or 100 mg. In a preferred embodiment the anti-IL-23 specific antibody is guselkumab at 100 mg/mL; 7.9% (w/v) sucrose, 4.0mM Histidine, 6.9 mM L-Histidine monohydrochloride monohydrate; 0.053% (w/v) Polysorbate 80 of the pharmaceutical composition; wherein the diluent is water at standard state.

In an embodiment, the psoriasis patient achieved the endpoints of achieving an IGA score of cleared or minimal disease (IGA 0/1) and 90% improvement in PASI response (PASI 90) or 100% improvement in PASI response (PASI 100) at week 16.

In another aspect of the invention the pharmaceutical composition comprises an isolated anti-IL23 specific antibody having the guselkumab CDR sequences comprising (i) the heavy chain CDR amino acid sequences of SEQ ID NO: 5, SEQ ID NO: 20, and SEQ ID NO: 44; and (ii) the light chain CDR amino acid sequences of SEQ ID NO: 50, SEQ ID NO: 56, and SEQ ID NO: 73 at 100 mg/mL; 7.9% (w/v) sucrose, 4.0mM Histidine, 6.9 mM L-Histidine monohydrochloride monohydrate; 0.053% (w/v) Polysorbate 80 of the pharmaceutical composition; wherein the diluent is water at standard state.

Another aspect of the method of the invention comprises administering a pharmaceutical composition comprising an isolated anti-IL-23 specific antibody having the guselkumab heavy chain variable region amino acid sequence of SEQ ID NO: 106 and the guselkumab light chain variable region amino acid sequence of SEQ ID NO: 116 at 100 mg/mL; 7.9% (w/v) sucrose, 4.0mM Histidine, 6.9 mM L-Histidine monohydrochloride monohydrate; 0.053% (w/v) Polysorbate 80 of the pharmaceutical composition; wherein the diluent is water at standard state.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the proportions of subjects achieving a PASI 90 response, a PASI 100 response, an IGA score of cleared (0), and an IGA score of cleared (0) or minimal (1) from Week 1 through Week 48.

Figure 2 is a diagram of the ECLIPSE study design.

Figure 3 shows serum levels of IL-17F in psoriasis patients treated with guselkumab and secukinumab.

Figure 4 shows serum levels of IL-22 in psoriasis patients treated with guselkumab and secukinumab.

Figure 5 shows serum levels of BD-2 in psoriasis patients treated with guselkumab and secukinumab.

Figure 6 shows the normalization of a subset of induced genes in psoriasis lesional skin.

Figure 7 shows the expression in psoriasis lesional skin of a group of genes associated with mucosal-associated invariant T (MAIT) cells

Figure 8 shows the frequency of CD8 TRM in PSO skin treated with guselkumab and secukinumab.

Figure 9 shows the frequency of regulatory T cells (Tregs) in PSO skin treated with guselkumab and secukinumab.

Figure 10 shows the ratio of regulatory T cells (Tregs) to CD8 tissue resident memory T cells (TRMs) in PSO skin treated with guselkumab and secukinumab.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

As used herein the method of treatment of psoriasis comprises administering isolated, recombinant and/or synthetic anti-IL-23 specific human antibodies and diagnostic and therapeutic compositions, methods and devices.

As used herein, an "anti-IL-23 specific antibody," "anti-IL-23 antibody," "antibody portion," or "antibody fragment" and/or "antibody variant" and the like include any protein or peptide containing molecule that comprises at least a portion of an immunoglobulin molecule, such as but not limited to, at least one complementarity determining region (CDR) of a heavy or light chain or a ligand binding portion thereof, a heavy chain or light chain variable region, a heavy chain or light chain constant region, a framework region, or any portion thereof, or at least one portion of an IL-23 receptor or binding protein, which can be incorporated into an antibody of the present invention. Such antibody optionally further affects a specific ligand, such as but not limited to, where such antibody modulates, decreases, increases, antagonizes, agonizes, mitigates, alleviates, blocks, inhibits, abrogates and/or interferes with at least one IL-23 activity or binding, or with IL-23 receptor activity or binding, *in vitro, in* situ and/or in *vivo*. As a non-limiting example, a suitable anti-IL-23 antibody, specified portion or variant of the present invention can bind at least one IL-23 molecule, or specified portions, variants or domains thereof. A suitable anti-IL-23 antibody, specified portion, or variant can also optionally affect at least one of IL-23 activity or function, such as but not limited to, RNA, DNA or protein synthesis, IL-23 release, IL-23 receptor signaling, membrane IL-23 cleavage, IL-23 activity, IL-23 production and/or synthesis.

The term “antibody” is further intended to encompass antibodies, digestion fragments, specified portions and variants thereof, including antibody mimetics or comprising portions of antibodies that mimic the structure and/or function of an antibody or specified fragment or portion thereof, including single chain antibodies and fragments thereof. Functional fragments include antigen-binding fragments that bind to a mammalian IL-23. For example, antibody fragments capable of binding to IL-23 or portions thereof, including, but not limited to, Fab (e.g., by papain digestion), Fab' (e.g., by pepsin digestion and partial reduction) and $F(ab')_2$ (e.g., by pepsin digestion), facb (e.g., by plasmin digestion), pFc’ (e.g., by pepsin or plasmin digestion), Fd (e.g., by pepsin digestion, partial reduction and reaggregation), Fv or scFv (e.g., by molecular biology techniques) fragments, are encompassed by the invention (see, e.g., Colligan, Immunology, supra).

Such fragments can be produced by enzymatic cleavage, synthetic or recombinant techniques, as known in the art and/or as described herein. Antibodies can also be produced in a variety of truncated forms using antibody genes in which one or more stop codons have been introduced upstream of the natural stop site. For example, a combination gene encoding a $F(ab')_2$ heavy chain portion can be designed to include DNA sequences encoding the C_H1 domain and/or hinge region of the heavy chain. The various portions of antibodies can be joined together chemically by conventional techniques, or can be prepared as a contiguous protein using genetic engineering techniques.

As used herein, the term “human antibody” refers to an antibody in which substantially every part of the protein (e.g., CDR, framework, C_L, C_H domains (e.g., C_H1, C_H2, C_H3), hinge, (V_L, V_H)) is substantially non-immunogenic in humans, with only minor sequence changes or variations. A “human antibody” may also be an antibody that is derived from or closely matches human germline immunoglobulin sequences. Human antibodies may include amino acid residues not encoded by germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo). Often, this means that the human antibody is substantially non-immunogenic in humans. Human antibodies have been classified into groupings based on their amino acid sequence similarities. Accordingly, using a sequence similarity search, an antibody with a similar linear sequence can be chosen as a template to create a human antibody. Similarly, antibodies designated primate (monkey, baboon, chimpanzee, etc.), rodent (mouse, rat, rabbit, guinea pig, hamster, and the like) and other mammals designate such species, sub-genus, genus, sub-family, and family specific antibodies. Further, chimeric antibodies can include any combination of the above. Such changes or variations optionally and preferably retain or reduce the immunogenicity in humans or other species relative to non-modified antibodies. Thus, a human antibody is distinct from a chimeric or humanized antibody.

It is pointed out that a human antibody can be produced by a non-human animal or prokaryotic or eukaryotic cell that is capable of expressing functionally rearranged human immunoglobulin (e.g., heavy chain and/or light chain) genes. Further, when a human antibody is a single chain antibody, it can comprise a linker peptide that is not found in native human antibodies. For example, an Fv can comprise a linker peptide, such as two to about eight glycine or other amino acid residues, which connects the variable region of the heavy chain and the variable region of the light chain. Such linker peptides are considered to be of human origin.

Bispecific, heterospecific, heteroconjugate or similar antibodies can also be used that are monoclonal, preferably, human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for at least one IL-23 protein, the other one is for any other antigen. Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy chain-light chain pairs, where the two heavy chains have different specificities (Milstein and Cuello, Nature 305:537 (1983)). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of 10 different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule, which is usually done by affinity chromatography steps, is rather cumbersome, and the product yields are low. Similar procedures are disclosed, e.g., in WO 93/08829, US Patent Nos, 6210668, 6193967, 6132992, 6106833, 6060285, 6037453, 6010902, 5989530, 5959084, 5959083, 5932448, 5833985, 5821333, 5807706, 5643759, 5601819, 5582996, 5496549, 4676980, WO 91/00360, WO 92/00373, EP 03089, Traunecker et al., EMBO J. 10:3655 (1991), Suresh et al., Methods in Enzymology 121:210 (1986), each entirely incorporated herein by reference.

Anti-IL-23 specific (also termed IL-23 specific antibodies) (or antibodies to IL-23) useful in the methods and compositions of the present invention can optionally be characterized by high affinity binding to IL-23 and, optionally and preferably, having low toxicity. In particular, an antibody, specified fragment or variant of the invention, where the individual components, such as the variable region, constant region and framework, individually and/or collectively, optionally and preferably possess low immunogenicity, is useful in the present invention. The antibodies that can be used in the invention are optionally characterized by their ability to treat patients for extended periods with measurable alleviation of symptoms and low and/or acceptable toxicity. Low or acceptable immunogenicity and/or high affinity, as well as other suitable properties, can contribute to the therapeutic results achieved. "Low immunogenicity" is defined herein as raising significant HAHA, HACA or HAMA responses in less than about 75%, or preferably less than about 50% of the patients treated and/or raising low titres in the patient treated (less than about 300, preferably less than about 100 measured with a double antigen enzyme immunoassay) (Elliott *et al.*, *Lancet 344*:1125-1127 (1994), entirely incorporated herein by reference). "Low immunogenicity" can also be defined as the incidence of titrable levels of antibodies to the anti-IL-23 antibody in patients treated with anti-IL-23 antibody as occurring in less than 25% of patients treated, preferably, in less than 10% of patients treated with the recommended dose for the recommended course of therapy during the treatment period.

The terms " clinically proven efficacy" and “clinically proven effective” as used herein in the context of a dose, dosage regimen, treatment or method refer to the effectiveness of a particular dose, dosage or treatment regimen. Efficacy can be measured based on change in the course of the disease in response to an agent of the present invention. For example, an anti-IL-23 antibody of the present invention (e.g., the anti-IL-23 antibody guselkumab) is administered to a patient in an amount and for a time sufficient to induce an improvement, preferably a sustained improvement, in at least one indicator that reflects the severity of the disorder that is being treated. Various indicators that reflect the extent of the subject's illness, disease or condition may be assessed for determining whether the amount and time of the treatment is sufficient. Such indicators include, for example, clinically recognized indicators of disease severity, symptoms, or manifestations of the disorder in question. The degree of improvement generally is determined by a physician, who may make this determination based on signs, symptoms, biopsies, or other test results, and who may also employ questionnaires that are administered to the subject, such as quality-of-life questionnaires developed for a given disease. For example, an anti-IL23 antibody of the present invention may be administered to achieve an improvement in a patient's condition related to psoriasis. Improvement may be indicated by an improvement in an index of disease activity, by amelioration of clinical symptoms or by any other measure of disease activity. Examples of such indices of disease are PASI75, PASI90, PASI100, IGA1 and IGA0. The Psoriasis Area and Severity Index (PASI) is a score used by doctors and nurses to record psoriasis severity and PASI75 is shorthand for a 75% reduction of the PASI score from the start to the end of the trial (with PASI90 meaning a 90% reduction and PASI100 meaning a 100% reduction). Investigator's Global Assesement (IGA) tool is a visual assessment that consists of a score ranging from 0 (clear) to 4 (severe). IGA0 signifies cleared and IGA1 signifies almost clear.

The term "clinically proven safe", as it relates to a dose, dosage regimen, treatment or method with an anti-IL-23 antibody of the present invention (e.g., the anti-IL-23 antibody guselkumab), refers to a favorable risk:benefit ratio with an acceptable frequency and/or acceptable severity of treatment-emergent adverse events (referred to as AEs or TEAEs) compared to the standard of care or to another comparator. An adverse event is an untoward medical occurrence in a patient administered a medicinal product. In particular, safe as it relates to a dose, dosage regimen or treatment with an anti-IL-23 antibody of the present invention refers to with an acceptable frequency and/or acceptable severity of adverse events associated with administration of the antibody if attribution is considered to be possible, probable, or very likely due to the use of the anti-IL23 antibody.

As used herein, unless otherwise noted, the term "clinically proven" (used independently or to modify the terms "safe" and/or "effective") shall mean that it has been proven by a clinical trial wherein the clinical trial has met the approval standards of U.S. Food and Drug Administration, EMEA or a corresponding national regulatory agency. For example, the clinical study may be an adequately sized, randomized, double-blinded study used to clinically prove the effects of the drug.

Utility

The isolated nucleic acids of the present invention can be used for production of at least one anti-IL-23 antibody or specified variant thereof, which can be used to measure or effect in an cell, tissue, organ or animal (including mammals and humans), to diagnose, monitor, modulate, treat, alleviate, help prevent the incidence of, or reduce the symptoms of psoriasis.

Such a method can comprise administering an effective amount of a composition or a pharmaceutical composition comprising at least one anti-IL-23 antibody to a cell, tissue, organ, animal or patient in need of such modulation, treatment, alleviation, prevention, or reduction in symptoms, effects or mechanisms. The effective amount can comprise an amount of about 0.001 to 500 mg/kg per single (e.g., bolus), multiple or continuous administration, or to achieve a serum concentration of 0.01-5000 μg/ml serum concentration per single, multiple, or continuous administration, or any effective range or value therein, as done and determined using known methods, as described herein or known in the relevant arts.

Citations

All publications or patents cited herein, whether or not specifically designated, are entirely incorporated herein by reference as they show the state of the art at the time of the present invention and/or to provide description and enablement of the present invention. Publications refer to any scientific or patent publications, or any other information available in any media format, including all recorded, electronic or printed formats. The following references are entirely incorporated herein by reference: Ausubel, et al., ed., Current Protocols in Molecular Biology, John Wiley & Sons, Inc., NY, NY (1987-2001); Sambrook, et al., Molecular Cloning: A Laboratory Manual, 2nd Edition, Cold Spring Harbor, NY (1989); Harlow and Lane, antibodies, a Laboratory Manual, Cold Spring Harbor, NY (1989); Colligan, et al., eds., Current Protocols in Immunology, John Wiley & Sons, Inc., NY (1994-2001); Colligan et al., Current Protocols in Protein Science, John Wiley & Sons, NY, NY, (1997-2001).

Antibodies of the Present Invention – Production and Generation

At least one anti-IL-23 antibody used in the method of the present invention can be optionally produced by a cell line, a mixed cell line, an immortalized cell or clonal population of immortalized cells, as well known in the art. See, e.g., Ausubel, et al., ed., Current Protocols in Molecular Biology, John Wiley & Sons, Inc., NY, NY (1987-2001); Sambrook, et al., Molecular Cloning: A Laboratory Manual, 2nd Edition, Cold Spring Harbor, NY (1989); Harlow and Lane, antibodies, a Laboratory Manual, Cold Spring Harbor, NY (1989); Colligan, et al., eds., Current Protocols in Immunology, John Wiley & Sons, Inc., NY (1994-2001); Colligan et al., Current Protocols in Protein Science, John Wiley & Sons, NY, NY, (1997-2001), each entirely incorporated herein by reference.

A preferred anti-IL-23 antibody is guselkumab (also referred to as CNTO1959) having the heavy chain variable region amino acid sequence of SEQ ID NO: 106 and the light chain variable region amino acid sequence of SEQ ID NO: 116 and having the heavy chain CDR amino acid sequences of SEQ ID NO: 5, SEQ ID NO: 20, and SEQ ID NO: 44; and the light chain CDR amino acid sequences of SEQ ID NO: 50, SEQ ID NO: 56, and SEQ ID NO: 73. Other anti-IL-23 antibodies have sequences listed herein and are described in U.S. Patent No. 7,935,344, the entire contents of which are incorporated herein by reference).

Human antibodies that are specific for human IL-23 proteins or fragments thereof can be raised against an appropriate immunogenic antigen, such as an isolated IL-23 protein and/or a portion thereof (including synthetic molecules, such as synthetic peptides). Other specific or general mammalian antibodies can be similarly raised. Preparation of immunogenic antigens, and monoclonal antibody production can be performed using any suitable technique.

In one approach, a hybridoma is produced by fusing a suitable immortal cell line (e.g., a myeloma cell line, such as, but not limited to, Sp2/0, Sp2/0-AG14, NSO, NS1, NS2, AE-1, L.5, L243, P3X63Ag8.653, Sp2 SA3, Sp2 MAI, Sp2 SS1, Sp2 SA5, U937, MLA 144, ACT IV, MOLT4, DA-1, JURKAT, WEHI, K-562, COS, RAJI, NIH 3T3, HL-60, MLA 144, NAMALWA, NEURO 2A, or the like, or heteromylomas, fusion products thereof, or any cell or fusion cell derived therefrom, or any other suitable cell line as known in the art) (see, e.g., www.atcc.org, www.lifetech.com., and the like), with antibody producing cells, such as, but not limited to, isolated or cloned spleen, peripheral blood, lymph, tonsil, or other immune or B cell containing cells, or any other cells expressing heavy or light chain constant or variable or framework or CDR sequences, either as endogenous or heterologous nucleic acid, as recombinant or endogenous, viral, bacterial, algal, prokaryotic, amphibian, insect, reptilian, fish, mammalian, rodent, equine, ovine, goat, sheep, primate, eukaryotic, genomic DNA, cDNA, rDNA, mitochondrial DNA or RNA, chloroplast DNA or RNA, hnRNA, mRNA, tRNA, single, double or triple stranded, hybridized, and the like or any combination thereof. See, e.g., Ausubel, supra, and Colligan, Immunology, supra, chapter 2, entirely incorporated herein by reference.

Antibody producing cells can also be obtained from the peripheral blood or, preferably, the spleen or lymph nodes, of humans or other suitable animals that have been immunized with the antigen of interest. Any other suitable host cell can also be used for expressing heterologous or endogenous nucleic acid encoding an antibody, specified fragment or variant thereof, of the present invention. The fused cells (hybridomas) or recombinant cells can be isolated using selective culture conditions or other suitable known methods, and cloned by limiting dilution or cell sorting, or other known methods. Cells which produce antibodies with the desired specificity can be selected by a suitable assay (e.g., ELISA).

Other suitable methods of producing or isolating antibodies of the requisite specificity can be used, including, but not limited to, methods that select recombinant antibody from a peptide or protein library (e.g., but not limited to, a bacteriophage, ribosome, oligonucleotide, RNA, cDNA, or the like, display library; e.g., as available from Cambridge antibody Technologies, Cambridgeshire, UK; MorphoSys, Martinsreid/Planegg, DE; Biovation, Aberdeen, Scotland, UK; BioInvent, Lund, Sweden; Dyax Corp., Enzon, Affymax/Biosite; Xoma, Berkeley, CA; Ixsys. See, e.g., EP 368,684, PCT/GB91/01134; PCT/GB92/01755; PCT/GB92/002240; PCT/GB92/00883; PCT/GB93/00605; US 08/350260(5/12/94); PCT/GB94/01422; PCT/GB94/02662; PCT/GB97/01835; (CAT/MRC); WO90/14443; WO90/14424; WO90/14430; PCT/US94/1234; WO92/18619; WO96/07754; (Scripps); WO96/13583, WO97/08320 (MorphoSys); WO95/16027 (BioInvent); WO88/06630; WO90/3809 (Dyax); US 4,704,692 (Enzon); PCT/US91/02989 (Affymax); WO89/06283; EP 371 998; EP 550 400; (Xoma); EP 229 046; PCT/US91/07149 (Ixsys); or stochastically generated peptides or proteins - US 5723323, 5763192, 5814476, 5817483, 5824514, 5976862, WO 86/05803, EP 590 689 (Ixsys, predecessor of Applied Molecular Evolution (AME), each entirely incorporated herein by reference)) or that rely upon immunization of transgenic animals (e.g., SCID mice, Nguyen et al., Microbiol. Immunol. 41:901-907 (1997); Sandhu et al., Crit. Rev. Biotechnol. 16:95-118 (1996); Eren et al., Immunol. 93:154-161 (1998), each entirely incorporated by reference as well as related patents and applications) that are capable of producing a repertoire of human antibodies, as known in the art and/or as described herein. Such techniques, include, but are not limited to, ribosome display (Hanes et al., Proc. Natl. Acad. Sci. USA, 94:4937-4942 (May 1997); Hanes et al., Proc. Natl. Acad. Sci. USA, 95:14130-14135 (Nov. 1998)); single cell antibody producing technologies (e.g., selected lymphocyte antibody method ("SLAM") (US pat. No. 5,627,052, Wen et al., J. Immunol. 17:887-892 (1987); Babcook et al., Proc. Natl. Acad. Sci. USA 93:7843-7848 (1996)); gel microdroplet and flow cytometry (Powell et al., Biotechnol. 8:333-337 (1990); One Cell Systems, Cambridge, MA; Gray et al., J. Imm. Meth. 182:155-163 (1995); Kenny et al., Bio/Technol. 13:787-790 (1995)); B-cell selection (Steenbakkers et al., Molec. Biol. Reports 19:125-134 (1994); Jonak et al., Progress Biotech, Vol. 5, In Vitro Immunization in Hybridoma Technology, Borrebaeck, ed., Elsevier Science Publishers B.V., Amsterdam, Netherlands (1988)).

Methods for engineering or humanizing non-human or human antibodies can also be used and are well known in the art. Generally, a humanized or engineered antibody has one or more amino acid residues from a source that is non-human, e.g., but not limited to, mouse, rat, rabbit, non-human primate or other mammal. These non-human amino acid residues are replaced by residues often referred to as "import" residues, which are typically taken from an "import" variable, constant or other domain of a known human sequence.

Known human Ig sequences are disclosed, e.g., www.ncbi.nlm.nih.gov/entrez/query.fcgi; www.ncbi.nih.gov/igblast; www.atcc.org/phage/hdb.html; www.mrc-cpe.cam.ac.uk/ALIGNMENTS.php; www.kabatdatabase.com/top.html; ftp.ncbi.nih.gov/repository/kabat; www.sciquest.com; www.abcam.com; www.antibodyresource.com/onlinecomp.html; www.public.iastate.edu/~pedro/research_tools.html; www.whfreeman.com/immunology/CH05/kuby05.htm;

www.hhmi.org/grants/lectures/1996/vlab; www.path.cam.ac.uk/~mrc7/mikeimages.html; mcb.harvard.edu/BioLinks/Immunology.html; www.immunologylink.com; pathbox.wustl.edu/~hcenter/index.html; www.appliedbiosystems.com; www.nal.usda.gov/awic/pubs/antibody; www.m.ehime-u.ac.jp/~yasuhito/Elisa.html; www.biodesign.com; www.cancerresearchuk.org; www.biotech.ufl.edu; www.isac-net.org; baserv.uci.kun.nl/~jraats/links1.html; www.recab.uni-hd.de/immuno.bme.nwu.edu; www.mrc-cpe.cam.ac.uk; www.ibt.unam.mx/vir/V_mice.html; http://www.bioinf.org.uk/abs; antibody.bath.ac.uk; www.unizh.ch; www.cryst.bbk.ac.uk/~ubcg07s; www.nimr.mrc.ac.uk/CC/ccaewg/ccaewg.html; www.path.cam.ac.uk/~mrc7/humanisation/TAHHP.html; www.ibt.unam.mx/vir/structure/stat_aim.html; www.biosci.missouri.edu/smithgp/index.html; www.jerini.de; Kabat et al., Sequences of Proteins of Immunological Interest, U.S. Dept. Health (1983), each entirely incorporated herein by reference.

Such imported sequences can be used to reduce immunogenicity or reduce, enhance or modify binding, affinity, on-rate, off-rate, avidity, specificity, half-life, or any other suitable characteristic, as known in the art. In general, the CDR residues are directly and most substantially involved in influencing antigen binding. Accordingly, part or all of the non-human or human CDR sequences are maintained while the non-human sequences of the variable and constant regions may be replaced with human or other amino acids.

Antibodies can also optionally be humanized or human antibodies engineered with retention of high affinity for the antigen and other favorable biological properties. To achieve this goal, humanized (or human) antibodies can be optionally prepared by a process of analysis of the parental sequences and various conceptual humanized products using three-dimensional models of the parental and humanized sequences. Three-dimensional immunoglobulin models are commonly available and are familiar to those skilled in the art. Computer programs are available which illustrate and display probable three-dimensional conformational structures of selected candidate immunoglobulin sequences. Inspection of these displays permits analysis of the likely role of the residues in the functioning of the candidate immunoglobulin sequence, i.e., the analysis of residues that influence the ability of the candidate immunoglobulin to bind its antigen. In this way, framework (FR) residues can be selected and combined from the consensus and import sequences so that the desired antibody characteristic, such as increased affinity for the target antigen(s), is achieved.

In addition, the human IL-23 specific antibody used in the method of the present invention may comprise a human germline light chain framework. In particular embodiments, the light chain germline sequence is selected from human VK sequences including, but not limited to, A1, A10, A11, A14, A17, A18, A19, A2, A20, A23, A26, A27, A3, A30, A5, A7, B2, B3, L1, L10, L11, L12, L14, L15, L16, L18, L19, L2, L20, L22, L23, L24, L25, L4/18a, L5, L6, L8, L9, O1, O11, O12, O14, O18, O2, O4, and O8. In certain embodiments, this light chain human germline framework is selected from V1-11, V1-13, V1-16, V1-17, V1-18, V1-19, V1-2, V1-20, V1-22, V1-3, V1-4, V1-5, V1-7, V1-9, V2-1, V2-11, V2-13, V2-14, V2-15, V2-17, V2-19, V2-6, V2-7, V2-8, V3-2, V3-3, V3-4, V4-1, V4-2, V4-3, V4-4, V4-6, V5-1, V5-2, V5-4, and V5-6.

In other embodiments, the human IL-23 specific antibody used in the method of the present invention may comprise a human germline heavy chain framework. In particular embodiments, this heavy chain human germline framework is selected from VH1-18, VH1-2, VH1-24, VH1-3, VH1-45, VH1-46, VH1-58, VH1-69, VH1-8, VH2-26, VH2-5, VH2-70, VH3-11, VH3-13, VH3-15, VH3-16, VH3-20, VH3-21, VH3-23, VH3-30, VH3-33, VH3-35, VH3-38, VH3-43, VH3-48, VH3-49, VH3-53, VH3-64, VH3-66, VH3-7, VH3-72, VH3-73, VH3-74, VH3-9, VH4-28, VH4-31, VH4-34, VH4-39, VH4-4, VH4-59, VH4-61, VH5-51, VH6-1, and VH7-81.

In particular embodiments, the light chain variable region and/or heavy chain variable region comprises a framework region or at least a portion of a framework region (e.g., containing 2 or 3 subregions, such as FR2 and FR3). In certain embodiments, at least FRL1, FRL2, FRL3, or FRL4 is fully human. In other embodiments, at least FRH1, FRH2, FRH3, or FRH4 is fully human. In some embodiments, at least FRL1, FRL2, FRL3, or FRL4 is a germline sequence (e.g., human germline) or comprises human consensus sequences for the particular framework (readily available at the sources of known human Ig sequences described above). In other embodiments, at least FRH1, FRH2, FRH3, or FRH4 is a germline sequence (e.g., human germline) or comprises human consensus sequences for the particular framework. In preferred embodiments, the framework region is a fully human framework region.

Humanization or engineering of antibodies of the present invention can be performed using any known method, such as but not limited to those described in, Winter (Jones et al., Nature 321:522 (1986); Riechmann et al., Nature 332:323 (1988); Verhoeyen et al., Science 239:1534 (1988)), Sims et al., J. Immunol. 151: 2296 (1993); Chothia and Lesk, J. Mol. Biol. 196:901 (1987), Carter et al., Proc. Natl. Acad. Sci. U.S.A. 89:4285 (1992); Presta et al., J. Immunol. 151:2623 (1993), US Patent Nos: 5723323, 5976862, 5824514, 5817483, 5814476, 5763192, 5723323, 5,766886, 5714352, 6204023, 6180370, 5693762, 5530101, 5585089, 5225539; 4816567, PCT/: US98/16280, US96/18978, US91/09630, US91/05939, US94/01234, GB89/01334, GB91/01134, GB92/01755; WO90/14443, WO90/14424, WO90/14430, EP 229246, each entirely incorporated herein by reference, included references cited therein.

In certain embodiments, the antibody comprises an altered (e.g., mutated) Fc region. For example, in some embodiments, the Fc region has been altered to reduce or enhance the effector functions of the antibody. In some embodiments, the Fc region is an isotype selected from IgM, IgA, IgG, IgE, or other isotype. Alternatively or additionally, it may be useful to combine amino acid modifications with one or more further amino acid modifications that alter C1q binding and/or the complement dependent cytotoxicity function of the Fc region of an IL-23 binding molecule. The starting polypeptide of particular interest may be one that binds to C1q and displays complement dependent cytotoxicity (CDC). Polypeptides with pre-existing C1q binding activity, optionally further having the ability to mediate CDC may be modified such that one or both of these activities are enhanced. Amino acid modifications that alter C1q and/or modify its complement dependent cytotoxicity function are described, for example, in WO0042072, which is hereby incorporated by reference.

As disclosed above, one can design an Fc region of the human IL-23 specific antibody of the present invention with altered effector function, e.g., by modifying C1q binding and/or FcγR binding and thereby changing complement dependent cytotoxicity (CDC) activity and/or antibody-dependent cell-mediated cytotoxicity (ADCC) activity. “Effector functions" are responsible for activating or diminishing a biological activity (e.g., in a subject). Examples of effector functions include, but are not limited to: C1q binding; CDC; Fc receptor binding; ADCC; phagocytosis; down regulation of cell surface receptors (e.g., B cell receptor; BCR), etc. Such effector functions may require the Fc region to be combined with a binding domain (e.g., an antibody variable domain) and can be assessed using various assays (e.g., Fc binding assays, ADCC assays, CDC assays, etc.).

For example, one can generate a variant Fc region of the human IL-23 (or anti-IL-23) antibody with improved C1q binding and improved FcγRIIIbinding (e.g., having both improved ADCC activity and improved CDC activity). Alternatively, if it is desired that effector function be reduced or ablated, a variant Fc region can be engineered with reduced CDC activity and/or reduced ADCC activity. In other embodiments, only one of these activities may be increased, and, optionally, also the other activity reduced (e.g., to generate an Fc region variant with improved ADCC activity, but reduced CDC activity and vice versa).

Fc mutations can also be introduced in engineer to alter their interaction with the neonatal Fc receptor (FcRn) and improve their pharmacokinetic properties. A collection of human Fc variants with improved binding to the FcRn have been described (Shields et al., (2001). High resolution mapping of the binding site on human IgG1 for FcγRI, FcγRII, FcγRIII, and FcRn and design of IgG1 variants with improved binding to the FcγR, J. Biol. Chem. 276:6591-6604).

Another type of amino acid substitution serves to alter the glycosylation pattern of the Fc region of the human IL-23 specific antibody. Glycosylation of an Fc region is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. O-linked glycosylation refers to the attachment of one of the sugars N-aceylgalactosamine, galactose, or xylose to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine may also be used. The recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain peptide sequences are asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline. Thus, the presence of either of these peptide sequences in a polypeptide creates a potential glycosylation site.

The glycosylation pattern may be altered, for example, by deleting one or more glycosylation site(s) found in the polypeptide, and/or adding one or more glycosylation sites that are not present in the polypeptide. Addition of glycosylation sites to the Fc region of a human IL-23 specific antibody is conveniently accomplished by altering the amino acid sequence such that it contains one or more of the above-described tripeptide sequences (for N-linked glycosylation sites). An exemplary glycosylation variant has an amino acid substitution of residue Asn 297 of the heavy chain. The alteration may also be made by the addition of, or substitution by, one or more serine or threonine residues to the sequence of the original polypeptide (for O-linked glycosylation sites). Additionally, a change of Asn 297 to Ala can remove one of the glycosylation sites.

In certain embodiments, the human IL-23 specific antibody of the present invention is expressed in cells that express beta (1,4)-N-acetylglucosaminyltransferase III (GnT III), such that GnT III adds GlcNAc to the human IL-23 antibody. Methods for producing antibodies in such a fashion are provided in WO/9954342, WO/03011878, patent publication 20030003097A1, and Umana et al., Nature Biotechnology, 17:176-180, Feb. 1999; all of which are herein specifically incorporated by reference in their entireties.

The anti-IL-23 antibody can also be optionally generated by immunization of a transgenic animal (e.g., mouse, rat, hamster, non-human primate, and the like) capable of producing a repertoire of human antibodies, as described herein and/or as known in the art. Cells that produce a human anti-IL-23 antibody can be isolated from such animals and immortalized using suitable methods, such as the methods described herein.

Transgenic mice that can produce a repertoire of human antibodies that bind to human antigens can be produced by known methods (e.g., but not limited to, U.S. Pat. Nos: 5,770,428, 5,569,825, 5,545,806, 5,625,126, 5,625,825, 5,633,425, 5,661,016 and 5,789,650 issued to Lonberg *et al.*; Jakobovits *et al.* WO 98/50433, Jakobovits *et al.* WO 98/24893, Lonberg *et al.* WO 98/24884, Lonberg *et al.* WO 97/13852, Lonberg *et al.* WO 94/25585, Kucherlapate *et al.* WO 96/34096, Kucherlapate *et al.* EP 0463 151 B1, Kucherlapate *et al.* EP 0710 719 A1, Surani *et al.* US. Pat. No. 5,545,807, Bruggemann *et al.* WO 90/04036, Bruggemann *et al.* EP 0438 474 B1, Lonberg *et al.* EP 0814 259 A2, Lonberg *et al.* GB 2 272 440 A, Lonberg *et al. Nature* 368:856-859 (1994), Taylor *et al., Int. Immunol.* 6(4)579-591 (1994), Green *et al, Nature Genetics* 7:13-21 (1994), Mendez *et al., Nature Genetics* 15:146-156 (1997), Taylor *et al.,* *Nucleic Acids Research* 20(23):6287-6295 (1992), Tuaillon *et al., Proc Natl Acad Sci USA* 90(8)3720-3724 (1993), Lonberg *et al., Int Rev Immunol* 13(1):65-93 (1995) and Fishwald *et al., Nat Biotechnol* 14(7):845-851 (1996), which are each entirely incorporated herein by reference). Generally, these mice comprise at least one transgene comprising DNA from at least one human immunoglobulin locus that is functionally rearranged, or which can undergo functional rearrangement. The endogenous immunoglobulin loci in such mice can be disrupted or deleted to eliminate the capacity of the animal to produce antibodies encoded by endogenous genes.

Screening antibodies for specific binding to similar proteins or fragments can be conveniently achieved using peptide display libraries. This method involves the screening of large collections of peptides for individual members having the desired function or structure. Antibody screening of peptide display libraries is well known in the art. The displayed peptide sequences can be from 3 to 5000 or more amino acids in length, frequently from 5-100 amino acids long, and often from about 8 to 25 amino acids long. In addition to direct chemical synthetic methods for generating peptide libraries, several recombinant DNA methods have been described. One type involves the display of a peptide sequence on the surface of a bacteriophage or cell. Each bacteriophage or cell contains the nucleotide sequence encoding the particular displayed peptide sequence. Such methods are described in PCT Patent Publication Nos. 91/17271, 91/18980, 91/19818, and 93/08278.

Other systems for generating libraries of peptides have aspects of both in vitro chemical synthesis and recombinant methods. See, PCT Patent Publication Nos. 92/05258, 92/14843, and 96/19256. See also, U.S. Patent Nos. 5,658,754; and 5,643,768. Peptide display libraries, vector, and screening kits are commercially available from such suppliers as Invitrogen (Carlsbad, CA), and Cambridge antibody Technologies (Cambridgeshire, UK). See, e.g., U.S. Pat. Nos. 4704692, 4939666, 4946778, 5260203, 5455030, 5518889, 5534621, 5656730, 5763733, 5767260, 5856456, assigned to Enzon; 5223409, 5403484, 5571698, 5837500, assigned to Dyax, 5427908, 5580717, assigned to Affymax; 5885793, assigned to Cambridge antibody Technologies; 5750373, assigned to Genentech, 5618920, 5595898, 5576195, 5698435, 5693493, 5698417, assigned to Xoma, Colligan, supra; Ausubel, *supra*; or Sambrook, *supra,* each of the above patents and publications entirely incorporated herein by reference.

Antibodies used in the method of the present invention can also be prepared using at least one anti-IL23 antibody encoding nucleic acid to provide transgenic animals or mammals, such as goats, cows, horses, sheep, rabbits, and the like, that produce such antibodies in their milk. Such animals can be provided using known methods. See, e.g., but not limited to, US Patent Nos. 5,827,690; 5,849,992; 4,873,316; 5,849,992; 5,994,616; 5,565,362; 5,304,489, and the like, each of which is entirely incorporated herein by reference.

Antibodies used in the method of the present invention can additionally be prepared using at least one anti-IL23 antibody encoding nucleic acid to provide transgenic plants and cultured plant cells (e.g., but not limited to, tobacco and maize) that produce such antibodies, specified portions or variants in the plant parts or in cells cultured therefrom. As a non-limiting example, transgenic tobacco leaves expressing recombinant proteins have been successfully used to provide large amounts of recombinant proteins, e.g., using an inducible promoter. See, e.g., Cramer et al., Curr. Top. Microbol. Immunol. 240:95-118 (1999) and references cited therein. Also, transgenic maize have been used to express mammalian proteins at commercial production levels, with biological activities equivalent to those produced in other recombinant systems or purified from natural sources. See, e.g., Hood et al., Adv. Exp. Med. Biol. 464:127-147 (1999) and references cited therein. Antibodies have also been produced in large amounts from transgenic plant seeds including antibody fragments, such as single chain antibodies (scFv's), including tobacco seeds and potato tubers. See, e.g., Conrad et al., Plant Mol. Biol. 38:101-109 (1998) and references cited therein. Thus, antibodies of the present invention can also be produced using transgenic plants, according to known methods. See also, e.g., Fischer et al., Biotechnol. Appl. Biochem. 30:99-108 (Oct.,1999), Ma et al., Trends Biotechnol. 13:522-7 (1995); Ma et al., Plant Physiol. 109:341-6 (1995); Whitelam et al., Biochem. Soc. Trans. 22:940-944 (1994); and references cited therein. Each of the above references is entirely incorporated herein by reference.

The antibodies used in the method of the invention can bind human IL-23 with a wide range of affinities (K_D). In a preferred embodiment, a human mAb can optionally bind human IL-23 with high affinity. For example, a human mAb can bind human IL-23 with a K_D equal to or less than about 10^{-7} M, such as but not limited to, 0.1-9.9 (or any range or value therein) X 10^{-7}, 10^{-8}, 10^{-9}, 10^{-10}, 10^{-11}, 10^{-12}, 10^{-13} or any range or value therein.

The affinity or avidity of an antibody for an antigen can be determined experimentally using any suitable method. (See, for example, Berzofsky, *et al.*, "Antibody-Antigen Interactions," In *Fundamental Immunology*, Paul, W. E., Ed., Raven Press: New York, NY (1984); Kuby, Janis *Immunology*, W. H. Freeman and Company: New York, NY (1992); and methods described herein). The measured affinity of a particular antibody-antigen interaction can vary if measured under different conditions (e.g., salt concentration, pH). Thus, measurements of affinity and other antigen-binding parameters (e.g., K_D, K_a, K_d) are preferably made with standardized solutions of antibody and antigen, and a standardized buffer, such as the buffer described herein.

Nucleic Acid Molecules

Using the information provided herein, for example, the nucleotide sequences encoding at least 70-100% of the contiguous amino acids of at least one of the light or heavy chain variable or CDR regions described herein, among other sequences disclosed herein, specified fragments, variants or consensus sequences thereof, or a deposited vector comprising at least one of these sequences, a nucleic acid molecule of the present invention encoding at least one anti-IL-23 antibody can be obtained using methods described herein or as known in the art.

Nucleic acid molecules of the present invention can be in the form of RNA, such as mRNA, hnRNA, tRNA or any other form, or in the form of DNA, including, but not limited to, cDNA and genomic DNA obtained by cloning or produced synthetically, or any combinations thereof. The DNA can be triple-stranded, double-stranded or single-stranded, or any combination thereof. Any portion of at least one strand of the DNA or RNA can be the coding strand, also known as the sense strand, or it can be the non-coding strand, also referred to as the anti-sense strand.

Isolated nucleic acid molecules used in the method of the present invention can include nucleic acid molecules comprising an open reading frame (ORF), optionally, with one or more introns, e.g., but not limited to, at least one specified portion of at least one CDR, such as CDR1, CDR2 and/or CDR3 of at least one heavy chain or light chain; nucleic acid molecules comprising the coding sequence for an anti-IL-23 antibody or variable region; and nucleic acid molecules which comprise a nucleotide sequence substantially different from those described above but which, due to the degeneracy of the genetic code, still encode at least one anti-IL-23 antibody as described herein and/or as known in the art. Of course, the genetic code is well known in the art. Thus, it would be routine for one skilled in the art to generate such degenerate nucleic acid variants that code for specific anti-IL-23 antibodies used in the method of the present invention. See, e.g., Ausubel, et al., *supra*, and such nucleic acid variants are included in the present invention. Non-limiting examples of isolated nucleic acid molecules include nucleic acids encoding HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3, respectively.

As indicated herein, nucleic acid molecules which comprise a nucleic acid encoding an anti-IL-23 antibody can include, but are not limited to, those encoding the amino acid sequence of an antibody fragment, by itself; the coding sequence for the entire antibody or a portion thereof; the coding sequence for an antibody, fragment or portion, as well as additional sequences, such as the coding sequence of at least one signal leader or fusion peptide, with or without the aforementioned additional coding sequences, such as at least one intron, together with additional, non-coding sequences, including but not limited to, non-coding 5' and 3' sequences, such as the transcribed, non-translated sequences that play a role in transcription, mRNA processing, including splicing and polyadenylation signals (for example, ribosome binding and stability of mRNA); an additional coding sequence that codes for additional amino acids, such as those that provide additional functionalities. Thus, the sequence encoding an antibody can be fused to a marker sequence, such as a sequence encoding a peptide that facilitates purification of the fused antibody comprising an antibody fragment or portion.

Polynucleotides Selectively Hybridizing to a Polynucleotide as Described Herein

The method of the present invention uses isolated nucleic acids that hybridize under selective hybridization conditions to a polynucleotide disclosed herein. Thus, the polynucleotides of this embodiment can be used for isolating, detecting, and/or quantifying nucleic acids comprising such polynucleotides. For example, polynucleotides of the present invention can be used to identify, isolate, or amplify partial or full-length clones in a deposited library. In some embodiments, the polynucleotides are genomic or cDNA sequences isolated, or otherwise complementary to, a cDNA from a human or mammalian nucleic acid library.

Preferably, the cDNA library comprises at least 80% full-length sequences, preferably, at least 85% or 90% full-length sequences, and, more preferably, at least 95% full-length sequences. The cDNA libraries can be normalized to increase the representation of rare sequences. Low or moderate stringency hybridization conditions are typically, but not exclusively, employed with sequences having a reduced sequence identity relative to complementary sequences. Moderate and high stringency conditions can optionally be employed for sequences of greater identity. Low stringency conditions allow selective hybridization of sequences having about 70% sequence identity and can be employed to identify orthologous or paralogous sequences.

Optionally, polynucleotides will encode at least a portion of an antibody. The polynucleotides embrace nucleic acid sequences that can be employed for selective hybridization to a polynucleotide encoding an antibody of the present invention. See, e.g., Ausubel, supra; Colligan, supra, each entirely incorporated herein by reference.

Construction of Nucleic Acids

The isolated nucleic acids can be made using (a) recombinant methods, (b) synthetic techniques, (c) purification techniques, and/or (d) combinations thereof, as well-known in the art.

The nucleic acids can conveniently comprise sequences in addition to a polynucleotide of the present invention. For example, a multi-cloning site comprising one or more endonuclease restriction sites can be inserted into the nucleic acid to aid in isolation of the polynucleotide. Also, translatable sequences can be inserted to aid in the isolation of the translated polynucleotide of the present invention. For example, a hexa-histidine marker sequence provides a convenient means to purify the proteins of the present invention. The nucleic acid of the present invention, excluding the coding sequence, is optionally a vector, adapter, or linker for cloning and/or expression of a polynucleotide of the present invention.

Additional sequences can be added to such cloning and/or expression sequences to optimize their function in cloning and/or expression, to aid in isolation of the polynucleotide, or to improve the introduction of the polynucleotide into a cell. Use of cloning vectors, expression vectors, adapters, and linkers is well known in the art. (See, e.g., Ausubel, *supra*; or Sambrook, *supra*)

Recombinant Methods for Constructing Nucleic Acids

The isolated nucleic acid compositions, such as RNA, cDNA, genomic DNA, or any combination thereof, can be obtained from biological sources using any number of cloning methodologies known to those of skill in the art. In some embodiments, oligonucleotide probes that selectively hybridize, under stringent conditions, to the polynucleotides of the present invention are used to identify the desired sequence in a cDNA or genomic DNA library. The isolation of RNA, and construction of cDNA and genomic libraries, are well known to those of ordinary skill in the art. (See, e.g., Ausubel, *supra*; or Sambrook, *supra*)

Nucleic Acid Screening and Isolation Methods

A cDNA or genomic library can be screened using a probe based upon the sequence of a polynucleotide used in the method of the present invention, such as those disclosed herein. Probes can be used to hybridize with genomic DNA or cDNA sequences to isolate homologous genes in the same or different organisms. Those of skill in the art will appreciate that various degrees of stringency of hybridization can be employed in the assay; and either the hybridization or the wash medium can be stringent. As the conditions for hybridization become more stringent, there must be a greater degree of complementarity between the probe and the target for duplex formation to occur. The degree of stringency can be controlled by one or more of temperature, ionic strength, pH and the presence of a partially denaturing solvent, such as formamide. For example, the stringency of hybridization is conveniently varied by changing the polarity of the reactant solution through, for example, manipulation of the concentration of formamide within the range of 0% to 50%. The degree of complementarity (sequence identity) required for detectable binding will vary in accordance with the stringency of the hybridization medium and/or wash medium. The degree of complementarity will optimally be 100%, or 70-100%, or any range or value therein. However, it should be understood that minor sequence variations in the probes and primers can be compensated for by reducing the stringency of the hybridization and/or wash medium.

Methods of amplification of RNA or DNA are well known in the art and can be used according to the present invention without undue experimentation, based on the teaching and guidance presented herein.

Known methods of DNA or RNA amplification include, but are not limited to, polymerase chain reaction (PCR) and related amplification processes (see, e.g., U.S. Patent Nos. 4,683,195, 4,683,202, 4,800,159, 4,965,188, to Mullis, et al.; 4,795,699 and 4,921,794 to Tabor, et al; 5,142,033 to Innis; 5,122,464 to Wilson, et al.; 5,091,310 to Innis; 5,066,584 to Gyllensten, et al; 4,889,818 to Gelfand, et al; 4,994,370 to Silver, et al; 4,766,067 to Biswas; 4,656,134 to Ringold) and RNA mediated amplification that uses anti-sense RNA to the target sequence as a template for double-stranded DNA synthesis (U.S. Patent No. 5,130,238 to Malek, et al, with the tradename NASBA), the entire contents of which references are incorporated herein by reference. (See, e.g., Ausubel, *supra*; or Sambrook, *supra.*)

For instance, polymerase chain reaction (PCR) technology can be used to amplify the sequences of polynucleotides used in the method of the present invention and related genes directly from genomic DNA or cDNA libraries. PCR and other in vitro amplification methods can also be useful, for example, to clone nucleic acid sequences that code for proteins to be expressed, to make nucleic acids to use as probes for detecting the presence of the desired mRNA in samples, for nucleic acid sequencing, or for other purposes. Examples of techniques sufficient to direct persons of skill through in vitro amplification methods are found in Berger, supra, Sambrook, supra, and Ausubel, supra, as well as Mullis, et al., U.S. Patent No. 4,683,202 (1987); and Innis, et al., PCR Protocols A Guide to Methods and Applications, Eds., Academic Press Inc., San Diego, CA (1990). Commercially available kits for genomic PCR amplification are known in the art. See, e.g., Advantage-GC Genomic PCR Kit (Clontech). Additionally, e.g., the T4 gene 32 protein (Boehringer Mannheim) can be used to improve yield of long PCR products.

Synthetic Methods for Constructing Nucleic Acids

The isolated nucleic acids used in the method of the present invention can also be prepared by direct chemical synthesis by known methods (see, e.g., Ausubel, et al., supra). Chemical synthesis generally produces a single-stranded oligonucleotide, which can be converted into double-stranded DNA by hybridization with a complementary sequence, or by polymerization with a DNA polymerase using the single strand as a template. One of skill in the art will recognize that while chemical synthesis of DNA can be limited to sequences of about 100 or more bases, longer sequences can be obtained by the ligation of shorter sequences.

Recombinant Expression Cassettes

The present invention uses recombinant expression cassettes comprising a nucleic acid. A nucleic acid sequence, for example, a cDNA or a genomic sequence encoding an antibody used in the method of the present invention, can be used to construct a recombinant expression cassette that can be introduced into at least one desired host cell. A recombinant expression cassette will typically comprise a polynucleotide operably linked to transcriptional initiation regulatory sequences that will direct the transcription of the polynucleotide in the intended host cell. Both heterologous and non-heterologous (i.e., endogenous) promoters can be employed to direct expression of the nucleic acids.

In some embodiments, isolated nucleic acids that serve as promoter, enhancer, or other elements can be introduced in the appropriate position (upstream, downstream or in the intron) of a non-heterologous form of a polynucleotide of the present invention so as to up or down regulate expression of a polynucleotide. For example, endogenous promoters can be altered *in vivo* or *in vitro* by mutation, deletion and/or substitution.

Vectors and Host Cells

The present invention also relates to vectors that include isolated nucleic acid molecules, host cells that are genetically engineered with the recombinant vectors, and the production of at least one anti-IL-23 antibody by recombinant techniques, as is well known in the art. See, e.g., Sambrook, et al., supra; Ausubel, et al., supra, each entirely incorporated herein by reference.

The polynucleotides can optionally be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it can be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

The DNA insert should be operatively linked to an appropriate promoter. The expression constructs will further contain sites for transcription initiation, termination and, in the transcribed region, a ribosome binding site for translation. The coding portion of the mature transcripts expressed by the constructs will preferably include a translation initiating at the beginning and a termination codon (e.g., UAA, UGA or UAG) appropriately positioned at the end of the mRNA to be translated, with UAA and UAG preferred for mammalian or eukaryotic cell expression.

Expression vectors will preferably but optionally include at least one selectable marker. Such markers include, e.g., but are not limited to, methotrexate (MTX), dihydrofolate reductase (DHFR, US Pat.Nos. 4,399,216; 4,634,665; 4,656,134; 4,956,288; 5,149,636; 5,179,017, ampicillin, neomycin (G418), mycophenolic acid, or glutamine synthetase (GS, US Pat.Nos. 5,122,464; 5,770,359; 5,827,739) resistance for eukaryotic cell culture, and tetracycline or ampicillin resistance genes for culturing in *E. coli* and other bacteria or prokaryotics (the above patents are entirely incorporated hereby by reference). Appropriate culture mediums and conditions for the above-described host cells are known in the art. Suitable vectors will be readily apparent to the skilled artisan. Introduction of a vector construct into a host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection or other known methods. Such methods are described in the art, such as Sambrook, supra, Chapters 1-4 and 16-18; Ausubel, supra, Chapters 1, 9, 13, 15, 16.

At least one antibody used in the method of the present invention can be expressed in a modified form, such as a fusion protein, and can include not only secretion signals, but also additional heterologous functional regions. For instance, a region of additional amino acids, particularly charged amino acids, can be added to the N-terminus of an antibody to improve stability and persistence in the host cell, during purification, or during subsequent handling and storage. Also, peptide moieties can be added to an antibody of the present invention to facilitate purification. Such regions can be removed prior to final preparation of an antibody or at least one fragment thereof. Such methods are described in many standard laboratory manuals, such as Sambrook, supra, Chapters 17.29-17.42 and 18.1-18.74; Ausubel, supra, Chapters 16, 17 and 18.

Those of ordinary skill in the art are knowledgeable in the numerous expression systems available for expression of a nucleic acid encoding a protein used in the method of the present invention. Alternatively, nucleic acids can be expressed in a host cell by turning on (by manipulation) in a host cell that contains endogenous DNA encoding an antibody. Such methods are well known in the art, e.g., as described in US patent Nos. 5,580,734, 5,641,670, 5,733,746, and 5,733,761, entirely incorporated herein by reference.

Illustrative of cell cultures useful for the production of the antibodies, specified portions or variants thereof, are mammalian cells. Mammalian cell systems often will be in the form of monolayers of cells although mammalian cell suspensions or bioreactors can also be used. A number of suitable host cell lines capable of expressing intact glycosylated proteins have been developed in the art, and include the COS-1 (e.g., ATCC CRL 1650), COS-7 (e.g., ATCC CRL-1651), HEK293, BHK21 (e.g., ATCC CRL-10), CHO (e.g., ATCC CRL 1610) and BSC-1 (e.g., ATCC CRL-26) cell lines, Cos-7 cells, CHO cells, hep G2 cells, P3X63Ag8.653, SP2/0-Ag14, 293 cells, HeLa cells and the like, which are readily available from, for example, American Type Culture Collection, Manassas, Va (www.atcc.org). Preferred host cells include cells of lymphoid origin, such as myeloma and lymphoma cells. Particularly preferred host cells are P3X63Ag8.653 cells (ATCC Accession Number CRL-1580) and SP2/0-Ag14 cells (ATCC Accession Number CRL-1851). In a particularly preferred embodiment, the recombinant cell is a P3X63Ab8.653 or a SP2/0-Ag14 cell.

Expression vectors for these cells can include one or more of the following expression control sequences, such as, but not limited to, an origin of replication; a promoter (e.g., late or early SV40 promoters, the CMV promoter (US Pat.Nos. 5,168,062; 5,385,839), an HSV tk promoter, a pgk (phosphoglycerate kinase) promoter, an EF-1 alpha promoter (US Pat.No. 5,266,491), at least one human immunoglobulin promoter; an enhancer, and/or processing information sites, such as ribosome binding sites, RNA splice sites, polyadenylation sites (e.g., an SV40 large T Ag poly A addition site), and transcriptional terminator sequences. See, e.g., Ausubel et al., supra; Sambrook, et al., supra. Other cells useful for production of nucleic acids or proteins of the present invention are known and/or available, for instance, from the American Type Culture Collection Catalogue of Cell Lines and Hybridomas (www.atcc.org) or other known or commercial sources.

When eukaryotic host cells are employed, polyadenlyation or transcription terminator sequences are typically incorporated into the vector. An example of a terminator sequence is the polyadenlyation sequence from the bovine growth hormone gene. Sequences for accurate splicing of the transcript can also be included. An example of a splicing sequence is the VP1 intron from

SV40 (Sprague, et al., J. Virol. 45:773-781 (1983)). Additionally, gene sequences to control replication in the host cell can be incorporated into the vector, as known in the art.

Purification of an Antibody

An anti-IL-23 antibody can be recovered and purified from recombinant cell cultures by well-known methods including, but not limited to, protein A purification, ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. High performance liquid chromatography ("HPLC") can also be employed for purification. See, e.g., Colligan, Current Protocols in Immunology, or Current Protocols in Protein Science, John Wiley & Sons, NY, NY, (1997-2001), e.g., Chapters 1, 4, 6, 8, 9, 10, each entirely incorporated herein by reference.

Antibodies used in the method of the present invention include naturally purified products, products of chemical synthetic procedures, and products produced by recombinant techniques from a eukaryotic host, including, for example, yeast, higher plant, insect and mammalian cells. Depending upon the host employed in a recombinant production procedure, the antibody can be glycosylated or can be non-glycosylated, with glycosylated preferred. Such methods are described in many standard laboratory manuals, such as Sambrook, supra, Sections 17.37-17.42; Ausubel, supra, Chapters 10, 12, 13, 16, 18 and 20, Colligan, Protein Science, supra, Chapters 12-14, all entirely incorporated herein by reference.

Anti-IL-23 Antibodies.

An anti-IL-23 antibody according to the present invention includes any protein or peptide containing molecule that comprises at least a portion of an immunoglobulin molecule, such as but not limited to, at least one ligand binding portion (LBP), such as but not limited to, a complementarity determining region (CDR) of a heavy or light chain or a ligand binding portion thereof, a heavy chain or light chain variable region, a framework region (e.g., FR1, FR2, FR3, FR4 or fragment thereof, further optionally comprising at least one substitution, insertion or deletion), a heavy chain or light chain constant region, (e.g., comprising at least one C_H1, hinge1, hinge2, hinge3, hinge4, C_H2, or C_H3 or fragment thereof, further optionally comprising at least one substitution, insertion or deletion), or any portion thereof, that can be incorporated into an antibody. An antibody can include or be derived from any mammal, such as but not limited to, a human, a mouse, a rabbit, a rat, a rodent, a primate, or any combination thereof, and the like.

The isolated antibodies used in the method of the present invention comprise the antibody amino acid sequences disclosed herein encoded by any suitable polynucleotide, or any isolated or prepared antibody. Preferably, the human antibody or antigen-binding fragment binds human IL-23 and, thereby, partially or substantially neutralizes at least one biological activity of the protein. An antibody, or specified portion or variant thereof, that partially or preferably substantially neutralizes at least one biological activity of at least one IL-23 protein or fragment can bind the protein or fragment and thereby inhibit activities mediated through the binding of IL-23 to the IL-23 receptor or through other IL-23-dependent or mediated mechanisms. As used herein, the term "neutralizing antibody" refers to an antibody that can inhibit an IL-23-dependent activity by about 20-120%, preferably by at least about 10, 20, 30, 40, 50, 55, 60, 65, 70, 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100% or more depending on the assay. The capacity of an anti-IL-23 antibody to inhibit an IL-23-dependent activity is preferably assessed by at least one suitable IL-23 protein or receptor assay, as described herein and/or as known in the art. A human antibody can be of any class (IgG, IgA, IgM, IgE, IgD, etc.) or isotype and can comprise a kappa or lambda light chain. In one embodiment, the human antibody comprises an IgG heavy chain or defined fragment, for example, at least one of isotypes, IgG1, IgG2, IgG3 or IgG4 (e.g., γ1, γ2, γ3, γ4). Antibodies of this type can be prepared by employing a transgenic mouse or other trangenic non-human mammal comprising at least one human light chain (e.g., IgG, IgA, and IgM) transgenes as described herein and/or as known in the art. In another embodiment, the anti-IL-23 human antibody comprises an IgG1 heavy chain and an IgG1 light chain.

An antibody binds at least one specified epitope specific to at least one IL-23 protein, subunit, fragment, portion or any combination thereof. The at least one epitope can comprise at least one antibody binding region that comprises at least one portion of the protein, which epitope is preferably comprised of at least one extracellular, soluble, hydrophillic, external or cytoplasmic portion of the protein.

Generally, the human antibody or antigen-binding fragment will comprise an antigen-binding region that comprises at least one human complementarity determining region (CDR1, CDR2 and CDR3) or variant of at least one heavy chain variable region and at least one human complementarity determining region (CDR1, CDR2 and CDR3) or variant of at least one light chain variable region. The CDR sequences may be derived from human germline sequences or closely match the germline sequences. For example, the CDRs from a synthetic library derived from the original non-human CDRs can be used. These CDRs may be formed by incorporation of conservative substitutions from the original non-human sequence. In another particular embodiment, the antibody or antigen-binding portion or variant can have an antigen-binding region that comprises at least a portion of at least one light chain CDR (i.e., CDR1, CDR2 and/or CDR3) having the amino acid sequence of the corresponding CDRs 1, 2 and/or 3.

Such antibodies can be prepared by chemically joining together the various portions (e.g., CDRs, framework) of the antibody using conventional techniques, by preparing and expressing a (i.e., one or more) nucleic acid molecule that encodes the antibody using conventional techniques of recombinant DNA technology or by using any other suitable method.

The anti-IL-23 specific antibody can comprise at least one of a heavy or light chain variable region having a defined amino acid sequence. For example, in a preferred embodiment, the anti-IL-23 antibody comprises at least one of at least one heavy chain variable region, optionally having the amino acid sequence of SEQ ID NO:106 and/or at least one light chain variable region, optionally having the amino acid sequence of SEQ ID NO:116. Antibodies that bind to human IL-23 and that comprise a defined heavy or light chain variable region can be prepared using suitable methods, such as phage display (Katsube, Y., *et al.*, *Int J Mol. Med*, 1(*5*):863-868 (1998)) or methods that employ transgenic animals, as known in the art and/or as described herein. For example, a transgenic mouse, comprising a functionally rearranged human immunoglobulin heavy chain transgene and a transgene comprising DNA from a human immunoglobulin light chain locus that can undergo functional rearrangement, can be immunized with human IL-23 or a fragment thereof to elicit the production of antibodies. If desired, the antibody producing cells can be isolated and hybridomas or other immortalized antibody-producing cells can be prepared as described herein and/or as known in the art. Alternatively, the antibody, specified portion or variant can be expressed using the encoding nucleic acid or portion thereof in a suitable host cell.

The invention also relates to antibodies, antigen-binding fragments, immunoglobulin chains and CDRs comprising amino acids in a sequence that is substantially the same as an amino acid sequence described herein. Preferably, such antibodies or antigen-binding fragments and antibodies comprising such chains or CDRs can bind human IL-23 with high affinity (e.g., K_D less than or equal to about 10^{-9} M). Amino acid sequences that are substantially the same as the sequences described herein include sequences comprising conservative amino acid substitutions, as well as amino acid deletions and/or insertions. A conservative amino acid substitution refers to the replacement of a first amino acid by a second amino acid that has chemical and/or physical properties (e.g., charge, structure, polarity, hydrophobicity/hydrophilicity) that are similar to those of the first amino acid. Conservative substitutions include, without limitation, replacement of one amino acid by another within the following groups: lysine (K), arginine (R) and histidine (H); aspartate (D) and glutamate (E); asparagine (N), glutamine (Q), serine (S), threonine (T), tyrosine (Y), K, R, H, D and E; alanine (A), valine (V), leucine (L), isoleucine (I), proline (P), phenylalanine (F), tryptophan (W), methionine (M), cysteine (C) and glycine (G); F, W and Y; C, S and T.

Amino Acid Codes

The amino acids that make up anti-IL-23 antibodies of the present invention are often abbreviated. The amino acid designations can be indicated by designating the amino acid by its single letter code, its three letter code, name, or three nucleotide codon(s) as is well understood in the art (see Alberts, B., et al., Molecular Biology of The Cell, Third Ed., Garland Publishing, Inc., New York, 1994):

Table 19

SINGLE LETTER CODE	THREE LETTER CODE	NAME	THREE NUCLEOTIDE CODON(S)
A	Ala	Alanine	GCA, GCC, GCG, GCU
C	Cys	Cysteine	UGC, UGU
D	Asp	Aspartic acid	GAC, GAU
E	Glu	Glutamic acid	GAA, GAG
F	Phe	Phenylanine	UUC, UUU
G	Gly	Glycine	GGA, GGC, GGG, GGU
H	His	Histidine	CAC, CAU
I	Ile	Isoleucine	AUA, AUC, AUU
K	Lys	Lysine	AAA, AAG
L	Leu	Leucine	UUA, UUG, CUA, CUC, CUG, CUU
M	Met	Methionine	AUG
N	Asn	Asparagine	AAC, AAU
P	Pro	Proline	CCA, CCC, CCG, CCU

Q	Gln	Glutamine	CAA, CAG
R	Arg	Arginine	AGA, AGG, CGA, CGC, CGG, CGU
S	Ser	Serine	AGC, AGU, UCA, UCC, UCG, UCU
T	Thr	Threonine	ACA, ACC, ACG, ACU
V	Val	Valine	GUA, GUC, GUG, GUU
W	Trp	Tryptophan	UGG
Y	Tyr	Tyrosine	UAC, UAU

An anti-IL-23 antibody used in the method of the present invention can include one or more amino acid substitutions, deletions or additions, either from natural mutations or human manipulation, as specified herein.

The number of amino acid substitutions a skilled artisan would make depends on many factors, including those described above. Generally speaking, the number of amino acid substitutions, insertions or deletions for any given anti-IL-23 antibody, fragment or variant will not be more than 40, 30, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, such as 1-30 or any range or value therein, as specified herein.

Amino acids in an anti-IL-23 specific antibody that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (e.g., Ausubel, supra, Chapters 8, 15; Cunningham and Wells, Science 244:1081-1085 (1989)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological activity, such as, but not limited to, at least one IL-23 neutralizing activity. Sites that are critical for antibody binding can also be identified by structural analysis, such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith, et al., J. Mol. Biol. 224:899-904 (1992) and de Vos, et al., Science 255:306-312 (1992)).

Anti-IL-23 antibodies can include, but are not limited to, at least one portion, sequence or combination selected from 5 to all of the contiguous amino acids of at least one of SEQ ID NOS: 5, 20, 44, 50, 56, and 73.

IL-23 antibodies or specified portions or variants can include, but are not limited to, at least one portion, sequence or combination selected from at least 3-5 contiguous amino acids of the SEQ ID NOs above; 5-17 contiguous amino acids of the SEQ ID NOs above, 5-10 contiguous amino acids of the SEQ ID NOs above, 5-11 contiguous amino acids of the SEQ ID NOs above, 5-7 contiguous amino acids of the SEQ ID NOs above; 5-9 contiguous amino acids of the SEQ ID NOs above.

An anti-IL-23 antibody can further optionally comprise a polypeptide of at least one of 70-100% of 5, 17, 10, 11, 7, 9, 119, or 108 contiguous amino acids of the SEQ ID NOs above. In one embodiment, the amino acid sequence of an immunoglobulin chain, or portion thereof (e.g., variable region, CDR) has about 70-100% identity (e.g., 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 or any range or value therein) to the amino acid sequence of the corresponding chain of at least one of the SEQ ID NOs above. For example, the amino acid sequence of a light chain variable region can be compared with the sequence of the SEQ ID NOs above, or the amino acid sequence of a heavy chain CDR3 can be compared with the SEQ ID NOs above. Preferably, 70-100% amino acid identity (i.e., 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 or any range or value therein) is determined using a suitable computer algorithm, as known in the art.

"Identity," as known in the art, is a relationship between two or more polypeptide sequences or two or more polynucleotide sequences, as determined by comparing the sequences. In the art, "identity" also means the degree of sequence relatedness between polypeptide or polynucleotide sequences, as determined by the match between strings of such sequences. "Identity" and "similarity" can be readily calculated by known methods, including, but not limited to, those described in Computational Molecular Biology, Lesk, A. M., ed., Oxford

University Press, New York, 1988; Biocomputing:Informatics and Genome Projects, Smith, D. W., ed., Academic Press, New York, 1993; Computer Analysis of Sequence Data, Part I, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey, 1994; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; and Carillo, H., and Lipman, D., Siam J. Applied Math., 48:1073 (1988). In addition, values for percentage identity can be obtained from amino acid and nucleotide sequence alignments generated using the default settings for the AlignX component of Vector NTI Suite 8.0 (Informax, Frederick, MD).

Preferred methods to determine identity are designed to give the largest match between the sequences tested. Methods to determine identity and similarity are codified in publicly available computer programs. Preferred computer program methods to determine identity and similarity between two sequences include, but are not limited to, the GCG program package (Devereux, J., et al., Nucleic Acids Research 12(1): 387 (1984)), BLASTP, BLASTN, and FASTA (Atschul, S. F. et al., J. Molec. Biol. 215:403-410 (1990)). The BLAST X program is publicly available from NCBI and other sources (BLAST Manual, Altschul, S., et al., NCBINLM NIH Bethesda, Md. 20894: Altschul, S., et al., J. Mol. Biol. 215:403-410 (1990). The well-known Smith Waterman algorithm may also be used to determine identity.

Preferred parameters for polypeptide sequence comparison include the following:
(1) Algorithm: Needleman and Wunsch, J. Mol Biol. 48:443-453 (1970) Comparison matrix: BLOSSUM62 from Hentikoff and Hentikoff, Proc. Natl. Acad. Sci, USA. 89:10915-10919 (1992)
Gap Penalty: 12
Gap Length Penalty: 4
A program useful with these parameters is publicly available as the "gap" program from Genetics Computer Group, Madison Wis. The aforementioned parameters are the default parameters for peptide sequence comparisons (along with no penalty for end gaps).

Preferred parameters for polynucleotide comparison include the following:
(1) Algorithm: Needleman and Wunsch, J. Mol Biol. 48:443-453 (1970)
Comparison matrix: matches=+10, mismatch=0

Gap Penalty: 50
Gap Length Penalty: 3
Available as: The "gap" program from Genetics Computer Group, Madison Wis. These are the default parameters for nucleic acid sequence comparisons.

By way of example, a polynucleotide sequence may be identical to another sequence, that is 100% identical, or it may include up to a certain integer number of nucleotide alterations as compared to the reference sequence. Such alterations are selected from the group consisting of at least one nucleotide deletion, substitution, including transition and transversion, or insertion, and wherein the alterations may occur at the 5' or 3' terminal positions of the reference nucleotide sequence or anywhere between those terminal positions, interspersed either individually among the nucleotides in the reference sequence or in one or more contiguous groups within the reference sequence. The number of nucleotide alterations is determined by multiplying the total number of nucleotides in the sequence by the numerical percent of the respective percent identity (divided by 100) and subtracting that product from the total number of nucleotides in the sequence, or:
n.sub.n.ltorsim.x.sub.n -(x.sub.n.y),
wherein n.sub.n is the number of nucleotide alterations, x.sub.n is the total number of nucleotides in sequence, and y is, for instance, 0.70 for 70%, 0.80 for 80%, 0.85 for 85%, 0.90 for 90%, 0.95 for 95%, etc., and wherein any non-integer product of x.sub.n and y is rounded down to the nearest integer prior to subtracting from x.sub.n.

Alterations of a polynucleotide sequence encoding the the SEQ ID NOs above may create nonsense, missense or frameshift mutations in this coding sequence and thereby alter the polypeptide encoded by the polynucleotide following such alterations. Similarly, a polypeptide sequence may be identical to the reference sequence of the SEQ ID NOs above, that is be 100% identical, or it may include up to a certain integer number of amino acid alterations as compared to the reference sequence such that the percentage identity is less than 100%. Such alterations are selected from the group consisting of at least one amino acid deletion, substitution, including conservative and non-conservative substitution, or insertion, and wherein the alterations may occur at the amino- or carboxy-terminal positions of the reference polypeptide sequence or anywhere between those terminal positions, interspersed either individually among the amino acids in the reference sequence or in one or more contiguous groups within the reference sequence. The number of amino acid alterations for a given % identity is determined by multiplying the total number of amino acids in the SEQ ID NOs above by the numerical percent of the respective percent identity (divided by 100) and then subtracting that product from the total number of amino acids in the SEQ ID NOs above, or:

n.sub.a.ltorsim.x.sub.a -(x.sub.a.y),

wherein n.sub.a is the number of amino acid alterations, x.sub.a is the total number of amino acids in the SEQ ID NOs above, and y is, for instance 0.70 for 70%, 0.80 for 80%, 0.85 for 85% etc., and wherein any non-integer produce of x.sub.a and y is rounded down to the nearest integer prior to subtracting it from x.sub.a.

Exemplary heavy chain and light chain variable regions sequences and portions thereof are provided in the SEQ ID NOs above. The antibodies of the present invention, or specified variants thereof, can comprise any number of contiguous amino acid residues from an antibody of the present invention, wherein that number is selected from the group of integers consisting of from 10-100% of the number of contiguous residues in an anti-IL-23 antibody. Optionally, this subsequence of contiguous amino acids is at least about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250 or more amino acids in length, or any range or value therein. Further, the number of such subsequences can be any integer selected from the group consisting of from 1 to 20, such as at least 2, 3, 4, or 5.

As those of skill will appreciate, the present invention includes at least one biologically active antibody of the present invention. Biologically active antibodies have a specific activity at least 20%, 30%, or 40%, and, preferably, at least 50%, 60%, or 70%, and, most preferably, at least 80%, 90%, or 95%-100% or more (including, without limitation, up to 10 times the specific activity) of that of the native (non-synthetic), endogenous or related and known antibody. Methods of assaying and quantifying measures of enzymatic activity and substrate specificity are well known to those of skill in the art.

In another aspect, the invention relates to human antibodies and antigen-binding fragments, as described herein, which are modified by the covalent attachment of an organic moiety. Such modification can produce an antibody or antigen-binding fragment with improved pharmacokinetic properties (e.g., increased *in vivo* serum half-life). The organic moiety can be a linear or branched hydrophilic polymeric group, fatty acid group, or fatty acid ester group. In particular embodiments, the hydrophilic polymeric group can have a molecular weight of about 800 to about 120,000 Daltons and can be a polyalkane glycol (e.g., polyethylene glycol (PEG), polypropylene glycol (PPG)), carbohydrate polymer, amino acid polymer or polyvinyl pyrolidone, and the fatty acid or fatty acid ester group can comprise from about eight to about forty carbon atoms.

The modified antibodies and antigen-binding fragments can comprise one or more organic moieties that are covalently bonded, directly or indirectly, to the antibody. Each organic moiety that is bonded to an antibody or antigen-binding fragment of the invention can independently be a hydrophilic polymeric group, a fatty acid group or a fatty acid ester group. As used herein, the term "fatty acid" encompasses mono-carboxylic acids and di-carboxylic acids. A "hydrophilic polymeric group," as the term is used herein, refers to an organic polymer that is more soluble in water than in octane. For example, polylysine is more soluble in water than in octane. Thus, an antibody modified by the covalent attachment of polylysine is encompassed by the invention. Hydrophilic polymers suitable for modifying antibodies of the invention can be linear or branched and include, for example, polyalkane glycols (e.g., PEG, monomethoxy-polyethylene glycol (mPEG), PPG and the like), carbohydrates (e.g., dextran, cellulose, oligosaccharides, polysaccharides and the like), polymers of hydrophilic amino acids (e.g., polylysine, polyarginine, polyaspartate and the like), polyalkane oxides (e.g., polyethylene oxide, polypropylene oxide and the like) and polyvinyl pyrolidone. Preferably, the hydrophilic polymer that modifies the antibody of the invention has a molecular weight of about 800 to about 150,000 Daltons as a separate molecular entity. For example, PEG_{5000} and $PEG_{20,000}$, wherein the subscript is the average molecular weight of the polymer in Daltons, can be used. The hydrophilic polymeric group can be substituted with one to about six alkyl, fatty acid or fatty acid ester groups. Hydrophilic polymers that are substituted with a fatty acid or fatty acid ester group can be prepared by employing suitable methods. For example, a polymer comprising an amine group can be coupled to a carboxylate of the fatty acid or fatty acid ester, and an activated carboxylate (e.g., activated with N, N-carbonyl diimidazole) on a fatty acid or fatty acid ester can be coupled to a hydroxyl group on a polymer.

Fatty acids and fatty acid esters suitable for modifying antibodies of the invention can be saturated or can contain one or more units of unsaturation. Fatty acids that are suitable for modifying antibodies of the invention include, for example, n-dodecanoate (C_{12}, laurate), n-tetradecanoate (C_{14}, myristate), n-octadecanoate (C_{18}, stearate), n-eicosanoate (C_{20}, arachidate), n-docosanoate (C_{22}, behenate), n-triacontanoate (C_{30}), n-tetracontanoate (C_{40}), *cis*-Δ9-octadecanoate (C_{18}, oleate), all *cis*-Δ5,8,11,14-eicosatetraenoate (C_{20}, arachidonate), octanedioic acid, tetradecanedioic acid, octadecanedioic acid, docosanedioic acid, and the like. Suitable fatty acid esters include mono-esters of dicarboxylic acids that comprise a linear or branched lower alkyl group. The lower alkyl group can comprise from one to about twelve, preferably, one to about six, carbon atoms.

The modified human antibodies and antigen-binding fragments can be prepared using suitable methods, such as by reaction with one or more modifying agents. A “modifying agent” as the term is used herein, refers to a suitable organic group (e.g., hydrophilic polymer, a fatty acid, a fatty acid ester) that comprises an activating group. An "activating group" is a chemical moiety or functional group that can, under appropriate conditions, react with a second chemical group thereby forming a covalent bond between the modifying agent and the second chemical group. For example, amine-reactive activating groups include electrophilic groups, such as tosylate, mesylate, halo (chloro, bromo, fluoro, iodo), N-hydroxysuccinimidyl esters (NHS), and the like. Activating groups that can react with thiols include, for example, maleimide, iodoacetyl, acrylolyl, pyridyl disulfides, 5-thiol-2-nitrobenzoic acid thiol (TNB-thiol), and the like. An aldehyde functional group can be coupled to amine- or hydrazide-containing molecules, and an azide group can react with a trivalent phosphorous group to form phosphoramidate or phosphorimide linkages. Suitable methods to introduce activating groups into molecules are known in the art (see for example, Hermanson, G. T., *Bioconjugate Techniques*, Academic Press: San Diego, CA (1996)). An activating group can be bonded directly to the organic group (e.g., hydrophilic polymer, fatty acid, fatty acid ester), or through a linker moiety, for example, a divalent C_1-C_{12} group wherein one or more carbon atoms can be replaced by a heteroatom, such as oxygen, nitrogen or sulfur. Suitable linker moieties include, for example, tetraethylene glycol, $-(CH_2)_3-$, $-NH-(CH_2)_6-NH-$, $-(CH_2)_2-NH-$ and $-CH_2-O-CH_2-CH_2-O-CH_2-CH_2-O-CH-NH-$. Modifying agents that comprise a linker moiety can be produced, for example, by reacting a mono-Boc-alkyldiamine (e.g., mono-Boc-ethylenediamine, mono-Boc-diaminohexane) with a fatty acid in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) to form an amide bond between the free amine and the fatty acid carboxylate. The Boc protecting group can be removed from the product by treatment with trifluoroacetic acid (TFA) to expose a primary amine that can be coupled to another carboxylate, as described, or can be reacted with maleic anhydride and the resulting product cyclized to produce an activated maleimido derivative of the fatty acid. (See, for example, Thompson, *et al.*, WO 92/16221, the entire teachings of which are incorporated herein by reference.)

The modified antibodies can be produced by reacting a human antibody or antigen-binding fragment with a modifying agent. For example, the organic moieties can be bonded to the antibody in a non-site specific manner by employing an amine-reactive modifying agent, for example, an NHS ester of PEG. Modified human antibodies or antigen-binding fragments can also be prepared by reducing disulfide bonds (e.g., intra-chain disulfide bonds) of an antibody or antigen-binding fragment. The reduced antibody or antigen-binding fragment can then be reacted with a thiol-reactive modifying agent to produce the modified antibody of the invention. Modified human antibodies and antigen-binding fragments comprising an organic moiety that is bonded to specific sites of an antibody of the present invention can be prepared using suitable methods, such as reverse proteolysis (Fisch *et al., Bioconjugate Chem.*, 3:147-153 (1992); Werlen *et al., Bioconjugate Chem.*, 5:411-417 (1994); Kumaran *et al., Protein Sci.* 6(10):2233-2241 (1997); Itoh *et al., Bioorg. Chem.*, 24(1): 59-68 (1996); Capellas *et al., Biotechnol. Bioeng.*, 56(4):456-463 (1997)), and the methods described in Hermanson, G. T., *Bioconjugate Techniques*, Academic Press: San Diego, CA (1996).

The method of the present invention also uses an anti-IL-23 antibody composition comprising at least one, at least two, at least three, at least four, at least five, at least six or more anti-IL-23 antibodies thereof, as described herein and/or as known in the art that are provided in a non-naturally occurring composition, mixture or form. Such compositions comprise non-naturally occurring compositions comprising at least one or two full length, C- and/or N-terminally deleted variants, domains, fragments, or specified variants, of the anti-IL-23 antibody amino acid sequence selected from the group consisting of 70-100% of the contiguous amino acids of the SEQ ID NOs above, or specified fragments, domains or variants thereof. Preferred anti-IL-23 antibody compositions include at least one or two full length, fragments, domains or variants as at least one CDR or LBP containing portions of the anti-IL-23 antibody sequence described herein, for example, 70-100% of the SEQ ID NOs above, or specified fragments, domains or variants thereof. Further preferred compositions comprise, for example, 40-99% of at least one of 70-100% of the SEQ ID NOs above, etc., or specified fragments, domains or variants thereof. Such composition percentages are by weight, volume, concentration, molarity, or molality as liquid or dry solutions, mixtures, suspension, emulsions, particles, powder, or colloids, as known in the art or as described herein.

Antibody Compositions Comprising Further Therapeutically Active Ingredients

The antibody compositions used in the method of the invention can optionally further comprise an effective amount of at least one compound or protein selected from at least one of an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplastic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug or the like. Such drugs are well known in the art, including formulations, indications, dosing and administration for each presented herein (see, e.g., Nursing 2001 Handbook of Drugs, 21st edition, Springhouse Corp., Springhouse, PA, 2001; Health Professional's Drug Guide 2001, ed., Shannon, Wilson, Stang, Prentice-Hall, Inc, Upper Saddle River, NJ; Pharmcotherapy Handbook, Wells et al., ed., Appleton & Lange, Stamford, CT, each entirely incorporated herein by reference).

By way of example of the drugs that can be combined with the antibodies for the method of the present invention, the anti-infective drug can be at least one selected from amebicides or at least one antiprotozoals, anthelmintics, antifungals, antimalarials, antituberculotics or at least one antileprotics, aminoglycosides, penicillins, cephalosporins, tetracyclines, sulfonamides, fluoroquinolones, antivirals, macrolide anti-infectives, and miscellaneous anti-infectives. The hormonal drug can be at least one selected from corticosteroids, androgens or at least one anabolic steroid, estrogen or at least one progestin, gonadotropin, antidiabetic drug or at least one glucagon, thyroid hormone, thyroid hormone antagonist, pituitary hormone, and parathyroid-like drug. The at least one cephalosporin can be at least one selected from cefaclor, cefadroxil, cefazolin sodium, cefdinir, cefepime hydrochloride, cefixime, cefmetazole sodium, cefonicid sodium, cefoperazone sodium, cefotaxime sodium, cefotetan disodium, cefoxitin sodium, cefpodoxime proxetil, cefprozil, ceftazidime, ceftibuten, ceftizoxime sodium, ceftriaxone sodium, cefuroxime axetil, cefuroxime sodium, cephalexin hydrochloride, cephalexin monohydrate, cephradine, and loracarbef.

The at least one coricosteroid can be at least one selected from betamethasone, betamethasone acetate or betamethasone sodium phosphate, betamethasone sodium phosphate, cortisone acetate, dexamethasone, dexamethasone acetate, dexamethasone sodium phosphate, fludrocortisone acetate, hydrocortisone, hydrocortisone acetate, hydrocortisone cypionate, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, methylprednisolone, methylprednisolone acetate, methylprednisolone sodium succinate, prednisolone, prednisolone acetate, prednisolone sodium phosphate, prednisolone tebutate, prednisone, triamcinolone, triamcinolone acetonide, and triamcinolone diacetate. The at least one androgen or anabolic steroid can be at least one selected from danazol, fluoxymesterone, methyltestosterone, nandrolone decanoate, nandrolone phenpropionate, testosterone, testosterone cypionate, testosterone enanthate, testosterone propionate, and testosterone transdermal system.

The at least one immunosuppressant can be at least one selected from azathioprine, basiliximab, cyclosporine, daclizumab, lymphocyte immune globulin, muromonab-CD3, mycophenolate mofetil, mycophenolate mofetil hydrochloride, sirolimus, and tacrolimus.

The at least one local anti-infective can be at least one selected from acyclovir, amphotericin B, azelaic acid cream, bacitracin, butoconazole nitrate, clindamycin phosphate, clotrimazole, econazole nitrate, erythromycin, gentamicin sulfate, ketoconazole, mafenide acetate, metronidazole (topical), miconazole nitrate, mupirocin, naftifine hydrochloride, neomycin sulfate, nitrofurazone, nystatin, silver sulfadiazine, terbinafine hydrochloride, terconazole, tetracycline hydrochloride, tioconazole, and tolnaftate. The at least one scabicide or pediculicide can be at least one selected from crotamiton, lindane, permethrin, and pyrethrins. The at least one topical corticosteroid can be at least one selected from betamethasone dipropionate, betamethasone valerate, clobetasol propionate, desonide, desoximetasone, dexamethasone, dexamethasone sodium phosphate, diflorasone diacetate, fluocinolone acetonide, fluocinonide, flurandrenolide, fluticasone propionate, halcionide, hydrocortisone, hydrocortisone acetate, hydrocortisone butyrate, hydrocorisone valerate, mometasone furoate, and triamcinolone acetonide. (See, e.g., pp. 1098-1136 of *Nursing 2001 Drug Handbook*.)

Anti-IL-23 antibody compositions can further comprise at least one of any suitable and effective amount of a composition or pharmaceutical composition comprising at least one anti-IL-23 antibody contacted or administered to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy, optionally further comprising at least one selected from at least one TNF antagonist (e.g., but not limited to a TNF chemical or protein antagonist, TNF monoclonal or polyclonal antibody or fragment, a soluble TNF receptor (e.g., p55, p70 or p85) or fragment, fusion polypeptides thereof, or a small molecule TNF antagonist, e.g., TNF binding protein I or II (TBP-1 or TBP-II), nerelimonmab, infliximab, eternacept, CDP-571, CDP-870, afelimomab, lenercept, and the like), an antirheumatic (e.g., methotrexate, auranofin, aurothioglucose, azathioprine, etanercept, gold sodium thiomalate, hydroxychloroquine sulfate, leflunomide, sulfasalzine), an immunization, an immunoglobulin, an immunosuppressive (e.g., basiliximab, cyclosporine, daclizumab), a cytokine or a cytokine antagonist. Non-limiting examples of such cytokines include, but are not limited to, any of IL-1 to IL-23 et al. (e.g., IL-1, IL-2, etc.). Suitable dosages are well known in the art. See, e.g., Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, CT (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, CA (2000), each of which references are entirely incorporated herein by reference.

Anti-IL-23 antibody compounds, compositions or combinations used in the method of the present invention can further comprise at least one of any suitable auxiliary, such as, but not limited to, diluent, binder, stabilizer, buffers, salts, lipophilic solvents, preservative, adjuvant or the like. Pharmaceutically acceptable auxiliaries are preferred. Non-limiting examples of, and methods of preparing such sterile solutions are well known in the art, such as, but limited to, Gennaro, Ed., *Remington's Pharmaceutical Sciences*, 18th Edition, Mack Publishing Co. (Easton, PA) 1990. Pharmaceutically acceptable carriers can be routinely selected that are suitable for the mode of administration, solubility and/or stability of the anti-IL-23 antibody, fragment or variant composition as well known in the art or as described herein.

Pharmaceutical excipients and additives useful in the present composition include, but are not limited to, proteins, peptides, amino acids, lipids, and carbohydrates (e.g., sugars, including monosaccharides, di-, tri-, tetra-, and oligosaccharides; derivatized sugars, such as alditols, aldonic acids, esterified sugars and the like; and polysaccharides or sugar polymers), which can be present singly or in combination, comprising alone or in combination 1-99.99% by weight or volume. Exemplary protein excipients include serum albumin, such as human serum albumin (HSA), recombinant human albumin (rHA), gelatin, casein, and the like. Representative amino acid/antibody components, which can also function in a buffering capacity, include alanine, glycine, arginine, betaine, histidine, glutamic acid, aspartic acid, cysteine, lysine, leucine, isoleucine, valine, methionine, phenylalanine, aspartame, and the like. One preferred amino acid is glycine.

Carbohydrate excipients suitable for use in the invention include, for example, monosaccharides, such as fructose, maltose, galactose, glucose, D-mannose, sorbose, and the like; disaccharides, such as lactose, sucrose, trehalose, cellobiose, and the like; polysaccharides, such as raffinose, melezitose, maltodextrins, dextrans, starches, and the like; and alditols, such as mannitol, xylitol, maltitol, lactitol, xylitol sorbitol (glucitol), myoinositol and the like. Preferred carbohydrate excipients for use in the present invention are mannitol, trehalose, and raffinose.

Anti-IL-23 antibody compositions can also include a buffer or a pH adjusting agent; typically, the buffer is a salt prepared from an organic acid or base. Representative buffers include organic acid salts, such as salts of citric acid, ascorbic acid, gluconic acid, carbonic acid, tartaric acid, succinic acid, acetic acid, or phthalic acid; Tris, tromethamine hydrochloride, or phosphate buffers. Preferred buffers for use in the present compositions are organic acid salts, such as citrate.

Additionally, anti-IL-23 antibody compositions can include polymeric excipients/additives, such as polyvinylpyrrolidones, ficolls (a polymeric sugar), dextrates (e.g., cyclodextrins, such as 2-hydroxypropyl-β-cyclodextrin), polyethylene glycols, flavoring agents, antimicrobial agents, sweeteners, antioxidants, antistatic agents, surfactants (e.g., polysorbates, such as “TWEEN 20” and “TWEEN 80”), lipids (*e.g.*, phospholipids, fatty acids), steroids (e.g., cholesterol), and chelating agents (e.g., EDTA).

These and additional known pharmaceutical excipients and/or additives suitable for use in the anti-IL-23 antibody, portion or variant compositions according to the invention are known in the art, e.g., as listed in "Remington: The Science & Practice of Pharmacy," 19th ed., Williams & Williams, (1995), and in the "Physician's Desk Reference," 52nd ed., Medical Economics, Montvale, NJ (1998), the disclosures of which are entirely incorporated herein by reference. Preferred carrier or excipient materials are carbohydrates (e.g., saccharides and alditols) and buffers (e.g., citrate) or polymeric agents. An exemplary carrier molecule is the mucopolysaccharide, hyaluronic acid, which may be useful for intraarticular delivery.

Formulations

As noted above, the invention provides for stable formulations, which preferably comprise a phosphate buffer with saline or a chosen salt, as well as preserved solutions and formulations containing a preservative as well as multi-use preserved formulations suitable for pharmaceutical or veterinary use, comprising at least one anti-IL-23 antibody in a pharmaceutically acceptable formulation. Preserved formulations contain at least one known preservative or optionally selected from the group consisting of at least one phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, phenylmercuric nitrite, phenoxyethanol, formaldehyde, chlorobutanol, magnesium chloride (e.g., hexahydrate), alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof in an aqueous diluent. Any suitable concentration or mixture can be used as known in the art, such as 0.001-5%, or any range or value therein, such as, but not limited to 0.001, 0.003, 0.005, 0.009, 0.01, 0.02, 0.03, 0.05, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.3, 4.5, 4.6, 4.7, 4.8, 4.9, or any range or value therein. Non-limiting examples include, no preservative, 0.1-2% m-cresol (e.g., 0.2, 0.3. 0.4, 0.5, 0.9, 1.0%), 0.1-3% benzyl alcohol (e.g., 0.5, 0.9, 1.1, 1.5, 1.9, 2.0, 2.5%), 0.001-0.5% thimerosal (e.g., 0.005, 0.01), 0.001-2.0% phenol (e.g., 0.05, 0.25, 0.28, 0.5, 0.9, 1.0%), 0.0005-1.0% alkylparaben(s) (e.g., 0.00075, 0.0009, 0.001, 0.002, 0.005, 0.0075, 0.009, 0.01, 0.02, 0.05, 0.075, 0.09, 0.1, 0.2, 0.3, 0.5, 0.75, 0.9, 1.0%), and the like.

As noted above, the method of the invention uses an article of manufacture, comprising packaging material and at least one vial comprising a solution of at least one anti-IL-23 specific antibody with the prescribed buffers and/or preservatives, optionally in an aqueous diluent, wherein said packaging material comprises a label that indicates that such solution can be held over a period of 1, 2, 3, 4, 5, 6, 9, 12, 18, 20, 24, 30, 36, 40, 48, 54, 60, 66, 72 hours or greater. The invention further uses an article of manufacture, comprising packaging material, a first vial comprising lyophilized anti-IL-23 specific antibody, and a second vial comprising an aqueous diluent of prescribed buffer or preservative, wherein said packaging material comprises a label that instructs a patient to reconstitute the anti-IL-23 specific antibody in the aqueous diluent to form a solution that can be held over a period of twenty-four hours or greater.

The anti-IL-23 specific antibody used in accordance with the present invention can be produced by recombinant means, including from mammalian cell or transgenic preparations, or can be purified from other biological sources, as described herein or as known in the art.

The range of the anti-IL-23 specific antibody includes amounts yielding upon reconstitution, if in a wet/dry system, concentrations from about 1.0 µg/ml to about 1000 mg/ml, although lower and higher concentrations are operable and are dependent on the intended delivery vehicle, e.g., solution formulations will differ from transdermal patch, pulmonary, transmucosal, or osmotic or micro pump methods.

Preferably, the aqueous diluent optionally further comprises a pharmaceutically acceptable preservative. Preferred preservatives include those selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof. The concentration of preservative used in the formulation is a concentration sufficient to yield an anti-microbial effect. Such concentrations are dependent on the preservative selected and are readily determined by the skilled artisan.

Other excipients, e.g., isotonicity agents, buffers, antioxidants, and preservative enhancers, can be optionally and preferably added to the diluent. An isotonicity agent, such as glycerin, is commonly used at known concentrations. A physiologically tolerated buffer is preferably added to provide improved pH control. The formulations can cover a wide range of pHs, such as from about pH 4 to about pH 10, and preferred ranges from about pH 5 to about pH 9, and a most preferred range of about 6.0 to about 8.0. Preferably, the formulations of the present invention have a pH between about 6.8 and about 7.8. Preferred buffers include phosphate buffers, most preferably, sodium phosphate, particularly, phosphate buffered saline (PBS).

Other additives, such as a pharmaceutically acceptable solubilizers like Tween 20 (polyoxyethylene (20) sorbitan monolaurate), Tween 40 (polyoxyethylene (20) sorbitan monopalmitate), Tween 80 (polyoxyethylene (20) sorbitan monooleate), Pluronic F68 (polyoxyethylene polyoxypropylene block copolymers), and PEG (polyethylene glycol) or non-ionic surfactants, such as polysorbate 20 or 80 or poloxamer 184 or 188, Pluronic® polyls, other block co-polymers, and chelators, such as EDTA and EGTA, can optionally be added to the formulations or compositions to reduce aggregation. These additives are particularly useful if a pump or plastic container is used to administer the formulation. The presence of pharmaceutically acceptable surfactant mitigates the propensity for the protein to aggregate.

The formulations can be prepared by a process which comprises mixing at least one anti-IL-23 specific antibody and a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben, (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal or mixtures thereof in an aqueous diluent. Mixing the at least one anti-IL-23 specific antibody and preservative in an aqueous diluent is carried out using conventional dissolution and mixing procedures. To prepare a suitable formulation, for example, a measured amount of at least one anti-IL-23 specific antibody in buffered solution is combined with the desired preservative in a buffered solution in quantities sufficient to provide the protein and preservative at the desired concentrations. Variations of this process would be recognized by one of ordinary skill in the art. For example, the order the components are added, whether additional additives are used, the temperature and pH at which the formulation is prepared, are all factors that can be optimized for the concentration and means of administration used.

The formulations can be provided to patients as clear solutions or as dual vials comprising a vial of lyophilized anti-IL-23 specific antibody that is reconstituted with a second vial containing water, a preservative and/or excipients, preferably, a phosphate buffer and/or saline and a chosen salt, in an aqueous diluent. Either a single solution vial or dual vial requiring reconstitution can be reused multiple times and can suffice for a single or multiple cycles of patient treatment and thus can provide a more convenient treatment regimen than currently available.

The present articles of manufacture are useful for administration over a period ranging from immediate to twenty-four hours or greater. Accordingly, the presently claimed articles of manufacture offer significant advantages to the patient. Formulations of the invention can optionally be safely stored at temperatures of from about 2°C to about 40°C and retain the biologically activity of the protein for extended periods of time, thus allowing a package label indicating that the solution can be held and/or used over a period of 6, 12, 18, 24, 36, 48, 72, or 96 hours or greater. If preserved diluent is used, such label can include use up to 1-12 months, one-half, one and a half, and/or two years.

The solutions of anti-IL-23 specific antibody can be prepared by a process that comprises mixing at least one antibody in an aqueous diluent. Mixing is carried out using conventional dissolution and mixing procedures. To prepare a suitable diluent, for example, a measured amount of at least one antibody in water or buffer is combined in quantities sufficient to provide the protein and, optionally, a preservative or buffer at the desired concentrations. Variations of this process would be recognized by one of ordinary skill in the art. For example, the order the components are added, whether additional additives are used, the temperature and pH at which the formulation is prepared, are all factors that can be optimized for the concentration and means of administration used.

The claimed products can be provided to patients as clear solutions or as dual vials comprising a vial of lyophilized at least one anti-IL-23 specific antibody that is reconstituted with a second vial containing the aqueous diluent. Either a single solution vial or dual vial requiring reconstitution can be reused multiple times and can suffice for a single or multiple cycles of patient treatment and thus provides a more convenient treatment regimen than currently available.

The claimed products can be provided indirectly to patients by providing to pharmacies, clinics, or other such institutions and facilities, clear solutions or dual vials comprising a vial of lyophilized at least one anti-IL-23 specific antibody that is reconstituted with a second vial containing the aqueous diluent. The clear solution in this case can be up to one liter or even larger in size, providing a large reservoir from which smaller portions of the at least one antibody solution can be retrieved one or multiple times for transfer into smaller vials and provided by the pharmacy or clinic to their customers and/or patients.

Recognized devices comprising single vial systems include pen-injector devices for delivery of a solution, such as BD Pens, BD Autojector®, Humaject®, NovoPen®, B-D®Pen, AutoPen®, and OptiPen®, GenotropinPen®, Genotronorm Pen®, Humatro Pen®, Reco-Pen®, Roferon Pen®, Biojector®, Iject®, J-tip Needle-Free Injector®, Intraject®, Medi-Ject®, Smartject® e.g., as made or developed by Becton Dickensen (Franklin Lakes, NJ, www.bectondickenson.com), Disetronic (Burgdorf, Switzerland, www.disetronic.com; Bioject, Portland, Oregon (www.bioject.com); National Medical Products, Weston Medical (Peterborough, UK, www.weston-medical.com), Medi-Ject Corp (Minneapolis, MN, www.mediject.com), and similary suitable devices. Recognized devices comprising a dual vial system include those pen-injector systems for reconstituting a lyophilized drug in a cartridge for delivery of the reconstituted solution, such as the HumatroPen®. Examples of other devices suitable include pre-filled syringes, auto-injectors, needle free injectors, and needle free IV infusion sets.

The products may include packaging material. The packaging material provides, in addition to the information required by the regulatory agencies, the conditions under which the product can be used. The packaging material of the present invention provides instructions to the patient, as applicable, to reconstitute the at least one anti-IL-23 antibody in the aqueous diluent to form a solution and to use the solution over a period of 2-24 hours or greater for the two vial, wet/dry, product. For the single vial, solution product, pre-filled syringe or auto-injector, the label indicates that such solution can be used over a period of 2-24 hours or greater. The products are useful for human pharmaceutical product use.

The formulations used in the method of the present invention can be prepared by a process that comprises mixing an anti-IL-23 antibody and a selected buffer, preferably, a phosphate buffer containing saline or a chosen salt. Mixing the anti-IL-23 antibody and buffer in an aqueous diluent is carried out using conventional dissolution and mixing procedures. To prepare a suitable formulation, for example, a measured amount of at least one antibody in water or buffer is combined with the desired buffering agent in water in quantities sufficient to provide the protein and buffer at the desired concentrations. Variations of this process would be recognized by one of ordinary skill in the art. For example, the order the components are added, whether additional additives are used, the temperature and pH at which the formulation is prepared, are all factors that can be optimized for the concentration and means of administration used.

The method of the invention provides pharmaceutical compositions comprising various formulations useful and acceptable for administration to a human or animal patient. Such pharmaceutical compositions are prepared using water at “standard state” as the diluent and routine methods well known to those of ordinary skill in the art. For example, buffering components such as histidine and histidine monohydrochloride hydrate, may be provided first followed by the addition of an appropriate, non-final volume of water diluent, sucrose and polysorbate 80 at “standard state.” Isolated antibody may then be added. Last, the volume of the pharmaceutical composition is adjusted to the desired final volume under “standard state” conditions using water as the diluent. Those skilled in the art will recognize a number of other methods suitable for the preparation of the pharmaceutical compositions.

The pharmaceutical compositions may be aqueous solutions or suspensions comprising the indicated mass of each constituent per unit of water volume or having an indicated pH at “standard state.” As used herein, the term “standard state” means a temperature of 25°C +/- 2°C and a pressure of 1 atmosphere. The term “standard state” is not used in the art to refer to a single art recognized set of temperatures or pressure, but is instead a reference state that specifies temperatures and pressure to be used to describe a solution or suspension with a particular composition under the reference "standard state" conditions. This is because the volume of a solution is, in part, a function of temperature and pressure. Those skilled in the art will recognize that pharmaceutical compositions equivalent to those disclosed here can be produced at other temperatures and pressures. Whether such pharmaceutical compositions are equivalent to those disclosed here should be determined under the "standard state" conditions defined above (*e.g.* 25°C +/- 2°C and a pressure of 1 atmosphere).

Importantly, such pharmaceutical compositions may contain component masses "about" a certain value (*e.g.* "about 0.53 mg L-histidine") per unit volume of the pharmaceutical composition or have pH values about a certain value. A component mass present in a pharmaceutical composition or pH value is "about" a given numerical value if the isolated antibody present in the pharmaceutical composition is able to bind a peptide chain while the isolated antibody is present in the pharmaceutical composition or after the isolated antibody has been removed from the pharmaceutical composition (*e.g.*, by dilution). Stated differently, a value, such as a component mass value or pH value, is "about" a given numerical value when the binding activity of the isolated antibody is maintained and detectable after placing the isolated antibody in the pharmaceutical composition.

Competition binding analysis is performed to determine if the IL-23 specific mAbs bind to similar or different epitopes and/or compete with each other. Abs are individually coated on ELISA plates. Competing mAbs are added, followed by the addition of biotinylated hrIL-23. For positive control, the same mAb for coating may be used as the competing mAb ("self-competition"). IL-23 binding is detected using streptavidin. These results demonstrate whether the mAbs recognize similar or partially overlapping epitopes on IL-23.

One aspect of the method of the invention administers to a patient a pharmaceutical composition comprising

In one embodiment of the pharmaceutical compositions, the isolated antibody concentration is from about 77 to about 104 mg per ml of the pharmaceutical composition. In another embodiment of the pharmaceutical compositions the pH is from about 5.5 to about 6.5.

The stable or preserved formulations can be provided to patients as clear solutions or as dual vials comprising a vial of lyophilized at least one anti-IL-23 antibody that is reconstituted with a second vial containing a preservative or buffer and excipients in an aqueous diluent. Either a single solution vial or dual vial requiring reconstitution can be reused multiple times and can suffice for a single or multiple cycles of patient treatment and thus provides a more convenient treatment regimen than currently available.

Other formulations or methods of stabilizing the anti-IL-23 antibody may result in other than a clear solution of lyophilized powder comprising the antibody. Among non-clear solutions are formulations comprising particulate suspensions, said particulates being a composition containing the anti-IL-23 antibody in a structure of variable dimension and known variously as a microsphere, microparticle, nanoparticle, nanosphere, or liposome. Such relatively homogenous, essentially spherical, particulate formulations containing an active agent can be formed by contacting an aqueous phase containing the active agent and a polymer and a nonaqueous phase followed by evaporation of the nonaqueous phase to cause the coalescence of particles from the aqueous phase as taught in U.S. 4,589,330. Porous microparticles can be prepared using a first phase containing active agent and a polymer dispersed in a continuous solvent and removing said solvent from the suspension by freeze-drying or dilution-extraction-precipitation as taught in U.S. 4,818,542. Preferred polymers for such preparations are natural or synthetic copolymers or polymers selected from the group consisting of gleatin agar, starch, arabinogalactan, albumin, collagen, polyglycolic acid, polylactic aced, glycolide-L(-) lactide poly(episilon-caprolactone, poly(epsilon-caprolactone-CO-lactic acid), poly(epsilon-caprolactone-CO-glycolic acid), poly(ß-hydroxy butyric acid), polyethylene oxide, polyethylene, poly(alkyl-2-cyanoacrylate), poly(hydroxyethyl methacrylate), polyamides, poly(amino acids), poly(2-hydroxyethyl DL-aspartamide), poly(ester urea), poly(L-phenylalanine/ethylene glycol/1,6-diisocyanatohexane) and poly(methyl methacrylate). Particularly preferred polymers are polyesters, such as polyglycolic acid, polylactic aced, glycolide-L(-) lactide poly(episilon-caprolactone, poly(epsilon-caprolactone-CO-lactic acid), and poly(epsilon-caprolactone-CO-glycolic acid. Solvents useful for dissolving the polymer and/or the active include: water, hexafluoroisopropanol, methylenechloride, tetrahydrofuran, hexane, benzene, or hexafluoroacetone sesquihydrate. The process of dispersing the active containing phase with a second phase may include pressure forcing said first phase through an orifice in a nozzle to affect droplet formation.

Dry powder formulations may result from processes other than lyophilization, such as by spray drying or solvent extraction by evaporation or by precipitation of a crystalline composition followed by one or more steps to remove aqueous or nonaqueous solvent. Preparation of a spray-dried antibody preparation is taught in U.S. 6,019,968. The antibody-based dry powder compositions may be produced by spray drying solutions or slurries of the antibody and, optionally, excipients, in a solvent under conditions to provide a respirable dry powder. Solvents may include polar compounds, such as water and ethanol, which may be readily dried. Antibody stability may be enhanced by performing the spray drying procedures in the absence of oxygen, such as under a nitrogen blanket or by using nitrogen as the drying gas. Another relatively dry formulation is a dispersion of a plurality of perforated microstructures dispersed in a suspension medium that typically comprises a hydrofluoroalkane propellant as taught in WO 9916419. The stabilized dispersions may be administered to the lung of a patient using a metered dose inhaler. Equipment useful in the commercial manufacture of spray dried medicaments are manufactured by Buchi Ltd. or Niro Corp.

An anti-IL-23 antibody in either the stable or preserved formulations or solutions described herein, can be administered to a patient in accordance with the present invention via a variety of delivery methods including SC or IM injection; transdermal, pulmonary, transmucosal, implant, osmotic pump, cartridge, micro pump, or other means appreciated by the skilled artisan, as well-known in the art.

Therapeutic Applications

The present invention also provides a method for modulating or treating psoriasis, in a cell, tissue, organ, animal, or patient, as known in the art or as described herein, using at least one IL-23 antibody of the present invention, e.g., administering or contacting the cell, tissue, organ, animal, or patient with a therapeutic effective amount of IL-23 specific antibody.

Any method of the present invention can comprise administering an effective amount of a composition or pharmaceutical composition comprising an anti-IL-23 antibody to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy. Such a method can optionally further comprise co-administration or combination therapy for treating such diseases or disorders, wherein the administering of said at least one anti-IL-23 antibody, specified portion or variant thereof, further comprises administering, before concurrently, and/or after, at least one selected from at least one TNF antagonist (e.g., but not limited to, a TNF chemical or protein antagonist, TNF monoclonal or polyclonal antibody or fragment, a soluble TNF receptor (e.g., p55, p70 or p85) or fragment, fusion polypeptides thereof, or a small molecule TNF antagonist, e.g., TNF binding protein I or II (TBP-1 or TBP-II), nerelimonmab, infliximab, eternacept (Enbrel™), adalimulab (Humira™), CDP-571, CDP-870, afelimomab, lenercept, and the like), an antirheumatic (e.g., methotrexate, auranofin, aurothioglucose, azathioprine, gold sodium thiomalate, hydroxychloroquine sulfate, leflunomide, sulfasalzine), a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial (e.g., aminoglycoside, an antifungal, an antiparasitic, an antiviral, a carbapenem, cephalosporin, a flurorquinolone, a macrolide, a penicillin, a sulfonamide, a tetracycline, another antimicrobial), an antipsoriatic, a corticosteriod, an anabolic steroid, a diabetes related agent, a mineral, a nutritional, a thyroid agent, a vitamin, a calcium related hormone, an antidiarrheal, an antitussive, an antiemetic, an antiulcer, a laxative, an anticoagulant, an erythropoietin (e.g., epoetin alpha), a filgrastim (e.g., G-CSF, Neupogen), a sargramostim (GM-CSF, Leukine), an immunization, an immunoglobulin, an immunosuppressive (e.g., basiliximab, cyclosporine, daclizumab), a growth hormone, a hormone replacement drug, an estrogen receptor modulator, a mydriatic, a cycloplegic, an alkylating agent, an antimetabolite, a mitotic inhibitor, a radiopharmaceutical, an antidepressant, antimanic agent, an antipsychotic, an anxiolytic, a hypnotic, a sympathomimetic, a stimulant, donepezil, tacrine, an asthma medication, a beta agonist, an inhaled steroid, a leukotriene inhibitor, a methylxanthine, a cromolyn, an epinephrine or analog, dornase alpha (Pulmozyme), a cytokine or a cytokine antagonist. Suitable dosages are well known in the art. See, e.g., Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, CT (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, CA (2000); Nursing 2001 Handbook of Drugs, 21st edition, Springhouse Corp., Springhouse, PA, 2001; Health Professional's Drug Guide 2001, ed., Shannon, Wilson, Stang, Prentice-Hall, Inc, Upper Saddle River, NJ, each of which references are entirely incorporated herein by reference.

Therapeutic Treatments

Typically, treatment of psoriasis is affected by administering an effective amount or dosage of an anti-IL-23 antibody composition that total, on average, a range from at least about 0.01 to 500 milligrams of an anti-IL-23 antibody per kilogram of patient per dose, and, preferably, from at least about 0.1 to 100 milligrams antibody/kilogram of patient per single or multiple administration, depending upon the specific activity of the active agent contained in the composition. Alternatively, the effective serum concentration can comprise 0.1-5000 µg/ml serum concentration per single or multiple administrations. Suitable dosages are known to medical practitioners and will, of course, depend upon the particular disease state, specific activity of the composition being administered, and the particular patient undergoing treatment. In some instances, to achieve the desired therapeutic amount, it can be necessary to provide for repeated administration, *i.e.*, repeated individual administrations of a particular monitored or metered dose, where the individual administrations are repeated until the desired daily dose or effect is achieved.

Preferred doses can optionally include 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 and/or 100-500 mg/kg/administration, or any range, value or fraction thereof, or to achieve a serum concentration of 0.1, 0.5, 0.9, 1.0, 1.1, 1.2, 1.5, 1.9, 2.0, 2.5, 2.9, 3.0, 3.5, 3.9, 4.0, 4.5, 4.9, 5.0, 5.5, 5.9, 6.0, 6.5, 6.9, 7.0, 7.5, 7.9, 8.0, 8.5, 8.9, 9.0, 9.5, 9.9, 10, 10.5, 10.9, 11, 11.5, 11.9, 20, 12.5, 12.9, 13.0, 13.5, 13.9, 14.0, 14.5, 4.9, 5.0, 5.5., 5.9, 6.0, 6.5, 6.9, 7.0, 7.5, 7.9, 8.0, 8.5, 8.9, 9.0, 9.5, 9.9, 10, 10.5, 10.9, 11, 11.5, 11.9, 12, 12.5, 12.9, 13.0, 13.5, 13.9, 14, 14.5, 15, 15.5, 15.9, 16, 16.5, 16.9, 17, 17.5, 17.9, 18, 18.5, 18.9, 19, 19.5, 19.9, 20, 20.5, 20.9, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 96, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, and/or 5000 μg/ml serum concentration per single or multiple administration, or any range, value or fraction thereof.

Alternatively, the dosage administered can vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent, and its mode and route of administration; age, health, and weight of the recipient; nature and extent of symptoms, kind of concurrent treatment, frequency of treatment, and the effect desired. Usually a dosage of active ingredient can be about 0.1 to 100 milligrams per kilogram of body weight. Ordinarily 0.1 to 50, and, preferably, 0.1 to 10 milligrams per kilogram per administration or in sustained release form is effective to obtain desired results.

As a non-limiting example, treatment of humans or animals can be provided as a one-time or periodic dosage of at least one antibody of the present invention 0.1 to 100 mg/kg, such as 0.5, 0.9, 1.0, 1.1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 40, 45, 50, 60, 70, 80, 90 or 100 mg/kg, per day, on at least one of day 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40, or, alternatively or additionally, at least one of week 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, or 52, or, alternatively or additionally, at least one of 1, 2, 3, 4, 5, 6,, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 years, or any combination thereof, using single, infusion or repeated doses.

Dosage forms (composition) suitable for internal administration generally contain from about 0.001 milligram to about 500 milligrams of active ingredient per unit or container. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-99.999% by weight based on the total weight of the composition.

For parenteral administration, the antibody can be formulated as a solution, suspension, emulsion, particle, powder, or lyophilized powder in association, or separately provided, with a pharmaceutically acceptable parenteral vehicle. Examples of such vehicles are water, saline, Ringer's solution, dextrose solution, and 1-10% human serum albumin. Liposomes and nonaqueous vehicles, such as fixed oils, can also be used. The vehicle or lyophilized powder can contain additives that maintain isotonicity (e.g., sodium chloride, mannitol) and chemical stability (e.g., buffers and preservatives). The formulation is sterilized by known or suitable techniques.

Suitable pharmaceutical carriers are described in the most recent edition of Remington's Pharmaceutical Sciences, A. Osol, a standard reference text in this field.

Alternative Administration

Many known and developed modes can be used according to the present invention for administering pharmaceutically effective amounts of an anti-IL-23 antibody. While pulmonary administration is used in the following description, other modes of administration can be used according to the present invention with suitable results. IL-23 specific antibodies of the present invention can be delivered in a carrier, as a solution, emulsion, colloid, or suspension, or as a dry powder, using any of a variety of devices and methods suitable for administration by inhalation or other modes described here within or known in the art.

Parenteral Formulations and Administration

Formulations for parenteral administration can contain as common excipients sterile water or saline, polyalkylene glycols, such as polyethylene glycol, oils of vegetable origin, hydrogenated naphthalenes and the like. Aqueous or oily suspensions for injection can be prepared by using an appropriate emulsifier or humidifier and a suspending agent, according to known methods. Agents for injection can be a non-toxic, non-orally administrable diluting agent, such as aqueous solution, a sterile injectable solution or suspension in a solvent. As the usable vehicle or solvent, water, Ringer's solution, isotonic saline, etc. are allowed; as an ordinary solvent or suspending solvent, sterile involatile oil can be used. For these purposes, any kind of involatile oil and fatty acid can be used, including natural or synthetic or semisynthetic fatty oils or fatty acids; natural or synthetic or semisynthtetic mono- or di- or tri-glycerides. Parental administration is known in the art and includes, but is not limited to, conventional means of injections, a gas pressured needle-less injection device as described in U.S. Pat. No. 5,851,198, and a laser perforator device as described in U.S. Pat. No. 5,839,446 entirely incorporated herein by reference.

Alternative Delivery

The invention further relates to the administration of an anti-IL-23 antibody by parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracerebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal means. An anti-IL-23 antibody composition can be prepared for use for parenteral (subcutaneous, intramuscular or intravenous) or any other administration particularly in the form of liquid solutions or suspensions; for use in vaginal or rectal administration particularly in semisolid forms, such as, but not limited to, creams and suppositories; for buccal, or sublingual administration, such as, but not limited to, in the form of tablets or capsules; or intranasally, such as, but not limited to, the form of powders, nasal drops or aerosols or certain agents; or transdermally, such as not limited to a gel, ointment, lotion, suspension or patch delivery system with chemical enhancers such as dimethyl sulfoxide to either modify the skin structure or to increase the drug concentration in the transdermal patch (Junginger, et al. In "Drug Permeation Enhancement;" Hsieh, D. S., Eds., pp. 59-90 (Marcel Dekker, Inc. New York 1994, entirely incorporated herein by reference), or with oxidizing agents that enable the application of formulations containing proteins and peptides onto the skin (WO 98/53847), or applications of electric fields to create transient transport pathways, such as electroporation, or to increase the mobility of charged drugs through the skin, such as iontophoresis, or application of ultrasound, such as sonophoresis (U.S. Pat. Nos. 4,309,989 and 4,767,402) (the above publications and patents being entirely incorporated herein by reference).

Method of Selling and/or Promoting

The invention further relates to a method of selling and/or promoting an approved pharmaceutical product (by the US FDA or equivalent ex-US regulatory agency) comprising an antibody to IL-23, such as an antibody described herein, e.g., guselkumab, comprising advertising, promoting and/or otherwise highlighting in connection with sales of guselkumab

(Tremfya®) the superiority of clinical endpoint results at week 44 and/or week 48 from initial treatment after continuous treatment with the antibody to IL-23 versus clinical endpoint results at week 44 and/or week 48 from initial treatment after continuous treatment with secukinumab in treated psoriasis patients.

Having generally described the invention, the same will be more readily understood by reference to the following Examples, which are provided by way of illustration and are not intended as limiting. Further details of the invention are illustrated by the following non-limiting Examples. The disclosures of all citations in the specification are expressly incorporated herein by reference.

Example 1: A Phase 3, Multicenter, Randomized, Double-blind Study Evaluating the Comparative Efficacy of CNTO 1959 (Guselkumab) and Secukinumab for the Treatment of Moderate to Severe Plaque-type Psorisis

Study Design:

- A Phase 3, randomized, double-blind, multicenter, active-comparator-controlled study in subjects with moderate to severe plaque-type psoriasis with 2 parallel treatment groups: guselkumab 100 mg and secukinumab 300 mg.

- Randomization: At Week 0, approximately 1040 subjects who satisfy all inclusion and exclusion criteria were planned to be randomized in a 1:1 ratio to 1 of 2 arms based on permuted block randomization with stratification by study site:

    - Group I (n=520): guselkumab 100 mg SC at Weeks 0, 4, 12, 20, and q8w thereafter through Week 44.

    - Group II (n=520): secukinumab 300 mg SC at Weeks 0, 1, 2, 3, 4, and q4w thereafter through Week 44.

- Treatment duration/Trial duration: Week 44 was the last dosing visit; subjects were followed for an additional 12 weeks after Week 44, with a final safety visit at Week 56. The end of the study was defined as the time when last subject completes the Week 56 visit. There was 1 database lock (DBL) in this study at Week 56.

A schematic of the study is shown below in Table 4.

Table 4

Overview of the Study

Randomization

Week	Guselkumab 100 mg SC (n=520)	Secukinumab 300 mg SC (n=520)
0	Guselkumab (one 100 mg injection + Placebo (one injection)	Secukinumab (two 150 mg injections)
1	Placebo (two injections)	Secukinumab (two 150 mg injections)
2	Placebo (two injections)	Secukinumab (two 150 mg injections)
3	Placebo (two injections)	Secukinumab (two 150 mg injections)
4	Guselkumab (one 100 mg injection + Placebo (one injection)	Secukinumab (two 150 mg injections)

8	Placebo (two injections)	Secukinumab (two 150 mg injections)
12	Guselkumab (one 100 mg injection + Placebo (one injection)	Secukinumab (two 150 mg injections)
16	Placebo (two injections)	Secukinumab (two 150 mg injections)
20	Guselkumab (one 100 mg injection + Placebo (one injection)	Secukinumab (two 150 mg injections)
24	Placebo (two injections)	Secukinumab (two 150 mg injections)
28	Guselkumab (one 100 mg injection + Placebo (one injection)	Secukinumab (two 150 mg injections)
32	Placebo (two injections)	Secukinumab (two 150 mg injections)
36	Guselkumab (one 100 mg injection + Placebo (one injection)	Secukinumab (two 150 mg injections)
40	Placebo (two injections)	Secukinumab (two 150 mg injections)
44	Guselkumab (one 100 mg injection + Placebo (one injection)	Secukinumab (two 150 mg injections)
48	Primary Endpoint	
56	Database Lock	

- Primary analysis set for efficacy: The primary efficacy analysis included all randomized subjects according to subjects' assigned treatment at Week 0, regardless of the treatment they actually received. This is also referred to as the full analysis set (FAS). The full analysis set was also used for all secondary efficacy analyses.

- Primary endpoint: the proportion of subjects who achieved a PASI 90 response at Week 48 (non-inferiority test followed by superiority)

- Major secondary efficacy variables: There were 6 major secondary endpoints in this study:

  - The proportion of subjects who achieved a PASI 75 response at both Week 12 and Week 48 (non-inferiority test followed by superiority)

  - The proportion of subjects who achieved a PASI 90 response at Week 12 (non-inferiority)

  - The proportion of subjects who achieved a PASI 75 response at Week 12 (non-inferiority)

  - The proportion of subjects who achieved a PASI 100 response at Week 48 (non-inferiority test followed by superiority)

  - The proportion of subjects who achieved an IGA score of cleared (0) at Week 48 (non-inferiority test followed by superiority)

  - The proportion of subjects who achieved an IGA score of cleared (0) or minimal (1) at Week 48 (non-inferiority test followed by superiority)
  - Non-inferiority margin was set to be 10% for all endpoints.

- To control the overall Type 1 error rate, it was specified that the primary analyses and major secondary analyses would be tested in a fixed sequence as ordered above. That is, the first major secondary endpoint would be tested only if the primary endpoint was positive, and the subsequent endpoint(s) would be tested only if the preceding endpoint in the sequence was positive.

- Planned sample size and power: A total of approximately 1,040 subjects randomized in a 1:1 ratio was expected to detect the differences between guselkumab group and secukinumab group with at least 92% power for PASI 90 response rate at Week 48 at a 2-sided significance level of 0.05. The assumptions for the sample size and power calculations, based on the data from the guselkumab CNTO1959PSO3001 and CNTO1959PSO3002 and the secukinumab Phase 3 studies (ERASURE and FIXTURE), were:

  - PASI 90 response rate at Week 48 was 70% to 80% for guselkumab group and 60% to 70% for secukinumab group.

Based on the above assumptions, the planned sample size, and a noninferiority margin of 10%, the power to demonstrate the non-inferiority for the primary endpoint of PASI 90 at Week 48 would be > 99%.

Primary Objective(s):

The primary objective is to evaluate the efficacy of guselkumab compared with secukinumab for the treatment of subjects with moderate to severe plaque-type psoriasis

Topline Results Summary

CNTO1959PSO3009 is a Phase 3, randomized, double-blind, multicenter, active-comparator-controlled study in subjects with moderate to severe plaque psoriasis, defined by a IGA ≥ 3, PASI ≥ 12, and BSA involvement of at least 10%, who were candidates for or previously received either systemic therapy or phototherapy. This database lock includes all data through Week 56 for all randomized subjects.

A total of 1200 subjects were screened of which 1048 subjects were randomized into guselkumab (n=534) or secukinumab (n=514) treatment groups. The study was conducted at 141 sites in 9 countries: Australia, Canada, Czech Republic, France, Germany, Hungary, Poland, Spain, and the US. The treatment groups were well balanced for baseline demographic and psoriasis characteristics. The majority of the subjects were white (93.4%) and male (67.5%). The median age was 46.0 years, and mean baseline weight was 89.2 kg (Appendix 1). Three subjects randomized to the secukinumab group did not receive any study agent due to violation of a study entry criterion. These 3 subjects were included in all efficacy analyses but excluded from the safety analyses.

Baseline disease characteristics were generally comparable between the treatment groups. The median duration of psoriasis was 16.1 years. The median percent of body surface area (BSA) involved was 20.0, with a median PASI score of 18.0. In addition, 76.1% subjects presented with an IGA = 3, and 23.8% of subjects had severe disease as defined by their baseline IGA score of 4 (Appendix 2).

The proportions of subjects receiving previous therapies in each previous psoriasis medication category were comparable between the treatment groups. Overall, 51.8% previously received phototherapy, 53.7% previously received systemic therapy and 29.1% previously received biologic therapy. Overall, 37.1% of subjects were naïve to non-biologic systemic and biologic therapies (Appendix 3).

The key baseline demographics, psoriasis disease characteristics and previous psoriasis medications/therapies are summarized in Table 1.

Table 1: Summary of Important Baseline Demographic, PSO Characteristics, and Previous Psoriasis Medications and Therapies by Medication Category

	Guselkumab	Secukinumab	Total
Analysis set: Subjects in full analysis set	534	514	1048
Weight (kg) (Mean)	89.3	89.1	89.2
PSO Characteristics			
BSA (Mean)	23.7	24.5	24.1
PASI Score (0-72) (Mean)	20.0	20.1	20.0
IGA score			
Mild (2)	0	0.2%	0.1%
Moderate (3)	76.2%	76.1%	76.1%
Severe (4)	23.8%	23.7%	23.8%
Previous Psoriasis Medications and Therapies			
Phototherapy (PUVA or UVB)	52.6%	50.9%	51.8%
Non-biologic systemics	51.7%	55.8%	53.7%
Biologics	29.2%	29.0%	29.1%
Naïve to non-biologic systemics and biologics	38.6%	35.6%	37.1%

Through Week 44, 5.1% of subjects in the guselkumab group and 9.3% of subjects in the secukinumab group discontinued study agent. The most common reason for study agent discontinuation was adverse event (1.7%) and withdrawal by subject (1.3%) in the guselkumab group, and withdrawal by subject (3.7%) and adverse events (2.1%) in the secukinumab group (Appendix 4).

Primary efficacy endpoints:

Significantly greater proportions of subjects in the guselkumab group achieved a PASI 90 response at Week 48 (84.5%) than in the secukinumab group (70.0%) (p-value < 0.001) (Table 2).

Table 2: Number of PASI 90 Responders at Week 48 (Superiority Analysis); Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab	Secukinumab
Analysis set: Full analysis set	534	514
PASI 90 responders	451 (84.5%)	360 (70.0%)
Treatment differences (95% CI)		14.2% (9.6%, 18.8%)
p-value		< 0.001

Note 1: Treatment difference and 95% CI were calculated adjusting for investigator site (pooled) using MH weights.
Note 2: P-value was based on CMH chi-square test stratified by the investigator site (pooled).

Major Secondary efficacy endpoints:

- Guselkumab is non-inferior to secukinumab for the proportion of subjects who achieved a PASI 75 response at both Week 12 and Week 48 [84.6% (guselknumab) vs. 80.2% (secukinumab); 95% CI: (-0.2%, 8.9%); p < 0.001] (Appendix 6); however, though the response rate of guselkumab group was numerically higher than that of the secukinumab group, the superiority test was not significant (p = 0.062) (Appendix 7). Therefore, because of the stipulation that the primary analyses and major secondary analyses would be tested in a fixed sequence to control the overall Type 1 error rate, the p-values reported for the rest of the major secondary endpoints are considered nominal.

- Non-inferiority for the proportion of subjects who achieved a PASI 90 response at Week 12 was not demonstrated [69.1% (guselknumab) vs. 76.1% (secukinumab); 95% CI: (-12.2%, -1.7%); p = 0.127] (Appendix 8).

- Guselkumab is non-inferior to secukinumab as assessed by the proportion of subjects who achieved a PASI 75 response at Week 12 [89.3% (guselkunumab) vs. 91.6% (secukinumab); 95% CI: (-6.0%, 1.2%); $p < 0.001$] (Appendix 9).

- The proportion of subjects who achieved a PASI 100 response at Week 48 was significantly higher in the guselkumab group compared to the secukinumab group [58.2% (guselkunumab) vs. 48.4% (secukinumab); $p = 0.001$)] (Appendix 10).

- The proportion of subjects who achieved an IGA score of cleared (0) at Week 48 was significantly higher in the guselkumab group compared to the secukinumab group [62.2% (guselkunumab) vs. 50.4% (secukinumab); $p < 0.001$] (Appendix 11).

- The proportion of subjects who achieved an IGA score of cleared (0) or minimal (1) at Week 48 was significantly higher in the guselkumab group compared to the secukinumab group [85.0% (guselkunumab) vs. 74.9% (secukinumab); $p < 0.001$] (Appendix 12).

<u>Other Efficacy Endpoints</u>:

- The proportion of subjects who achieved a PASI 90 response at all 7 visits from Week 24 through Week 48 was significantly higher in the guselkumab group compared to the secukinumab group [71.0% (guselkunumab) vs. 61.5% (secukinumab); $p < 0.001$] (Appendix 13).

- IGA and PASI responses over time

  The proportions of subjects achieving a PASI 90 response, a PASI 100 response, an IGA score of cleared (0), and an IGA score of cleared (0) or minimal (1) over time from Week 1 through Week 48 are summarized in Figure 1 below (also see Appendix 14 and 15).

  These curves highlight differences in the rate and maintenance of response over time between guselkumab and secukinumab. The PASI 90 figure panel, for example, shows that responses start occurring for both treatments at Weeks 2 and 3. Between Weeks 3 and 12, secukinumab PASI 90 response rates are higher than those for guselkumab. At Weeks 16 and 20, both drugs show similar PASI 90 response rates, and PASI 90 response rates for guselkumab are higher than those for secukinumab at all visits from Week 24 through Week 48. The guselkumab PASI 90 response rate curve reaches a plateau at Week 28, and then the response rate remains stable through Week 48. In contrast, the PASI 90 response rate curve for secukinumab plateaus earlier, at Week 20, and the response rate then declines steadily from Week 20 through Week 48. For the other 3 endpoints, the patterns of response rates are similar to that of PASI 90, although there is variability in the timing of when response rates plateau, and the visits at which the switch from higher response rates for secukinumab to higher rates for guselkumab occur.

Safety:

Safety was assessed among all randomized and treated subjects who received at least 1 dose of study agent (partial or complete) according to the actual treatment received during the study, irrespective of the treatment assigned at randomization. This is also referred to as the safety analysis set. Key safety events are summarized in Table 3.

Table 3: Key safety events; treated subjects

	Guselkumab	Secukinumab
Analysis set: Safety analysis set	534	511
Avg duration of follow-up (weeks)	54.90	53.67
Avg exposure (number of administrations)[a]	14.65	14.41
Avg number of active injections received	6.8	28.8
Subjects who discontinued study agent because of 1 or more adverse events	10 (1.9%)	12 (2.3%)
Subjects with 1 or more:		
Adverse events	416 (77.9%)	417 (81.6%)
Serious adverse events	33 (6.2%)	37 (7.2%)
Overall infections	313 (58.6%)	331 (64.8%)
Infections requiring treatment	118 (22.1%)	147 (28.8%)
Serious infections	6 (1.1%)	5 (1.0%)

Malignancy	7 (1.3%)	4 (0.8%)
NMSC	6 (1.1%)	2 (0.4%)
Other malignancy	1 (0.2%)	2 (0.4%)
MACE[b]	0	1 (0.2%)
Suicidal ideation or behavior[c]	8 (1.5%)	8 (1.6%)
Inflammatory bowel disease[d]	0	3 (0.6%)
Anaphylactic reaction or serum sickness-like reaction to active study agent	0	0
ISR to active study agent[e]	13 (2.4%)	20 (3.9%)
Total number of active injections	3644	14722
Active injections with ISR	19 (0.5%)	63 (0.4%)

[a] All administrations were counted regardless of whether they are active or placebo injections. Each administration includes two injections.

[b] MACE: investigator reported nonfatal myocardial infarction (MI), nonfatal stroke or CV death. One stroke (PT: cerebrovascular accident) was reported in the secukinumab group.

[c] Suicidal ideation and behavior data was collected by electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) at scheduled visits. When suicidal ideation or behavior-related adverse events occurred outside of a study visit, they were reported on the AE eCRF.

[d] Preferred terms of IBD: Crohn's disease and inflammatory bowel disease

[e] ISR: injection site reactions

- The proportion of subjects experiencing 1 or more adverse events categorized as infections by the investigator was lower in the guselkumab group compared with the secukinumab group (58.6% [313/534] in the guselkumab group, 64.8% [331/511] in the secukinumab group) (Appendix 19).
  - The most common infections were PTs of nasopharyngitis [21.9% (guselkumab) vs. 24.5% (secukinumab)] and upper respiratory tract infection [15.5% (guselkumab) vs. 18.0% (secukinumab)].
  - Individual PTs representing fungal infections reported in >2% of subjects included tinea pedis (1.1% vs. 3.1%), oral candidiasis (0.9% vs. 2.2%) and vulvovaginal candidiasis (0.9% vs 2.5%) for the guselkumab and secukinumab groups.

  - All serious infections were single events in both treatment groups and there was no pattern or trend for either treatment group. No cases of active tuberculosis or opportunistic infections were reported during the study (Appendix 21).

- A total of 3 BCCs (0.6%) were reported in the guselkumab group versus 2 BCCs (0.4%) in the secukinumab group.

  - Two skin squamous cell carcinomas and 1 Bowen's disease were reported in the guselkumab group.

- One subject in the guselkumab group was diagnosed with invasive ductal breast carcinoma. One subject in the secukinumab group was diagnosed with non-small cell lung cancer and another subject was diagnosed with mycosis fungoides.

- A total of 3 subjects in the secukinumab group reported an event of Crohn's disease, IBD or colitis:

  - One subject, was diagnosed with a serious AE of Crohn's disease. This subject received 5 scheduled doses of study agent.

  - Two subjects reported a non-serious AE of IBD.

    - One subject, with a history of chronic IBD that was not identified in screening was randomized and received 5 doses of study agent before being discontinued upon confirmation of Crohn's colitis.

A second subject, approximately a month after completing the 44 weeks of treatment presented with symptoms that were suggestive of, and later confirmed to be Crohn's disease.

Analysis of Patients with PsA

Post hoc analyses examined the subgroup of patients with self-reported Psoriatic Arthritis (PsA). For the PsA subpopulation, treatment differences and 95% confidence intervals (CIs) were calculated. Missing data were imputed as non-response. Both efficacy and safety were assessed through Week 56. Overall, treatment groups [GUS (n=534), SEC (n=514)] were comparable at baseline: weight 89kg, 24% body surface area PsO, and Investigator Global Assessment (IGA) moderate (76%) or severe (24%). These characteristics were similar to those of subgroups with self-reported PsA [GUS (n=97), SEC (n=79)]. In the overall population, the primary endpoint of PASI 90 response at Week 48 was reached by 84.5% GUS patients vs 70.0% SEC patients (P<0.001). Results of the first major secondary endpoint (proportion of patients with a PASI 75 response at both Week 12 and 48) showed non-inferiority of GUS vs SEC (GUS-84.6% vs SEC-80.2% of patients, p<0.001), but superiority was not demonstrated (p=0.062). Among patients with PsA, the primary endpoint of Week-48 PASI 90 response was reached by 82.5% GUS vs 63.3% SEC patients (treatment difference 19.2% [95% CI=5.0, 33.4]). In both the overall population and the subgroup of patients with PsA, peak PASI 90 response rates were achieved between Weeks 16 and 24 for both drugs. GUS-treated patients sustained this response through Week 48, whereas SEC patients demonstrated reduction in response rate from Weeks 24 to 48. Adverse events observed in the overall population were generally consistent with the established safety profiles for GUS and SEC. Safety results among patients with PsA were consistent with that of the overall population. In the subset of patients with self-reported PsA in the ECLIPSE study, GUS demonstrated higher long-term efficacy and maintenance of response compared with SEC in the treatment of moderate to severe plaque PsO, consistent with the overall trial population with plaque PsO.

Weight Quartile Analysis

Efficacy data were analyzed by baseline body weight quartiles (Q1, ≤74kg; Q2, >74 to ≤87kg; Q3, >87 to ≤100kg; Q4, >100kg) and BMI categories (normal, <25kg/m^2; overweight, ≥25 to <30kg/m^2; obese, ≥30kg/m^2). This post-hoc analysis evaluated efficacy by baseline body weight quartiles and body mass index (BMI) categories. There were no body weight restrictions for enrollment in the study.

The data are shown in Tables 12-16 below. Missing data were imputed as non-response after applying treatment failure rules. The proportions of patients achieving a PASI90 response at Week48 in the guselkumab and secukinumab groups, respectively were as follows: by baseline body weight quartiles—Q1, 86.7% vs 75.6% (11.1% [0.9%-21.3%]); Q2, 89.1% vs 73.0% (16.0% [6.0%-26.0%]); Q3, 80.3% vs 71.0% (9.3% [–1.9%-20.6%]); Q4, 82.1% vs 61.3% (20.9% [9.4%-32.3%]); by BMI categories—normal, 88.1% vs 75.2% (12.8% [2.2%-23.5%]); overweight, 84.1% vs 73.4% (10.6% [1.6%-19.7%]); obese, 82.5% vs 65.3% (17.2% [8.8%-

25.6%]) (percent difference [95% CI]). These results are consistent with the primary endpoint of PASI90 at Week 48 in the overall study population (guselkumab, 84.5% vs secukinumab, 70.0% [14.2% (9.2%-19.2%)]). Similar results were observed across all body weight quartiles and BMI categories for PASI100, IGA0, and IGA0/1 responses, with all between-treatment differences numerically favoring guselkumab. In conclusion, across baseline body weight quartiles and BMI categories, efficacy outcome response rates at Week48 were consistently numerically greater for guselkumab compared to secukinumab in the treatment of moderate to severe psoriasis.

Body Region Analysis

As shown in Table 17, guselkumab showed numerically greater levels of efficacy than secukinumab through 48 weeks in body region components of the PASI, including head and neck, trunk, and upper and lower extremities, compared with secukinumab in the treatment of moderate to severe psoriasis. Improvement in body region components of PASI, including the head and neck, trunk, and upper and lower extremities, was also evaluated. Missing data were imputed as nonresponse.

At Week 48, numerically greater proportions of patients achieved improvement (100% improvement and ≥90% improvement) with guselkumab than with secukinumab for the PASI components of head and neck, trunk, and upper and lower extremities (Table 17).

Patient Geograhic Area Analysis

Patients from North America (United States, Canada; n=391), Eastern Europe (Czech Republic, Hungary, Poland; n=338), Western Europe (France, Germany, Spain; n=248), and Australia (n=71) were randomized to receive guselkumab 100 mg subcutaneous (SC) at Weeks 0, 4, 12, then every 8 weeks (n=534), or secukinumab 300 mg SC at Weeks 0, 1, 2, 3, 4, then every 4 weeks (n=514), both through Week 44. The primary endpoint was the proportion of patients achieving a PASI 90 response at Week 48. Missing data were imputed as nonresponse.

As shown in Table 18, regardless of geographic region, PASI 90 response rates with guselkumab treatment were higher at Week 48 compared with secukinumab in the treatment of moderate to severe psoriasis. Subgroup analyses by geographical region showed higher PASI 90 response rates among guselkumab-treated patients versus secukinumab-treated patients in all regions: North America (guselkumab 78.9% vs secukinumab 60.4%); Eastern Europe (guselkumab 90.6% vs secukinumab 76.0%); Western Europe (guselkumab 82.9% vs secukinumab 74.8%); and Australia (guselkumab 91.4% vs secukinumab 77.8%) (Table 18).

Example 2 – Assessment of the Treatment Effect of Anti-IL-23 and Anti-IL-17A on Immune Cell Populations in Skin and Serum IL-17F and IL-22 levels

Skin biopsies were collected at wks 0, 4 and 24. Skin gene expression profiles were generated in whole biopsy via RNAseq. The composition of T cells was determined by immunophenotyping of cell suspensions from dissociated biopsies using flow cytometry combined with unbiased clustering analysis. Serum was collected at wks 0, 4, 24 and 48 and analyzed by ultrasensitive immunoassays for IL17A, IL17F, IL22, IL23 and beta defensin-2 (BD-2) levels. In addition, the numbers of $CD4^+$ and $CD8^+$ T cells were measured in skin lesions.

Results

Serum IL17A, IL17F and IL22 levels were reduced at wks 4, 24, and 48 after guselkumab treatment. In contrast, treatment with secukinumab reduced IL17F levels less efficiently than guselkumab ($p<0.0001$, all timepoints) and had no effect on IL22 levels (free IL17A levels in SEC cohort could not be measured with the assay used). Accordingly, there was a greater reduction in serum levels of IL-17F and IL-22 from guselkumab treatment versus secukinumab treatment at weeks 4, 24 and 48.

Reduction in levels of BD-2, a biomarker highly correlated with skin inflammation, was greater with secukinumab vs guselkumab treatment at wk 4 ($p<0.0001$), and was equivalent at wk 24; however, BD-2 increased in secukinumab arm but remained reduced in the guselkumab arm at wk 48 ($p<0.05$) such that there was a greater reduction in BD-2 levels by guselkumab versus secukinumab at wk 48. Normalization of skin transcriptional changes was more pronounced in the secukinumab vs guselkumab group at wk 4, but equivalent at wk 24. Normalization of increased skin gene expression of IL17A, IL22 and IL23 was comparable between both treatments at wk 4 and 24, while expression of IL23R was significantly reduced by guselkumab only ($p<0.01$). At wk 24 of treatment, the numbers of $CD4^+$ and $CD8^+$ T cells decreased in skin lesions in both cohorts. However, the frequency of $CD8^+$ TRMs ($CD3^+$, $CD8^+$, $CD103^+$ and/or $CD49a^+$) decreased relative to baseline with guselkumab ($p=0.036$) but not with secukinumab. The reduction in $IL17A^+/CD8^+$

TRMs in lesional skin did not differ between treatments. In contrast, the frequency of regulatory T cells (Tregs) ($FoxP3^+$, $CD25^+$, $IL17A^-$) was higher in the guselkumab arm at wk 24 (p=0.042).

Genes that are part of the psoriasis transcriptome that are better normalized by GUS vs SEC, including IL23R were identified

Increased expression in PSO lesional skin of a group of genes associated with mucosal-associated invariant T cells (MAIT) (including IL23R) was better normalized by GUS vs SEC at Week 24

Frequency of CD8+ tissue resident memory cells (TRMs) (CD3+, CD8+, CD103+ and/or CD49a+) was decreased relative to lesional baseline with GUS treatment ($p<0.05$) but not with SEC at week 24 Frequency of regulatory T cells (Tregs) (CD3+, FoxP3+,CD25+,IL17A-) were higher in the GUS arm compared to SEC arm at week 24 ($p<0.05$)

Analysis of IL-23+APC indicated that CD14+CD64+DC were responsible for majority of IL-23 expression in PsO lesional skin. Expansion of CD4 T cells were associated with relative increase of non-TRM (CD103-CD49a-). Expansion of CD8 T cells were associated with relative increase in the frequency of TRMs (CD103+and/or CD49a+). A large increase in CD8 TRMs and non-TRMs and CD4 non TRMs in PsO SkinCD4+non-TRM and CD8+TRMs are the major contributors of IL-17A in PsO (Baseline). The frequency of Treg population in T cells is significantly increased in PsO lesions. 2 distinct clusters of Tregs were identified, one IL17A+and one IL17A-N. An increased frequency of IL17A expression within T cell subsets in lesional vs non-lesional skin. CD4+T cells making IL-17A were mostly non-TRMs while CD8+T cells making IL-17A were mostly TRMs. Tregs contribute to a low amount of IL17A expression in PsO skin. A more significant decrease in the frequency of TRMs in CD8+ T cells in response to guselkumab vs secukinumab in cohort at wk 24. No difference in the frequency of TRMs in CD4+ T cell subsets in response to guselkumab vs secukinumab at wk 24. No difference in non-TRM CD4+ or non-TRM CD8+ T cell subsets between guselkumab or secukinumab treatments at wk 24. IL17A was reduced significantly in guselkumab group (measurement in SEC cohort complicated by inability of assay to differentiate SEC bound vs free IL17A resulting in increases in IL17A). An increased frequency of IL17A expression within CD8TRMs in lesional skin at baseline seems to be associated with not achieving PASI>90 at week 48 (regardless of treatment arm). No similar pattern observed in non lesional skin at baseline.

Figure 2 shows the ECLIPSE study design through Week 48 and samples collected for biomarker sub-studies. Blood samples for the serum protein biomarker sub-study were collected from all participated subjects at Weeks 0, 4, 24, and 48. Skin samples, including a pair of non-lesional skin and lesional skin at Week 0, and lesional skin after Weeks 4 and 24, were collected from a subset of subjects (19 GUS-treated and 16 SEC treated) for a skin transcriptome biomarker sub-study. Separately, skin samples, including a pair of non-lesional skin and lesional skin at Week 0, and lesional skin after Weeks 4 and 24, were collected from another subset of subjects (11 GUS-treated and 9 SEC treated) for immunophenotyping of skin immune cells sub-study.

As shown in Figure 3, elevated serum levels of IL-17F in psoriasis patients were reduced by both treatments, with faster and greater reduction by guselkumab. Compared to healthy controls (n=25), serum levels of IL-17F were elevated in psoriasis patients (n=200), with 5.2 fold and $p<0.0001$. Reduction in elevated serum IL-17F was greater in guselkumab treated samples (n=100) vs secukinumab treated samples (n=100) at all visits after week 4: 2.26 fold vs 1.12 fold, $p<0.0001$ at Week 4; 5.32 fold vs 2.31 fold, $p<0.0001$ at Week 24; and 5.28 fold vs 2.33 fold, $p<0.0001$ at Week 48. Serum IL-17F was normalized to the level of healthy controls in guselkumab-treated patients at Weeks 24 and 48. LS Means: Least Squares Means; CI: confidence intervals. LS Means and 95% CI were computed based on log transformed concentration using a mixed-effects model with repeated-measures, where the treatment (guselkumab and secukinumab) and visits (Weeks 0, 4, 24, and 48) are fixed effects, and subject is a random effect.

As shown in Figure 4, elevated serum levels of IL-22 in psoriasis were reduced by both treatments, with faster and greater reduction by guselkumab. Compared to healthy controls (n=25), serum levels of IL-22 were elevated in psoriasis patients (n=200), with 6.0 fold and $p<0.0001$. Reduction in elevated serum IL-22 was greater by guselkumab (n=100) vs secukinumab (n=100) at all visits after week 4: 1.74 fold vs 1.28 fold, $p=0.057$ at Week 4; 2.79 fold vs 1.25 fold, $p<0.0001$ at Week 24; and 2.85 fold vs 1.24 fold, $p<0.0001$ at Week 48. LS Means: Least Squares Means; CI: confidence intervals. LS Means and 95% CI were computed based on log transformed concentration using a mixed-effects model with repeated-measures, where the treatment (guselkumab and secukinumab) and visits (Weeks 0, 4, 24, and 48) are fixed effects, and subject is a random effect.

As shown in Figure 5, elevated serum levels of beta defensin-2 (BD-2) in psoriasis were reduced by both treatments, with faster reduction by secukinumab but more sustained reduction by guselkumab. Compared to healthy controls (n=25), serum levels of BD-2 were elevated in psoriasis patients (n=200), with >32 fold and p<0.0001. Reduction in elevated serum BD-2 was greater with secukinumab (n=100) vs guselkumab (n=100) (13.1 fold vs 5.0 fold, p<0.0001) at Week 4, and was equivalent (18.4 fold vs 17.3 fold, p=0.99) at Week 24, but was reversed (18.9 fold with guselkumab vs. 13.7 fold with secukinumab, p<0.05) at Week 48.
LS Means: Least Squares Means; CI: confidence intervals. LS Means and 95% CI were computed based on log transformed concentration using a mixed-effects model with repeated-measures, where the treatment (guselkumab and secukinumab) and visits (Weeks 0, 4, 24, and 48) are fixed effects, and subject is a random effect.

As shown in Figure 6, a subset of induced genes in psoriasis lesional skin were better normalized by guselkumab than secukinumab at Week 24. Quantification of gene expression in individual skin biopsies were computed as log2 transformed Transcripts per Million (TPM) from RNA-Seq Differential gene expression between lesional skin (LS) and non-lesional skin (NL) at baseline were calculated as the log2 transformed ratios based on paired t test among 35 psoriasis patients. 1655 genes had increased expression in LS, with fold change >1.5 and false discovery rate (FDR) <0.05. Differential gene expression in LS in response to treatment at Week 4 and 24 were computed as log2 transformed ratio using a mixed-effects model with repeated-measures, where the treatment (guselkumab and secukinumab) and visits (Weeks 4 and 24) are fixed effects, subject is a random effect, and the differential gene expression at baseline (between lesional skin and non-lesional skin) is a covariate. For a given gene, % of improvement in response to a treatment at a given visit is calculated as the negative ratio of the log2 transformed ratio for the response in LS vs the log2 transformed ratio of the difference between LS and NL at baseline. Among the 1655 genes had increased expression in LS at baseline, 328 (19.8%) had greater improvement in response to guselkumab than secukinumab at Week 24, as defined as >50% improvement in response to guselkumab, and >25% of difference in improvement between guselkumab vs secukinumab. Light grey lines represent individual genes, and the thick black line represents the average of % improvement among 328 genes in response to guselkumab (126%) vs secukinumab (76%). GUS: guselkumab, SEC: secukinumab

As shown in Figure 7, increased expression in psoriasis lesional skin of a group of genes associated with mucosal-associated invariant T (MAIT) cells was better normalized by guselkumab than secukinumab at Week 24. Light grey lines represent individual genes. GUS: guselkumab, SEC: secukinumab.

PsO is a T cell driven disease where skin resident T cells that produce multiple inflammatory cytokines are believed to play an important role in orchestrating the inflammatory immune response that leads to activation and proliferation of keratinocytes and culminates in hyperkeratosis, erythema and scaling, hallmarks of PsO inflamed skin. Inflammatory T cells in the skin and other tissues are believed to express IL23R and are dependent on IL-23 for becoming immunopathogenic. To better understand the mechanism of action of guselkumab, we sought to characterize PsO skin T cells by flow cytometry-based immunophenotyping of cell suspensions from dissociated biopsies. Using this approach, we showed that the frequency of CD8+ tissue resident memory T cells (TRMs) in lesional skin at week 24 was decreased relative to baseline levels in the GUS cohort (p=0.036) but not in the secukinumab. This leads to higher frequency of CD8 TRMs in the secukinumab cohort compared to guselkumab cohort at week 24 (p=0.0048).

Table 20

Summary of P values - Frequency of CD8 TRM within CD3 T cells

Treatment	Week	P values
Guselkumab	Week 0-NL vs Week 0-L	0.021683
Guselkumab	Week 0-NL vs Week 4	0.028696
Guselkumab	Week 0-NL vs Week 24	0.83748
Guselkumab	Week 0-L vs Week 4	0.909182
Guselkumab	Week 0-L vs Week 24	0.035655
Guselkumab	Week 4 vs Week 24	0.046409
Secukinumab	Week 0-NL vs Week 0-L	0.800505
Secukinumab	Week 0-NL vs Week 4	0.18244
Secukinumab	Week 0-NL vs Week 24	0.300364
Secukinumab	Week 0-L vs Week 4	0.278196
Secukinumab	Week 0-L vs Week 24	0.432394
Secukinumab	Week 4 vs Week 24	0.762684

Treatment	Week	P values
Guselkumab vs Secukinumab	0-NL	0.048327
Guselkumab vs Secukinumab	0-L	0.961635
Guselkumab vs Secukinumab	4	0.196808
Guselkumab vs Secukinumab	24	0.004842

As shown in Figure 8, the frequency of CD8 TRM in PSO skin was reduced by guselkumab, but not by secukinumab at Week 24. Characterization of PSO skin T cells was done by immunophenotyping of cell suspension obtained from dissociated biopsy. Compared to baseline lesional skin, frequency of CD8 TRMs ($CD3^+$, $CD8^+$, $CD103^+$ and/or $CD49a^+$) was reduced at Week 24 in the guselkumab arm (n=11, $p < 0.05$) but not in the secukinumab arm (n=9). Statistical analysis was performed using SAS 9.4 software using longitudinal regression model with difference from lesion at baseline as response, lesion at baseline as predictor, treatment and week as factor and interaction term between treatment and week, and AR1 as covariance structure. Data was plotted as change from baseline lesion using least square means and 95% confidence interval.

IL23 has also been reported to have an antagonistic effect on the function of regulatory T cells (Treg). Treg in PsO blood and skin have been reported to be increased but are defective in function. To better understand the mechanism of action of guselkumab, we sought to characterize PsO skin T cells by flow cytometry-based immunophenotyping of cell suspensions from dissociated biopsies. Using this novel approach, we showed that the frequency of Treg ($CD3^+$, $FoxP3^+$, $CD25^+$) in the GUS arm was maintained relative to baseline levels at week 24. In comparison, in the cohort treated with secukinumab, the levels of Tregs were reduced relative to baseline at week 24 (p=0.00013). Thus, GUS was able to maintain the relative frequency of Treg during the course of treatment.

Table 21

Summary of P values - Frequency of Tregs within CD3 T cells		
Treatment	**Week**	**P values**
Guselkumab	Week 0-NL vs Week 0-L	0.00704
Guselkumab	Week 0-NL vs Week 4	0.055978
Guselkumab	Week 0-NL vs Week 24	0.065898
Guselkumab	Week 0-L vs Week 4	0.408284
Guselkumab	Week 0-L vs Week 24	0.36752
Guselkumab	Week 4 vs Week 24	0.94038
Secukinumab	Week 0-NL vs Week 0-L	8.3E-06
Secukinumab	Week 0-NL vs Week 4	0.029787
Secukinumab	Week 0-NL vs Week 24	0.457042
Secukinumab	Week 0-L vs Week 4	0.011765
Secukinumab	Week 0-L vs Week 24	0.000126
Secukinumab	Week 4 vs Week 24	0.146146

Treatment	Week	P values
Guselkumab vs Secukinumab	0-NL	0.346175
Guselkumab vs Secukinumab	0-L	0.161581
Guselkumab vs Secukinumab	4	0.636662
Guselkumab vs Secukinumab	24	0.059004

As shown in Figure 9, the frequency of regulatory T cells (Tregs) was reduced in the secukinumab arm but not in guselkumab arm at Week 24. Characterization of PSO skin T cells by immunophenotyping of skin cells showed that compared to baseline, the frequency of Treg population was maintained in the guselkumab arm (n=11), but was reduced in the secukinumab arm (n=9, p<0.001) at Week 24. Statistical analysis was performed using SAS 9.4 software using longitudinal regression model with difference from lesion at baseline as response, lesion at baseline as predictor, treatment and week as factor and interaction term between treatment and week, and AR1 as covariance structure. Data was plotted as change from baseline lesion using least square means and 95% confidence interval.

To better understand the mechanism of action of Guselkumab (GUS) (trademark name TREMFYA), we sought to characterize PsO skin T cells by flow cytometry-based immunophenotyping of cell suspensions from dissociated biopsies. Using this approach, we showed that the relative frequency of Treg to CD8+ tissue resident memory T cells (TRMs) in PsO skin was higher in the guselkumab cohort compared to the cohort treated with IL17A mAb blocker, secukinumab (COSENTYX), at week 24 (p=0.006).

Table 22

Summary of P values - Ratio of Tregs to CD8TRM

Treatment	Week	P values
Guselkumab	Week 0-NL vs Week 0-L	0.617381
Guselkumab	Week 0-NL vs Week 4	0.770112
Guselkumab	Week 0-NL vs Week 24	0.085235
Guselkumab	Week 0-L vs Week 4	0.835498
Guselkumab	Week 0-L vs Week 24	0.217772
Guselkumab	Week 4 vs Week 24	0.150912
Secukinumab	Week 0-NL vs Week 0-L	0.061484
Secukinumab	Week 0-NL vs Week 4	0.594812
Secukinumab	Week 0-NL vs Week 24	0.993097
Secukinumab	Week 0-L vs Week 4	0.176379
Secukinumab	Week 0-L vs Week 24	0.060335
Secukinumab	Week 4 vs Week 24	0.588851

Treatment	Week	P values
Guselkumab vs Secukinumab	0-NL	0.247194
Guselkumab vs Secukinumab	0-L	0.729469
Guselkumab vs Secukinumab	4	0.379056
Guselkumab vs Secukinumab	24	0.006053

As shown in Figure 10, there are a higher relative frequency of regulatory T cells (Tregs) to CD8 tissue resident memory T cells (TRMs) in guselkumab arm compared to secukinumab arm at Week 24. Characterization of PSO skin T cells by immunophenotyping of skin cells showed that the ratio of Treg population to CD8 TRM population was higher in the guselkumab arm (n=11) compared to secukinumab arm (n=9, p<0.01) at Week 24. Statistical analysis was performed using SAS 9.4 software using longitudinal regression model with difference from lesion at baseline as response, lesion at baseline as predictor, treatment and week as factor and interaction term between treatment and week, and AR1 as covariance structure. Data was plotted as change from baseline lesion using least square means and 95% confidence interval.

Appendix

Appendix 1: Summary of Demographics and Baseline Characteristics; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg	Total
Analysis set: Full analysis set	534	514	1048
Age, years			
N	534	514	1048
Mean (SD)	46.3 (13.67)	45.3 (13.57)	45.8 (13.63)
Median	47.0	44.0	46.0
Range	(18; 87)	(18; 76)	(18; 87)
IQ range	(37.0; 56.0)	(35.0; 55.0)	(36.0; 55.0)
< 45 years	226 (42.3%)	262 (51.0%)	488 (46.6%)
≥ 45 to < 65 years	254 (47.6%)	207 (40.3%)	461 (44.0%)
≥ 65 years	54 (10.1%)	45 (8.8%)	99 (9.4%)
Sex			
N	534	514	1048
Female	169 (31.6%)	172 (33.5%)	341 (32.5%)
Male	365 (68.4%)	342 (66.5%)	707 (67.5%)
Race			
N	534	514	1048
American Indian or Alaska Native	2 (0.4%)	2 (0.4%)	4 (0.4%)
Asian	18 (3.4%)	12 (2.3%)	30 (2.9%)
Black or African American	5 (0.9%)	11 (2.1%)	16 (1.5%)
Native Hawaiian or Other Pacific Islander	0	3 (0.6%)	3 (0.3%)

Appendix 1: Summary of Demographics and Baseline Characteristics; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg	Total
White	499 (93.4%)	480 (93.4%)	979 (93.4%)
Other	6 (1.1%)	6 (1.2%)	12 (1.1%)
Multiple	4 (0.7%)	0	4 (0.4%)
Ethnicity			
N	534	514	1048
Hispanic or Latino	27 (5.1%)	36 (7.0%)	63 (6.0%)
Not Hispanic or Latino	502 (94.0%)	472 (91.8%)	974 (92.9%)
Not Reported	5 (0.9%)	4 (0.8%)	9 (0.9%)
Unknown	0	2 (0.4%)	2 (0.2%)
Weight, kg			
N	534	512	1046
Mean (SD)	89.31 (22.953)	89.13 (20.212)	89.23 (21.645)
Median	87.60	87.00	87.00
Range	(42.4; 201.1)	(42.8; 177.6)	(42.4; 201.1)
IQ range	(73.10; 101.30)	(75.00; 100.00)	(74.00; 100.60)
≤ 90kg	297 (55.6%)	292 (57.0%)	589 (56.3%)
> 90kg	237 (44.4%)	220 (43.0%)	457 (43.7%)
Height, cm			
N	533	511	1044
Mean (SD)	172.9 (10.27)	172.3 (9.63)	172.6 (9.96)
Median	173.0	172.5	172.8
Range	(149; 198)	(143; 205)	(143; 205)
IQ range	(166.0; 180.0)	(165.1; 179.0)	(165.2; 180.0)

Appendix 1: Summary of Demographics and Baseline Characteristics; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg	Total
Body mass index, kg/m^2			
N	533	511	1044
Mean (SD)	29.8 (7.10)	30.0 (6.33)	29.9 (6.73)
Median	28.4	29.2	28.8
Range	(16; 70)	(16; 65)	(16; 70)
IQ range	(25.0; 33.4)	(25.5; 33.6)	(25.1; 33.6)
Normal < 25 kg/m^2	134 (25.1%)	109 (21.3%)	243 (23.3%)
Overweight ≥ 25 to < 30 kg/m^2	176 (33.0%)	177 (34.6%)	353 (33.8%)
Obese ≥ 30 kg/m^2	223 (41.8%)	225 (44.0%)	448 (42.9%)

Key: IQ = Interquartile

[TSIDEM01.RTF] [CNTO1959\PSO3009\DBR_WEEK_056\RE_WEEK_056_CSR\PROD\TSIDEM01.SAS] 23OCT2018, 12:56

Appendix 2: Summary of Psoriasis Baseline Clinical Disease Characteristics; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg	Total
Analysis set: Full analysis set	534	514	1048
Psoriasis disease duration (years)			
N	534	514	1048
Mean (SD)	18.5 (12.16)	18.3 (12.67)	18.4 (12.41)
Median	17.0	15.7	16.1
Range	(1; 60)	(1; 68)	(1; 68)
IQ range	(9.0; 27.0)	(9.0; 25.0)	(9.0; 26.0)
Psoriasis disease duration (years)			
N	534	514	1048

Appendix 2: Summary of Psoriasis Baseline Clinical Disease Characteristics; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg	Total
< 15 years	222 (41.6%)	239 (46.5%)	461 (44.0%)
≥ 15 years	312 (58.4%)	275 (53.5%)	587 (56.0%)
Age at diagnosis (years)			
N	534	514	1048
Mean (SD)	27.9 (14.72)	27.1 (15.05)	27.5 (14.88)
Median	26.0	25.0	25.0
Range	(0; 84)	(0; 76)	(0; 84)
IQ range	(16.0; 38.0)	(16.0; 37.0)	(16.0; 37.0)
Age at diagnosis (years)			
N	534	514	1048
< 25 years	253 (47.4%)	255 (49.6%)	508 (48.5%)
≥ 25 years	281 (52.6%)	259 (50.4%)	540 (51.5%)
Psoriatic arthritis			
N	534	514	1048
Yes	97 (18.2%)	79 (15.4%)	176 (16.8%)
No	437 (81.8%)	435 (84.6%)	872 (83.2%)
BSA (%)			
N	534	514	1048
Mean (SD)	23.7 (12.85)	24.5 (14.59)	24.1 (13.73)
Median	20.0	20.0	20.0
Range	(10; 86)	(10; 95)	(10; 95)
IQ range	(14.0; 29.0)	(15.0; 30.0)	(15.0; 29.0)

Appendix 2: Summary of Psoriasis Baseline Clinical Disease Characteristics; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg	Total
BSA			
N	534	514	1048
< 20%	249 (46.6%)	240 (46.7%)	489 (46.7%)
≥ 20%	285 (53.4%)	274 (53.3%)	559 (53.3%)
IGA score			
N	534	514	1048
Cleared (0)	0	0	0
Minimal (1)	0	0	0
Mild (2)	0	1 (0.2%)	1 (0.1%)
Moderate (3)	407 (76.2%)	391 (76.1%)	798 (76.1%)
Severe (4)	127 (23.8%)	122 (23.7%)	249 (23.8%)
IGA score			
N	534	514	1048
< 4	407 (76.2%)	392 (76.3%)	799 (76.2%)
= 4	127 (23.8%)	122 (23.7%)	249 (23.8%)
PASI score (0-72)			
N	534	514	1048
Mean (SD)	20.0 (7.38)	20.1 (7.63)	20.0 (7.50)
Median	18.0	17.8	18.0
Range	(12; 59)	(5; 65)	(5; 65)
IQ range	(15.0; 22.4)	(15.2; 22.2)	(15.1; 22.3)

Appendix 2: Summary of Psoriasis Baseline Clinical Disease Characteristics; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg	Total
PASI score			
N	534	514	1048
< 20	344 (64.4%)	326 (63.4%)	670 (63.9%)
≥ 20	190 (35.6%)	188 (36.6%)	378 (36.1%)

Key: IQ = Interquartile

[TSIDEM04.RTF] [CNTO1959\PSO3009\DBR_WEEK_056\RE_WEEK_056_CSR\PROD\TSIDEM04.SAS] 23OCT2018, 12:56

Appendix 3: Summary of Previous Psoriasis Medications and Therapies by Medication Category; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg	Total
Analysis set: Full analysis set	534	514	1048
Topical agents			
N	531	514	1045
Never Used	22 (4.1%)	34 (6.6%)	56 (5.4%)
Ever Used	509 (95.9%)	480 (93.4%)	989 (94.6%)
Phototherapy {PUVA or UVB}			
N	534	513	1047
Never Used	253 (47.4%)	252 (49.1%)	505 (48.2%)
Ever Used	281 (52.6%)	261 (50.9%)	542 (51.8%)
Non-biologic systemic {PUVA, methotrexate, cyclosporine, acitretin, apremilast, or tofacitinib}			
N	534	514	1048
Never Used	258 (48.3%)	227 (44.2%)	485 (46.3%)
≥ 1 therapy	276 (51.7%)	287 (55.8%)	563 (53.7%)
≥ 2 therapies	126 (23.6%)	132 (25.7%)	258 (24.6%)
≥ 3 therapies	46 (8.6%)	53 (10.3%)	99 (9.4%)
≥ 4 therapies	10 (1.9%)	4 (0.8%)	14 (1.3%)
Biologics (etanercept, infliximab, alefacept, efalizumab, ustekinumab, briakinumab, ixekizumab, adalimumab, brodalumab, tildrakizumab, or risankizumab}			
N	534	514	1048
Never Used	378 (70.8%)	365 (71.0%)	743 (70.9%)
Ever Used	156 (29.2%)	149 (29.0%)	305 (29.1%)

Appendix 3: Summary of Previous Psoriasis Medications and Therapies by Medication Category; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg	Total
Non-biologic systemic or biologics			
N	534	514	1048
Never Used	206 (38.6%)	183 (35.6%)	389 (37.1%)
Ever Used	328 (61.4%)	331 (64.4%)	659 (62.9%)
Anti-TNFα agent (etanercept, infliximab, adalimumab)			
N	534	514	1048
Never Used	452 (84.6%)	429 (83.5%)	881 (84.1%)
Ever Used	82 (15.4%)	85 (16.5%)	167 (15.9%)
IL-12/23 inhibitors (ustekinumab, briakinumab, tildrakizumab, risankizumab)			
N	534	514	1048
Never Used	489 (91.6%)	470 (91.4%)	959 (91.5%)
Ever Used	45 (8.4%)	44 (8.6%)	89 (8.5%)
IL-17 inhibitors (ixekizumab, brodalumab)			
N	534	514	1048
Never Used	465 (87.1%)	445 (86.6%)	910 (86.8%)
Ever Used	69 (12.9%)	69 (13.4%)	138 (13.2%)

[TSICM01A.RTF] [CNTO1959\PSO3009\DBR_WEEK_056\RE_WEEK_056_CSR\PROD\TSICM01A.SAS] 23OCT2018, 12:57

Appendix 4: Treatment Disposition Through Week 44; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg	Total
Analysis set: Full analysis set	534	514	1048
Discontinued study treatment	27 (5.1%)	48 (9.3%)	75 (7.2%)
Reason for discontinuation			
Adverse event	9 (1.7%)	11 (2.1%)	20 (1.9%)
Worsening of Psoriasis	1 (0.2%)	1 (0.2%)	2 (0.2%)
Other Adverse event	8 (1.5%)	10 (1.9%)	18 (1.7%)
Death	0	0	0
Lack of Efficacy	2 (0.4%)	7 (1.4%)	9 (0.9%)
Lost to Follow-Up	2 (0.4%)	2 (0.4%)	4 (0.4%)
Non-Compliance with Study Drug	2 (0.4%)	0	2 (0.2%)
Product Quality Complaint	0	0	0
Study Terminated by Sponsor	0	0	0
Trial Site Terminated by Sponsor	0	0	0
Withdrawal by Subject	7 (1.3%)	19 (3.7%)	26 (2.5%)
Pregnancy	1 (0.2%)	1 (0.2%)	2 (0.2%)
Protocol Violation	2 (0.4%)	6 (1.2%)	8 (0.8%)
Other	2 (0.4%)	2 (0.4%)	4 (0.4%)

[TSIDS02.RTF] [CNTO1959\PSO3009\DBR_WEEK_056\RE_WEEK_056_CSR\PROD\TSIDS02.SAS] 23OCT2018, 12:56

Appendix 5: Summary of Exposure to Study Agent Through Week 44; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Analysis set: Safety analysis set	534	511
Total number of active injections received		
N	534	511
Mean (SD)	6.8 (0.86)	28.8 (4.18)
Median	7.0	30.0
Range	(1; 9)	(2; 30)
Total number of active injections received		
1	4 (0.7%)	0
2	6 (1.1%)	2 (0.4%)
3	3 (0.6%)	0
4	3 (0.6%)	0
5	7 (1.3%)	0
6	9 (1.7%)	2 (0.4%)
7	499 (93.4%)	0
8	2 (0.4%)	1 (0.2%)
9	1 (0.2%)	0
10	0	4 (0.8%)
11	0	0
12	0	4 (0.8%)
13	0	0
14	0	4 (0.8%)
15	0	0
16	0	5 (1.0%)
17	0	0

Appendix 5: Summary of Exposure to Study Agent Through Week 44; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
18	0	6 (1.2%)
19	0	0
20	0	3 (0.6%)
21	0	0
22	0	3 (0.6%)
23	0	0
24	0	1 (0.2%)
25	0	0
26	0	3 (0.6%)
27	0	0
28	0	26 (5.1%)
29	0	0
30	0	447 (87.5%)
Total dose of study agent, mg		
N	534	511
Mean (SD)	682.4 (86.14)	4321.5 (627.48)
Median	700.0	4500.0
Range	(100; 900)	(300; 4500)

[TSIEX01.RTF] [CNTO1959\PSO3009\DBR_WEEK_056\RE_WEEK_056_CSR\PROD\TSIEX01.SAS] 23OCT2018, 12:58

Efficacy

Appendix 6: Number of PASI 75 Responders at Both Week 12 and Week 48 (Non-Inferiority Analysis); Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Analysis set: Full analysis set	534	514
PASI 75 responders	452 (84.6%)	412 (80.2%)
Treatment difference (95% CI)		4.3% (-0.2%, 8.9%)
p-value		< 0.001

Note 1: Treatment difference was calculated adjusting for investigator site (pooled) using MH weights and 95% CI was calculated adjusting for investigator site (pooled) with MH weights using Miettinen-Nurminen method.
Note 2: P-value was based on 1-sided MH Z-test adjusted for investigator site (pooled).

[TEFPASI03A.RTF] [CNTO1959\PSO3009\DBR_WEEK_056\RE_WEEK_056_CSR\PROD\TEFPASI03A.SAS] 23OCT2018, 13:06

Appendix 7: Number of PASI 75 Responders at Both Week 12 and Week 48 (Superiority Analysis); Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Analysis set: Full analysis set	534	514
PASI 75 responders	452 (84.6%)	412 (80.2%)
Treatment differences (95% CI)		4.3% (0.1%, 8.5%)
p-value		0.062

Note 1: Treatment difference and 95% CI were calculated adjusting for investigator site (pooled) using MH weights.
Note 2: P-value was based on 1-sided CMH chi-square test stratified by the investigator site (pooled).

[TEFPASI03B.RTF] [CNTO1959\PSO3009\DBR_WEEK_056\RE_WEEK_056_CSR\PROD\TEFPASI03B.SAS] 23OCT2018, 13:06

Appendix 8: Number of PASI 90 Responders at Week 12 (Non-Inferiority Analysis); Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Analysis set: Full analysis set	534	514
PASI 90 responders	369 (69.1%)	391 (76.1%)
Treatment difference (95% CI)		-7.0% (-12.2%, -1.7%)
p-value		0.127

Note 1: Treatment difference was calculated adjusting for investigator site (pooled) using MH weights and 95% CI was calculated adjusting for investigator site (pooled) with MH weights using Miettinen-Nurminen method.
Note 2: P-value was based on 1-sided MH Z-test adjusted for investigator site (pooled).

[TEFPASI04A.RTF] [CNTO1959\PSO3009\DBR_WEEK_056\RE_WEEK_056_CSR\PROD\TEFPASI04A.SAS] 23OCT2018, 13:10

Appendix 9: Number of PASI 75 Responders at Week 12 (Non-Inferiority Analysis); Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Analysis set: Full analysis set	534	514
PASI 75 responders	477 (89.3%)	471 (91.6%)
Treatment difference (95% CI)		-2.3% (-6.0%, 1.2%)
p-value		< 0.001

Note 1: Treatment difference was calculated adjusting for investigator site (pooled) using MH weights and 95% CI was calculated adjusting for investigator site (pooled) with MH weights using Miettinen-Nurminen method.
Note 2: P-value was based on 1-sided MH Z-test adjusted for investigator site (pooled).

[TEFPASI05A.RTF] [CNTO1959\PSO3009\DBR_WEEK_056\RE_WEEK_056_CSR\PROD\TEFPASI05A.SAS] 23OCT2018, 13:13

Appendix 10: Number of PASI 100 Responders at Week 48 (Superiority Analysis); Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Analysis set: Full analysis set	534	514
PASI 100 responders	311 (58.2%)	249 (48.4%)
Treatment differences (95% CI)		9.7% (4.2%, 15.1%)
p-value		0.001

Note 1: Treatment difference and 95% CI were calculated adjusting for investigator site (pooled) using MH weights.
Note 2: P-value was based on CMH chi-square test stratified by the investigator site (pooled).

[TEFPASI06B.RTF] [CNTO1959\PSO3009\DBR_WEEK_056\RE_WEEK_056_CSR\PROD\TEFPASI06B.SAS] 23OCT2018, 13:17

Appendix 11: Number of Subjects With IGA Score of Cleared (0) at Week 48 (Superiority Analysis); Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Analysis set: Full analysis set	534	514
Subjects with IGA score of cleared (0)	332 (62.2%)	259 (50.4%)
Treatment difference (95% CI)		11.6% (6.2%, 17.1%)
p-value		< 0.001

Note 1: Treatment difference and 95% CI were calculated adjusting for investigator site (pooled) using MH weights.
Note 2: P-value was based on CMH chi-square test stratified by the investigator site (pooled).

[TEFIGA01B.RTF] [CNTO1959\PSO3009\DBR_WEEK_056\RE_WEEK_056_CSR\PROD\TEFIGA01B.SAS] 23OCT2018, 13:20

Appendix 12: Number of Subjects With IGA Score of Cleared (0) or Minimal (1) at Week 48 (Superiority Analysis); Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Analysis set: Full analysis set	534	514
Subjects with IGA score of cleared (0) or minimal (1)	454 (85.0%)	385 (74.9%)
Treatment difference (95% CI)		9.7% (5.3%, 14.0%)
p-value		< 0.001

Note 1: Treatment difference and 95% CI were calculated adjusting for investigator site (pooled) using MH weights.
Note 2: P-value was based on CMH chi-square test stratified by the investigator site (pooled).

[TEFIGA02B.RTF] [CNTO1959\PSO3009\DBR_WEEK_056\RE_WEEK_056_CSR\PROD\TEFIGA02B.SAS] 23OCT2018, 13:24

Appendix 13: Number of Subjects Achieving a PASI 90 Response at All 7 Visits From Week 24 Through Week 48 (Superiority Analysis); Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Analysis set: Full analysis set	534	514
PASI 90 responders	379 (71.0%)	316 (61.5%)
Treatment difference (95% CI)		9.8% (4.6%, 14.9%)
p-value		< 0.001

Note 1: Treatment difference and 95% CI were calculated adjusting for investigator site (pooled) using MH weights.
Note 2: P-value was based on CMH chi-square test stratified by the investigator site (pooled).

[TEFPASI10B.RTF] [CNTO1959\PSO3009\DBR_WEEK_056\RE_WEEK_056_CSR\PROD\TEFPASI10B.SAS] 23OCT2018, 13:28

Appendix 14: Summary of PASI Responses Through Week 56 by Visit; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Analysis set: Full analysis set	534	514
Week 1		
N	534	514
100% improvement	0	0
≥ 90% improvement	0	0
≥ 75% improvement	11 (2.1%)	9 (1.8%)
≥ 50% improvement	57 (10.7%)	66 (12.8%)
Week 2		
N	534	514
100% improvement	1 (0.2%)	3 (0.6%)
≥ 90% improvement	6 (1.1%)	14 (2.7%)
≥ 75% improvement	34 (6.4%)	59 (11.5%)
≥ 50% improvement	165 (30.9%)	216 (42.0%)
Week 3		
N	534	514
100% improvement	9 (1.7%)	8 (1.6%)
≥ 90% improvement	30 (5.6%)	44 (8.6%)
≥ 75% improvement	104 (19.5%)	146 (28.4%)
≥ 50% improvement	301 (56.4%)	344 (66.9%)
Week 4		
N	534	514
100% improvement	22 (4.1%)	26 (5.1%)

Appendix 14: Summary of PASI Responses Through Week 56 by Visit; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
≥ 90% improvement	70 (13.1%)	112 (21.8%)
≥ 75% improvement	210 (39.3%)	258 (50.2%)
≥ 50% improvement	392 (73.4%)	439 (85.4%)
Week 8		
N	534	514
100% improvement	107 (20.0%)	140 (27.2%)
≥ 90% improvement	260 (48.7%)	319 (62.1%)
≥ 75% improvement	408 (76.4%)	443 (86.2%)
≥ 50% improvement	509 (95.3%)	498 (96.9%)
Week 12		
N	534	514
100% improvement	202 (37.8%)	216 (42.0%)
≥ 90% improvement	369 (69.1%)	391 (76.1%)
≥ 75% improvement	477 (89.3%)	471 (91.6%)
≥ 50% improvement	517 (96.8%)	494 (96.1%)
Week 16		
N	534	514
100% improvement	255 (47.8%)	237 (46.1%)
≥ 90% improvement	419 (78.5%)	409 (79.6%)
≥ 75% improvement	495 (92.7%)	477 (92.8%)
≥ 50% improvement	521 (97.6%)	495 (96.3%)
Week 20		
N	534	514

Appendix 14: Summary of PASI Responses Through Week 56 by Visit; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
100% improvement	274 (51.3%)	250 (48.6%)
≥ 90% improvement	428 (80.1%)	417 (81.1%)
≥ 75% improvement	500 (93.6%)	475 (92.4%)
≥ 50% improvement	521 (97.6%)	489 (95.1%)
Week 24		
N	534	514
100% improvement	292 (54.7%)	259 (50.4%)
≥ 90% improvement	444 (83.1%)	402 (78.2%)
≥ 75% improvement	503 (94.2%)	464 (90.3%)
≥ 50% improvement	522 (97.8%)	478 (93.0%)
Week 28		
N	534	514
100% improvement	305 (57.1%)	262 (51.0%)
≥ 90% improvement	456 (85.4%)	397 (77.2%)
≥ 75% improvement	502 (94.0%)	464 (90.3%)
≥ 50% improvement	519 (97.2%)	478 (93.0%)
Week 32		
N	534	514
100% improvement	307 (57.5%)	258 (50.2%)
≥ 90% improvement	453 (84.8%)	398 (77.4%)
≥ 75% improvement	502 (94.0%)	459 (89.3%)
≥ 50% improvement	518 (97.0%)	478 (93.0%)

Appendix 14: Summary of PASI Responses Through Week 56 by Visit; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Week 36		
N	534	514
100% improvement	313 (58.6%)	257 (50.0%)
≥ 90% improvement	451 (84.5%)	389 (75.7%)
≥ 75% improvement	500 (93.6%)	447 (87.0%)
≥ 50% improvement	519 (97.2%)	474 (92.2%)
Week 40		
N	534	514
100% improvement	311 (58.2%)	250 (48.6%)
≥ 90% improvement	452 (84.6%)	379 (73.7%)
≥ 75% improvement	496 (92.9%)	441 (85.8%)
≥ 50% improvement	512 (95.9%)	467 (90.9%)
Week 44		
N	534	514
100% improvement	313 (58.6%)	254 (49.4%)
≥ 90% improvement	449 (84.1%)	373 (72.6%)
≥ 75% improvement	493 (92.3%)	438 (85.2%)
≥ 50% improvement	503 (94.2%)	470 (91.4%)
Week 48		
N	534	514
100% improvement	311 (58.2%)	249 (48.4%)
≥ 90% improvement	451 (84.5%)	360 (70.0%)
≥ 75% improvement	492 (92.1%)	429 (83.5%)

Appendix 14: Summary of PASI Responses Through Week 56 by Visit; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
≥ 50% improvement	502 (94.0%)	459 (89.3%)
Week 56		
N	534	514
100% improvement	269 (50.4%)	139 (27.0%)
≥ 90% improvement	413 (77.3%)	264 (51.4%)
≥ 75% improvement	470 (88.0%)	362 (70.4%)
≥ 50% improvement	486 (91.0%)	422 (82.1%)

[TEFPASI13A.RTF] [CNTO1959\PSO3009\DBR_WEEK_056\RE_WEEK_056_CSR\PROD\TEFPASI13A.SAS] 23OCT2018, 13:29

Appendix 15: Summary of IGA Responses Through Week 56 by Visit; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Analysis set: Full analysis set	534	514
Week 1		
N	534	514
IGA of cleared (0)	0	0
IGA of cleared (0) or minimal (1)	18 (3.4%)	13 (2.5%)
IGA of mild or better (≤2)	145 (27.2%)	176 (34.2%)
Week 2		
N	534	514
IGA of cleared (0)	1 (0.2%)	4 (0.8%)
IGA of cleared (0) or minimal (1)	66 (12.4%)	104 (20.2%)
IGA of mild or better (≤2)	289 (54.1%)	328 (63.8%)
Week 3		
N	534	514
IGA of cleared (0)	14 (2.6%)	17 (3.3%)
IGA of cleared (0) or minimal (1)	145 (27.2%)	205 (39.9%)
IGA of mild or better (≤2)	402 (75.3%)	424 (82.5%)
Week 4		
N	534	514
IGA of cleared (0)	36 (6.7%)	50 (9.7%)
IGA of cleared (0) or minimal (1)	236 (44.2%)	305 (59.3%)
IGA of mild or better (≤2)	457 (85.6%)	474 (92.2%)

Appendix 15: Summary of IGA Responses Through Week 56 by Visit; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Week 8		
N	534	514
IGA of cleared (0)	156 (29.2%)	184 (35.8%)
IGA of cleared (0) or minimal (1)	409 (76.6%)	429 (83.5%)
IGA of mild or better (≤2)	514 (96.3%)	495 (96.3%)
Week 12		
N	534	514
IGA of cleared (0)	247 (46.3%)	258 (50.2%)
IGA of cleared (0) or minimal (1)	457 (85.6%)	444 (86.4%)
IGA of mild or better (≤2)	517 (96.8%)	490 (95.3%)
Week 16		
N	534	514
IGA of cleared (0)	296 (55.4%)	275 (53.5%)
IGA of cleared (0) or minimal (1)	463 (86.7%)	445 (86.6%)
IGA of mild or better (≤2)	517 (96.8%)	487 (94.7%)
Week 20		
N	534	514
IGA of cleared (0)	304 (56.9%)	277 (53.9%)
IGA of cleared (0) or minimal (1)	469 (87.8%)	440 (85.6%)
IGA of mild or better (≤2)	509 (95.3%)	479 (93.2%)
Week 24		
N	534	514
IGA of cleared (0)	326 (61.0%)	288 (56.0%)

Appendix 15: Summary of IGA Responses Through Week 56 by Visit; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
IGA of cleared (0) or minimal (1)	473 (88.6%)	425 (82.7%)
IGA of mild or better (≤2)	514 (96.3%)	471 (91.6%)
Week 28		
N	534	514
IGA of cleared (0)	332 (62.2%)	289 (56.2%)
IGA of cleared (0) or minimal (1)	469 (87.8%)	426 (82.9%)
IGA of mild or better (≤2)	510 (95.5%)	467 (90.9%)
Week 32		
N	534	514
IGA of cleared (0)	337 (63.1%)	280 (54.5%)
IGA of cleared (0) or minimal (1)	473 (88.6%)	419 (81.5%)
IGA of mild or better (≤2)	510 (95.5%)	465 (90.5%)
Week 36		
N	534	514
IGA of cleared (0)	324 (60.7%)	276 (53.7%)
IGA of cleared (0) or minimal (1)	462 (86.5%)	409 (79.6%)
IGA of mild or better (≤2)	510 (95.5%)	457 (88.9%)
Week 40		
N	534	514
IGA of cleared (0)	337 (63.1%)	269 (52.3%)
IGA of cleared (0) or minimal (1)	461 (86.3%)	401 (78.0%)
IGA of mild or better (≤2)	500 (93.6%)	452 (87.9%)

Appendix 15: Summary of IGA Responses Through Week 56 by Visit; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Week 44		
N	534	514
IGA of cleared (0)	332 (62.2%)	267 (51.9%)
IGA of cleared (0) or minimal (1)	459 (86.0%)	393 (76.5%)
IGA of mild or better (≤2)	493 (92.3%)	450 (87.5%)
Week 48		
N	534	514
IGA of cleared (0)	332 (62.2%)	259 (50.4%)
IGA of cleared (0) or minimal (1)	454 (85.0%)	385 (74.9%)
IGA of mild or better (≤2)	495 (92.7%)	446 (86.8%)
Week 56		
N	534	514
IGA of cleared (0)	290 (54.3%)	151 (29.4%)
IGA of cleared (0) or minimal (1)	421 (78.8%)	299 (58.2%)
IGA of mild or better (≤2)	467 (87.5%)	392 (76.3%)

[TEFIGA05A.RTF] [CNTO1959\PSO3009\DBR_WEEK_056\RE_WEEK_056_CSR\PROD\TEFIGA05A.SAS] 23OCT2018, 13:28

Safety

Appendix 16: Number of Subjects With Treatment-Emergent Adverse Events Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Analysis set: Safety analysis set	534	511
Avg duration of follow-up (weeks)	54.90	53.67
Avg exposure (number of administrations)	14.65	14.41
Subjects with 1 or more AEs	416 (77.9%)	417 (81.6%)
System organ class		
Preferred term		
Infections and infestations	310 (58.1%)	324 (63.4%)
Nasopharyngitis	118 (22.1%)	125 (24.5%)
Upper respiratory tract infection	83 (15.5%)	92 (18.0%)
Pharyngitis	24 (4.5%)	22 (4.3%)
Influenza	20 (3.7%)	13 (2.5%)
Bronchitis	17 (3.2%)	15 (2.9%)
Oral herpes	11 (2.1%)	14 (2.7%)
Urinary tract infection	11 (2.1%)	11 (2.2%)
Gastroenteritis	10 (1.9%)	9 (1.8%)
Sinusitis	10 (1.9%)	12 (2.3%)
Gastroenteritis viral	9 (1.7%)	8 (1.6%)
Rhinitis	9 (1.7%)	13 (2.5%)
Viral upper respiratory tract infection	9 (1.7%)	8 (1.6%)

Appendix 16: Number of Subjects With Treatment-Emergent Adverse Events Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Folliculitis	8 (1.5%)	10 (2.0%)
Tonsillitis	7 (1.3%)	15 (2.9%)
Tinea pedis	6 (1.1%)	16 (3.1%)
Gastrointestinal infection	5 (0.9%)	0
Oral candidiasis	5 (0.9%)	11 (2.2%)
Tooth abscess	5 (0.9%)	3 (0.6%)
Tooth infection	5 (0.9%)	2 (0.4%)
Vulvovaginal candidiasis	5 (0.9%)	13 (2.5%)
Acute sinusitis	4 (0.7%)	0
Cellulitis	4 (0.7%)	3 (0.6%)
Conjunctivitis	4 (0.7%)	17 (3.3%)
Respiratory tract infection	4 (0.7%)	2 (0.4%)
Tinea versicolour	4 (0.7%)	5 (1.0%)
Gastrointestinal viral infection	3 (0.6%)	1 (0.2%)
Periodontitis	3 (0.6%)	5 (1.0%)
Pneumonia	3 (0.6%)	6 (1.2%)
Cystitis	2 (0.4%)	2 (0.4%)
Ear infection	2 (0.4%)	5 (1.0%)
Helicobacter gastritis	2 (0.4%)	0
Hordeolum	2 (0.4%)	8 (1.6%)
Laryngitis	2 (0.4%)	2 (0.4%)
Localised infection	2 (0.4%)	1 (0.2%)
Otitis media	2 (0.4%)	6 (1.2%)
Postoperative wound infection	2 (0.4%)	0
Skin candida	2 (0.4%)	3 (0.6%)
Tinea cruris	2 (0.4%)	4 (0.8%)
Wound infection	2 (0.4%)	1 (0.2%)

Appendix 16: Number of Subjects With Treatment-Emergent Adverse Events Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Acarodermatitis	1 (0.2%)	2 (0.4%)
Anal abscess	1 (0.2%)	0
Anal fistula infection	1 (0.2%)	0
Appendicitis	1 (0.2%)	0
Arthritis infective	1 (0.2%)	0
Bacterial rhinitis	1 (0.2%)	0
Bacterial vulvovaginitis	1 (0.2%)	0
Candida infection	1 (0.2%)	0
Conjunctivitis bacterial	1 (0.2%)	0
Dermatitis infected	1 (0.2%)	2 (0.4%)
Dermo-hypodermitis	1 (0.2%)	0
Diverticulitis	1 (0.2%)	3 (0.6%)
Enterobiasis	1 (0.2%)	0
Erysipelas	1 (0.2%)	0
Fungal skin infection	1 (0.2%)	0
Furuncle	1 (0.2%)	2 (0.4%)
Gangrene	1 (0.2%)	0
Gastroenteritis yersinia	1 (0.2%)	0
Genital herpes	1 (0.2%)	3 (0.6%)
Gingivitis	1 (0.2%)	2 (0.4%)
Impetigo	1 (0.2%)	4 (0.8%)
Labyrinthitis	1 (0.2%)	0
Mastitis	1 (0.2%)	0
Nasal herpes	1 (0.2%)	1 (0.2%)
Ophthalmic herpes zoster	1 (0.2%)	0
Paronychia	1 (0.2%)	2 (0.4%)
Peritonsillar abscess	1 (0.2%)	0

Appendix 16: Number of Subjects With Treatment-Emergent Adverse Events Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Pilonidal cyst	1 (0.2%)	0
Pyoderma	1 (0.2%)	0
Salmonellosis	1 (0.2%)	0
Sepsis	1 (0.2%)	0
Skin bacterial infection	1 (0.2%)	0
Upper respiratory tract infection bacterial	1 (0.2%)	0
Urinary tract infection bacterial	1 (0.2%)	0
Viral pharyngitis	1 (0.2%)	0
Abscess	0	1 (0.2%)
Abscess limb	0	1 (0.2%)
Angular cheilitis	0	3 (0.6%)
Application site cellulitis	0	1 (0.2%)
Bacterial vaginosis	0	1 (0.2%)
Balanitis candida	0	2 (0.4%)
Blister infected	0	1 (0.2%)
Body tinea	0	2 (0.4%)
Bullous impetigo	0	1 (0.2%)
Dermatophytosis	0	1 (0.2%)
Eczema impetiginous	0	1 (0.2%)
Eczema infected	0	2 (0.4%)
Groin abscess	0	1 (0.2%)
Helicobacter infection	0	1 (0.2%)
Herpes simplex	0	1 (0.2%)
Herpes zoster	0	4 (0.8%)
Neuroborreliosis	0	1 (0.2%)
Onychomycosis	0	1 (0.2%)
Otitis externa	0	3 (0.6%)

Appendix 16: Number of Subjects With Treatment-Emergent Adverse Events Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Otitis media acute	0	1 (0.2%)
Perianal streptococcal infection	0	1 (0.2%)
Peritonsillitis	0	1 (0.2%)
Pharyngitis streptococcal	0	4 (0.8%)
Pharyngotonsillitis	0	1 (0.2%)
Pulpitis dental	0	2 (0.4%)
Pyelonephritis	0	1 (0.2%)
Respiratory syncytial virus infection	0	1 (0.2%)
Respiratory tract infection viral	0	1 (0.2%)
Sialoadenitis	0	1 (0.2%)
Soft tissue infection	0	1 (0.2%)
Staphylococcal skin infection	0	3 (0.6%)
Subcutaneous abscess	0	2 (0.4%)
Tracheobronchitis	0	1 (0.2%)
Vaginal infection	0	2 (0.4%)
Vulvovaginal mycotic infection	0	2 (0.4%)
Musculoskeletal and connective tissue disorders	98 (18.4%)	93 (18.2%)
Arthralgia	30 (5.6%)	25 (4.9%)
Back pain	29 (5.4%)	18 (3.5%)
Myalgia	11 (2.1%)	7 (1.4%)
Musculoskeletal pain	7 (1.3%)	7 (1.4%)
Psoriatic arthropathy	7 (1.3%)	3 (0.6%)
Osteoarthritis	6 (1.1%)	4 (0.8%)
Joint swelling	5 (0.9%)	3 (0.6%)
Tendonitis	5 (0.9%)	2 (0.4%)
Muscle spasms	4 (0.7%)	5 (1.0%)

Appendix 16: Number of Subjects With Treatment-Emergent Adverse Events Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Neck pain	4 (0.7%)	5 (1.0%)
Joint effusion	3 (0.6%)	1 (0.2%)
Pain in extremity	3 (0.6%)	6 (1.2%)
Musculoskeletal chest pain	2 (0.4%)	2 (0.4%)
Plantar fasciitis	2 (0.4%)	0
Spinal pain	2 (0.4%)	3 (0.6%)
Arthritis	1 (0.2%)	1 (0.2%)
Chondropathy	1 (0.2%)	0
Enthesopathy	1 (0.2%)	0
Exostosis	1 (0.2%)	0
Fibromyalgia	1 (0.2%)	0
Groin pain	1 (0.2%)	1 (0.2%)
Intervertebral disc degeneration	1 (0.2%)	0
Joint stiffness	1 (0.2%)	1 (0.2%)
Muscle tightness	1 (0.2%)	0
Myofascial pain syndrome	1 (0.2%)	0
Rotator cuff syndrome	1 (0.2%)	2 (0.4%)
Spinal osteoarthritis	1 (0.2%)	3 (0.6%)
Synovial cyst	1 (0.2%)	0
Synovitis	1 (0.2%)	0
Trigger finger	1 (0.2%)	0
Bursitis	0	3 (0.6%)
Costochondritis	0	1 (0.2%)
Flank pain	0	1 (0.2%)
Intervertebral disc disorder	0	3 (0.6%)
Intervertebral disc protrusion	0	2 (0.4%)
Musculoskeletal stiffness	0	1 (0.2%)

Appendix 16: Number of Subjects With Treatment-Emergent Adverse Events Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Osteopenia	0	1 (0.2%)
Periarthritis	0	1 (0.2%)
Sacroiliitis	0	1 (0.2%)
Spinal column stenosis	0	1 (0.2%)
Spondylolisthesis	0	1 (0.2%)
Temporomandibular joint syndrome	0	1 (0.2%)
Tenosynovitis stenosans	0	1 (0.2%)
Nervous system disorders	79 (14.8%)	71 (13.9%)
Headache	49 (9.2%)	48 (9.4%)
Sciatica	8 (1.5%)	6 (1.2%)
Migraine	6 (1.1%)	4 (0.8%)
Hypoaesthesia	3 (0.6%)	2 (0.4%)
Paraesthesia	3 (0.6%)	0
Presyncope	2 (0.4%)	1 (0.2%)
Aphonia	1 (0.2%)	0
Burning sensation	1 (0.2%)	0
Carpal tunnel syndrome	1 (0.2%)	2 (0.4%)
Cervicobrachial syndrome	1 (0.2%)	0
Cluster headache	1 (0.2%)	0
Disturbance in attention	1 (0.2%)	0
Dizziness postural	1 (0.2%)	0
Dysaesthesia	1 (0.2%)	1 (0.2%)
Facial neuralgia	1 (0.2%)	0
Hyperaesthesia	1 (0.2%)	0
Memory impairment	1 (0.2%)	0
Nerve compression	1 (0.2%)	0
Piriformis syndrome	1 (0.2%)	0

Appendix 16: Number of Subjects With Treatment-Emergent Adverse Events Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Spinal cord infarction	1 (0.2%)	0
Spinal meningeal cyst	1 (0.2%)	0
Syncope	1 (0.2%)	4 (0.8%)
Tension headache	1 (0.2%)	0
Tremor	1 (0.2%)	0
Vertebral artery stenosis	1 (0.2%)	0
White matter lesion	1 (0.2%)	0
Cerebral cyst	0	1 (0.2%)
Cerebrovascular accident	0	1 (0.2%)
Dizziness	0	5 (1.0%)
Dysgeusia	0	1 (0.2%)
Facial paralysis	0	1 (0.2%)
Head discomfort	0	1 (0.2%)
Lethargy	0	1 (0.2%)
Neuralgia	0	3 (0.6%)
Neuropathy peripheral	0	1 (0.2%)
Post herpetic neuralgia	0	1 (0.2%)
Post-traumatic headache	0	1 (0.2%)
Gastrointestinal disorders	78 (14.6%)	77 (15.1%)
Diarrhoea	27 (5.1%)	20 (3.9%)
Abdominal pain upper	10 (1.9%)	7 (1.4%)
Gastrooesophageal reflux disease	7 (1.3%)	8 (1.6%)
Abdominal pain	6 (1.1%)	7 (1.4%)
Nausea	6 (1.1%)	8 (1.6%)
Vomiting	6 (1.1%)	2 (0.4%)
Toothache	5 (0.9%)	4 (0.8%)
Constipation	3 (0.6%)	4 (0.8%)

Appendix 16: Number of Subjects With Treatment-Emergent Adverse Events Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Enteritis	3 (0.6%)	0
Flatulence	3 (0.6%)	1 (0.2%)
Gastritis	3 (0.6%)	2 (0.4%)
Dental caries	2 (0.4%)	0
Frequent bowel movements	2 (0.4%)	1 (0.2%)
Umbilical hernia	2 (0.4%)	1 (0.2%)
Abdominal discomfort	1 (0.2%)	1 (0.2%)
Abdominal distension	1 (0.2%)	0
Abdominal pain lower	1 (0.2%)	0
Anal fissure	1 (0.2%)	0
Anal fistula	1 (0.2%)	0
Colitis microscopic	1 (0.2%)	0
Diverticulum intestinal	1 (0.2%)	0
Dry mouth	1 (0.2%)	0
Dyspepsia	1 (0.2%)	2 (0.4%)
Glossitis	1 (0.2%)	0
Haematochezia	1 (0.2%)	1 (0.2%)
Haemorrhoidal haemorrhage	1 (0.2%)	0
Haemorrhoids	1 (0.2%)	2 (0.4%)
Hyperchlorhydria	1 (0.2%)	0
Inguinal hernia	1 (0.2%)	0
Irritable bowel syndrome	1 (0.2%)	1 (0.2%)
Large intestine polyp	1 (0.2%)	1 (0.2%)
Leukoplakia oral	1 (0.2%)	0
Mucous stools	1 (0.2%)	0
Palatal oedema	1 (0.2%)	0
Rectal polyp	1 (0.2%)	0

Appendix 16: Number of Subjects With Treatment-Emergent Adverse Events Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Abdominal hernia	0	1 (0.2%)
Anal pruritus	0	1 (0.2%)
Aphthous ulcer	0	8 (1.6%)
Apical granuloma	0	1 (0.2%)
Burning mouth syndrome	0	1 (0.2%)
Chronic gastritis	0	1 (0.2%)
Colitis	0	1 (0.2%)
Crohn's disease	0	1 (0.2%)
Dysphagia	0	3 (0.6%)
Food poisoning	0	2 (0.4%)
Functional gastrointestinal disorder	0	1 (0.2%)
Gingival bleeding	0	1 (0.2%)
Gingival recession	0	1 (0.2%)
Hiatus hernia	0	1 (0.2%)
Inflammatory bowel disease	0	2 (0.4%)
Odynophagia	0	2 (0.4%)
Tooth impacted	0	1 (0.2%)
Skin and subcutaneous tissue disorders	76 (14.2%)	92 (18.0%)
Pruritus	17 (3.2%)	12 (2.3%)
Acne	4 (0.7%)	3 (0.6%)
Dermatitis	4 (0.7%)	7 (1.4%)
Dermatitis contact	4 (0.7%)	8 (1.6%)
Eczema	4 (0.7%)	7 (1.4%)
Psoriasis	4 (0.7%)	11 (2.2%)
Skin lesion	3 (0.6%)	2 (0.4%)
Urticaria	3 (0.6%)	9 (1.8%)
Actinic keratosis	2 (0.4%)	2 (0.4%)

Appendix 16: Number of Subjects With Treatment-Emergent Adverse Events Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Alopecia	2 (0.4%)	4 (0.8%)
Blister	2 (0.4%)	0
Chronic cutaneous lupus erythematosus	2 (0.4%)	0
Drug eruption	2 (0.4%)	1 (0.2%)
Dry skin	2 (0.4%)	3 (0.6%)
Eczema asteatotic	2 (0.4%)	2 (0.4%)
Hyperkeratosis	2 (0.4%)	0
Papule	2 (0.4%)	1 (0.2%)
Photosensitivity reaction	2 (0.4%)	0
Polymorphic light eruption	2 (0.4%)	0
Pruritus generalised	2 (0.4%)	2 (0.4%)
Rash	2 (0.4%)	1 (0.2%)
Angioedema	1 (0.2%)	0
Cafe au lait spots	1 (0.2%)	2 (0.4%)
Dermal cyst	1 (0.2%)	3 (0.6%)
Dermatitis atopic	1 (0.2%)	1 (0.2%)
Erythema	1 (0.2%)	2 (0.4%)
Ingrowing nail	1 (0.2%)	0
Ingrown hair	1 (0.2%)	0
Intertrigo	1 (0.2%)	8 (1.6%)
Lentigo	1 (0.2%)	0
Milia	1 (0.2%)	0
Miliaria	1 (0.2%)	1 (0.2%)
Night sweats	1 (0.2%)	1 (0.2%)
Onycholysis	1 (0.2%)	1 (0.2%)
Perioral dermatitis	1 (0.2%)	0
Pityriasis	1 (0.2%)	0

Appendix 16: Number of Subjects With Treatment-Emergent Adverse Events Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Pityriasis rosea	1 (0.2%)	0
Rash morbilliform	1 (0.2%)	0
Rash papular	1 (0.2%)	2 (0.4%)
Rosacea	1 (0.2%)	0
Seborrhoeic dermatitis	1 (0.2%)	8 (1.6%)
Skin burning sensation	1 (0.2%)	0
Skin exfoliation	1 (0.2%)	0
Skin ulcer	1 (0.2%)	1 (0.2%)
Solar dermatitis	1 (0.2%)	0
Alopecia scarring	0	1 (0.2%)
Dermatitis allergic	0	1 (0.2%)
Diffuse alopecia	0	1 (0.2%)
Dyshidrotic eczema	0	2 (0.4%)
Eczema nummular	0	1 (0.2%)
Ephelides	0	1 (0.2%)
Hair growth rate abnormal	0	1 (0.2%)
Hand dermatitis	0	1 (0.2%)
Hyperhidrosis	0	1 (0.2%)
Idiopathic urticaria	0	1 (0.2%)
Keratolysis exfoliativa acquired	0	1 (0.2%)
Keratosis pilaris	0	1 (0.2%)
Myxoid cyst	0	1 (0.2%)
Neurodermatitis	0	3 (0.6%)
Photodermatosis	0	1 (0.2%)
Pruritus allergic	0	1 (0.2%)
Rash maculo-papular	0	1 (0.2%)
Skin fissures	0	3 (0.6%)

Appendix 16: Number of Subjects With Treatment-Emergent Adverse Events Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Skin texture abnormal	0	1 (0.2%)
Stasis dermatitis	0	1 (0.2%)
Urticaria pressure	0	1 (0.2%)
Respiratory, thoracic and mediastinal disorders	59 (11.0%)	59 (11.5%)
Cough	20 (3.7%)	21 (4.1%)
Oropharyngeal pain	12 (2.2%)	11 (2.2%)
Nasal congestion	7 (1.3%)	6 (1.2%)
Rhinorrhoea	6 (1.1%)	9 (1.8%)
Rhinitis allergic	4 (0.7%)	0
Sinus congestion	4 (0.7%)	3 (0.6%)
Dysphonia	2 (0.4%)	0
Dyspnoea	2 (0.4%)	2 (0.4%)
Productive cough	2 (0.4%)	1 (0.2%)
Asthma	1 (0.2%)	3 (0.6%)
Catarrh	1 (0.2%)	0
Dry throat	1 (0.2%)	0
Dyspnoea exertional	1 (0.2%)	0
Epistaxis	1 (0.2%)	0
Interstitial lung disease	1 (0.2%)	0
Nasal cyst	1 (0.2%)	0
Nasal polyps	1 (0.2%)	0
Oropharyngeal discomfort	1 (0.2%)	0
Pneumonia aspiration	1 (0.2%)	0
Respiratory disorder	1 (0.2%)	0
Sneezing	1 (0.2%)	0
Upper respiratory tract congestion	1 (0.2%)	0
Adenoidal hypertrophy	0	1 (0.2%)

Appendix 16: Number of Subjects With Treatment-Emergent Adverse Events Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Asthmatic crisis	0	1 (0.2%)
Bronchial hyperreactivity	0	1 (0.2%)
Chronic obstructive pulmonary disease	0	1 (0.2%)
Lower respiratory tract congestion	0	1 (0.2%)
Nasal ulcer	0	1 (0.2%)
Pulmonary embolism	0	1 (0.2%)
Sleep apnoea syndrome	0	1 (0.2%)
Throat irritation	0	2 (0.4%)
General disorders and administration site conditions	56 (10.5%)	58 (11.4%)
Fatigue	10 (1.9%)	7 (1.4%)
Injection site erythema	10 (1.9%)	7 (1.4%)
Injection site haematoma	6 (1.1%)	5 (1.0%)
Injection site pain	6 (1.1%)	7 (1.4%)
Injection site pruritus	5 (0.9%)	0
Non-cardiac chest pain	5 (0.9%)	6 (1.2%)
Pyrexia	5 (0.9%)	6 (1.2%)
Oedema peripheral	4 (0.7%)	4 (0.8%)
Influenza like illness	3 (0.6%)	5 (1.0%)
Injection site bruising	3 (0.6%)	2 (0.4%)
Injection site swelling	3 (0.6%)	1 (0.2%)
Adverse drug reaction	2 (0.4%)	0
Asthenia	2 (0.4%)	2 (0.4%)
Cyst	2 (0.4%)	1 (0.2%)
Injection site induration	2 (0.4%)	0
Calcinosis	1 (0.2%)	0
Chest pain	1 (0.2%)	1 (0.2%)

Appendix 16: Number of Subjects With Treatment-Emergent Adverse Events Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Face oedema	1 (0.2%)	0
General physical health deterioration	1 (0.2%)	0
Generalised oedema	1 (0.2%)	0
Hernia pain	1 (0.2%)	0
Injection site extravasation	1 (0.2%)	0
Injection site haemorrhage	1 (0.2%)	2 (0.4%)
Injection site oedema	1 (0.2%)	2 (0.4%)
Injection site rash	1 (0.2%)	0
Malaise	1 (0.2%)	0
Pain	1 (0.2%)	0
Tenderness	1 (0.2%)	0
Xerosis	1 (0.2%)	2 (0.4%)
Axillary pain	0	1 (0.2%)
Chest discomfort	0	1 (0.2%)
Discomfort	0	2 (0.4%)
Exercise tolerance decreased	0	1 (0.2%)
Feeling cold	0	2 (0.4%)
Injection site inflammation	0	1 (0.2%)
Injury associated with device	0	1 (0.2%)
Nodule	0	1 (0.2%)
Swelling	0	1 (0.2%)
Vessel puncture site haemorrhage	0	1 (0.2%)
Injury, poisoning and procedural complications	56 (10.5%)	54 (10.6%)
Laceration	7 (1.3%)	6 (1.2%)
Ligament sprain	5 (0.9%)	4 (0.8%)
Procedural pain	4 (0.7%)	1 (0.2%)
Arthropod sting	3 (0.6%)	0

Appendix 16: Number of Subjects With Treatment-Emergent Adverse Events Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Contusion	3 (0.6%)	8 (1.6%)
Limb injury	3 (0.6%)	1 (0.2%)
Arthropod bite	2 (0.4%)	1 (0.2%)
Hand fracture	2 (0.4%)	1 (0.2%)
Joint dislocation	2 (0.4%)	0
Ligament rupture	2 (0.4%)	1 (0.2%)
Meniscus injury	2 (0.4%)	1 (0.2%)
Muscle strain	2 (0.4%)	6 (1.2%)
Rib fracture	2 (0.4%)	2 (0.4%)
Tooth fracture	2 (0.4%)	1 (0.2%)
Tooth injury	2 (0.4%)	0
Wound	2 (0.4%)	0
Animal scratch	1 (0.2%)	0
Arterial injury	1 (0.2%)	0
Chest injury	1 (0.2%)	0
Clavicle fracture	1 (0.2%)	0
Concussion	1 (0.2%)	0
Craniocerebral injury	1 (0.2%)	1 (0.2%)
Electrical burn	1 (0.2%)	0
Foot fracture	1 (0.2%)	1 (0.2%)
Foreign body in eye	1 (0.2%)	0
Joint injury	1 (0.2%)	1 (0.2%)
Overdose	1 (0.2%)	0
Procedural hypertension	1 (0.2%)	0
Radius fracture	1 (0.2%)	1 (0.2%)
Skin abrasion	1 (0.2%)	5 (1.0%)
Skull fracture	1 (0.2%)	0

Appendix 16: Number of Subjects With Treatment-Emergent Adverse Events Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Spinal column injury	1 (0.2%)	0
Thermal burn	1 (0.2%)	4 (0.8%)
Venomous sting	1 (0.2%)	0
Bone contusion	0	2 (0.4%)
Dental restoration failure	0	1 (0.2%)
Ear abrasion	0	1 (0.2%)
Epicondylitis	0	3 (0.6%)
Eye contusion	0	1 (0.2%)
Femoral neck fracture	0	1 (0.2%)
Palate injury	0	1 (0.2%)
Post procedural diarrhoea	0	1 (0.2%)
Post-traumatic neck syndrome	0	1 (0.2%)
Soft tissue injury	0	2 (0.4%)
Tendon rupture	0	2 (0.4%)
Upper limb fracture	0	1 (0.2%)
Wrist fracture	0	1 (0.2%)
Investigations	37 (6.9%)	32 (6.3%)
Alanine aminotransferase increased	15 (2.8%)	10 (2.0%)
Aspartate aminotransferase increased	10 (1.9%)	6 (1.2%)
Blood pressure increased	6 (1.1%)	4 (0.8%)
Blood bilirubin increased	3 (0.6%)	0
Blood glucose increased	2 (0.4%)	1 (0.2%)
Electrocardiogram T wave amplitude decreased	2 (0.4%)	0
Faecal calprotectin increased	2 (0.4%)	0
Hepatic enzyme increased	2 (0.4%)	3 (0.6%)
Transaminases increased	2 (0.4%)	2 (0.4%)

Appendix 16: Number of Subjects With Treatment-Emergent Adverse Events Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Blood iron decreased	1 (0.2%)	0
C-reactive protein increased	1 (0.2%)	0
Electrocardiogram T wave inversion	1 (0.2%)	0
Electrocardiogram repolarisation abnormality	1 (0.2%)	0
Liver function test increased	1 (0.2%)	0
Serum ferritin decreased	1 (0.2%)	0
Weight increased	1 (0.2%)	1 (0.2%)
Blood alkaline phosphatase increased	0	2 (0.4%)
Blood creatine phosphokinase increased	0	1 (0.2%)
Blood creatinine increased	0	1 (0.2%)
Blood pressure systolic increased	0	1 (0.2%)
Blood triglycerides increased	0	1 (0.2%)
Computerised tomogram coronary artery abnormal	0	1 (0.2%)
Ejection fraction abnormal	0	1 (0.2%)
Neutrophil count decreased	0	2 (0.4%)
Occult blood	0	1 (0.2%)
Platelet count decreased	0	1 (0.2%)
Ultrasound liver abnormal	0	1 (0.2%)
Weight decreased	0	2 (0.4%)
White blood cell count decreased	0	1 (0.2%)
Vascular disorders	33 (6.2%)	33 (6.5%)
Hypertension	22 (4.1%)	22 (4.3%)
Hypertensive crisis	2 (0.4%)	0
Peripheral arterial occlusive disease	2 (0.4%)	0
Aortic aneurysm	1 (0.2%)	0
Arteriosclerosis	1 (0.2%)	0

Appendix 16: Number of Subjects With Treatment-Emergent Adverse Events Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Haematoma	1 (0.2%)	1 (0.2%)
Hot flush	1 (0.2%)	2 (0.4%)
Hypotension	1 (0.2%)	2 (0.4%)
Varicose vein	1 (0.2%)	0
Vein rupture	1 (0.2%)	0
Deep vein thrombosis	0	1 (0.2%)
Diastolic hypertension	0	1 (0.2%)
Flushing	0	1 (0.2%)
Lymphoedema	0	1 (0.2%)
Orthostatic hypotension	0	1 (0.2%)
Peripheral vascular disorder	0	1 (0.2%)
Phlebitis superficial	0	1 (0.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	24 (4.5%)	19 (3.7%)
Skin papilloma	6 (1.1%)	3 (0.6%)
Melanocytic naevus	5 (0.9%)	4 (0.8%)
Basal cell carcinoma	3 (0.6%)	2 (0.4%)
Squamous cell carcinoma of skin	2 (0.4%)	0
Acrochordon	1 (0.2%)	0
Anogenital warts	1 (0.2%)	0
Bowen's disease	1 (0.2%)	0
Colon adenoma	1 (0.2%)	1 (0.2%)
Dysplastic naevus	1 (0.2%)	2 (0.4%)
Fibroma	1 (0.2%)	0
Invasive ductal breast carcinoma	1 (0.2%)	0
Lipoma	1 (0.2%)	1 (0.2%)
Ductal adenocarcinoma of pancreas	0	1 (0.2%)

Appendix 16: Number of Subjects With Treatment-Emergent Adverse Events Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Haemangioma	0	1 (0.2%)
Kidney angiomyolipoma	0	1 (0.2%)
Mycosis fungoides	0	1 (0.2%)
Non-small cell lung cancer	0	1 (0.2%)
Seborrhoeic keratosis	0	2 (0.4%)
Uterine leiomyoma	0	2 (0.4%)
Psychiatric disorders	24 (4.5%)	27 (5.3%)
Anxiety	8 (1.5%)	9 (1.8%)
Depression	5 (0.9%)	4 (0.8%)
Insomnia	4 (0.7%)	7 (1.4%)
Suicidal ideation	3 (0.6%)	3 (0.6%)
Alcoholism	1 (0.2%)	0
Borderline personality disorder	1 (0.2%)	0
Depressed mood	1 (0.2%)	1 (0.2%)
Grief reaction	1 (0.2%)	0
Psychotic disorder	1 (0.2%)	0
Restlessness	1 (0.2%)	0
Sleep disorder	1 (0.2%)	0
Stress	1 (0.2%)	2 (0.4%)
Adjustment disorder with depressed mood	0	1 (0.2%)
Intentional self-injury	0	1 (0.2%)
Irritability	0	1 (0.2%)
Mental disorder	0	1 (0.2%)
Mixed anxiety and depressive disorder	0	1 (0.2%)
Panic attack	0	1 (0.2%)
Seasonal affective disorder	0	1 (0.2%)
Suicide attempt	0	1 (0.2%)

Appendix 16: Number of Subjects With Treatment-Emergent Adverse Events Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Metabolism and nutrition disorders	22 (4.1%)	16 (3.1%)
Hyperglycaemia	9 (1.7%)	1 (0.2%)
Hyperlipidaemia	3 (0.6%)	0
Abnormal loss of weight	1 (0.2%)	0
Decreased appetite	1 (0.2%)	2 (0.4%)
Diabetes mellitus	1 (0.2%)	3 (0.6%)
Gout	1 (0.2%)	2 (0.4%)
Haemochromatosis	1 (0.2%)	0
Hypercholesterolaemia	1 (0.2%)	0
Hyperkalaemia	1 (0.2%)	1 (0.2%)
Hypertriglyceridaemia	1 (0.2%)	0
Hyperuricaemia	1 (0.2%)	0
Hypokalaemia	1 (0.2%)	2 (0.4%)
Increased appetite	1 (0.2%)	1 (0.2%)
Overweight	1 (0.2%)	0
Type 2 diabetes mellitus	1 (0.2%)	2 (0.4%)
Dehydration	0	1 (0.2%)
Diabetes mellitus inadequate control	0	1 (0.2%)
Glucose tolerance impaired	0	1 (0.2%)
Hyperhomocysteinaemia	0	1 (0.2%)
Hypoglycaemia	0	1 (0.2%)
Hyponatraemia	0	1 (0.2%)
Polydipsia	0	1 (0.2%)
Type 1 diabetes mellitus	0	1 (0.2%)
Vitamin D deficiency	0	1 (0.2%)
Cardiac disorders	20 (3.7%)	11 (2.2%)
Tachycardia	5 (0.9%)	1 (0.2%)

Appendix 16: Number of Subjects With Treatment-Emergent Adverse Events Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Atrial fibrillation	4 (0.7%)	2 (0.4%)
Bundle branch block left	3 (0.6%)	0
Palpitations	2 (0.4%)	0
Aortic valve stenosis	1 (0.2%)	0
Bundle branch block right	1 (0.2%)	0
Coronary artery occlusion	1 (0.2%)	0
Defect conduction intraventricular	1 (0.2%)	0
Sinus bradycardia	1 (0.2%)	0
Supraventricular tachycardia	1 (0.2%)	0
Ventricular extrasystoles	1 (0.2%)	0
Wolff-Parkinson-White syndrome	1 (0.2%)	0
Atrial thrombosis	0	1 (0.2%)
Atrioventricular block complete	0	1 (0.2%)
Atrioventricular block first degree	0	2 (0.4%)
Cardiac disorder	0	1 (0.2%)
Cardiac failure congestive	0	1 (0.2%)
Coronary artery disease	0	1 (0.2%)
Extrasystoles	0	1 (0.2%)
Left ventricular dilatation	0	1 (0.2%)
Sinus tachycardia	0	2 (0.4%)
Eye disorders	18 (3.4%)	17 (3.3%)
Cataract	5 (0.9%)	2 (0.4%)
Conjunctivitis allergic	3 (0.6%)	3 (0.6%)
Dry eye	2 (0.4%)	2 (0.4%)
Blepharitis	1 (0.2%)	4 (0.8%)
Cataract subcapsular	1 (0.2%)	0
Chalazion	1 (0.2%)	0

Appendix 16: Number of Subjects With Treatment-Emergent Adverse Events Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Conjunctival haemorrhage	1 (0.2%)	1 (0.2%)
Conjunctival hyperaemia	1 (0.2%)	0
Diabetic retinopathy	1 (0.2%)	0
Episcleritis	1 (0.2%)	0
Eye oedema	1 (0.2%)	0
Eye swelling	1 (0.2%)	0
Glaucoma	1 (0.2%)	0
Macular fibrosis	1 (0.2%)	0
Ocular hyperaemia	1 (0.2%)	0
Ocular hypertension	1 (0.2%)	0
Retinal degeneration	1 (0.2%)	0
Vitreous detachment	1 (0.2%)	0
Blepharospasm	0	1 (0.2%)
Eczema eyelids	0	1 (0.2%)
Eye discharge	0	1 (0.2%)
Myopia	0	1 (0.2%)
Pupils unequal	0	1 (0.2%)
Visual acuity reduced	0	2 (0.4%)
Ear and labyrinth disorders	13 (2.4%)	13 (2.5%)
Vertigo	7 (1.3%)	6 (1.2%)
Ear pain	3 (0.6%)	3 (0.6%)
Cerumen impaction	1 (0.2%)	0
Ear canal erythema	1 (0.2%)	0
Ear discomfort	1 (0.2%)	0
Ear pruritus	1 (0.2%)	0
Tinnitus	1 (0.2%)	1 (0.2%)
Deafness unilateral	0	1 (0.2%)

Appendix 16: Number of Subjects With Treatment-Emergent Adverse Events Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Ear canal stenosis	0	1 (0.2%)
Hypoacusis	0	1 (0.2%)
Middle ear effusion	0	1 (0.2%)
Blood and lymphatic system disorders	10 (1.9%)	9 (1.8%)
Lymphadenopathy	3 (0.6%)	2 (0.4%)
Anaemia	2 (0.4%)	0
Leukocytosis	2 (0.4%)	0
Thrombocytopenia	2 (0.4%)	0
Neutrophilia	1 (0.2%)	0
Pancytopenia	1 (0.2%)	0
Erythropenia	0	1 (0.2%)
Leukopenia	0	1 (0.2%)
Lymphopenia	0	2 (0.4%)
Neutropenia	0	4 (0.8%)
Reproductive system and breast disorders	9 (1.7%)	12 (2.3%)
Dysmenorrhoea	2 (0.4%)	1 (0.2%)
Bartholin's cyst	1 (0.2%)	0
Benign prostatic hyperplasia	1 (0.2%)	2 (0.4%)
Breast cyst	1 (0.2%)	0
Breast mass	1 (0.2%)	1 (0.2%)
Endometriosis	1 (0.2%)	0
Erectile dysfunction	1 (0.2%)	0
Varicocele	1 (0.2%)	0
Acquired phimosis	0	1 (0.2%)
Endometrial disorder	0	2 (0.4%)
Prostatomegaly	0	1 (0.2%)
Vulvovaginal dryness	0	1 (0.2%)

Appendix 16: Number of Subjects With Treatment-Emergent Adverse Events Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Vulvovaginal inflammation	0	1 (0.2%)
Vulvovaginal pruritus	0	2 (0.4%)
Hepatobiliary disorders	7 (1.3%)	10 (2.0%)
Hepatic steatosis	3 (0.6%)	5 (1.0%)
Biliary colic	2 (0.4%)	0
Cholelithiasis	2 (0.4%)	3 (0.6%)
Cholecystitis acute	1 (0.2%)	0
Cholangitis	0	1 (0.2%)
Cholecystitis	0	1 (0.2%)
Drug-induced liver injury	0	1 (0.2%)
Gallbladder polyp	0	1 (0.2%)
Hepatomegaly	0	1 (0.2%)
Jaundice	0	1 (0.2%)
Immune system disorders	6 (1.1%)	9 (1.8%)
Seasonal allergy	4 (0.7%)	6 (1.2%)
Allergy to arthropod bite	1 (0.2%)	2 (0.4%)
Drug hypersensitivity	1 (0.2%)	0
Anaphylactoid reaction	0	1 (0.2%)
Renal and urinary disorders	6 (1.1%)	8 (1.6%)
Nephrolithiasis	4 (0.7%)	2 (0.4%)
Acute kidney injury	1 (0.2%)	1 (0.2%)
Haematuria	1 (0.2%)	0
Cystitis noninfective	0	1 (0.2%)
Glycosuria	0	1 (0.2%)
Incontinence	0	1 (0.2%)
Ketonuria	0	1 (0.2%)
Leukocyturia	0	1 (0.2%)

Appendix 16: Number of Subjects With Treatment-Emergent Adverse Events Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Micturition urgency	0	1 (0.2%)
Pollakiuria	0	2 (0.4%)
Congenital, familial and genetic disorders	2 (0.4%)	0
Dermoid cyst	1 (0.2%)	0
Hydrocele	1 (0.2%)	0
Endocrine disorders	2 (0.4%)	3 (0.6%)
Hyperthyroidism	1 (0.2%)	1 (0.2%)
Hypothyroidism	1 (0.2%)	0
Androgen deficiency	0	1 (0.2%)
Autoimmune thyroiditis	0	1 (0.2%)
Pregnancy, puerperium and perinatal conditions	1 (0.2%)	3 (0.6%)
Pregnancy	1 (0.2%)	2 (0.4%)
Unintended pregnancy	0	1 (0.2%)
Social circumstances	1 (0.2%)	2 (0.4%)
Pregnancy of partner	1 (0.2%)	2 (0.4%)
Product issues	0	3 (0.6%)
Device dislocation	0	1 (0.2%)
Device loosening	0	1 (0.2%)
Device material opacification	0	1 (0.2%)
Surgical and medical procedures	0	1 (0.2%)
Finger amputation	0	1 (0.2%)

Key: AE = adverse event, Avg = average.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 21.0.

[TSFAE01.RTF] [CNTO1959\PSO3009\DBR_WEEK_056\RE_WEEK_056_CSR\PROD\TSFAE01.SAS] 23OCT2018, 12:58

Appendix 17: Number of Subjects With Treatment-Emergent Serious Adverse Events Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Analysis set: Safety analysis set	534	511
Avg duration of follow-up (weeks)	54.90	53.67
Avg exposure (number of administrations)	14.65	14.41
Subjects with 1 or more SAEs	33 (6.2%)	37 (7.2%)
System organ class		
Preferred term		
Infections and infestations	4 (0.7%)	5 (1.0%)
Appendicitis	1 (0.2%)	0
Cellulitis	1 (0.2%)	1 (0.2%)
Labyrinthitis	1 (0.2%)	0
Pneumonia	1 (0.2%)	1 (0.2%)
Abscess limb	0	1 (0.2%)
Neuroborreliosis	0	1 (0.2%)
Pyelonephritis	0	1 (0.2%)
Injury, poisoning and procedural complications	4 (0.7%)	4 (0.8%)
Clavicle fracture	1 (0.2%)	0
Ligament rupture	1 (0.2%)	0
Meniscus injury	1 (0.2%)	0
Skull fracture	1 (0.2%)	0
Femoral neck fracture	0	1 (0.2%)
Foot fracture	0	1 (0.2%)
Tendon rupture	0	1 (0.2%)

Appendix 17: Number of Subjects With Treatment-Emergent Serious Adverse Events Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Upper limb fracture	0	1 (0.2%)
Respiratory, thoracic and mediastinal disorders	4 (0.7%)	1 (0.2%)
Interstitial lung disease	1 (0.2%)	0
Nasal cyst	1 (0.2%)	0
Nasal polyps	1 (0.2%)	0
Pneumonia aspiration	1 (0.2%)	0
Pulmonary embolism	0	1 (0.2%)
Cardiac disorders	3 (0.6%)	3 (0.6%)
Atrial fibrillation	1 (0.2%)	1 (0.2%)
Coronary artery occlusion	1 (0.2%)	0
Wolff-Parkinson-White syndrome	1 (0.2%)	0
Atrioventricular block complete	0	1 (0.2%)
Cardiac failure congestive	0	1 (0.2%)
Gastrointestinal disorders	3 (0.6%)	2 (0.4%)
Constipation	1 (0.2%)	0
Leukoplakia oral	1 (0.2%)	0
Umbilical hernia	1 (0.2%)	0
Crohn's disease	0	1 (0.2%)
Haemorrhoids	0	1 (0.2%)
Skin and subcutaneous tissue disorders	3 (0.6%)	1 (0.2%)
Chronic cutaneous lupus erythematosus	1 (0.2%)	0
Drug eruption	1 (0.2%)	0
Rash morbilliform	1 (0.2%)	0
Psoriasis	0	1 (0.2%)
General disorders and administration site conditions	2 (0.4%)	3 (0.6%)
General physical health deterioration	1 (0.2%)	0

Appendix 17: Number of Subjects With Treatment-Emergent Serious Adverse Events Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Non-cardiac chest pain	1 (0.2%)	1 (0.2%)
Chest pain	0	1 (0.2%)
Exercise tolerance decreased	0	1 (0.2%)
Hepatobiliary disorders	2 (0.4%)	3 (0.6%)
Cholecystitis acute	1 (0.2%)	0
Cholelithiasis	1 (0.2%)	1 (0.2%)
Cholecystitis	0	1 (0.2%)
Drug-induced liver injury	0	1 (0.2%)
Musculoskeletal and connective tissue disorders	2 (0.4%)	5 (1.0%)
Osteoarthritis	1 (0.2%)	1 (0.2%)
Rotator cuff syndrome	1 (0.2%)	0
Intervertebral disc protrusion	0	2 (0.4%)
Spinal column stenosis	0	1 (0.2%)
Spinal osteoarthritis	0	1 (0.2%)
Reproductive system and breast disorders	2 (0.4%)	2 (0.4%)
Bartholin's cyst	1 (0.2%)	0
Endometriosis	1 (0.2%)	0
Benign prostatic hyperplasia	0	1 (0.2%)
Prostatomegaly	0	1 (0.2%)
Vascular disorders	2 (0.4%)	1 (0.2%)
Arteriosclerosis	1 (0.2%)	0
Hypotension	1 (0.2%)	0
Deep vein thrombosis	0	1 (0.2%)
Eye disorders	1 (0.2%)	0
Macular fibrosis	1 (0.2%)	0
Investigations	1 (0.2%)	0

Appendix 17: Number of Subjects With Treatment-Emergent Serious Adverse Events Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Electrocardiogram repolarisation abnormality	1 (0.2%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.2%)	1 (0.2%)
Invasive ductal breast carcinoma	1 (0.2%)	0
Non-small cell lung cancer	0	1 (0.2%)
Nervous system disorders	1 (0.2%)	1 (0.2%)
Headache	1 (0.2%)	0
Cerebrovascular accident	0	1 (0.2%)
Syncope	0	1 (0.2%)
Psychiatric disorders	1 (0.2%)	2 (0.4%)
Anxiety	1 (0.2%)	1 (0.2%)
Depression	0	1 (0.2%)
Mixed anxiety and depressive disorder	0	1 (0.2%)
Renal and urinary disorders	1 (0.2%)	2 (0.4%)
Acute kidney injury	1 (0.2%)	1 (0.2%)
Nephrolithiasis	0	1 (0.2%)
Immune system disorders	0	1 (0.2%)
Anaphylactoid reaction	0	1 (0.2%)
Surgical and medical procedures	0	1 (0.2%)
Finger amputation	0	1 (0.2%)

Key: AE = adverse event, Avg = average.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 21.0.

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Appendix 18: Number of Subjects With Treatment-Emergent Adverse Events Leading to Discontinuation of Study Agent Through Week 44 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Analysis set: Safety analysis set	534	511
Avg duration of follow-up (weeks)	54.90	53.67
Avg exposure (number of administrations)	14.65	14.41
Subjects with 1 or more AEs leading to discontinuation of study agent	10 (1.9%)	12 (2.3%)
System organ class		
Preferred term		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (0.7%)	2 (0.4%)
Squamous cell carcinoma of skin	2 (0.4%)	0
Bowen's disease	1 (0.2%)	0
Invasive ductal breast carcinoma	1 (0.2%)	0
Mycosis fungoides	0	1 (0.2%)
Non-small cell lung cancer	0	1 (0.2%)
Skin and subcutaneous tissue disorders	3 (0.6%)	2 (0.4%)
Drug eruption	1 (0.2%)	0
Psoriasis	1 (0.2%)	1 (0.2%)
Rash morbilliform	1 (0.2%)	0
Rash maculo-papular	0	1 (0.2%)
Gastrointestinal disorders	1 (0.2%)	2 (0.4%)
Colitis microscopic	1 (0.2%)	0
Crohn's disease	0	1 (0.2%)

Appendix 18: Number of Subjects With Treatment-Emergent Adverse Events Leading to Discontinuation of Study Agent Through Week 44 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Inflammatory bowel disease	0	1 (0.2%)
Investigations	1 (0.2%)	1 (0.2%)
Transaminases increased	1 (0.2%)	0
Platelet count decreased	0	1 (0.2%)
Pregnancy, puerperium and perinatal conditions	1 (0.2%)	1 (0.2%)
Pregnancy	1 (0.2%)	1 (0.2%)
Hepatobiliary disorders	0	1 (0.2%)
Drug-induced liver injury	0	1 (0.2%)
Infections and infestations	0	1 (0.2%)
Abscess limb	0	1 (0.2%)
Nervous system disorders	0	1 (0.2%)
Cerebrovascular accident	0	1 (0.2%)
Vascular disorders	0	1 (0.2%)
Deep vein thrombosis	0	1 (0.2%)

Key: AE = adverse event, Avg = average.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 21.0.

[TSFAE05.RTF] [CNTO1959\PSO3009\DBR_WEEK_056\RE_WEEK_056_CSR\PROD\TSFAE05.SAS] 23OCT2018, 12:58

Appendix 19: Number of Subjects With Treatment-Emergent Infections Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Analysis set: Safety analysis set	534	511
Avg duration of follow-up (weeks)	54.90	53.67
Avg exposure (number of administrations)	14.65	14.41
Subjects with 1 or more infections	313 (58.6%)	331 (64.8%)
System organ class		
Preferred term		
Infections and infestations	308 (57.7%)	323 (63.2%)
Nasopharyngitis	117 (21.9%)	125 (24.5%)
Upper respiratory tract infection	83 (15.5%)	92 (18.0%)
Pharyngitis	24 (4.5%)	22 (4.3%)
Influenza	20 (3.7%)	13 (2.5%)
Bronchitis	17 (3.2%)	15 (2.9%)
Oral herpes	11 (2.1%)	14 (2.7%)
Urinary tract infection	11 (2.1%)	11 (2.2%)
Gastroenteritis	10 (1.9%)	9 (1.8%)
Sinusitis	10 (1.9%)	12 (2.3%)
Gastroenteritis viral	9 (1.7%)	8 (1.6%)
Viral upper respiratory tract infection	9 (1.7%)	8 (1.6%)
Folliculitis	8 (1.5%)	9 (1.8%)
Rhinitis	8 (1.5%)	13 (2.5%)
Tonsillitis	7 (1.3%)	15 (2.9%)

Appendix 19: Number of Subjects With Treatment-Emergent Infections Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Tinea pedis	6 (1.1%)	16 (3.1%)
Gastrointestinal infection	5 (0.9%)	0
Oral candidiasis	5 (0.9%)	11 (2.2%)
Tooth abscess	5 (0.9%)	3 (0.6%)
Tooth infection	5 (0.9%)	2 (0.4%)
Vulvovaginal candidiasis	5 (0.9%)	13 (2.5%)
Acute sinusitis	4 (0.7%)	0
Cellulitis	4 (0.7%)	3 (0.6%)
Conjunctivitis	4 (0.7%)	16 (3.1%)
Respiratory tract infection	4 (0.7%)	2 (0.4%)
Tinea versicolour	4 (0.7%)	5 (1.0%)
Gastrointestinal viral infection	3 (0.6%)	1 (0.2%)
Periodontitis	3 (0.6%)	4 (0.8%)
Pneumonia	3 (0.6%)	6 (1.2%)
Cystitis	2 (0.4%)	2 (0.4%)
Ear infection	2 (0.4%)	5 (1.0%)
Helicobacter gastritis	2 (0.4%)	0
Laryngitis	2 (0.4%)	2 (0.4%)
Localised infection	2 (0.4%)	1 (0.2%)
Otitis media	2 (0.4%)	6 (1.2%)
Postoperative wound infection	2 (0.4%)	0
Skin candida	2 (0.4%)	3 (0.6%)
Tinea cruris	2 (0.4%)	4 (0.8%)
Wound infection	2 (0.4%)	1 (0.2%)
Anal abscess	1 (0.2%)	0
Anal fistula infection	1 (0.2%)	0
Appendicitis	1 (0.2%)	0

Appendix 19: Number of Subjects With Treatment-Emergent Infections Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Arthritis infective	1 (0.2%)	0
Bacterial rhinitis	1 (0.2%)	0
Bacterial vulvovaginitis	1 (0.2%)	0
Candida infection	1 (0.2%)	0
Conjunctivitis bacterial	1 (0.2%)	0
Dermatitis infected	1 (0.2%)	2 (0.4%)
Dermo-hypodermitis	1 (0.2%)	0
Diverticulitis	1 (0.2%)	2 (0.4%)
Enterobiasis	1 (0.2%)	0
Erysipelas	1 (0.2%)	0
Furuncle	1 (0.2%)	2 (0.4%)
Gangrene	1 (0.2%)	0
Gastroenteritis yersinia	1 (0.2%)	0
Genital herpes	1 (0.2%)	3 (0.6%)
Gingivitis	1 (0.2%)	2 (0.4%)
Hordeolum	1 (0.2%)	8 (1.6%)
Impetigo	1 (0.2%)	4 (0.8%)
Labyrinthitis	1 (0.2%)	0
Mastitis	1 (0.2%)	0
Nasal herpes	1 (0.2%)	1 (0.2%)
Ophthalmic herpes zoster	1 (0.2%)	0
Paronychia	1 (0.2%)	2 (0.4%)
Peritonsillar abscess	1 (0.2%)	0
Pyoderma	1 (0.2%)	0
Salmonellosis	1 (0.2%)	0
Sepsis	1 (0.2%)	0
Skin bacterial infection	1 (0.2%)	0

Appendix 19: Number of Subjects With Treatment-Emergent Infections Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Upper respiratory tract infection bacterial	1 (0.2%)	0
Urinary tract infection bacterial	1 (0.2%)	0
Viral pharyngitis	1 (0.2%)	0
Abscess	0	1 (0.2%)
Abscess limb	0	1 (0.2%)
Acarodermatitis	0	2 (0.4%)
Angular cheilitis	0	2 (0.4%)
Application site cellulitis	0	1 (0.2%)
Bacterial vaginosis	0	1 (0.2%)
Balanitis candida	0	1 (0.2%)
Blister infected	0	1 (0.2%)
Body tinea	0	2 (0.4%)
Bullous impetigo	0	1 (0.2%)
Eczema impetiginous	0	1 (0.2%)
Eczema infected	0	2 (0.4%)
Groin abscess	0	1 (0.2%)
Helicobacter infection	0	1 (0.2%)
Herpes simplex	0	1 (0.2%)
Herpes zoster	0	4 (0.8%)
Neuroborreliosis	0	1 (0.2%)
Onychomycosis	0	1 (0.2%)
Otitis externa	0	3 (0.6%)
Otitis media acute	0	1 (0.2%)
Perianal streptococcal infection	0	1 (0.2%)
Peritonsillitis	0	1 (0.2%)
Pharyngitis streptococcal	0	4 (0.8%)
Pharyngotonsillitis	0	1 (0.2%)

Appendix 19: Number of Subjects With Treatment-Emergent Infections Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Pulpitis dental	0	1 (0.2%)
Pyelonephritis	0	1 (0.2%)
Respiratory syncytial virus infection	0	1 (0.2%)
Respiratory tract infection viral	0	1 (0.2%)
Soft tissue infection	0	1 (0.2%)
Staphylococcal skin infection	0	3 (0.6%)
Subcutaneous abscess	0	2 (0.4%)
Tracheobronchitis	0	1 (0.2%)
Vaginal infection	0	2 (0.4%)
Vulvovaginal mycotic infection	0	2 (0.4%)
Respiratory, thoracic and mediastinal disorders	12 (2.2%)	11 (2.2%)
Cough	5 (0.9%)	1 (0.2%)
Oropharyngeal pain	3 (0.6%)	3 (0.6%)
Rhinorrhoea	2 (0.4%)	5 (1.0%)
Nasal congestion	1 (0.2%)	0
Pneumonia aspiration	1 (0.2%)	0
Respiratory disorder	1 (0.2%)	0
Nasal ulcer	0	1 (0.2%)
Sinus congestion	0	1 (0.2%)
Gastrointestinal disorders	7 (1.3%)	3 (0.6%)
Diarrhoea	3 (0.6%)	0
Enteritis	3 (0.6%)	0
Dental caries	1 (0.2%)	0
Aphthous ulcer	0	2 (0.4%)
Apical granuloma	0	1 (0.2%)
General disorders and administration site conditions	5 (0.9%)	8 (1.6%)

Appendix 19: Number of Subjects With Treatment-Emergent Infections Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Influenza like illness	3 (0.6%)	5 (1.0%)
Pyrexia	2 (0.4%)	2 (0.4%)
Nodule	0	1 (0.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (0.7%)	2 (0.4%)
Skin papilloma	3 (0.6%)	2 (0.4%)
Anogenital warts	1 (0.2%)	0
Skin and subcutaneous tissue disorders	4 (0.7%)	10 (2.0%)
Acne	1 (0.2%)	0
Intertrigo	1 (0.2%)	7 (1.4%)
Onycholysis	1 (0.2%)	0
Skin ulcer	1 (0.2%)	1 (0.2%)
Dermal cyst	0	1 (0.2%)
Psoriasis	0	1 (0.2%)
Congenital, familial and genetic disorders	1 (0.2%)	0
Dermoid cyst	1 (0.2%)	0
Reproductive system and breast disorders	1 (0.2%)	0
Bartholin's cyst	1 (0.2%)	0
Eye disorders	0	2 (0.4%)
Blepharitis	0	2 (0.4%)
Nervous system disorders	0	1 (0.2%)
Post herpetic neuralgia	0	1 (0.2%)
Renal and urinary disorders	0	1 (0.2%)
Cystitis noninfective	0	1 (0.2%)
Vascular disorders	0	1 (0.2%)
Phlebitis superficial	0	1 (0.2%)

Appendix 19: Number of Subjects With Treatment-Emergent Infections Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg

Key: Avg = average.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 21.0.

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Appendix 20: Number of Subjects With Treatment-Emergent Infections Requiring Oral or Parenteral Antimicrobial Treatment Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Analysis set: Safety analysis set	534	511
Avg duration of follow-up (weeks)	54.90	53.67
Avg exposure (number of administrations)	14.65	14.41
Subjects with 1 or more infections requiring treatment	118 (22.1%)	147 (28.8%)
System organ class		
Preferred term		
Infections and infestations	116 (21.7%)	139 (27.2%)
Upper respiratory tract infection	19 (3.6%)	28 (5.5%)
Bronchitis	14 (2.6%)	12 (2.3%)
Pharyngitis	13 (2.4%)	10 (2.0%)
Nasopharyngitis	11 (2.1%)	12 (2.3%)
Urinary tract infection	9 (1.7%)	9 (1.8%)
Tonsillitis	5 (0.9%)	13 (2.5%)
Cellulitis	4 (0.7%)	3 (0.6%)
Sinusitis	4 (0.7%)	4 (0.8%)
Tooth abscess	4 (0.7%)	3 (0.6%)
Tooth infection	4 (0.7%)	1 (0.2%)
Acute sinusitis	3 (0.6%)	0
Influenza	3 (0.6%)	2 (0.4%)

Appendix 20: Number of Subjects With Treatment-Emergent Infections Requiring Oral or Parenteral Antimicrobial Treatment Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Pneumonia	3 (0.6%)	6 (1.2%)
Respiratory tract infection	3 (0.6%)	0
Viral upper respiratory tract infection	3 (0.6%)	1 (0.2%)
Folliculitis	2 (0.4%)	3 (0.6%)
Gastroenteritis	2 (0.4%)	0
Localised infection	2 (0.4%)	1 (0.2%)
Periodontitis	2 (0.4%)	2 (0.4%)
Postoperative wound infection	2 (0.4%)	0
Wound infection	2 (0.4%)	0
Arthritis infective	1 (0.2%)	0
Bacterial rhinitis	1 (0.2%)	0
Bacterial vulvovaginitis	1 (0.2%)	0
Conjunctivitis bacterial	1 (0.2%)	0
Cystitis	1 (0.2%)	2 (0.4%)
Dermo-hypodermitis	1 (0.2%)	0
Diverticulitis	1 (0.2%)	2 (0.4%)
Ear infection	1 (0.2%)	4 (0.8%)
Erysipelas	1 (0.2%)	0
Gastroenteritis yersinia	1 (0.2%)	0
Gingivitis	1 (0.2%)	2 (0.4%)
Helicobacter gastritis	1 (0.2%)	0
Hordeolum	1 (0.2%)	2 (0.4%)
Impetigo	1 (0.2%)	2 (0.4%)
Laryngitis	1 (0.2%)	1 (0.2%)
Mastitis	1 (0.2%)	0
Ophthalmic herpes zoster	1 (0.2%)	0

Appendix 20: Number of Subjects With Treatment-Emergent Infections Requiring Oral or Parenteral Antimicrobial Treatment Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Oral candidiasis	1 (0.2%)	1 (0.2%)
Otitis media	1 (0.2%)	6 (1.2%)
Paronychia	1 (0.2%)	1 (0.2%)
Peritonsillar abscess	1 (0.2%)	0
Pyoderma	1 (0.2%)	0
Salmonellosis	1 (0.2%)	0
Sepsis	1 (0.2%)	0
Skin bacterial infection	1 (0.2%)	0
Upper respiratory tract infection bacterial	1 (0.2%)	0
Urinary tract infection bacterial	1 (0.2%)	0
Viral pharyngitis	1 (0.2%)	0
Abscess	0	1 (0.2%)
Abscess limb	0	1 (0.2%)
Application site cellulitis	0	1 (0.2%)
Blister infected	0	1 (0.2%)
Bullous impetigo	0	1 (0.2%)
Conjunctivitis	0	5 (1.0%)
Dermatitis infected	0	1 (0.2%)
Furuncle	0	1 (0.2%)
Gastroenteritis viral	0	1 (0.2%)
Gastrointestinal viral infection	0	1 (0.2%)
Groin abscess	0	1 (0.2%)
Helicobacter infection	0	1 (0.2%)
Herpes zoster	0	1 (0.2%)
Neuroborreliosis	0	1 (0.2%)
Otitis media acute	0	1 (0.2%)

Appendix 20: Number of Subjects With Treatment-Emergent Infections Requiring Oral or Parenteral Antimicrobial Treatment Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Perianal streptococcal infection	0	1 (0.2%)
Peritonsillitis	0	1 (0.2%)
Pharyngitis streptococcal	0	3 (0.6%)
Pharyngotonsillitis	0	1 (0.2%)
Pulpitis dental	0	1 (0.2%)
Pyelonephritis	0	1 (0.2%)
Respiratory syncytial virus infection	0	1 (0.2%)
Rhinitis	0	1 (0.2%)
Soft tissue infection	0	1 (0.2%)
Staphylococcal skin infection	0	1 (0.2%)
Subcutaneous abscess	0	2 (0.4%)
Tracheobronchitis	0	1 (0.2%)
Vaginal infection	0	1 (0.2%)
Vulvovaginal candidiasis	0	1 (0.2%)
Skin and subcutaneous tissue disorders	3 (0.6%)	4 (0.8%)
Acne	1 (0.2%)	0
Intertrigo	1 (0.2%)	1 (0.2%)
Skin ulcer	1 (0.2%)	1 (0.2%)
Dermal cyst	0	1 (0.2%)
Psoriasis	0	1 (0.2%)
Gastrointestinal disorders	1 (0.2%)	1 (0.2%)
Diarrhoea	1 (0.2%)	0
Apical granuloma	0	1 (0.2%)
General disorders and administration site conditions	1 (0.2%)	1 (0.2%)
Influenza like illness	1 (0.2%)	0
Pyrexia	0	1 (0.2%)

Appendix 20: Number of Subjects With Treatment-Emergent Infections Requiring Oral or Parenteral Antimicrobial Treatment Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Reproductive system and breast disorders	1 (0.2%)	0
Bartholin's cyst	1 (0.2%)	0
Respiratory, thoracic and mediastinal disorders	1 (0.2%)	4 (0.8%)
Pneumonia aspiration	1 (0.2%)	0
Nasal ulcer	0	1 (0.2%)
Oropharyngeal pain	0	3 (0.6%)
Renal and urinary disorders	0	1 (0.2%)
Cystitis noninfective	0	1 (0.2%)
Vascular disorders	0	1 (0.2%)
Phlebitis superficial	0	1 (0.2%)

Key: Avg = average.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 21.0.

[TSFINFE03.RTF] [CNTO1959\PSO3009\DBR_WEEK_056\RE_WEEK_056_CSR\PROD\TSFINFE03.SAS] 23OCT2018, 12:59

Appendix 21: Number of Subjects With Treatment-Emergent Serious Infections Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Analysis set: Safety analysis set	534	511
Avg duration of follow-up (weeks)	54.90	53.67
Avg exposure (number of administrations)	14.65	14.41
Subjects with 1 or more serious infections	6 (1.1%)	5 (1.0%)
System organ class		
Preferred term		
Infections and infestations	4 (0.7%)	5 (1.0%)
Appendicitis	1 (0.2%)	0
Cellulitis	1 (0.2%)	1 (0.2%)
Labyrinthitis	1 (0.2%)	0
Pneumonia	1 (0.2%)	1 (0.2%)
Abscess limb	0	1 (0.2%)
Neuroborreliosis	0	1 (0.2%)
Pyelonephritis	0	1 (0.2%)
Reproductive system and breast disorders	1 (0.2%)	0
Bartholin's cyst	1 (0.2%)	0
Respiratory, thoracic and mediastinal disorders	1 (0.2%)	0
Pneumonia aspiration	1 (0.2%)	0

Appendix 21: Number of Subjects With Treatment-Emergent Serious Infections Through Week 56 by System Organ Class and Preferred Term; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg

Key: Avg = average.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 21.0.

[TSFINFE02.RTF] [CNTO1959\PSO3009\DBR_WEEK_056\RE_WEEK_056_CSR\PROD\TSFINFE02.SAS] 23OCT2018, 12:59

Appendix 22: Number of Subjects With Treatment-Emergent Adverse Events of Psoriasis Through Week 56 by MedDRA Lower Level Term Category; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Analysis set: Safety analysis set	534	511
Avg duration of follow-up (weeks)	54.90	53.67
Avg exposure (number of administrations)	14.65	14.41
Subjects with 1 or more AEs of psoriasis	4 (0.7%)	11 (2.2%)
Lower level term category		
Worsening or exacerbation of psoriasis	4 (0.7%)	11 (2.2%)

Key: AE = adverse event, Avg = average.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 21.0.

[TSFAE08.RTF] [CNTO1959\PSO3009\DBR_WEEK_056\RE_WEEK_056_CSR\PROD\TSFAE08.SAS] 23OCT2018, 12:59

Appendix 23: Summary of Injection-Site Reactions Through Week 56 by Intensity; Treated Subjects by Study Agent Injection Received (Study CNTO1959PSO3009)

	Placebo Injections	Guselkumab Injections	Secukinumab Injections
Analysis set: Treated subjects by study agent injection received	534	534	511
Avg number of injections	22.5	6.8	28.8
Subjects with 1 or more injection-site reactions	20 (3.7%)	13 (2.4%)	20 (3.9%)
Total number of injections	11998	3644	14722
Injections with injection-site reactions	32 (0.3%)	19 (0.5%)	63 (0.4%)
Mild	30 (0.3%)	19 (0.5%)	55 (0.4%)
Moderate	2 (<0.1%)	0	8 (0.1%)
Severe	0	0	0

[TSFIR01.RTF] [CNTO1959\PSO3009\DBR_WEEK_056\RE_WEEK_056_CSR\PROD\TSFIR01.SAS] 23OCT2018, 12:59

Appendix 24: Summary of Injection-Site Reactions Through Week 56 by System Organ Class and Preferred Term; Treated Subjects by Study Agent Injection Received (Study CNTO1959PSO3009)

	Placebo Injections	Guselkumab Injections	Secukinumab Injections
Analysis set: Treated subjects by study agent injection received	534	534	511
Avg number of injections	22.5	6.8	28.8
Total number of injections	11998	3644	14722
Injections with injection-site reactions	32 (0.3%)	19 (0.5%)	63 (0.4%)
Subjects with 1 or more injection-site reactions	20 (3.7%)	13 (2.4%)	20 (3.9%)
System organ class			
Preferred term			
General disorders and administration site conditions	20 (3.7%)	13 (2.4%)	20 (3.9%)
Injection site erythema	8 (1.5%)	6 (1.1%)	7 (1.4%)
Injection site pruritus	3 (0.6%)	4 (0.7%)	0
Injection site haematoma	3 (0.6%)	3 (0.6%)	5 (1.0%)
Injection site swelling	3 (0.6%)	3 (0.6%)	1 (0.2%)
Injection site pain	5 (0.9%)	2 (0.4%)	6 (1.2%)
Injection site extravasation	0	1 (0.2%)	0
Injection site induration	2 (0.4%)	1 (0.2%)	0
Injection site rash	0	1 (0.2%)	0
Injection site bruising	3 (0.6%)	0	2 (0.4%)
Injection site haemorrhage	1 (0.2%)	0	2 (0.4%)
Injection site inflammation	0	0	1 (0.2%)

Appendix 24: Summary of Injection-Site Reactions Through Week 56 by System Organ Class and Preferred Term; Treated Subjects by Study Agent Injection Received (Study CNTO1959PSO3009)

	Placebo Injections	Guselkumab Injections	Secukinumab Injections
Injection site oedema	1 (0.2%)	0	2 (0.4%)

[TSFIR02.RTF] [CNTO1959\PSO3009\DBR_WEEK_056\RE_WEEK_056_CSR\PROD\TSFIR02.SAS] 23OCT2018, 12:59

Appendix 25: Number of Subjects with 1 or More Post-Baseline Suicidal Ideation or Suicidal Behavior Through Week 56; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Analysis set: Safety analysis set	534	511
Suicidal ideation or behavior	8 (1.5%)	8 (1.6%)
Suicidal ideation	5 (0.9%)	4 (0.8%)
1 - Wish to be dead	2 (0.4%)	3 (0.6%)
2 - Non-specific active suicidal thoughts	1 (0.2%)	1 (0.2%)
3 - Active suicidal ideation with any methods (not plan) without intent to act	1 (0.2%)	0
4 - Active suicidal ideation with some intent to act, without specific plan	0	0
5 - Active suicidal ideation with specific plan and intent	0	0
Suicidal behavior	3 (0.6%)	4 (0.8%)
6 - Preparatory acts or behavior	1 (0.2%)	1 (0.2%)
7 - Aborted attempt	1 (0.2%)	0
8 - Interrupted attempt	1 (0.2%)	0

Appendix 25: Number of Subjects with 1 or More Post-Baseline Suicidal Ideation or Suicidal Behavior Through Week 56; Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
9 - Non-fatal suicide attempt	0	2 (0.4%)
10 - Completed suicide	0	0

Note 1: Each subject is counted only once in the above table, based on the most severe postbaseline eC-SSRS score.
Note 2: The categories of suicidal ideation or behavior, suicidal ideation, and suicidal behavior are based on the eC-SSRS and AE.
Note 3: Score 1 to 9 are only based the eC-SSRS, not including AE. Completed suicide is from AE.

[TSFECSSRS01.RTF] [CNTO1959\PSO3009\DBR_WEEK_056\RE_WEEK_056_CSR\PROD\TSFECSSRS01.SAS] 23OCT2018, 13:02

Data Summary of Patients with psoriatic arthritis (PsA) in addition to PsO:

Table 5

Table 5 - TEFPASI13A_PSA: Summary of PASI Responses Through Week 56 by Visit; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Full analysis set with PSA	97	79
Week 1		
N	97	79
100% improvement	0	0
≥ 90% improvement	0	0
≥ 75% improvement	0	0
≥ 50% improvement	6 (6.2%)	5 (6.3%)
Week 2		
N	97	79
100% improvement	1 (1.0%)	1 (1.3%)
≥ 90% improvement	1 (1.0%)	1 (1.3%)
≥ 75% improvement	2 (2.1%)	5 (6.3%)
≥ 50% improvement	28 (28.9%)	28 (35.4%)
Week 3		
N	97	79
100% improvement	3 (3.1%)	1 (1.3%)
≥ 90% improvement	8 (8.2%)	5 (6.3%)
≥ 75% improvement	20 (20.6%)	13 (16.5%)
≥ 50% improvement	46 (47.4%)	47 (59.5%)
Week 4		

Table 5 - TEFPASI13A_PSA: Summary of PASI Responses Through Week 56 by Visit; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
N	97	79
100% improvement	6 (6.2%)	3 (3.8%)
≥ 90% improvement	14 (14.4%)	7 (8.9%)
≥ 75% improvement	33 (34.0%)	30 (38.0%)
≥ 50% improvement	68 (70.1%)	60 (75.9%)
Week 8		
N	97	79
100% improvement	17 (17.5%)	19 (24.1%)
≥ 90% improvement	41 (42.3%)	44 (55.7%)
≥ 75% improvement	71 (73.2%)	64 (81.0%)
≥ 50% improvement	92 (94.8%)	77 (97.5%)
Week 12		
N	97	79
100% improvement	37 (38.1%)	31 (39.2%)
≥ 90% improvement	69 (71.1%)	57 (72.2%)
≥ 75% improvement	89 (91.8%)	72 (91.1%)
≥ 50% improvement	96 (99.0%)	76 (96.2%)
Week 16		
N	97	79
100% improvement	42 (43.3%)	37 (46.8%)
≥ 90% improvement	70 (72.2%)	59 (74.7%)
≥ 75% improvement	91 (93.8%)	74 (93.7%)
≥ 50% improvement	95 (97.9%)	76 (96.2%)

Table 5 - TEFPASI13A_PSA: Summary of PASI Responses Through Week 56 by Visit; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Week 20		
N	97	79
100% improvement	47 (48.5%)	43 (54.4%)
≥ 90% improvement	74 (76.3%)	60 (75.9%)
≥ 75% improvement	89 (91.8%)	71 (89.9%)
≥ 50% improvement	95 (97.9%)	74 (93.7%)
Week 24		
N	97	79
100% improvement	56 (57.7%)	36 (45.6%)
≥ 90% improvement	76 (78.4%)	59 (74.7%)
≥ 75% improvement	92 (94.8%)	70 (88.6%)
≥ 50% improvement	95 (97.9%)	71 (89.9%)
Week 28		
N	97	79
100% improvement	53 (54.6%)	38 (48.1%)
≥ 90% improvement	80 (82.5%)	61 (77.2%)
≥ 75% improvement	89 (91.8%)	72 (91.1%)
≥ 50% improvement	94 (96.9%)	72 (91.1%)
Week 32		
N	97	79
100% improvement	53 (54.6%)	38 (48.1%)
≥ 90% improvement	80 (82.5%)	58 (73.4%)
≥ 75% improvement	92 (94.8%)	68 (86.1%)
≥ 50% improvement	95 (97.9%)	72 (91.1%)

Table 5 - TEFPASI13A_PSA: Summary of PASI Responses Through Week 56 by Visit; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Week 36		
N	97	79
100% improvement	54 (55.7%)	36 (45.6%)
≥ 90% improvement	78 (80.4%)	59 (74.7%)
≥ 75% improvement	92 (94.8%)	68 (86.1%)
≥ 50% improvement	94 (96.9%)	71 (89.9%)
Week 40		
N	97	79
100% improvement	53 (54.6%)	36 (45.6%)
≥ 90% improvement	79 (81.4%)	56 (70.9%)
≥ 75% improvement	90 (92.8%)	67 (84.8%)
≥ 50% improvement	95 (97.9%)	69 (87.3%)
Week 44		
N	97	79
100% improvement	55 (56.7%)	34 (43.0%)
≥ 90% improvement	79 (81.4%)	55 (69.6%)
≥ 75% improvement	91 (93.8%)	68 (86.1%)
≥ 50% improvement	95 (97.9%)	70 (88.6%)
Week 48		
N	97	79
100% improvement	55 (56.7%)	35 (44.3%)
≥ 90% improvement	80 (82.5%)	50 (63.3%)
≥ 75% improvement	93 (95.9%)	65 (82.3%)

Table 5 - TEFPASI13A_PSA: Summary of PASI Responses Through Week 56 by Visit; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
≥ 50% improvement	95 (97.9%)	68 (86.1%)
Week 56		
N	97	79
100% improvement	39 (40.2%)	24 (30.4%)
≥ 90% improvement	66 (68.0%)	33 (41.8%)
≥ 75% improvement	81 (83.5%)	50 (63.3%)
≥ 50% improvement	87 (89.7%)	61 (77.2%)

[TEFPASI13A.RTF] [CNTO1959\PSO3009\DBR_WEEK_056\RE_WEEK_056_CSR\PDEV\TEFPASI13A_PSA.SAS] 07DEC2018, 18:12

Table 6

Table 6 - TSICM01A_PSA: Summary of Previous Psoriasis Medications and Therapies by Medication Category; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg	Total
Full analysis set with PSA	97	79	176
Topical agents			
N	97	79	176
Never Used	3 (3.1%)	6 (7.6%)	9 (5.1%)
Ever Used	94 (96.9%)	73 (92.4%)	167 (94.9%)
Phototherapy {PUVA or UVB}			
N	97	78	175
Never Used	40 (41.2%)	42 (53.8%)	82 (46.9%)
Ever Used	57 (58.8%)	36 (46.2%)	93 (53.1%)
Non-biologic systemic {PUVA, methotrexate, cyclosporine, acitretin, apremilast, or tofacitinib}			
N	97	79	176
Never Used	26 (26.8%)	18 (22.8%)	44 (25.0%)
≥ 1 therapy	71 (73.2%)	61 (77.2%)	132 (75.0%)
≥ 2 therapies	41 (42.3%)	33 (41.8%)	74 (42.0%)
≥ 3 therapies	18 (18.6%)	17 (21.5%)	35 (19.9%)
≥ 4 therapies	3 (3.1%)	1 (1.3%)	4 (2.3%)
Biologics (etanercept, infliximab, alefacept, efalizumab, ustekinumab, briakinumab, ixekizumab, adalimumab, brodalumab, tildrakizumab, or risankizumab}			
N	97	79	176

Table 6 - TSICM01A_PSA: Summary of Previous Psoriasis Medications and Therapies by Medication Category; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg	Total
Never Used	56 (57.7%)	45 (57.0%)	101 (57.4%)
Ever Used	41 (42.3%)	34 (43.0%)	75 (42.6%)
Non-biologic systemic or biologics			
N	97	79	176
Never Used	19 (19.6%)	11 (13.9%)	30 (17.0%)
Ever Used	78 (80.4%)	68 (86.1%)	146 (83.0%)
Anti-TNFα agent (etanercept, infliximab, adalimumab)			
N	97	79	176
Never Used	67 (69.1%)	54 (68.4%)	121 (68.8%)
Ever Used	30 (30.9%)	25 (31.6%)	55 (31.3%)
IL-12/23 inhibitors (ustekinumab, briakinumab, tildrakizumab, risankizumab)			
N	97	79	176
Never Used	85 (87.6%)	66 (83.5%)	151 (85.8%)
Ever Used	12 (12.4%)	13 (16.5%)	25 (14.2%)
IL-17 inhibitors (ixekizumab, brodalumab)			
N	97	79	176
Never Used	81 (83.5%)	64 (81.0%)	145 (82.4%)
Ever Used	16 (16.5%)	15 (19.0%)	31 (17.6%)

[TSICM01A.RTF] [CNTO1959\PSO3009\DBR_WEEK_056\RE_WEEK_056_CSR\PDEV\TSICM01A_PSA.SAS] 07DEC2018, 18:00

Table 7

Table 7 - TSIDEM01_PSA: Summary of Demographics and Baseline Characteristics; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg	Total
Full analysis set with PSA	97	79	176
Age, years			
N	97	79	176
Mean (SD)	50.7 (12.01)	46.9 (14.04)	49.0 (13.06)
Median	52.0	47.0	48.5
Range	(20; 77)	(20; 74)	(20; 77)
IQ range	(41.0; 59.0)	(35.0; 59.0)	(40.0; 59.0)
< 45 years	29 (29.9%)	38 (48.1%)	67 (38.1%)
≥ 45 to < 65 years	53 (54.6%)	33 (41.8%)	86 (48.9%)
≥ 65 years	15 (15.5%)	8 (10.1%)	23 (13.1%)
Sex			
N	97	79	176
Female	30 (30.9%)	33 (41.8%)	63 (35.8%)
Male	67 (69.1%)	46 (58.2%)	113 (64.2%)
Race			
N	97	79	176
American Indian or Alaska Native	0	1 (1.3%)	1 (0.6%)
Asian	2 (2.1%)	3 (3.8%)	5 (2.8%)
Black or African American	2 (2.1%)	0	2 (1.1%)
White	91 (93.8%)	75 (94.9%)	166 (94.3%)
Other	2 (2.1%)	0	2 (1.1%)

Table 7 - TSIDEM01_PSA: Summary of Demographics and Baseline Characteristics; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg	Total
Ethnicity			
N	97	79	176
Hispanic or Latino	4 (4.1%)	4 (5.1%)	8 (4.5%)
Not Hispanic or Latino	93 (95.9%)	75 (94.9%)	168 (95.5%)
Weight, kg			
N	97	79	176
Mean (SD)	89.20 (21.231)	87.96 (21.376)	88.64 (21.244)
Median	89.00	85.10	86.75
Range	(50.0; 158.9)	(53.8; 177.6)	(50.0; 177.6)
IQ range	(73.50; 100.00)	(73.00; 98.30)	(73.25; 100.00)
≤ 90kg	52 (53.6%)	47 (59.5%)	99 (56.3%)
> 90kg	45 (46.4%)	32 (40.5%)	77 (43.8%)
Height, cm			
N	97	79	176
Mean (SD)	174.1 (10.05)	171.5 (8.79)	172.9 (9.57)
Median	174.4	172.0	173.0
Range	(152; 192)	(148; 196)	(148; 196)
IQ range	(168.0; 182.8)	(165.1; 177.0)	(167.0; 179.0)
Body mass index, kg/m^2			
N	97	79	176
Mean (SD)	29.3 (6.04)	29.8 (6.81)	29.6 (6.38)
Median	28.4	28.8	28.7
Range	(17; 48)	(20; 65)	(17; 65)
IQ range	(25.4; 32.3)	(25.1; 33.2)	(25.2; 32.8)

Table 7 - TSIDEM01_PSA: Summary of Demographics and Baseline Characteristics; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg	Total
Normal < 25 kg/m^2	20 (20.6%)	18 (22.8%)	38 (21.6%)
Overweight ≥ 25 to < 30 kg/m^2	41 (42.3%)	24 (30.4%)	65 (36.9%)
Obese ≥ 30 kg/m^2	36 (37.1%)	37 (46.8%)	73 (41.5%)

Key: IQ = Interquartile

[TSIDEM01.RTF] [CNTO1959\PSO3009\DBR_WEEK_056\RE_WEEK_056_CSR\PDEV\TSIDEM01_PSA.SAS] 07DEC2018, 17:53

Table 8

Table 8 - TEFPASI13A_PSA: Summary of PASI Responses Through Week 56 by Visit; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Full analysis set with PSA	97	79
Week 1		
N	97	79
100% improvement	0	0
≥ 90% improvement	0	0
≥ 75% improvement	0	0
≥ 50% improvement	6 (6.2%)	5 (6.3%)
Week 2		
N	97	79
100% improvement	1 (1.0%)	1 (1.3%)
≥ 90% improvement	1 (1.0%)	1 (1.3%)
≥ 75% improvement	2 (2.1%)	5 (6.3%)
≥ 50% improvement	28 (28.9%)	28 (35.4%)
Week 3		
N	97	79
100% improvement	3 (3.1%)	1 (1.3%)
≥ 90% improvement	8 (8.2%)	5 (6.3%)
≥ 75% improvement	20 (20.6%)	13 (16.5%)
≥ 50% improvement	46 (47.4%)	47 (59.5%)
Week 4		
N	97	79
100% improvement	6 (6.2%)	3 (3.8%)

Table 8 - TEFPASI13A_PSA: Summary of PASI Responses Through Week 56 by Visit; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
≥ 90% improvement	14 (14.4%)	7 (8.9%)
≥ 75% improvement	33 (34.0%)	30 (38.0%)
≥ 50% improvement	68 (70.1%)	60 (75.9%)
Week 8		
N	97	79
100% improvement	17 (17.5%)	19 (24.1%)
≥ 90% improvement	41 (42.3%)	44 (55.7%)
≥ 75% improvement	71 (73.2%)	64 (81.0%)
≥ 50% improvement	92 (94.8%)	77 (97.5%)
Week 12		
N	97	79
100% improvement	37 (38.1%)	31 (39.2%)
≥ 90% improvement	69 (71.1%)	57 (72.2%)
≥ 75% improvement	89 (91.8%)	72 (91.1%)
≥ 50% improvement	96 (99.0%)	76 (96.2%)
Week 16		
N	97	79
100% improvement	42 (43.3%)	37 (46.8%)
≥ 90% improvement	70 (72.2%)	59 (74.7%)
≥ 75% improvement	91 (93.8%)	74 (93.7%)
≥ 50% improvement	95 (97.9%)	76 (96.2%)
Week 20		
N	97	79

Table 8 - TEFPASI13A_PSA: Summary of PASI Responses Through Week 56 by Visit; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
100% improvement	47 (48.5%)	43 (54.4%)
≥ 90% improvement	74 (76.3%)	60 (75.9%)
≥ 75% improvement	89 (91.8%)	71 (89.9%)
≥ 50% improvement	95 (97.9%)	74 (93.7%)
Week 24		
N	97	79
100% improvement	56 (57.7%)	36 (45.6%)
≥ 90% improvement	76 (78.4%)	59 (74.7%)
≥ 75% improvement	92 (94.8%)	70 (88.6%)
≥ 50% improvement	95 (97.9%)	71 (89.9%)
Week 28		
N	97	79
100% improvement	53 (54.6%)	38 (48.1%)
≥ 90% improvement	80 (82.5%)	61 (77.2%)
≥ 75% improvement	89 (91.8%)	72 (91.1%)
≥ 50% improvement	94 (96.9%)	72 (91.1%)
Week 32		
N	97	79
100% improvement	53 (54.6%)	38 (48.1%)
≥ 90% improvement	80 (82.5%)	58 (73.4%)
≥ 75% improvement	92 (94.8%)	68 (86.1%)
≥ 50% improvement	95 (97.9%)	72 (91.1%)
Week 36		

Table 8 - TEFPASI13A_PSA: Summary of PASI Responses Through Week 56 by Visit; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
N	97	79
100% improvement	54 (55.7%)	36 (45.6%)
≥ 90% improvement	78 (80.4%)	59 (74.7%)
≥ 75% improvement	92 (94.8%)	68 (86.1%)
≥ 50% improvement	94 (96.9%)	71 (89.9%)
Week 40		
N	97	79
100% improvement	53 (54.6%)	36 (45.6%)
≥ 90% improvement	79 (81.4%)	56 (70.9%)
≥ 75% improvement	90 (92.8%)	67 (84.8%)
≥ 50% improvement	95 (97.9%)	69 (87.3%)
Week 44		
N	97	79
100% improvement	55 (56.7%)	34 (43.0%)
≥ 90% improvement	79 (81.4%)	55 (69.6%)
≥ 75% improvement	91 (93.8%)	68 (86.1%)
≥ 50% improvement	95 (97.9%)	70 (88.6%)
Week 48		
N	97	79
100% improvement	55 (56.7%)	35 (44.3%)
≥ 90% improvement	80 (82.5%)	50 (63.3%)
≥ 75% improvement	93 (95.9%)	65 (82.3%)
≥ 50% improvement	95 (97.9%)	68 (86.1%)

Table 8 - TEFPASI13A_PSA: Summary of PASI Responses Through Week 56 by Visit; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Week 56		
N	97	79
100% improvement	39 (40.2%)	24 (30.4%)
≥ 90% improvement	66 (68.0%)	33 (41.8%)
≥ 75% improvement	81 (83.5%)	50 (63.3%)
≥ 50% improvement	87 (89.7%)	61 (77.2%)

[TEFPASI13A.RTF] [CNTO1959\PSO3009\DBR_WEEK_056\RE_WEEK_056_CSR\PDEV\TEFPASI13A_PSA.SAS] 07DEC2018, 18:12

Table 9

Table 9 - TSFAE_PSA: Number of Subjects with Treatment-Emergent Adverse Events Through Week 56; PSA Subjects in Safety Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg
Safety analysis set, with PSA	97	79
Avg duration of follow-up (weeks)	55.36	52.68
Avg exposure (number of administrations)	14.76	14.13
Subjects with 1 or more AEs	73 (75.3%)	67 (84.8%)
Subjects with 1 or more SAEs	3 (3.1%)	11 (13.9%)
Subjects with 1 or more AEs leading to discontinuation of study agent	1 (1.0%)	3 (3.8%)
Subjects with 1 or more infections	54 (55.7%)	54 (68.4%)
Subjects with 1 or more serious infections	0	2 (2.5%)

Key: AE = adverse event, Avg = average.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 21.0.

[TSFAE01.RTF] [CNTO1959\PSO3009\DBR_WEEK_056\RE_WEEK_056_CSR\PDEV\TSFAE_PSA.SAS] 07DEC2018, 12:37

Table 10

Table 10 - TSIDEM04_PSA: Summary of Psoriasis Baseline Clinical Disease Characteristics; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg	Total
Full analysis set with PSA	97	79	176
Psoriasis disease duration (years)			
N	97	79	176
Mean (SD)	21.9 (11.25)	20.0 (13.46)	21.1 (12.29)
Median	21.0	17.0	20.0
Range	(1; 48)	(1; 57)	(1; 57)
IQ range	(14.7; 27.0)	(10.0; 28.0)	(12.0; 27.5)
Psoriasis disease duration (years)			
N	97	79	176
< 15 years	25 (25.8%)	31 (39.2%)	56 (31.8%)
≥ 15 years	72 (74.2%)	48 (60.8%)	120 (68.2%)
Age at diagnosis (years)			
N	97	79	176
Mean (SD)	28.9 (13.37)	26.9 (13.28)	28.0 (13.33)
Median	27.0	25.0	27.0
Range	(5; 67)	(6; 61)	(5; 67)
IQ range	(18.0; 37.0)	(16.0; 34.0)	(17.5; 36.0)
Age at diagnosis (years)			
N	97	79	176
< 25 years	40 (41.2%)	36 (45.6%)	76 (43.2%)
≥ 25 years	57 (58.8%)	43 (54.4%)	100 (56.8%)

Table 10 - TSIDEM04_PSA: Summary of Psoriasis Baseline Clinical Disease Characteristics; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg	Total
Psoriatic arthritis			
N	97	79	176
Yes	97 (100.0%)	79 (100.0%)	176 (100.0%)
No	0	0	0
BSA (%)			
N	97	79	176
Mean (SD)	27.3 (13.16)	25.0 (13.29)	26.3 (13.24)
Median	23.0	21.0	23.0
Range	(10; 74)	(10; 68)	(10; 74)
IQ range	(17.0; 36.0)	(15.0; 32.0)	(16.5; 34.5)
BSA			
N	97	79	176
< 20%	26 (26.8%)	36 (45.6%)	62 (35.2%)
≥ 20%	71 (73.2%)	43 (54.4%)	114 (64.8%)
IGA score			
N	97	79	176
Cleared (0)	0	0	0
Minimal (1)	0	0	0
Mild (2)	0	0	0
Moderate (3)	69 (71.1%)	57 (72.2%)	126 (71.6%)
Severe (4)	28 (28.9%)	22 (27.8%)	50 (28.4%)
IGA score			
N	97	79	176

Table 10 - TSIDEM04_PSA: Summary of Psoriasis Baseline Clinical Disease Characteristics; Full Analysis Set (Study CNTO1959PSO3009)

	Guselkumab 100 mg	Secukinumab 300 mg	Total
< 4	69 (71.1%)	57 (72.2%)	126 (71.6%)
= 4	28 (28.9%)	22 (27.8%)	50 (28.4%)
PASI score (0-72)			
N	97	79	176
Mean (SD)	21.6 (8.29)	20.2 (7.03)	21.0 (7.76)
Median	18.8	18.0	18.6
Range	(12; 59)	(12; 50)	(12; 59)
IQ range	(15.7; 25.5)	(16.0; 22.0)	(15.9; 24.3)
PASI score			
N	97	79	176
< 20	53 (54.6%)	51 (64.6%)	104 (59.1%)
≥ 20	44 (45.4%)	28 (35.4%)	72 (40.9%)

Key: IQ = Interquartile

[TSIDEM04.RTF] [CNTO1959\PSO3009\DBR_WEEK_056\RE_WEEK_056_CSR\PDEV\TSIDEM04_PSA.SAS] 07DEC2018, 17:53

Table 11

Table 11 - TEFFECACY_PSA: _

Efficacy Endpoint	Guselkumab 100 mg	Secukinumab 300 mg	Difference	95% CI
PASI 90 at WEEK 48	84.5% (451/534)	70.0% (360/514)	14.4	(9.2, 19.6)
- Psoriatic arthritis	82.5% (80/97)	63.3% (50/79)	19.2	(5.0, 33.4)
			.	
PASI 75 at WEEK 12 AND WEEK 48	84.6% (452/534)	80.2% (412/514)	4.5	(-0.3, 9.3)
- Psoriatic arthritis	90.7% (88/97)	78.5% (62/79)	12.2	(0.3, 24.1)
			.	
PASI 90 at WEEK 12	69.1% (369/534)	76.1% (391/514)	-7	(-12.5, -1.4)
- Psoriatic arthritis	71.1% (69/97)	72.2% (57/79)	-1	(-15.5, 13.5)
			.	
PASI 75 at WEEK 12	89.3% (477/534)	91.6% (471/514)	-2.3	(-6.0, 1.4)
- Psoriatic arthritis	91.8% (89/97)	91.1% (72/79)	0.6	(-8.9, 10.1)
			.	
PASI 100 at WEEK 48	58.2% (311/534)	48.4% (249/514)	9.8	(3.6, 16.0)
- Psoriatic arthritis	56.7% (55/97)	44.3% (35/79)	12.4	(-3.5, 28.3)
			.	
IGA 0 at WEEK 48	62.2% (332/534)	50.4% (259/514)	11.8	(5.6, 17.9)
- Psoriatic arthritis	58.8% (57/97)	45.6% (36/79)	13.2	(-2.7, 29.1)
			.	
IGA 0/1 at WEEK 48	85.0% (454/534)	74.9% (385/514)	10.1	(5.1, 15.1)
- Psoriatic arthritis	88.7% (86/97)	73.4% (58/79)	15.2	(2.5, 28.0)
			.	

[TEFFECACY_PSA.RTF] [CNTO1959\PSO3009\DBR_WEEK_056\RE_WEEK_056_CSR\PDEV\TEFFECACY_PSA.SAS] 08DEC2018, 10:03

PASI 90/PASI 100 and IGA 0/1 Organized by Weight Quartiles

Table 12 - PASI 90 at Week 48 by weight quartiles

Weight Category (kg)	Guselkumab 100 mg	Secukinumab 300 mg	Treatment Difference	Lower Limit	Upper Limit
<=74	86.7% (124/143)	75.6% (93/123)	11.1%	0.9%	21.3%
>74 - <=87	89.1% (106/119)	73.0% (103/141)	16.0%	6.0%	26.0%
>87 - <=100	80.3% (106/132)	71.0% (88/124)	9.3%	-1.9%	20.6%
>100	82.1% (115/140)	61.3% (76/124)	20.9%	9.4%	32.3%

Table 13 - PASI 100 at Week 48 by weight quartiles

Weight Category (kg)	Guselkumab 100 mg	Secukinumab 300 mg	Treatment Difference	Lower Limit	Upper Limit
<=74	58.7% (84/143)	56.1% (69/123)	2.6%	-10.0%	15.3%
>74 - <=87	66.4% (79/119)	51.8% (73/141)	14.6%	2.0%	27.2%
>87 - <=100	59.1% (78/132)	47.6% (59/124)	11.5%	-1.4%	24.4%
>100	50.0% (70/140)	38.7% (48/124)	11.3%	-1.4%	24.0%

Table 14 - IGA 0/1 at Week 48 by weight quartiles

Weight Category (kg)	Guselkumab 100 mg	Secukinumab 300 mg	Treatment Difference	Lower Limit	Upper Limit
<=74	84.6% (121/143)	78.0% (96/123)	6.6%	-3.6%	16.7%
>74 - <=87	89.9% (107/119)	78.7% (111/141)	11.2%	1.8%	20.6%
>87 - <=100	83.3% (110/132)	80.6% (100/124)	2.7%	-7.5%	12.9%
>100	82.9% (116/140)	62.9% (78/124)	20.0%	8.6%	31.3%

Table 15 - IGA 0 at Week 48 by weight quartiles

Weight Category (kg)	Guselkumab 100 mg	Secukinumab 300 mg	Treatment Difference	Lower Limit	Upper Limit
<=74	61.5% (88/143)	58.5% (72/123)	3.0%	-9.6%	15.6%
>74 - <=87	71.4% (85/119)	53.9% (76/141)	17.5%	5.2%	29.9%
>87 - <=100	61.4% (81/132)	50.0% (62/124)	11.4%	-1.5%	24.2%
>100	55.7% (78/140)	39.5% (49/124)	16.2%	3.5%	28.9%

Note: There were two patients in Secukinumab 300 mg group without baseline weight such that Secukinumab group only has 512 patients listed, instead of 514 patients.

Table 16 - IGA0/1 by BMI category

Baseline BMI Group 1	Guselkumab 100 mg	Secukinumab 300 mg	Treatment Difference	Lower Limit	Upper Limit
Normal (< 25)	85.8% (115/134)	77.1% (84/109)	8.8%	-1.9%	19.4%
Overweight (>= 25 to < 30)	86.9% (153/176)	81.9% (145/177)	5.0%	-3.1%	13.1%
Obese (>= 30)	83.0% (185/223)	69.3% (156/225)	13.6%	5.4%	21.9%

Note: There was one patient in gueselkumab 100 mg group without baseline height such that it only has 533 patients listed in the above analysis, instead of 534 patients. Secukinumab 300 mg group only had 511 patients with baseline height such that it only has 511 patients listed in the above analysis instead of 514 patients.

Table 17. Summary of PASI component responses at Week 48		
	Guselkumab 100 mg	**Secukinumab 300 mg**
Full analysis set, n	534	514
Head and neck, n	499	481
100% improvement, n (%)	399 (80.0)	360 (74.8)
≥90% improvement, n (%)	424 (85.0)	371 (77.1)
Trunk, n	512	494
100% improvement, n (%)	432 (84.4)	384 (77.7)
≥90% improvement, n (%)	444 (86.7)	395 (80.0)
Upper extremities, n	532	510
100% improvement, n (%)	422 (79.3)	322 (63.1)
≥90% improvement, n (%)	435 (81.8)	341 (66.9)
Lower extremities, n	534	513

100% improvement, n (%)	400 (74.9)	315 (61.4)
≥90% improvement, n (%)	433 (81.1)	343 (66.9)

Table 18. Proportion of patients achieving PASI 90 response at Week 48 with guselkumab (GUS) or secukinumab (SEC) by geographic region

	North America		**Eastern Europe**		**Western Europe**		**Australia**		**Overall**	
	GUS 100mg	**SEC 300mg**	**GUS 100mg**	**SEC 300mg**	**GUS 100mg**	**SEC 300mg**	**GUS 100mg**	**SEC 300mg**	**GUS 100mg**	**SEC 300mg**
Randomized patients, n	199	192	171	167	129	119	35	36	534	514
PASI 90 responders, n (%)	157 (78.9)	116 (60.4)	155 (90.6)	127 (76.0)	107 (82.9)	89 (74.8)	32 (91.4)	28 (77.8)	451 (84.5)	360 (70.0)

CLAIMS

What is claimed is:

1. A method of treating psoriasis in a patient, comprising administering an antibody to IL-23 to the patient in a clinically proven safe and clinically proven effective amount, wherein the antibody to IL-23 comprises a light chain variable region and a heavy chain variable region, said light chain variable region comprising:

a complementarity determining region light chain 1 (CDRL1) amino acid sequence of SEQ ID NO:50;

a CDRL2 amino acid sequence of SEQ ID NO:56; and

a CDRL3 amino acid sequence of SEQ ID NO:73,

said heavy chain variable region comprising:

a complementarity determining region heavy chain 1 (CDRH1) amino acid sequence of SEQ ID NO:5;

a CDRH2 amino acid sequence of SEQ ID NO:20; and

a CDRH3 amino acid sequence of SEQ ID NO:44, wherein the patient is treated with the antibody to IL-23 for at least 44 weeks to demonstrate greater efficacy in a psoriasis clinical endpoint than a patient treated with the antibody secukinumab.

2. The method of claim 1, wherein the psoriasis clinical endpoint is PASI90, PASI100, IGA 0 and/or IGA 1.

3. The method of claim 2, wherein the psoriasis clinical endpoint is measured 44 and/or 48 weeks after initial treatment with the antibody to IL-23.

4. The method of claim 3, wherein the psoriasis clinical endpoint is measured 48 weeks after initial treatment with the antibody to IL-23.

5. The method of claim 1, wherein the antibody to IL-23 is administered in an initial dose, 4 weeks after the initial dose and every 8 weeks after the dose at 4 weeks.

5. The method of claim 1, wherein the secukinumab antibody is administered in an initial dose, 1 week after the initial dose, 2 weeks after the initial dose, 3 weeks after the initial dose, 4 weeks after the initial dose and every 4 weeks after the dose at 4 weeks.

6. The method of claim 1, wherein the antibody to IL-23 is administered at a dose of 100 mg.

7. The method of claim 6, wherein the antibody to IL-23 is safe and effective treating psoriasis at an area of a patient selected from the group consisting of scalp, nails, hands and feet.

8. The method of claim 6, wherein the antibody to IL-23 is in a composition comprising 100 mg/mL of antibody; 7.9% (w/v) sucrose, 4.0mM Histidine, 6.9 mM L-Histidine monohydrochloride monohydrate; 0.053% (w/v) Polysorbate 80 of the pharmaceutical composition; wherein the diluent is water at standard state.

9. The method of claim 8, further comprising administering to the patient one or more additional drugs used to treat psoriasis.

10. The method of claim 9, wherein the additional drug is selected from the group consisting of: immunosuppressive agents, non-steroidal anti-inflammatory drugs (NSAIDs), methotrexate (MTX), anti-B-cell surface marker antibodies, anti-CD20 antibodies, rituximab, TNF-inhibitors, corticosteroids, and co-stimulatory modifiers.

11. The method of claim 1, wherein the antibody to IL-23 is effective to reduce a symptom of psoriasis in the patient, induce clinical response, induce or maintain clinical remission, inhibit disease progression, or inhibit a disease complication in the patient.

12. The method of claim 1, wherein the patient is treated for moderate to severe psoriasis.

13. The method of claim 1, further comprising the step of discontinuing treatment of a patient previously treated with at least one dose of secukinumab and deciding to treat the patient with guselkumab.

14. The method of claim 13, further comprising the step of measuring the psoriasis clinical endpoint PASI90, PASI100, IGA 0 and/or IGA 1 at 44 and/or 48 weeks after initial treatment and discontinuing treatment of a patient previously treated with at least one dose of secukinumab and treating the patient with guselkumab.

15. The method of claim 1, wherein the patient has psoriatic arthritis.

16. A method of treating psoriasis in a patient, comprising administering an antibody to IL-23 to the patient in a clinically proven safe and clinically proven effective amount, the antibody to IL-23 comprising a light chain variable region of the amino acid sequence of SEQ ID NO: 116 and a heavy chain variable region of the amino acid sequence of SEQ ID NO: 106, wherein the patient is treated with the antibody to IL-23 for at least 44 weeks to demonstrate greater efficacy in a psoriasis clinical endpoint than a patient treated with the antibody secukinumab.

17. The method of claim 16, wherein the psoriasis clinical endpoint is PASI90, PASI100, IGA 0 and/or IGA 1.

18. The method of claim 17, wherein the psoriasis clinical endpoint is measured 44 and/or 48 weeks after initial treatment with the antibody to IL-23.

19. The method of claim 18, wherein the psoriasis clinical endpoint is measured 48 weeks after initial treatment with the antibody to IL-23.

20. The method of claim 16, wherein the antibody to IL-23 is administered in an initial dose, 4 weeks after the initial dose and every 8 weeks after the dose at 4 weeks.

21. The method of claim 16, wherein the secukinumab antibody is administered in an initial dose, 1 week after the initial dose, 2 weeks after the initial dose, 3 weeks after the initial dose, 4 weeks after the initial dose and every 4 weeks after the dose at 4 weeks.

22. The method of claim 16, wherein the antibody to IL-23 is administered at a dose of 100 mg.

23. The method of claim 22, wherein the antibody to IL-23 is safe and effective treating psoriasis at an area of a patient selected from the group consisting of scalp, nails, hands and feet.

24. The method of claim 22, wherein the antibody to IL-23 is in a composition comprising 100 mg/mL of antibody; 7.9% (w/v) sucrose, 4.0mM Histidine, 6.9 mM L-Histidine monohydrochloride monohydrate; 0.053% (w/v) Polysorbate 80 of the pharmaceutical composition; wherein the diluent is water at standard state.

25. The method of claim 24, further comprising administering to the patient one or more additional drugs used to treat psoriasis.

26. The method of claim 25, wherein the additional drug is selected from the group consisting of: immunosuppressive agents, non-steroidal anti-inflammatory drugs (NSAIDs), methotrexate (MTX), anti-B-cell surface marker antibodies, anti-CD20 antibodies, rituximab, TNF-inhibitors, corticosteroids, and co-stimulatory modifiers.

27. The method of claim 16, wherein the antibody to IL-23 is effective to reduce a symptom of psoriasis in the patient, induce clinical response, induce or maintain clinical remission, inhibit disease progression, or inhibit a disease complication in the patient.

28. The method of claim 16, wherein the patient is treated for moderate to severe psoriasis.

29. The method of claim 16, further comprising the step of discontinuing treatment of a patient previously treated with at least one dose of secukinumab and deciding to treat the patient with guselkumab.

30. The method of claim 29, further comprising the step of measuring the psoriasis clinical endpoint PASI90, PASI100, IGA 0 and/or IGA 1 at 44 and/or 48 weeks after initial treatment and discontinuing treatment of a patient previously treated with at least one dose of secukinumab and treating the patient with guselkumab.

31. The method of claim 16, wherein the patient has psoriatic arthritis.

32. A method of treating moderate-to-severe plaque psoriasis in an adult patient who is a candidate for systemic therapy or phototherapy, comprising administering an antibody to IL-23 to the patient in a clinically proven safe and clinically proven effective amount, wherein the antibody comprises a light chain variable region of the amino acid sequence of SEQ ID NO: 116 and a heavy chain variable region of the amino acid sequence of SEQ ID NO: 106, the dosage is 100 mg administered by subcutaneous injection at Week 0, Week 4 and every 8 weeks thereafter and the antibody is at a concentration of 100 mg/mL in a single-dose prefilled syringe comprising 7.9% (w/v) sucrose, 4.0mM Histidine, 6.9 mM L-Histidine monohydrochloride monohydrate; 0.053% (w/v) Polysorbate 80 and the diluent is water at standard state, wherein the patient is treated with the antibody to IL-23 for at least 44 weeks to demonstrate greater efficacy in a psoriasis clinical endpoint than a patient treated with the antibody secukinumab, the psoriasis clinical endpoint selected from the group consisting of PASI90, PASI100, IGA 0 and IGA 1.

33. A method of selling and/or promoting an approved pharmaceutical product comprising an antibody to IL-23, the method comprising advertising superiority of clinical endpoint results at week 44 from initial treatment after continuous treatment with the antibody to IL-23 versus clinical endpoint results at week 44 from initial treatment after continuous treatment with secukinumab, wherein the antibody to IL-23 comprises a light chain variable region of the amino acid sequence of SEQ ID NO: 116 and a heavy chain variable region of the amino acid sequence of SEQ ID NO: 106.

FIG. 1

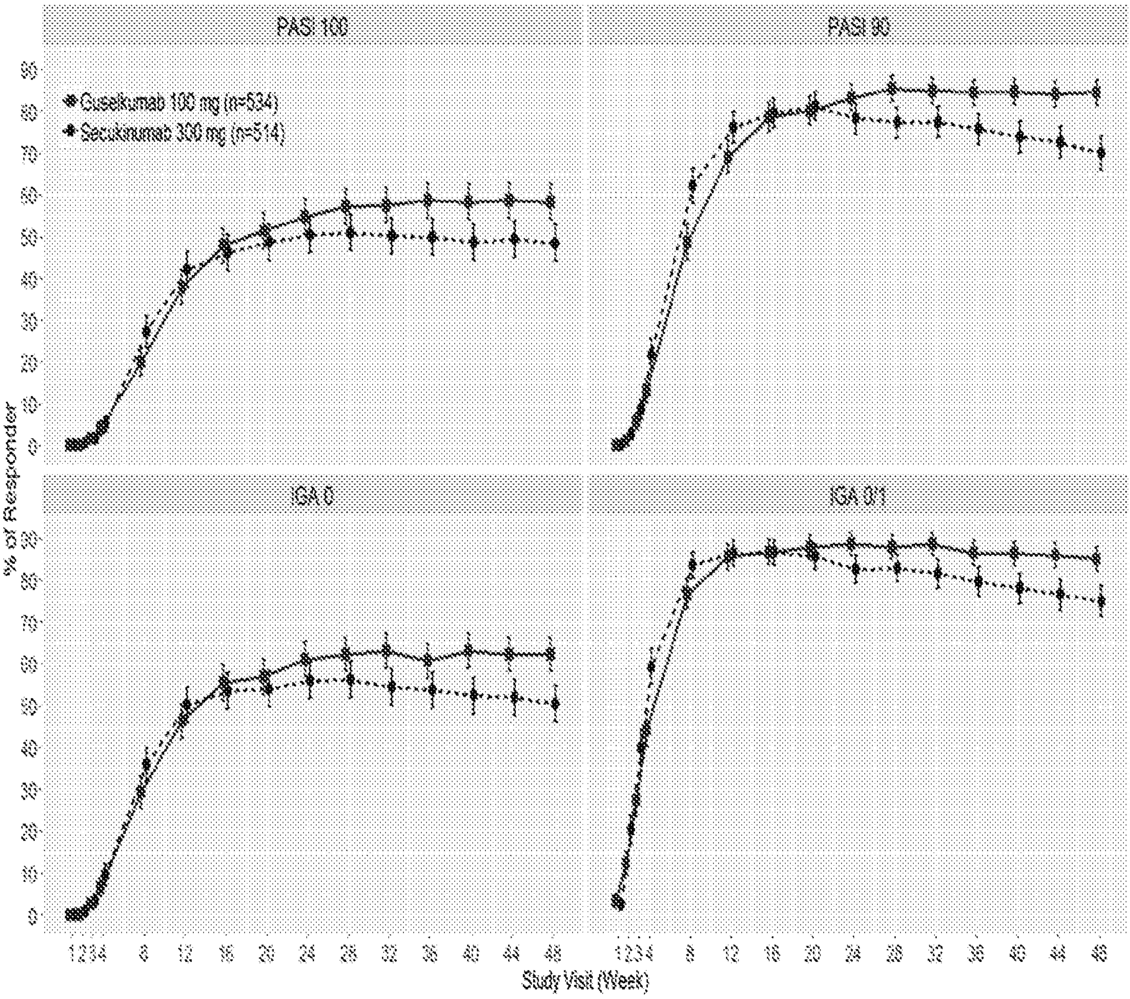

PASI 100
PASI 90
IGA 0
IGA 0/1
Guselkumab 100 mg (n=534)
Secukinumab 300 mg (n=514)
% of Responder
Study Visit (Week)

FIG. 2

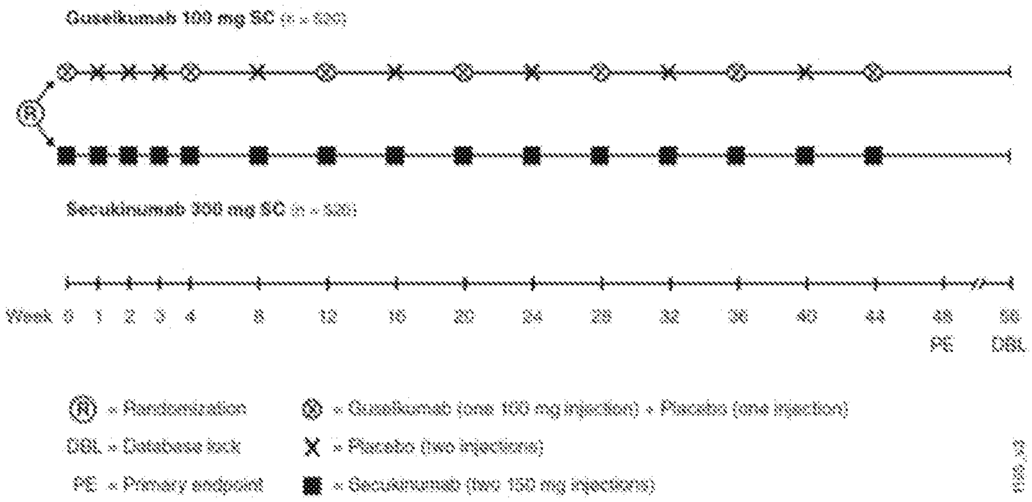

Guselkumab 100 mg SC
Secukinumab 300 mg SC
Week 0 1 2 3 4 8 12 16 20 24 28 32 36 40 44
PE
DBL
R = Randomization
DBL = Database lock
PE = Primary endpoint
= Guselkumab (one 100 mg injection) + Placebo (one injection)
= Placebo (two injections)
= Secukinumab (two 150 mg injections)

FIG. 3

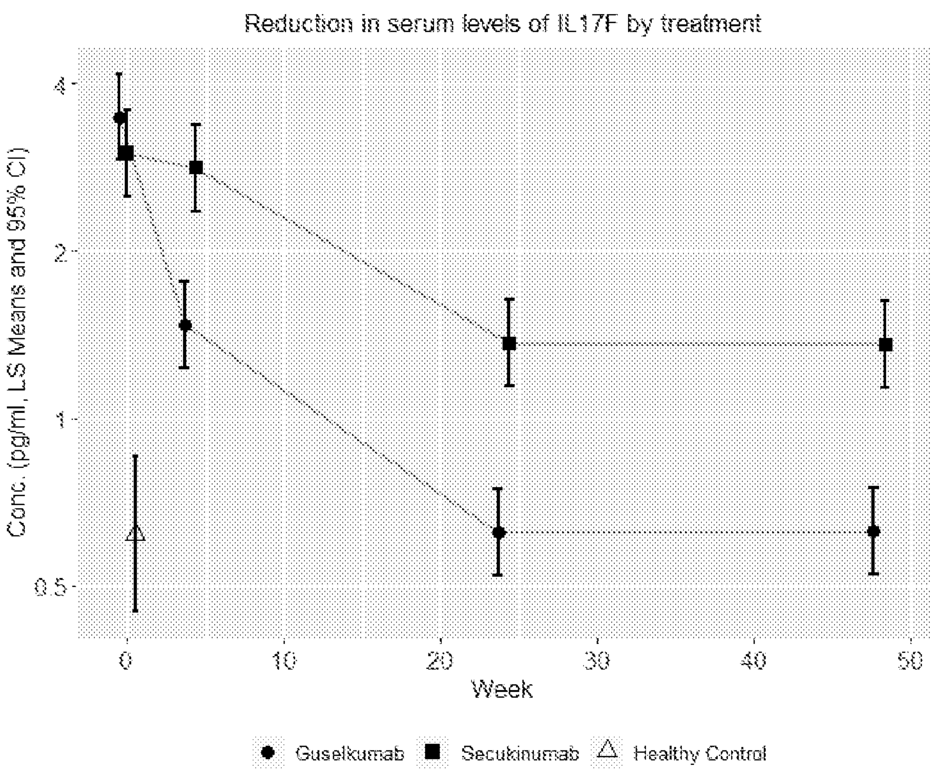

Reduction in serum levels of IL17F by treatment
Conc. (pg/ml, LS Means and 95% CI)
4
2
1
0.5
0
10
20
30
40
50
Week
Guselkumab
Secukinumab
Healthy Control

FIG. 4

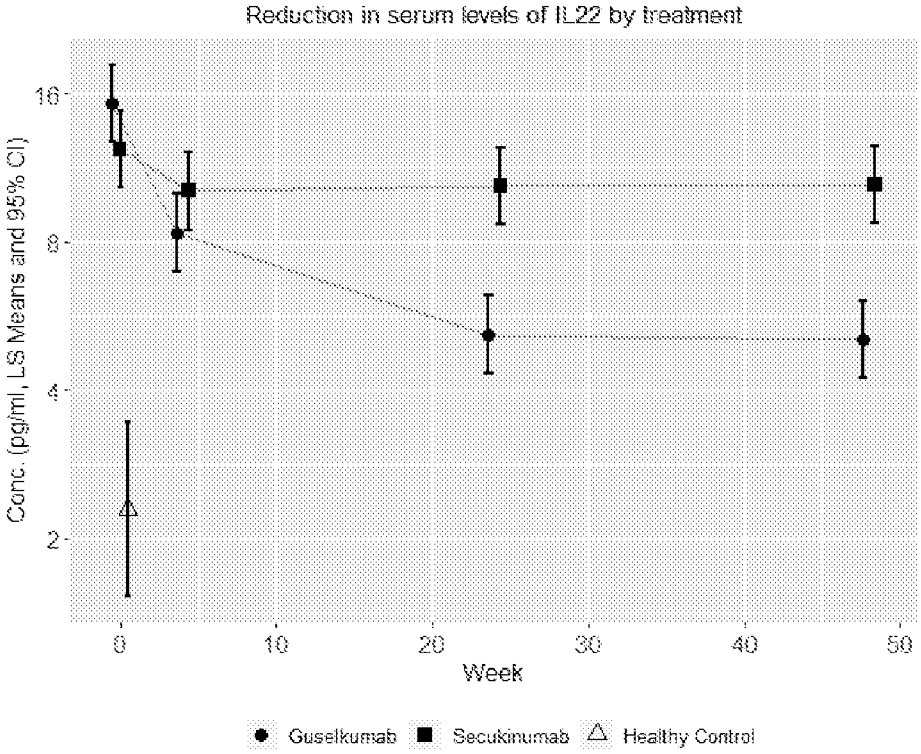

Reduction in serum levels of IL22 by treatment
16
8
4
2
Conc. (pg/ml, LS Means and 95% CI)
0
10
20
30
40
50
Week
Guselkumab
Secukinumab
Healthy Control

FIG. 5

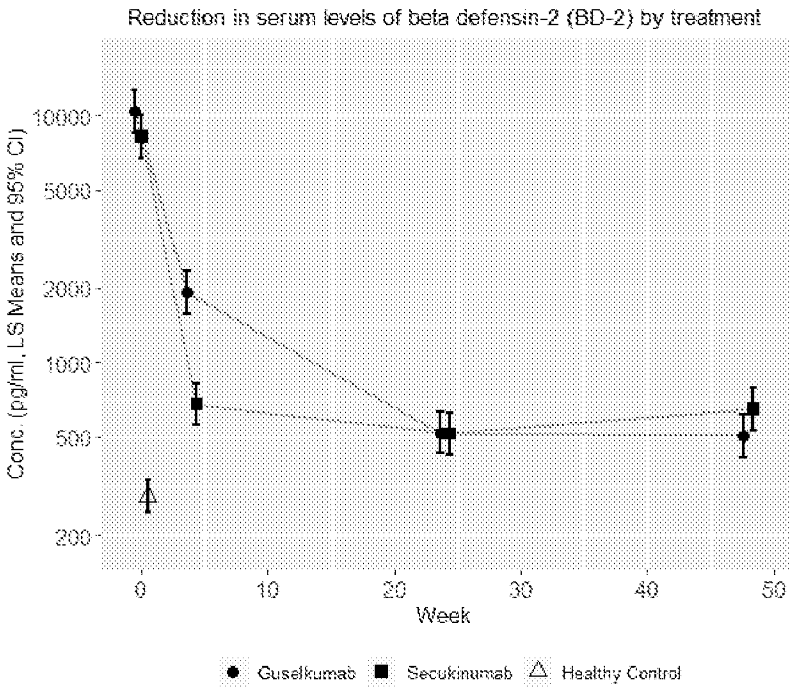

Reduction in serum levels of beta defensin-2 (BD-2) by treatment
Conc. (pg/ml, LS Means and 95% CI)
10000
5000
2000
1000
500
200
0
10
20
30
40
50
Week
Guselkumab
Secukinumab
Healthy Control

FIG. 6


A subset of induced genes in psoriasis lesional skin were better normalized by GUS vs SEC at Week 24
% Improvement at WK24 from WK0
250
200
150
100
50
0
GUS
SEC

FIG. 7

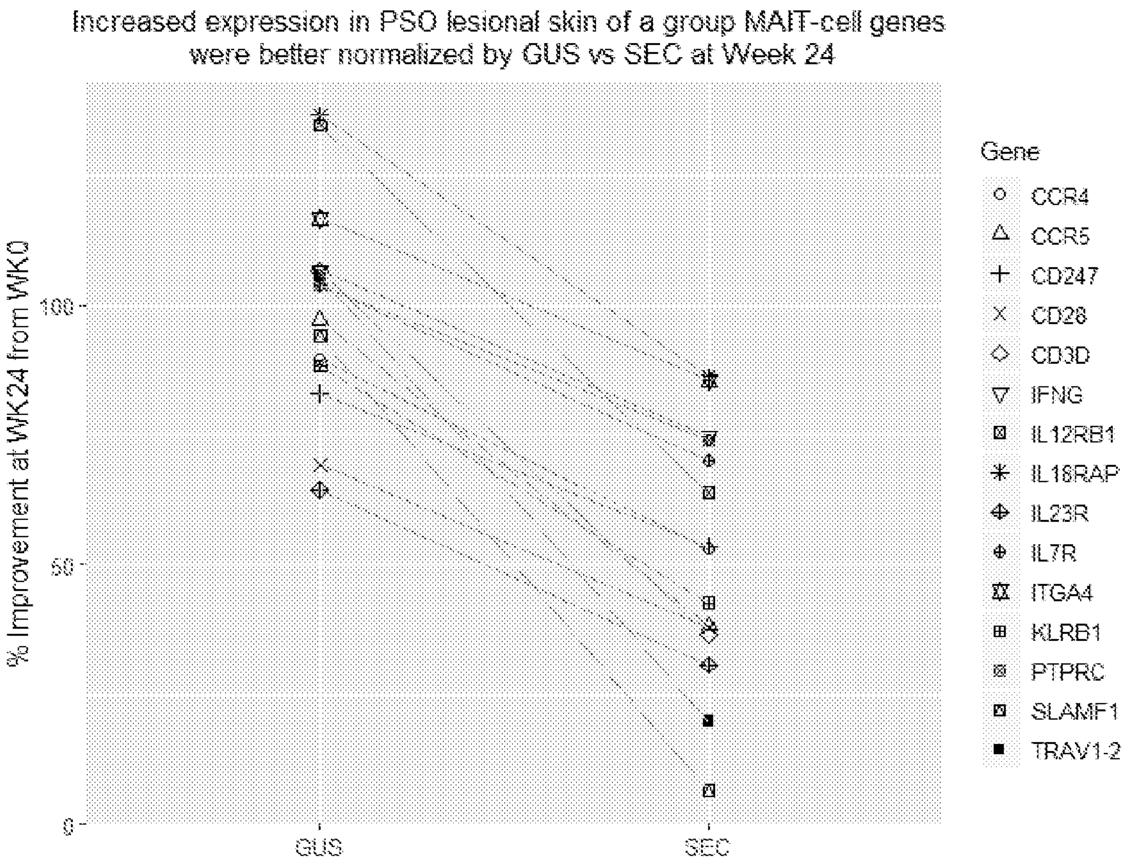

Increased expression in PSO lesional skin of a group MAIT-cell genes were better normalized by GUS vs SEC at Week 24
% Improvement at WK24 from WK0
100
50
0
GUS
SEC
Gene
CCR4
CCR5
CD247
CD28
CD3D
IFNG
IL12RB1
IL18RAP
IL23R
IL7R
ITGA4
KLRB1
PTPRC
SLAMF1
TRAV1-2

FIG. 8

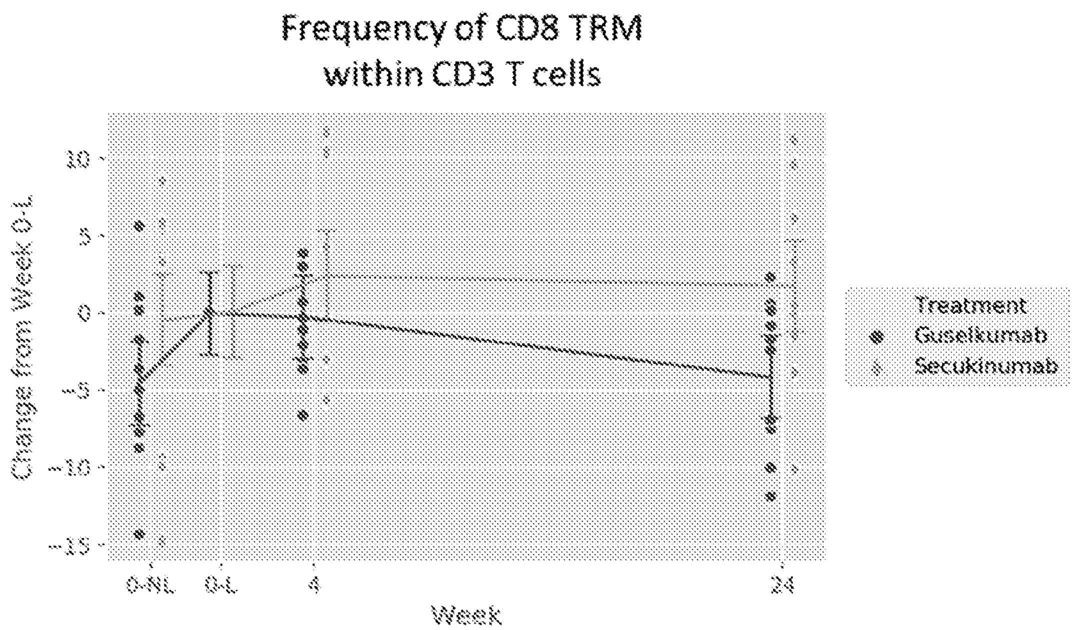

Frequency of CD8 TRM within CD3 T cells
Change from Week 0-L
10
5
0
-5
-10
-15
0-NL
0-L
4
24
Week
Treatment
Guselkumab
Secukinumab

FIG. 9

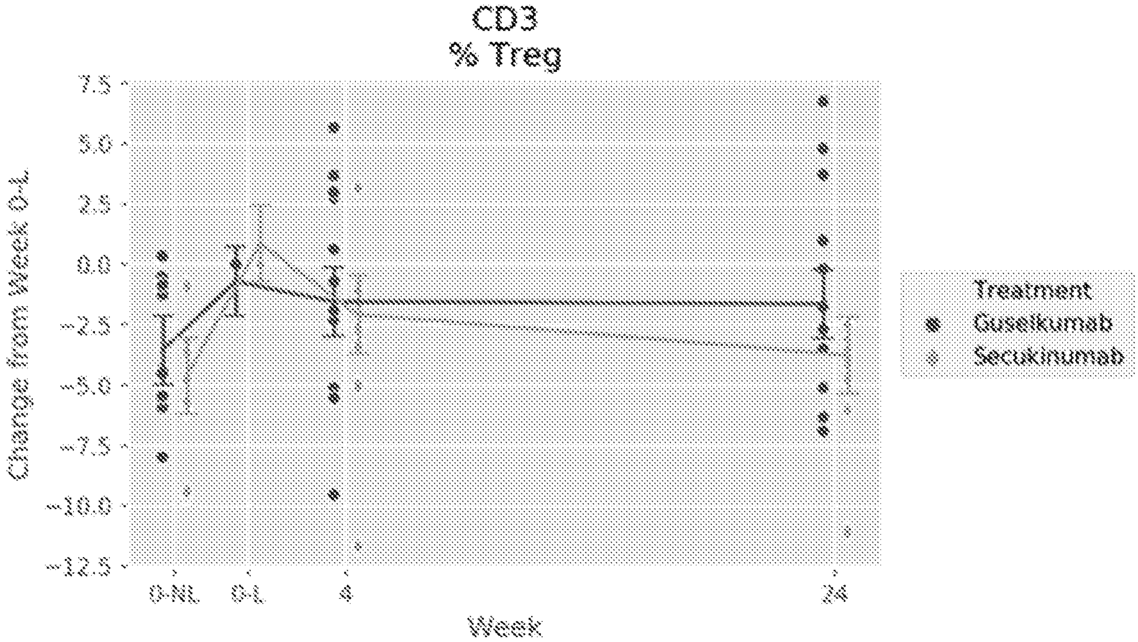

CD3
% Treg
Change from Week 0-L
7.5
5.0
2.5
0.0
−2.5
−5.0
−7.5
−10.0
−12.5
0-NL
0-L
4
24
Week
Treatment
Guselkumab
Secukinumab

FIG. 10

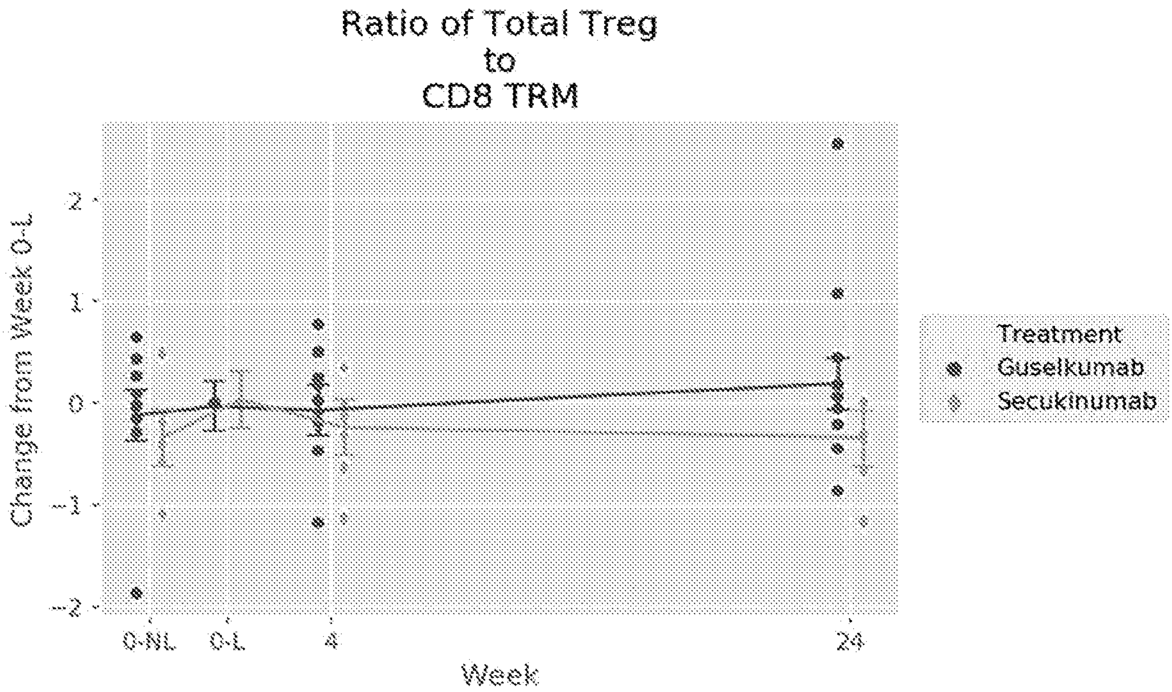
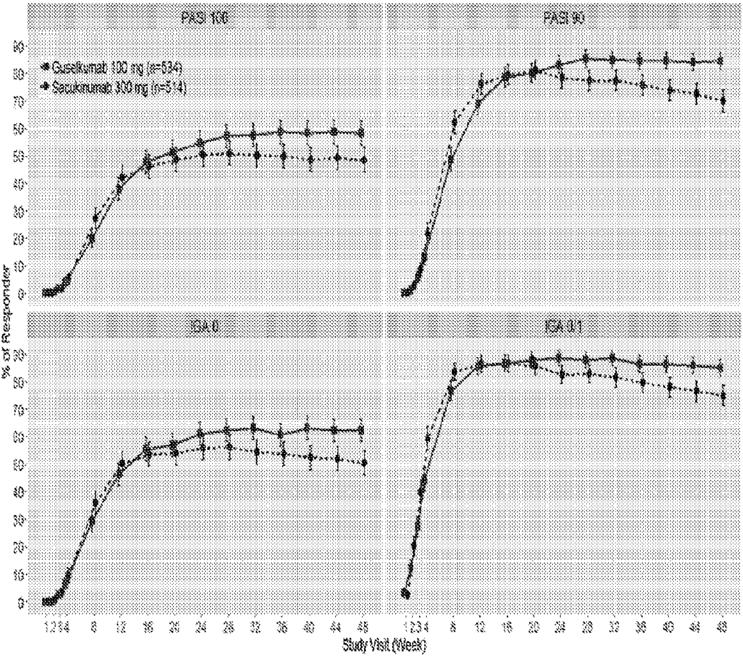

Ratio of Total Treg
to
CD8 TRM
Change from Week 0-L
2
1
0
−1
−2
0-NL
0-L
4
24
Week
Treatment
Guselkumab
Secukinumab

FIG. 1



PASI 100
PASI 90
IGA 0
IGA 0/1
Guselkumab 100 mg (n=534)
Secukinumab 300 mg (n=514)
% of Responder
Study Visit (Week)