

- [00229] In some aspects, the amount or frequency of the IL23 antagonist administered to the patient (e.g., an anti-IL23 antibody targeting, e.g., the p19 subunit of IL23, such as MEDI2070, or an antigen-binding fragment thereof) can be maintained or reduced if the patient's IL22 and/or LCN2 level in the second sample is lower than or about the same as the IL22 and/or LCN2 level in the first sample.
- [00230] In certain aspects, in all the treatment methods disclosed herein, a "loading" dose of an IL23 antagonist (e.g., an anti-IL23 antibody targeting, e.g., the p19 subunit of IL23, such as MEDI2070, or an antigen-binding fragment thereof) is administered to achieve a desired therapeutic level in the patient. If the loading dose does not affect the patient's IL22 and/or LCN2 levels (e.g., protein expression levels or gene expression levels) significantly or the patient's IL22 and/or LCN2 levels rise, a decision could be made to discontinue treatment – e.g., to use a non-IL23 antagonist therapy.
- [00231] If the loading dose results in a reduced IL22 and/or LCN2 level in the patient a decision could be made to reduce the dose size or frequency to a "maintenance" dose. It is important to note that the methods provided here are guidelines for a healthcare provider to administer treatment, and the ultimate treatment decision will be based on the healthcare provider's sound judgment.
- [00232] In some aspects, results of an immunoassay as provided herein can be submitted to a healthcare benefits provider for determination of whether the patient's insurance will cover treatment with an IL23 antagonist (e.g., an anti-IL23 antibody targeting, e.g., the p19 subunit of IL23, such as MEDI2070, or an antigen-binding fragment thereof).
- [00233] In some aspects, this disclosure includes a method of treating a patient having an IL23-mediated disease comprising: measuring, e.g., in a clinical laboratory, the IL22 and/or LCN2 level (e.g., protein expression level or gene expression level) in a first sample obtained from a patient having an IL23-mediated disease, e.g., a sample provided by a healthcare provider, wherein the patient's IL22 and/or LCN2 level in the first sample is, for example, measured in an immunoassay, including, e.g., an immunoassay described in Example 3, employing one or more anti-IL22 and/or anti-LCN2 antibodies or antigen binding fragments thereof which recognize human IL22 and/or human LCN2, determining whether the patient's IL22 and/or LCN2 level in the first sample is above a predetermined IL22 and/or LCN2 level, or is elevated relative to the IL22 and/or LCN2 level in one or more control samples;

and advising a healthcare provider to administer an IL23 antagonist (e.g., an anti-IL23 antibody targeting, e.g., the p19 subunit of IL23, such as MEDI2070, or an antigen-binding fragment thereof) to the patient if the patient's IL22 and/or LCN2 level are above a predetermined IL22 and/or LCN2 threshold level, or are elevated relative to the IL22 and/or LCN2 level in one or more control samples.

[00234] In some aspects, these methods can further comprise: measuring the IL22 and/or LCN2 levels (e.g., protein expression level or gene expression level) in a second sample obtained from the patient, e.g., a sample provided by a healthcare provider, wherein the patient's IL22 and/or LCN2 level is again measured, for example, in an immunoassay, including, e.g., an immunoassay described in Example 3, employing one or more anti-IL22 and/or anti-LCN2 antibodies or antigen binding fragments thereof which recognize human IL22 and/or human LCN2; determining whether the patient's IL22 and/or LCN2 level in the second sample is higher than, about the same as, or lower than the IL22 and/or LCN2 level measured in the first sample; and advising a healthcare provider to adjust the IL23 antagonist therapy (e.g., a therapy comprising the administration of an anti-IL23 antibody targeting, e.g., the p19 subunit of IL23, such as MEDI2070, or an antigen-binding fragment thereof) if indicated, e.g., to increase or maintain the amount or frequency of the IL23 antagonist administered to the patient, or discontinuing IL23 antagonist therapy, if the patient's IL22 and/or LCN2 level in the second sample is higher than the IL22 and/or LCN2 level in the first sample, or to maintain or reduce the amount or frequency of the IL23 antagonist administered to the patient if the patient's IL22 and/or LCN2 level in the second sample is lower than or about the same as the IL22 and/or LCN2 level in the first sample.

[00235] In some aspects, a sample is obtained from the patient and is submitted, e.g., to a clinical laboratory, for measurement of the IL22 and/or LCN2 level (e.g., protein expression level or gene expression level) in the sample, e.g., using an immunoassay. In some aspects, the clinical laboratory performing the assay will advise the healthcare provide as to whether the patient can benefit from treatment with an IL23 antagonist (e.g., an anti-IL23 antibody targeting, e.g., the p19 subunit of IL23, such as MEDI2070, or an antigen-binding fragment thereof) based on whether the patient's IL22 and/or LCN2 level (e.g., protein expression level or gene expression level) is above a predetermined IL22 and/or LCN2 threshold value or is elevated relative to one or more control samples.

[00236] In some aspects, methods of treatment contemplated herein (e.g., for an IL23-mediated disease such as Crohn's disease) comprise administering to the subject an antibody or antigen-binding fragment thereof targeting IL23 (e.g., to the p19 subunit of IL23, such as MEDI2070) in a sufficient amount and/or at sufficient interval to achieve and/or maintain a certain quantity of IL23-specific antibody per volume of serum, using, for example, an assay as described herein.

[00237] For example, the antibody or antigen-binding fragment thereof targeting IL23 (e.g., to the p19 subunit of IL23, such as MEDI2070) can be given to achieve at least 25 ng/ml, 30 ng/ml, 35 ng/ml, 40 ng/ml, 45 ng/ml, 50 ng/ml, 55 ng/ml, 60 ng/ml, 65 ng/ml, 70 ng/ml, 75 ng/ml, 80 ng/ml, 85 ng/ml, 90 ng/ml, 95 ng/ml, 100 ng/ml, 150 ng/ml, 200 ng/ml, 250 ng/ml, 300 ng/ml, 350 ng/ml, 400 ng/ml, 450 ng/ml, 500 ng/ml, 550 ng/ml, 600 ng/ml, 650 ng/ml, 700 ng/ml, 750 ng/ml, 800 ng/ml, 850 ng/ml, 900 ng/ml, 950 ng/ml or 1000 ng/ml in serum.

[00238] In a further embodiment, the antibody or antigen-binding fragment thereof targeting IL23 (e.g., to the p19 subunit of IL23, such as MEDI2070) can be given to achieve a concentration of IL23-specific antibody in serum from about 12.5 ng/ml to about 1000 ng/ml. Those of skill in the art will understand that the amounts given here apply to a full-length antibody or immunoglobulin molecule; if an antigen binding fragment thereof is used, the absolute quantity will differ from that given in a manner that can be calculated based on the molecular weight of the fragment.

[00239] In some aspects, methods of treatment contemplated herein (e.g., for an IL23-mediated disease such as Crohn's disease) comprise administering to the subject an IL23 antagonist (e.g., an anti-IL23 antibody targeting, e.g., the p19 subunit of IL23, such as MEDI2070, or an antigen-binding fragment thereof) in an amount and at an interval of: 15–54 mg every 0.5–1.5 months; 55–149 mg every 1.5–4.5 months; 150–299 mg every 4–8 months; or 300–1100 mg every 4–12 months. In some aspects, the amount and interval are: 15–21 mg every 0.5–1.0 month; 55–70 mg every 1.5–3.0 months; 150–260 mg every 4–6 months; or 300–700 mg every 4–8 months. In some aspects, the amount and interval are: 21 mg every month; 70 mg every 3 months; 210 mg every 6 months; or 700 mg every 6 months. In some aspects, the amount and interval are: 210 mg every 3 months or 700 mg every 3 months. In some aspects, the amount and interval are: 210 mg every 1 month or 700 mg every 1 month.

[00240] In some aspects of the methods, the IL23 antagonist (e.g., an anti-IL23 antibody targeting, e.g., the p19 subunit of IL23, such as MEDI2070, or an antigen-binding fragment thereof) is administered intravenously (IV). In some aspects of the methods, the IL23 antagonist (e.g., an anti-IL23 antibody targeting, e.g., the p19 subunit of IL23, such as MEDI2070, or an antigen-binding fragment thereof) is administered subcutaneously (SC).

[00241] In some aspects, the IL23 antagonist (e.g., an anti-IL23 antibody targeting, e.g., the p19 subunit of IL23, such as MEDI2070, or an antigen-binding fragment thereof) is administered in one or more fixed doses. In some aspects, the doses as administered every week, every two weeks, every three weeks, every 4 weeks, every 5 weeks, every 6 weeks, every 7 weeks, every 8 weeks, every 9 weeks every 10 weeks, or every 12 weeks. In some aspects, the dose comprises about 1 mg, 2 mg, 3mg, 4 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 310 mg, 320 mg, 330 mg, 340 mg, 350 mg, 360 mg, 370 mg, 380 mg, 390 mg, 400 mg, 410 mg, 420 mg, 430 mg, 440 mg, 450 mg, 460 mg, 470 mg, 480 mg, 490 mg, 500 mg, 510 mg, 520 mg, 530 mg, 540 mg, 550 mg, 560 mg, 570 mg, 580 mg, 590 mg, 600 mg, 610 mg, 620 mg, 630 mg, 640 mg, 650 mg, 660 mg , 670 mg, 680 mg, 690 mg, 700 mg, 710 mg, 720 mg, 730 mg, 740 mg, 750 mg, 760 mg, 770 mg, 780 mg, 790 mg, 800 mg, 810 mg, 820 mg, 830 mg, 840 mg, 850 mg, 860 mg, 870 mg, 880 mg, 890 mg, 900 mg, 910 mg, 920 mg, 930 mg, 940 mg, 950 mg, 960 mg, 970 mg, 980 mg, 990 mg or 1000 mg. In some aspects, the dose is higher than 1000 mg.

[00242] In some aspects, the dose is about 210 mg of IL23 antagonist (e.g., an anti-IL23 antibody targeting, e.g., the p19 subunit of IL23, such as MEDI2070, or an antigen-binding fragment thereof) administered SC.

[00243] In other aspects, the dose is about 700 mg of IL23 antagonist (e.g., an anti-IL23 antibody targeting, e.g., the p19 subunit of IL23, such as MEDI2070, or an antigen-binding fragment thereof) administered IV.

[00244] In some aspects, two, three, 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 or 50 doses are administered.

[00245] In one specific aspect, the anti-IL23 antibody (e.g., MEDI2070) is administered at a fixed dose of 210 mg Q4W for 26 doses. In another specific aspects, the anti-IL23 antibody (e.g., MEDI2070) is administered at a fixed dose of 700 mg IV Q4W for 12-weeks. In some aspects, the IV administration is followed by administration of the anti-IL23 antibody (e.g., MEDI2070) at a fixed dose of 210 mg SC Q4W for 100-weeks.

[00246] The formulation, dosage regimen, and route of administration of a therapeutic agent, e.g., and IL23 antagonist (e.g., an anti-IL23 antibody targeting, e.g., the p19 subunit of IL23, such as MEDI2070, or an antigen-binding fragment thereof), can be adjusted to provide an effective amount for an optimum therapeutic response according to the method disclosed herein. With regard to the administration of an IL23 antagonist, the antagonist may be administered through any suitable means, compositions and routes known in the art. With regard to dosage regimens, a single bolus can be administered, several divided doses can be administered over time or the dose can be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation.

[00247] The IL23 antagonist (e.g., an anti-IL23 antibody targeting, e.g., the p19 subunit of IL23, such as MEDI2070, or an antigen-binding fragment thereof) may be administered by any suitable technique, including but not limited to, parenterally, topically, or by inhalation. If injected, the pharmaceutical composition can be administered, for example, via intra-articular, intravenous, intramuscular, intralesional, intraperitoneal or cutaneous routes (including intra-, trans- or sub- dermal, and subcutaneous), by bolus injection, or continuous infusion. In some aspects, the pharmaceutical composition is administered by an intravenous route. In some aspects the pharmaceutical composition is administered by a subcutaneous route. In further aspects, the compositions are administered by oral, buccal, rectal, intratracheal, gastric, or intracranial routes. Localized administration, *e.g.* at a site of disease or injury is contemplated, for example, by enema or suppository for conditions involving the gastrointestinal tract. Also contemplated are transdermal delivery and sustained release from implants. Delivery by inhalation includes, for example, nasal or oral inhalation, use of a nebulizer, inhalation of the antagonist in aerosol form, and the like. Other alternatives include eyedrops; oral preparations including pills, syrups, lozenges or chewing gum; and topical preparations such as lotions, gels, sprays, and ointments, prefilled syringes and autoinjectors.

[00248] Advantageously, the IL23 antagonist (e.g., an anti-IL23 antibody targeting, e.g., the p19 subunit of IL23, such as MEDI2070, or an antigen-binding fragment thereof) can be administered in the form of a composition comprising one or more additional components such as a physiologically acceptable carrier, excipient or diluent. Optionally, the composition additionally comprises one or more physiologically active agents for combination therapy.

[00249] A pharmaceutical composition may comprise an IL23 antagonist (e.g., an anti-IL23 antibody targeting, e.g., the p19 subunit of IL23, such as MEDI2070, or an antigen-binding fragment thereof) together with one or more substances selected from the group consisting of a buffer, an antioxidant such as ascorbic acid, a low molecular weight polypeptide (such as those having fewer than 10 amino acids), a protein, an amino acid, a carbohydrate such as glucose, sucrose or dextrans, a chelating agent such as EDTA, glutathione, a stabilizer, and an excipient. Neutral buffered saline or saline mixed with conspecific serum albumin are examples of appropriate diluents. In accordance with appropriate industry standards, preservatives such as benzyl alcohol may also be added. The composition may be formulated as a lyophilizate using appropriate excipient solutions (e.g., sucrose) as diluents.

[00250] In some aspects, the IL23 antagonist (e.g., an anti-IL23 antibody targeting, e.g., the p19 subunit of IL23, such as MEDI2070, or an antigen-binding fragment thereof) can be provided at a concentration of about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195 or 200 mg/ml.

[00251] Exemplary formulations useful for the present invention are those that include a glutamic acid, citric acid or acetic acid buffer at an appropriate pH, from 4.5 to 5.2, an excipient such as sucrose, glycine, proline, glycerol, and/or sorbitol at an appropriate concentration such as 1 to 20% (w/v), and a surfactant such as a non-ionic surfactant like polysorbate (polysorbate 20 or 80) or poloxamers (poloxamer 1888) at an appropriate concentration of 0.001% - 0.1% (w/v). Such formulations are disclosed in US Patent No. 6171586 and WIPO Published Applications Nos. WO20100027766 and WO2011088120. In some aspects, the formulations comprise sodium acetate, sucrose and polysorbate 20. In some aspects, the formulations comprise 70 mg/mL anti-IL23 antibody (e.g., MEDI2070), 10 mM sodium acetate, 9% (w/v) sucrose and 0.004% (w/v) polysorbate 20, at pH 5.2. Suitable components are nontoxic to recipients at the dosages and concentrations employed. Further

examples of components that may be employed in pharmaceutical formulations are presented in any Remington's Pharmaceutical Sciences including the 21st Ed. (2005), Mack Publishing Company, Easton, PA.

VI. Combination Treatments

[00252] Particular aspects of methods of the invention involve the use of an anti-IL23 antibody (e.g., an anti-IL23 antibody targeting, e.g., the p19 subunit of IL23, such as MEDI2070, or an antigen-binding fragment thereof) and one or more additional IL23 antagonists as described in the section of the description entitled "IL23 Antagonists" in combination with additional therapeutic agents.

[00253] In some aspects, the IL23 antagonist is an anti-IL23 antibody which can specifically bind to the p19 subunit of IL23 (SEQ ID NO: 13), to the p40 subunit of IL23 (SEQ ID NO: 14), or both.

[00254] In some aspects, the anti-IL23 antibody or antigen-binding fragment thereof comprises the heavy chain (HC) (SEQ ID NO: 15) and/or the light chain (SEQ ID NO: 16) of MEDI2070, or an antigen-binding fragment, variant, or derivative thereof. In some aspects, the anti-IL23 antibody or antigen-binding fragment thereof comprises the heavy chain variable region (VH) (SEQ ID NO: 5) and/or the light chain variable region (VL) (SEQ ID NO: 6) of MEDI2070. In some aspects, the anti-IL23 antibody or antigen-binding fragment thereof comprises at least one of the complementarity determining regions of MEDI2070 (SEQ ID NOS: 31-36). In some aspects, the anti-IL23 antibody or antigen-binding fragment thereof comprises a VH region comprising the sequence of SEQ ID NO: 43 and/or a VL region comprising the sequence of SEQ ID NO: 44, or an antigen-binding fragment, variant, or derivative thereof. In some aspects, the anti-IL23 antibody or antigen-binding fragment thereof comprises at least one of the complementarity determining regions of SEQ ID NOS:45-47 (CDRs of the VH of SEQ ID NO:43) and/or SEQ ID NOS: 48-50 (CDRs of the VL of SEQ ID NO:44).

[00255] In other aspects, the IL23 antagonist is an anti-IL23 antibody selected from ustekinumab or briakinumab (targeting the p40 subunit of IL23), guselkumab, tildrakizumab, BI-655066 or LY-3074828 (targeting the p19 subunit of IL23), an antigen-binding fragment thereof, or a combination thereof. In other aspects, the IL23 antagonist is a molecule (e.g., an

antibody) that competes for binding to IL23 with ustekinumab or briakinumab (targeting the p40 subunit of IL23), guselkumab, tildrakizumab, BI-655066 or LY-3074828 (targeting the p19 subunit of IL23), an antigen-binding fragment thereof, or a combination thereof.

[00256] Examples include using combinations of an anti-IL23 antibody and one or more other therapeutic moiety having anti-inflammatory properties (for example, non-steroidal anti-inflammatory agents, steroids, and/or immunomodulators), or of an anti-IL23 antibody and one or more other treatments (*e.g.*, surgery, ultrasound, or treatment effective to reduce inflammation). Useful agents that may be combined with an anti-IL23 antibody include those used to treat, for example, Crohn's disease or ulcerative colitis, such as aminosalicylate (for example, mesalamine or substances that are metabolized to mesalamine, including, for example, ASACOL®, SALOFALK®, PENTASA®, DIPENTUM®, COLAZIDE®, LIALDA® and ROWASA®), corticosteroids/glucocorticoids (including prednisolone methasulfobenzoate, tixocortol pivalate, fluticasone propionate, beclomethasone dipropionate, and budesonide), antibiotics such as metronidazole or ciprofloxacin (or other antibiotics useful for treating, for example, patients afflicted with fistulas), and immunosuppressives such as azathioprine (for example, IMURAN® and AZASAN®), 6-mercaptopurine (for example, PURINETHOL®), methotrexate (for example, TREXALL®, RHEUMATREX®), tacrolimus (for example, PROGRAF®) and cyclosporine (for example, GENGRAF®, NEORAL®, and SANDIMMUNE®). Such agent(s) may be administered orally or by another route, for example via suppository or enema, at dosages and intervals that are known in the art and described in the prescribing information.

[00257] Furthermore, IL23 antibodies or antibody derivatives, or the aforesaid combinations, can be used in conjunction with one or more molecules or other treatments, wherein the other molecule(s) and/or treatment(s) do not directly bind to or affect IL23, but which combination is effective for treating or preventing the condition being treated. For example, an anti-IL23 antibody can be used in combination with probiotic therapy, or other therapy used to restore or maintain normal gut flora, including gut flora transplant. In one embodiment, one or more of the molecule(s) and/or treatment(s) treats or prevents a condition that is caused by one or more of the other molecule(s) or treatment(s) in the course of therapy, *e.g.*, nausea, fatigue, alopecia, cachexia, insomnia, *etc.* Such agent(s) or therapies may be administered by routes,

and at dosages and intervals, that are known in the art and described in the prescribing information.

[00258] In some aspects, IL23 antibodies or antibody derivatives, or the aforesaid combinations, can be used in conjunction with one or more elemental diet treatment. See, e.g., Voitek et al. Arch Surg 107:329 (1973); Yamamoto et al. Int J Colorectal Dis 28:335–340 (2013).

[00259] Additional supportive therapies are included in possible combination treatment with IL23 antagonists (e.g., an anti-IL23 antibody targeting, e.g., the p19 subunit of IL23, such as MEDI2070, or an antigen-binding fragment thereof); such supportive therapies as (without limitation), analgesics, and anticholinergic and antidiarrheal agents. Combining such supportive therapies can be useful in the beginning of a treatment regimen in reducing a patient's symptoms and improving their quality of life. Supportive therapies include administering oral iron, folate, and vitamin B₁₂. Antidiarrheal agents include, but are not limited to diphenoxylate, codeine, loperamide, and anticholinergics (or pharmacological equivalents thereof), which can be administered to patients with mild disease to reduce the frequency of bowel movements and relieve rectal urgency. Cholestyramine can be used in patients to prevent bile salt-induced colonic secretion in patients who have already undergone limited ileocolic resections. Anticholinergic agents include, but are not limited to, clidinium bromide, dicyclomine hydrochloride, tincture of belladonna and the like, and are useful to reduce abdominal cramps, pain and rectal urgency. Supportive or therapies may be administered by routes, and at dosages and intervals, that are known in the art and described in the prescribing information

[00260] In every case where a combination of molecules and/or other treatments is used, the individual molecule(s) and/or treatment(s) can be administered in any order, over any length of time, which is effective, e.g., simultaneously, consecutively, or alternately. In one embodiment, the method of treatment comprises completing a first course of treatment with one molecule or other treatment before beginning a second course of treatment. The length of time between the end of the first course of treatment and beginning of the second course of treatment can be any length of time that allows the total course of therapy to be effective, e.g., seconds, minutes, hours, days, weeks, months, or even years.

VII. Kits and Assays for Detecting IL23 Pathway Biomarkers

- [00261] This disclosure also provides kits for detecting IL23 pathway biomarkers, e.g., IL22, LCN2, or combinations thereof (*e.g.*, protein expression level or gene expression level), for example, through an immunoassay method. Such kits can comprise containers, each with one or more of the various reagents (*e.g.*, in concentrated form) utilized in the method, including, for example, one or more anti-IL22 and/or anti-LCN2 antibodies. One or more anti-IL22 antibodies and/or anti-LCN2 antibodies, *e.g.*, capture antibodies, can be provided already attached to a solid support. One or more antibodies anti-IL22 antibodies and/or anti-LCN2 antibodies, *e.g.*, detection antibodies, can be provided already conjugated to a detectable label, *e.g.*, biotin or a ruthenium chelate.
- [00262] The kit can also provide reagents for coupling a detectable label to an antibody (as well as the label itself), buffers, and/or reagents and instrumentation to support the practice of the assays provided herein. In certain aspects, a labeled secondary antibody can be provided that binds to the detection antibody. A kit provided according to this disclosure can further comprise suitable containers, plates, and any other reagents or materials necessary to practice the assays provided herein.
- [00263] In some aspects, a kit comprises one or more nucleic acid probes (*e.g.*, oligonucleotides comprising naturally occurring and/or chemically modified nucleotide units) capable of hybridizing a subsequence of the *IL22* or *LCN2* gene sequences under high stringency conditions. In some aspects, one or more nucleic acid probes (*e.g.*, oligonucleotides comprising naturally occurring and/or chemically modified nucleotide units) capable of hybridizing a subsequence of the *IL22* or *LCN2* gene sequence under high stringency conditions are attached to a microarray chip.
- [00264] A kit provided according to this disclosure can also comprise brochures or instructions describing the process. For IL22 or LCN2 detection immunoassays, and in particular sandwich immunoassays, *e.g.*, an ELISA assay or an ECL assay, the sandwich immunoassay process comprises a first anti-IL22 or anti-LCN2 "capture" antibody or antigen-binding fragment thereof attached to a solid support, and a second anti-IL22 or anti-LCN2 "detection" antibody or antigen binding fragment thereof. The immunoassay can be performed by methods provided herein or methods well known and understood by those of ordinary skill in the art. In one aspect, the immunoassay comprises attaching a capture

antibody or fragment thereof to a solid support; applying the test sample or a control sample, allowing IL22 or LCN2, if present in the sample, to bind to the capture antibody or fragment thereof; applying the detection antibody or fragment thereof, which can bind to IL22 or LCN2 already bound to the capture antibody or fragment thereof; and measuring the amount of detection antibody or fragment thereof bound to IL22 or LCN2. In certain aspects, the assay can further include washing steps, blocking steps and incubation steps.

[00265] Test kits can include instructions for carrying out one or more IL22 or LCN2 detection assays, *e.g.*, immunoassays or nucleic acid detection assays. Instructions included in the kits can be affixed to packaging material or can be included as a package insert. While the instructions are typically written or printed materials they are not limited to such. Any medium capable of storing such instructions and communicating them to an end user is contemplated. Such media include, but are not limited to, electronic storage media (*e.g.*, magnetic discs, tapes, cartridges, chips), optical media (*e.g.*, CD ROM), and the like. As used herein, the term "instructions" can include the address of an internet site that provides the instructions.

VIII. Companion Diagnostic System

[00266] The methods disclosed herein can be provided as a companion diagnostic, for example available via a web server, to inform the clinician or patient about potential treatment choices. The methods disclosed herein can comprise collecting or otherwise obtaining a biological sample and performing an analytical method to detect and measure the levels of IL23 pathway biomarkers disclosed herein (*e.g.*, protein expression levels or gene expression levels of IL22, LCN2, and/or combinations thereof) alone or in combination with other biomarkers (*e.g.*, other components of the IL23 pathway, biomarkers downstream from the IL23 pathway, or components of inflammation pathways known in the art). Exemplary biomarkers that can be combined with IL22, LCN2, and combinations thereof are discussed above in the specification.

[00267] Levels of IL22, LCN2, and combinations thereof (*e.g.*, protein expression levels or gene expression levels) or normalized scores derived from measured levels can be used alone (*e.g.*, for treatment, diagnostic, prognostic, or monitoring purposes), or in combination with levels or normalized scores derived from other biomarkers (*e.g.*, a panel a genes used to

derive a gene signature). These scores can also be combined with other scores corresponding, for example, to clinical biomarkers such as (i) gender, (ii) age, (iii) body mass index, (iv) smoking status, (v) concomitant drugs, (vi) health assessment quality (HAQ), or a combination of two or more to yield a diagnostic score. In this approach, the diagnostic score may be a single number determined from the sum of all the marker calculations that is compared to a preset threshold value that is an indication of the presence or absence of disease. Or the diagnostic score may be a series of bars that each represent a biomarker value and the pattern of the responses may be compared to a pre-set pattern for determination of the presence or absence of disease.

[00268] At least some aspects of the methods described herein, due to the complexity of the calculations involved, a method comprising the use of IL22, LCN2, and combinations thereof as biomarkers can be implemented with the use of a computer. In some aspects, the computer system comprises hardware elements that are electrically coupled via bus, including a processor, input device, output device, storage device, computer-readable storage media reader, communications system, processing acceleration (e.g., DSP or special-purpose processors), and memory. The computer-readable storage media reader can be further coupled to computer-readable storage media, the combination comprehensively representing remote, local, fixed and/or removable storage devices plus storage media, memory, etc. for temporarily and/or more permanently containing computer-readable information, which can include storage device, memory and/or any other such accessible system resource.

[00269] A single architecture might be utilized to implement one or more servers that can be further configured in accordance with currently desirable protocols, protocol variations, extensions, etc. However, it will be apparent to those skilled in the art that embodiments may well be utilized in accordance with more specific application requirements. Customized hardware might also be utilized and/or particular elements might be implemented in hardware, software or both. Further, while connection to other computing devices such as network input/output devices (not shown) may be employed, it is to be understood that wired, wireless, modem, and/or other connection or connections to other computing devices might also be utilized.

[00270] In one aspect, the system further comprises one or more devices for providing input data to the one or more processors. The system further comprises a memory for storing a data

set of ranked data elements. In another aspect, the device for providing input data comprises a detector for detecting the characteristic of the data element, e.g., such as a fluorescent plate reader, mass spectrometer, or gene chip reader.

[00271] The system additionally may comprise a database management system. User requests or queries can be formatted in an appropriate language understood by the database management system that processes the query to extract the relevant information from the database of training sets. The system may be connectable to a network to which a network server and one or more clients are connected. The network may be a local area network (LAN) or a wide area network (WAN), as is known in the art. Preferably, the server includes the hardware necessary for running computer program products (e.g., software) to access database data for processing user requests. The system can be in communication with an input device for providing data regarding data elements to the system (e.g., expression values). In one aspect, the input device can include a gene expression profiling system including, e.g., a mass spectrometer, gene chip or array reader, and the like.

[00272] Some aspects described herein can be implemented so as to include a computer program product. A computer program product may include a computer readable medium having computer readable program code embodied in the medium for causing an application program to execute on a computer with a database. As used herein, a "computer program product" refers to an organized set of instructions in the form of natural or programming language statements that are contained on a physical media of any nature (e.g., written, electronic, magnetic, optical or otherwise) and that may be used with a computer or other automated data processing system. Such programming language statements, when executed by a computer or data processing system, cause the computer or data processing system to act in accordance with the particular content of the statements.

[00273] Computer program products include without limitation: programs in source and object code and/or test or data libraries embedded in a computer readable medium. Furthermore, the computer program product that enables a computer system or data processing equipment device to act in pre-selected ways may be provided in a number of forms, including, but not limited to, original source code, assembly code, object code, machine language, encrypted or compressed versions of the foregoing and any and all equivalents.

[00274] In one aspect, a computer program product is provided to implement the treatment, diagnostic, prognostic, or monitoring methods disclosed herein, for example, to determine whether to administer an IL23 antagonist (e.g., an anti-IL23 antibody targeting, e.g., the p19 subunit of IL23, such as MEDI2070, or an antigen-binding fragment thereof) to a patient in need thereof if the level of IL23 pathway biomarkers in a sample taken from the patient are above or below predetermined threshold levels, e.g., if IL22 and/or LCN2 levels are above respective predetermined threshold levels.

[00275] In some aspects, the IL23 antagonist is an anti-IL23 antibody which can specifically bind to the p19 subunit of IL23 (SEQ ID NO: 13), to the p40 subunit of IL23 (SEQ ID NO: 14), or both.

[00276] In some aspects, the anti-IL23 antibody or antigen-binding fragment thereof comprises the heavy chain (HC) (SEQ ID NO: 15) and/or the light chain (SEQ ID NO: 16) of MEDI2070, or an antigen-binding fragment, variant, or derivative thereof. In some aspects, the anti-IL23 antibody or antigen-binding fragment thereof comprises the heavy chain variable region (VH) (SEQ ID NO: 5) and/or the light chain variable region (VL) (SEQ ID NO: 6) of MEDI2070. In some aspects, the anti-IL23 antibody or antigen-binding fragment thereof comprises at least one of the complementarity determining regions of MEDI2070 (SEQ ID NOS: 31-36). In some aspects, the anti-IL23 antibody or antigen-binding fragment thereof comprises a VH region comprising the sequence of SEQ ID NO: 43 and/or a VL region comprising the sequence of SEQ ID NO: 44, or an antigen-binding fragment, variant, or derivative thereof. In some aspects, the anti-IL23 antibody or antigen-binding fragment thereof comprises at least one of the complementarity determining regions of SEQ ID NOS:45-47 (CDRs of the VH of SEQ ID NO:43) and/or SEQ ID NOS: 48-50 (CDRs of the VL of SEQ ID NO:44).

[00277] In other aspects, the IL23 antagonist is an anti-IL23 antibody selected from ustekinumab or briakinumab (targeting the p40 subunit of IL23), guselkumab, tildrakizumab, BI-655066 or LY-3074828 (targeting the p19 subunit of IL23), an antigen-binding fragment thereof, or a combination thereof. In other aspects, the IL23 antagonist is a molecule (e.g., an antibody) that competes for binding to IL23 with ustekinumab or briakinumab (targeting the p40 subunit of IL23), guselkumab, tildrakizumab, BI-655066 or LY-3074828 (targeting the p19 subunit of IL23), an antigen-binding fragment thereof, or a combination thereof.

[00278] The computer program product includes a computer readable medium embodying program code executable by a processor of a computing device or system, the program code comprising: (a) code that retrieves data attributed to a biological sample from a subject, wherein the data comprises IL23 pathway biomarker (e.g., IL22, and/or LCN2) levels values (presence/absence, amount, or data otherwise derived from these level values) alone or combination with values corresponding to other biomarkers in the biological sample (e.g., biological markers or clinical markers). These values can also be combined with values corresponding to clinical biomarkers, for example, indicative of the severity of the disease or disorder or to the patient's predisposition to have such disease or disorder; and, (b) code that executes a classification method that indicates, e.g., whether to administer an IL23 antagonist (e.g., an anti-IL23 antibody targeting, e.g., the p19 subunit of IL23, such as MEDI2070, or an antigen-binding fragment thereof) to a patient in need thereof.

[00279] While various aspects have been described as methods or apparatuses, it should be understood that aspects can be implemented through code coupled with a computer, e.g., code resident on a computer or accessible by the computer. For example, software and databases could be utilized to implement many of the methods discussed above. Thus, in addition to aspects accomplished by hardware, it is also noted that these aspects can be accomplished through the use of an article of manufacture comprised of a computer usable medium having a computer readable program code embodied therein, which causes the enablement of the functions disclosed in this description. Therefore, it is desired that aspects also be considered protected by this patent in their program code means as well.

[00280] Furthermore, some aspects can be code stored in a computer-readable memory of virtually any kind including, without limitation, RAM, ROM, magnetic media, optical media, or magneto-optical media. Even more generally, some aspects could be implemented in software, or in hardware, or any combination thereof including, but not limited to, software running on a general purpose processor, microcode, PLAs, or ASICs.

[00281] It is also envisioned that some aspects could be accomplished as computer signals embodied in a carrier wave, as well as signals (e.g., electrical and optical) propagated through a transmission medium. Thus, the various types of information discussed above could be formatted in a structure, such as a data structure, and transmitted as an electrical signal through a transmission medium or stored on a computer readable medium.

IX. Embodiments

- [00282]** E1. A method of treating an interleukin-23 (IL23)-mediated disease in a patient, comprising administering an IL23 antagonist to a patient if the patient is determined or identified to have (i) a higher or increased level of interleukin-22 (IL22) and/or (ii) a higher or increased level of lipocalin 2 (LCN2) in one or more samples taken from the patient compared to a predetermined IL22 and/or LCN2 threshold level, or compared to a IL22 and/or LCN2 level in one or more control samples.
- [00283]** E2. A method of treating a patient having an IL23-mediated disease comprising suspending or not initiating the administration of an IL23 antagonist to a patient if the is determined or identified to have (i) a lower or decreased level of interleukin-22 (IL22) and/or (ii) a lower or decreased level of lipocalin 2 (LCN2) in one or more samples taken from the patient compared to a predetermined IL22 and/or LCN2 threshold level, or compared to a IL22 and/or LCN2 level in one or more control samples.
- [00284]** E3. A method of treating an interleukin-23 (IL23)-mediated disease in a patient, wherein the patient failed, was non-responsive or intolerant to treatment with an anti-TNF agent comprising administering an IL23 antagonist to the patient if the patient is determined or identified to have (i) a higher or increased level of interleukin-22 (IL22) and/or (ii) a higher or increased level of lipocalin 2 (LCN2) in one or more samples taken from the patient compared to a predetermined IL22 and/or LCN2 threshold level, or compared to a IL22 and/or LCN2 level in one or more control samples.
- [00285]** E4. A method of determining whether to treat a patient having an IL23-mediated disease with an IL-23 antagonist, comprising determining to treat the patient if the patient is determined or identified to have (i) a higher or increased level of interleukin-22 (IL22) and/or (ii) a higher or increased level of lipocalin 2 (LCN2) in one or more samples taken from the patient compared to a predetermined IL22 and/or LCN2 threshold level, or compared to a IL22 and/or LCN2 level in one or more control samples.
- [00286]** E5. A method of selecting a patient diagnosed with an IL23-mediated disease as a candidate for treatment with an IL23 antagonist, comprising selecting the patient for treatment if the patient is determined or identified to have (i) a higher or increased level of interleukin-22 (IL22) and/or (ii) a higher or increased level of lipocalin 2 (LCN2) in one or

more samples taken from the patient compared to a predetermined IL22 and/or LCN2 threshold level, or compared to a IL22 and/or LCN2 level in one or more control samples.

[00287] E6. The method according to any one of embodiments E1 to E5, further comprising measuring the level of IL22 and/or LCN2 in one or more of the samples obtained from the patient or instructing a clinical laboratory or healthcare provider to measure the level of IL22 and/or LCN2 in the sample and/or submitting the one or more samples obtained from the patient to a clinical laboratory or healthcare provider to measure the level of IL22 and/or LCN2 in the sample.

[00288] E7. The method according to any one of embodiments E1 to E6, further comprising determining the level of IL22 and/or LCN2 in the one or more samples obtained from the patient.

[00289] E8. The method according to any one of embodiments E1 to E7 further comprising advising a healthcare provider to administer an IL23 antagonist to the patient if the patient is determined or identified to have (i) a higher or increased level of IL22 and/or (ii) a higher or increased level of LCN2 in one or more of the samples compared to a predetermined IL22 and/or LCN2 threshold level, or compared to a IL22 and/or LCN2 level in one or more control samples, or to suspend, not initiate or deny the administration of an IL23 antagonist to the patient if the patient is determined or identified to have (i) a lower or decreased level of IL22 and/or (ii) a lower or decreased level of LCN2 in one or more of the samples compared to a predetermined IL22 and/or LCN2 threshold level, or compared to a IL22 and/or LCN2 level in one or more control samples

[00290] E9. A method of measuring the efficacy or pharmacodynamics of an IL23 antagonist in a patient diagnosed with an IL23-mediated disease, comprising: (a) measuring the level of IL22 and/or LCN2 in a first sample taken from the patient; (b) administering an IL23 antagonist; and (c) measuring the level of IL22 and/or LCN2 in a second sample taken from the patient, wherein a reduction in the level of IL22 and/or LCN2 in the second sample compared to the patient's level IL22 and/or LCN2 in the first sample indicates that the patient is responding to treatment.

[00291] E10. The method according to embodiment E9, wherein the second sample is taken 1, 2, 4, 8, 12, or 28 weeks, or at intervening times, after administering the IL23 antagonist.

- [00292] E11. The method according to any one of embodiments E1 to E10, wherein the IL23 antagonist is an anti-IL23 antibody or antigen-binding fragment thereof.
- [00293] E12. The method of embodiment E11, wherein the anti-IL23 antibody or antigen-binding fragment thereof binds to the p19 subunit of IL23 (SEQ ID NO: 13), to the p40 subunit of IL23 (SEQ ID NO: 14), or both.
- [00294] E13. The method according to any one of embodiments E11 or E12, wherein the anti-IL23 antibody or antigen-binding fragment thereof comprises ustekinumab, briakinumab, guselkumab, BI-655066, tildrakinumab, LY-3074828, or an antigen-binding fragment thereof.
- [00295] E14. The method according to embodiment 11, wherein the anti-IL23 antibody or antigen-binding fragment thereof comprises (i) a variable region (VH) comprising or consisting of SEQ ID NO: 5 and/or a light chain variable region (VL) comprising or consisting of SEQ ID NO: 6, or (ii) a variable region (VH) comprising or consisting of SEQ ID NO: 43 and/or a light chain variable region (VL) comprising or consisting of SEQ ID NO: 44.
- [00296] E15. The method according to embodiment 11, wherein the anti-IL23 antibody or antigen-binding fragment thereof comprises at least one, two, three, four, five or six complementarity determining regions selected from SEQ ID NOS: 31-36 or SEQ ID NOS:45-50.
- [00297] E16. The method according to any one of embodiments E14 or E15, wherein the antibody is administered at a fixed dose.
- [00298] E17. The method according to embodiment E16, wherein the fixed dose is between 10 and 1000 mg/dose.
- [00299] E18. The method according to embodiment E16, wherein the fixed dose is about 210 mg/dose or about 700 mg/dose.
- [00300] E19. The method according to any one of embodiments E1 to E18 wherein the patient has been treated before, during, after, or alternatively to the administration of an IL23 antagonist or anti-IL23 antibody or antigen-binding fragment with one or more additional therapies for the treatment of the IL23-mediated disease or disorder.

- [00301] E20. The method according to any one of embodiments E1 to E19, wherein the one or more samples taken from the patient and/or the one or more control samples are one or more selected from the group consisting of: whole blood, blood serum, plasma, saliva, sputum, bronchoalveolar lavage fluid, cerebrospinal fluid, pleural fluid, pericardial fluid, ascites, synovial fluid, epithelial cells, urine, stool, skin, tissue biopsy, or a combination thereof.
- [00302] E21. The method according to any one of embodiments E1 to E20, wherein the one or more control samples are (i) a sample or samples obtained from normal healthy individuals; (ii) a sample or samples obtained from patients with a non-IL23-mediated disease; or (iii) a combination thereof.
- [00303] E22. The method according to any one of embodiments E1 to E21, wherein the patient's level of IL22 and/or LCN2 is measured in an immunoassay, including an immunoassay described in Example 3.
- [00304] E23. The method according to any one of embodiments E1 to E22, further comprising determining the level of one or more IL23 Pathway Biomarker selected from the group consisting of IL17F, IL17A/F, IL23R, IL12B, IL6, IL21, TNF, CCR6, CCL22, IL1R1, IFN γ , S100A12, DEFB-2, DEFB-4, IL1, SERPINB3, PI3/Elafin, LL37, ROR γ , ROR γ T, IL26, S100A7, DEFB103B, and GM-CSF.
- [00305] E24. The method according to any one any one of embodiments E1 to E23, wherein the predetermined threshold level of IL22 and/or LCN2 is selected from the group consisting of: (a) about the mean level of IL22 and/or LCN2; (b) about the median level of IL22 and/or LCN2; and (c) about the 1st, 2nd, 3rd, 4th, 5th, 6th, 7th, 8th, or 9th decile baseline level of IL22 and/or LCN2 as described in TABLES 4 or 5; and as measured in the serum using an immunoassay from a plurality of (i) normal healthy patients, (ii) patients with a non-IL23-mediated disease, and/or (iii) patients with an IL23-mediated disease.
- [00306] E25. The method according to any one of embodiments E1 to E24, wherein the IL23-mediated disease or disorder is a pulmonary disease, an inflammatory bowel disease, a chronic inflammatory skin disease, an inflammatory disease, an autoimmune disease, a neurodegenerative disease, an infection, or a cancer.

- [00307] E26. The method according to any one of embodiments E1 to E25, wherein the IL23-mediated disease or disorder is selected from the group consisting of: asthma, IPF, COPD, Crohn's disease, ulcerative colitis (UC), celiac disease, atopic dermatitis, allergic contact dermatitis, eczema, psoriasis, alopecia areata, palmoplantar pustulosis, psoriatic arthritis, ankylosing spondylitis, arthritis, rheumatoid arthritis (RA), a rheumatic disorder, ANCA vasculitis, Bechet's disease, autoimmune thyroiditis, type 1 diabetes, multiple sclerosis (MS), Sjogren's syndrome (SS), systemic lupus erythematosus (SLE), Alzheimer's disease, mycobacterial disease, leishmaniasis, gastric cancer, colorectal cancer, esophageal cancer, leukemia, hepatitis B virus (HBV)-related hepatocellular carcinoma, breast cancer, lung cancer, and nasopharyngeal cancer.
- [00308] E27. The method according to embodiment E25, wherein the inflammatory bowel disease is Crohn's disease, UC or Celiac Disease.
- [00309] E28. The method according to embodiment E27, wherein the patient is determined to have a level of CRP ≥ 5 mg/L and/or a level of FCP ≥ 250 μ g/g, a level of FCP ≥ 200 μ g/g, a level of FCP ≥ 150 μ g/g, a level of FCP ≥ 100 μ g/g, or a level of FCP at least about 100 μ g/g to at least about 250 μ g/g in one or more samples taken from the patient.
- [00310] E29. The method according to any one of embodiments E1 to E28, wherein (a) the predetermined IL22 threshold level is at least about 7.9 pg/mL to at least about 31.4 pg/mL as measured using an immunoassay; and/or (b) the predetermined LCN2 threshold level is at least about 143 ng/mL to at least about 261 ng/mL as measured using an immunoassay.
- [00311] E30. The method according to embodiment E29, wherein (a) the predetermined IL22 threshold level is about 15.6 pg/mL as measured using an immunoassay; and/or, (b) the predetermined LCN2 threshold level is about 215 ng/mL as measured using an immunoassay.
- [00312] E31. The method according to any one of embodiments E1 to E28 wherein (a) the predetermined IL22 threshold level is about 7.9 pg/mL, about 11.3 pg/mL, about 12.7 pg/mL, about 15.6 pg/mL, about 19.6 pg/mL, about 23.1 pg/mL, about 31.4 pg/mL or about 46.8 pg/mL in serum as measured using a IL22 immunoassay; and/or (b) the predetermined LCN2 threshold level is about 142.8 ng/mL, about 163.6 ng/mL, about 184.3 ng/mL, about 201.3

ng/mL, about 214.6 ng/mL, about 233.4 ng/mL, about 261.1 ng/mL, about 294.8 ng/mL, or about 326.6 ng/mL in serum as measured using a LCN2 immunoassay.

[00313] E32. The method according to any one of embodiments E27 to E31, wherein administration of the IL23 antagonist or anti-IL23 antibody or antigen-binding fragment thereof results in a Crohn's Disease Activity Index (CDAI) response score reduction of at least 100 points, or reduction of the total CDAI score to below 150 points after first administering the anti-IL23 antibody or antigen-binding fragment thereof.

[00314] E33. The method according to embodiment E32, wherein the CDAI response score reduction of at least 100 points, or reduction of the total CDAI score to below 150 points occurs within 1, 2, 4, 8, 12, 16 or 24 weeks or later after first administering the IL23 antagonist or anti-IL23 antibody or antigen-binding fragment thereof.

[00315] E34. A method of treating an interleukin-23 (IL23)-mediated disease in a patient, comprising administering an IL23 antagonist (including, e.g., an anti-IL23 antibody) to a patient if the patient is determined or identified to have an IL23 pathway with increased or higher activity in one or more samples taken from the patient compared to a predetermined IL23 pathway activity threshold level, or compared to a IL23 pathway activity level in one or more control samples.

[00316] E35. The method according to embodiment E34, further comprising determining the level of one or more IL23 Pathway Biomarkers selected from the group consisting of IL22, LCN2, CCL20, IL17F, IL17A/F, IL23R, IL12B, IL6, IL21, TNF, CCR6, CCL22, IL1R1, IFN γ , S100A12, DEFB-2, DEFB-4, IL1, SERPINB3, PI3/Elafin, LL37, ROR γ , ROR γ T, IL26, S100A7, DEFB103B, and GM-CSF; wherein an increased or higher level of one or more of the IL23 Pathway Biomarkers in one or more samples taken from the patient compared to a predetermined IL23 Pathway Biomarker threshold level, or compared to a IL23 Pathway Biomarker level in one or more control samples indicates an IL23 pathway with increased or higher activity.

LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ADA(s)	anti-drug antibody/ antibodies

Abbreviation or Specialized Term	Definition
AE	adverse event
ANCOVA	analysis of covariance
AS	ankylosing spondylitis
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CRP	C-reactive protein
DNA	deoxyribonucleic acid
GI	Gastrointestinal
IBD	inflammatory bowel disease
IBDQ	inflammatory bowel disease questionnaire
IFN	Interferon
IgG2	immunoglobulin G2
IL	Interleukin
IM	Immunogenicity
IV	Intravenous
LOCF	last observation carried forward
Mab	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MS	multiple sclerosis
NK	natural killer
PD	Pharmacodynamics
PK	pharmacokinetic(s)
PP	per protocol
PROs	Patient Reported Outcomes
PsO	Psoriasis
Q4W	every 4 weeks
RA	rheumatoid arthritis
RNA	ribonucleic acid
SAE	serious adverse event
SC	subcutaneous(ly)
Th	T helper
TNF α	tumor necrosis factor-alpha

Abbreviation or Specialized Term	Definition
UC	ulcerative colitis
w/v	weight per volume

SEQUENCES

SEQ ID NO	Description	Sequence
1	IL22 gene (mRNA)	CGACCAGGTTCTCCTTCCCCAGTCACCAGTTGCTCGAGTTAGAATTGTCT GCAATGGCCGCCCTGCAGAAATCTGTGAGCTCTTTCCTTATGGGGACCC GGCCACCAGCTGCCTCCTTCTCTTGGCCCTCTTGGTACAGGGAGGAGCAG CTGCGCCCATCAGCTCCCACTGCAGGCTTGACAAGTCCAACCTCCAGCAG CCCTATATCACCAACCGCACCTTCATGCTGGCTAAGGAGGCTAGCTTGGC TGATAACAACACAGACGTTCTGCTCATTGGGGAGAACTGTTCCACGGAG TCAGTATGAGTGAGCGCTGCTATCTGATGAAGCAGGTGCTGAACCTCACC CTTGAAGAAGTGCTGTTCCCTCAATCTGATAGGTTCCAGCCTTATATGCA GGAGGTGGTGGCCTTCCCTGGCCAGGCTCAGCAACAGGCTAAGCACATGTC ATATTGAAGGTGATGACCTGCATATCCAGAGGAATGTGCAAAAGCTGAAG GACACAGTGAAAAAGCTTGGAGAGAGTGGAGAGATCAAAGCAATTGGAGA ACTGGATTGCTGTTTATGTCTCTGAGAAATGCCTGCATTTGACCAGAGC AAAGCTGAAAAATGAATAACTAACCCCTTTCCCTGCTAGAAATAACAAT TAGATGCCCCAAAGCGATTTTTTTTAAACCAAAAGGAAGATGGGAAGCCAA ACTCCATCATGATGGGTGGATTCCAAATGAACCCCTGCGTTAGTTACAAA GGAAACCAATGCCACTTTTGTATAAGACCAGAAGGTAGACTTTCTAAG CATAGATATTTATTGATAACATTTTATTGTAAGTGGTGTCTATACACAG AAAACAATTTATTTTTTAAATAATTGTCTTTTCCATAAAAAAGATTACT TTCCATTCCCTTAGGGGAAAAAACCCCTAAATAGCTTCATGTTTCCATAA TCAGTACTTTATATTTATAAATGTATTTATTATTATTATAAGACTGCATT TTATTTATATCATTTTATTAATATGGATTTATTATAGAAACATCATTCG ATATTGCTACTTGAGTGTAAGGCTAATATTGATATTATGACAATAATTA TAGAGCTATAACATGTTTATTATTGACCTCAATAAACACTTGGATATCC
2	IL22 protein	MAALQKSVSSFLMGTLATSLLLLALLVQGGAAAPISSHCRLDKSNFQQP YITNRTFMLAKEASLADNNTDVRLLIGEKLFGVSMSERCYLMKQVLNFTL EEVLFPSDRFPYMQEVVPFLARLSNRLSTCHIEGDDLHIQRNVQKLKD TVKKLGESGEIKAIGELDLLFMSLRNACI
3	LCN2 gene (mRNA)	ACTCGCCACCTCCTCTTCCACCCCTGCCAGGCCAGCAGCCACCACAGCG CCTGCTTCCTCGGCCCTGAAATCATGCCCTAGGTCTCCTGTGGCTGGGC CTAGCCCTGTTGGGGGCTCTGCATGCCAGGCCAGGACTCCACCTCAGA CCTGATCCCAGCCCCACCTCTGAGCAAGTCCCTCTGCAGCAGAACTTC AGGACAACCAATTCCAGGGGAAGTGGTATGTGGTAGGCCTGGCAGGGAAT GCAATTCTCAGAGAAGACAAAGACCCGCAAAAGATGTATGCCACCATCTA TGAGCTGAAAGAAGACAAGAGCTACAATGTCACCTCCGTCCTGTTTAGGA AAAAGAAGTGTGACTACTGGATCAGGACTTTTGTTCAGGTTGCCAGCCC GGCGAGTTCACGCTGGGCAACATTAAGAGTTACCTTGATTAACGAGTTA CCTCGTCCGAGTGGTGAGCACCAACTACAACCAGCATGCTATGGTGTCTCT TCAAGAAAGTTTCTCAAAACAGGGAGTACTTCAAGATCACCTCTACGGG AGAACCAAGGAGCTGACTTCGGAATAAAGGAGAACTTCATCCGCTTCTC CAAATCTCTGGGCCTCCCTGAAAACACATCGTCTTCCCTGTCCCAATCG ACCAGTGTATCGACGGCTGAGTGCACAGGTGCCGCCAGCTGCCGCACCAG CCCGAACACCATGAGGGAGCTGGGAGACCTCCCCACAGTGCCACCCAT GCAGCTGCTCCCCAGGCCACCCGCTGATGGAGCCCCACCTTGTCTGCTA

SEQ ID NO	Description	Sequence
		AATAAACATGTGCCCTCAGGCCAAAAAAAAAAAAAAAAAAAA
4	LCN2 protein	MPLGLLWLGLALLGALHAQAQDSTSDLPAPPLSKVPLQQNFQDNQFQ GK WYVVGLAGNAILREDKDPQKMYATIIYELKEDKSYNVTSVLFRKKKCDYWI RTFVPGCQPGFETLGNIKSYPLTSLYLRVVSTNYNQHAMVFFKKVSQNR EYFKITLYGRTELKELTSELKENFIRFSKSLGLPENHIVFPVPIDQCIDG
5	MEDI2070 VH	QVQLVESGGGVVQPGRSRLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAV IWYDGSNEYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARDR GYTSSWYPDAFDIWQGQTMVTVSS
6	MEDI2070 VL	QSVLTQPPSVSGAPGQRVTISCTGSSSNTGAGYDVHWYQQVPGTAPKLLI YGSNRPSPGVPDRFSGSKSGTSASLAITGLQAEDEADYYCQSYDSSLGSGW VFGGGTRLTVL
7	CRP gene (mRNA)	AAGGCAAGAGATCTAGGACTTCTAGCCCCTGAACCTTCAGCCGAATACAT CTTTTCCAAAGGAGTGAATTCAGGCCCTTGATCACTGGCAGCAGGACGT GACCATGGAGAAGCTGTTGTGTTTCTTGGTCTTGACCAGCCTCTCTCATG CTTTTGGCCAGACAGACATGTCGAGGAAGGCTTTTGTGTTTCCAAAGAG TCGGATACTTCCTATGTATCCCTCAAAGCACCGTTAACGAAGCCTCTCAA AGCCTTCACTGTGTGCCTCCACTTCTACACGGAACGTCTCTCGACCCGTG GGTACAGTATTTTCTCGTATGCCACCAAGAGACAAGACAATGAGATTCTC ATATTTTGGTCTAAGGATATAGGATACAGTTTTACAGTGGGTGGGTCTGA AATATTATTCGAGGTTCCTGAAGTCACAGTAGCTCCAGTACACATTTGTA CAAGCTGGGAGTCCGCCTCAGGGATCGTGGAGTTCTGGGTAGATGGGAAG CCCAGGGTGAGGAAGAGTCTGAAGAAGGGATACACTGTGGGGGCAGAAGC AAGCATCATCTTGGGGCAGGAGCAGGATTCCCTTCGGTGGGAACCTTTGAAG GAAGCCAGTCCCTGGTGGGAGACATTGGAAATGTGAACATGTGGGACTTT GTGCTGTCCACAGATGAGATTAACACCATCTATCTTGGCGGGCCCTTCAG TCCTAATGTCTGAACCTGGCGGGCACTGAAGTATGAAGTGCAAGGCGAAG TGTTTACCAAACCCAGCTGTGGCCCTGAGGCCAGCTGTGGGTCTCTGAA GGTACCTCCCGGTTTTTTTACACCGCATGGGCCCCACGTCTCTGTCTCTGG TACCTCCCGCTTTTTTACACTGCATGGTTCCACAGTCTCTGTCTCTGGGC CTTTGTTCCCTATATGCATTGCAGGCCTGCTCCACCCTCCTCAGCGCCT GAGAATGGAGGTAAAGTGTCTGGTCTGGGAGCTCGTTAACTATGCTGGGA AACGGTCCAAAAGAATCAGAATTTGAGGTGTTTTGTTTTTCATTTTTATTT CAAGTTGGACAGATCTTGGAGATAATTTCTTACCTCACATAGATGAGAAA ACTAACACCCAGAAAGGAGAAATGATGTTATAAAAAAATCATAAGGCAAG AGCTGAGAAGGAAGCGCTGATCTTCTATTTAATTTCCCAACCATGACCCC CAGAAAGCAGGAGGGCATTGCCACATTACAGGGCTCTTCAGTCTCAGA ATCAGGACACTGGCCAGGTGTCTGGTTTGGGTCCAGAGTGCTCATCATCA TGTCATAGAAGTCTGGGCCCAGGTCTCCTGAAATGGGAAGCCCAGCAAT ACCACGCAGTCCCTCCACTTTCTCAAAGCACACTGGAAAGGCCATTAGAA TTGCCCCAGCAGAGCAGATCTGCTTTTTTTCCAGAGCAAAATGAAGCACT AGGTATAAATATGTTGTTACTGCCAAGAACCTTAAATGACTGGTTTTTGT TGCTTGCACTGCTTTCTTAATTTTATGGCTCTTCTGGGAAACTCCTCCCC TTTTCCACACGAACCTTGTGGGGCTGTGAATTTCTTCTCATCCCCGCAT TCCCAATATACCCAGGCCACAAGAGTGGACGTGAACACAGGGTGTCTCTG TCAGAGGAGCCCATCTCCCATCTCCCCAGCTCCCTATCTGGAGGATAGTT GGATAGTTACGTGTTCTTAGCAGGACCAACTACAGTCTTCCCAAGGATTG AGTTATGGACTTTGGGAGTGAGACATCTTCTTGCTGCTGGATTTCCAAGC TGAGAGGACGTGAACCTGGGACCACAGTAGCCATCTTGTGTTGCCACATG GAGAGAGACTGTGAGGACAGAAGCCAACTGGAAGTGAGGAGGCCAAGGG ATTGACAAACAACAGAGCCTTGACCACGTGGAGTCTCTGAATCAGCCTTG TCTGGAACCAAGATCTACACCTGGACTGCCAGGTCTATAAGCCAATAAAG CCCCTGTTTACTTGAAAAAAAAA
8	CRP protein	MEKLLCFVLVLSLSHAFGQTDMSRKAFVFPKESDTSYVSLKAPLTKPLKA

SEQ ID NO	Description	Sequence
		FTVCLHFYTELSSTRGYSIFSATKRQDNEILIFWSKDIGYSFTVGGSEI LFEVPEVTAPVHICTSWESASGIVEFWVDGKPRVRKSLKKGYTVGAES IILGQEQDSFGNFEGSQSLVGDIGNVNMWDFVLSPEINTIYLGPFSP NVLNWRALKYEVQGEVFTKPQLWP
9	Calprotectin S100A8 subunit (mRNA)	ATGTCTCTTGTGCTGCTCTTTTCAAGAAGACCTGGTGGGGCAAGTCCGTGG GCATCATGTTGACCGAGCTGGAGAAAGCCTTGAACCTATCATCGACGTC TACCACAAGTACTCCCTGATAAAGGGGAATTTCCATGCCGTCTACAGGGA TGACCTGAAGAAATTGCTAGAGACCGAGTGTCTCAGTATATCAGGAAAA AGGGTGCAGACGCTCTGGTTCAAAGAGTTGGATATCAACACTGATGGTGCA GTAACTTCCAGGAGTTCTCTATTCTGGTGATAAAGATGGGCGTGGCAGC CCACAAAAAAGCCATGAAGAAAGCCACAAAGAGTAGCTGAGTTACTGGG CCCAGAGGCTGGGCCCCCTGGACATGTACCTGCAGAATAATAAAGTCATCA ATACCTCAAAAAAAAAAAAAAAAAAAAAA
10	Calprotectin S100A8 subunit	MLTELEKALNSIIDVYHKYSLIKGNFHAVYRDDLLKLLLETECPQYIRKKG ADVWFKELDINTDGAVNFQEFLLILVIKMGVAAHKSHEESHKE
11	Calprotectin S100A9 subunit (mRNA)	AAACACTCTGTGTGGCTCCTCGGCTTTGACAGAGTGCAAGACGATGACTT GCAAAATGTCGAGCTGGAACGCAACATAGAGACCATCATCAACACCTTC CACCAATACTCTGTGAAGCTGGGGCAGCCAGACACCTGAACCAGGGGGA ATTCAAAGAGCTGGTGCAGAAAAGATCTGCAAAATTTTCTCAAGAAGGAGA ATAAGAATGAAAAGGTGATAGAACACATCATGGAGGACCTGGACACAAAT GCAGACAAGCAGCTGAGCTTCGAGGAGTTCATCATGCTGATGGCGAGGCT AACCTGGGCCTCCACGAGAAGATGCACGAGGGTGACGAGGGCCCTGGCC ACCACCATAAGCCAGGCTCGGGGAGGGCACCCCTAAGACCACAGTGGC CAAGATCACAGTGGCCACGGCCACGGCCACAGTCATGGTGGCCACGGCCA CAGCCACTAATCAGGAGGCCAGGCCACCCTGCCTCTACCCAACCAGGGCC CCGGGGCCTGTTATGTCAAACCTGTCTTGGCTGTGGGGCTAGGGGCTGGGG CCAAATAAAGTCTCTTCTCCAAGTCAAAAAAAAAA
12	Calprotectin S100A9 subunit	MTCKMSQLERNIETIINTFHQYSVKLGHPDTLNQGEFKELVRKDLQNFLK KENKNEKVIEHIMEDLDTNADKQLSFEFIMLMARLTWASHEKMHEGDEG PGHHKPGLEGTEP
13	IL-23 alpha subunit (p19)	MLGSRVMLLLLLPWTAAQGRAVPGSSPAWTQCQQLSQKLCTLAWSAHLVGHMDLREEG DEETTNDVPHIQCGDGDPPQGLRDNSQFCLQRHQGLIFYEKLKLGSDIFTGEPSSLPDSP VGQLHASLLGLSQLLQPEGHHWETQQIPSLSPSPQWQRLRLRFKILRSLQAFVAVAAARVF AHGAATLSP
14	IL-12 beta subunit (p40)	MCHQQLVISWFSVLFLASPLVAIWELKKDVYVVELDWYDPDAPGEMVVLTCDTPEEDGITW TLDQSSEVLGSGKTLTIQVKEFGDAGQYTCHKGGEVLSHSLLLHKKEDGIWSTDILKDQ KEPKNKTFLRCEAKNYSGRFTCWWLTITISTDLTFSVKSSRGSSDPQGVTCGAATLSAERV RGDNKEYEYSVEQEDSACPAAEESLPIEVMVDAVHKLKYENYTSSFFIRDIIKPDPPKN LQLKPLKNSRQVEVSWEYPTWSTPHSYFSLTFVQVQVQKSKREKKDRVFTDKTSATVIC RKNASISVRAQDRYSSSWSEWASVPCS
15	MEDI2070 HC	QVQLVESGGGVVQPGSRSLRLSAAAGFTSSYGMHWVRQAPGKLEWVAVIWDGSNEYAD SVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARDRGYTSSWYDAFDIWGQGMVTVSS ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVTVPSNFGTQTYTCNVDHKPSNTKVDKTKVERKCCVECPPCAPPVAGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVSVLT VVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTTPMLDSGGSFFLYSKLTVDKSRWQQGNVSCSVMHEA LHNHYTQKSLSLSPGK
16	MEDI2070 LC	QSVLTQPPSVSGAPGQRTVISTGSSSNTGAGYDVHWYQQVPGTAPKLLIYGSNGRPSGVPD RFSGSKSGTSASLAITGLQAEDADYYCQSYDSSLSGWVFGGGTRLTVLQGPKAAPSVTLFPP PSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNKNYAASSYLSLT PEQWKSRSYSCQVTHEGSTVEKTVAPTECS

SEQ ID NO	Description	Sequence
17	Ustekinumab HC	EVQLVQSGAEVKKPGESLKISCKGSGYSFTTYWLGWVRQMPGKGLDWIGIMSPVDSDIRY SPSFQGGVTMSVDKSIITAYLQWNSLKASDTAMYYCARRRPGQGYDFWGGQTLVTVSSS STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVKVEPKSCDKTHTCPPCPAPELLGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMEALHNHYTQKSLSLSPGK
18	Ustekinumab LC	DIQMTQSPSSLSASVGDRVTITCRASQGISWLAHYQQKPEKAPKSLIYAASSLQSGVPS RFGSGSGTDFTLTISLQPEDFATYYCQQYNIYPYTFGGQTKLEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
19	Vedolizumab HC	QVQLVQSGAEVKKPGASVKVSCKSGYFTTSYWMHWVRQAPGQRLEWIGEIDPSESNTNY NQKFKGRVTLTVDISASTAYMELSSLRSEDATVYYCARGGYDGWDYAIDYWGQTLVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVKVEPKSCDKTHTCPPCPAPELAG APSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRD ELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMEALHNHYTQKSLSLSPGK
20	Vedolizumab LC	DVVMTQSPSLPVPTEGEPASISCRSSQSLAKSYGNTYLSWYLQKPGQSPQLLIYGISNRF SGVPDRFSGSGSGTDFTLKISRVEAEDGVVYCLQGTQHPYTFGGQTKVEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
21	Adalimumab HC	EVQLVESGGGLVQPGGSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSAITWNSGHIDY ADSVKGRFTISRDNKNSLYLQMNSLRAEDATVYYCAKVSYLSTASSLDYWGQTLVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVKVEPKSCDKTHTCPPCPAPELLG GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRD ELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMEALHNHYTQKSLSLSPGK
22	Adalimumab LC	DIQMTQSPSSLSASVGDRVTITCRASQIRNYLAHYQQKPGKAPKLLIYAASLTQSGVPS RFGSGSGTDFTLTISLQPEDVATYYCQRYNRAPYTFGGQTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
23	Certolizumab HC	EVQLVESGGGLVQPGGSLRLSCAASGYVFTDYGMNWVRQAPGKGLEWMGWINTYIGEPY ADSVKGRFTFSLDTSKSTAYLQMNSLRAEDATVYYCARGYRSYAMDYWGQTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVKVEPKSCDKTHTCAA
24	Certolizumab LC	DIQMTQSPSSLSASVGDRVTITCKASQNVGTNVAWYQQKPGKAPKALIYSASFLYSGVPY RFGSGSGTDFTLTISLQPEDFATYYCQQYNIYPLTFGGQTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
25	Briakinumab HC	QVQLVESGGGVVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAFIRYDGSNKYY ADSVKGRFTISRDNKNTLYLQMNSLRAEDATVYYCKTHGSHDNWGQGTMTVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVKVEPKSCDKTHTCPPCPAPELLGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
26	Briakinumab	QSVLTQPPSVSGAPGQRVTISCSGSRNIGSNTVKWYQQLPGTAPKLLIYYNDQRP SGVP

SEQ ID NO	Description	Sequence
	LC	DRFSGSKSGTSASLAITGLQAEDEADYYCQSYDRYTHPALLFGTGKVTVLGQPKAAPSV TLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNKYAAS SYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
27	Tildrakizuma b HC	QVQLVQSGAEVKKPGASVKVSKASGYIFITYWMTWVRQAPGGLEWMGQIFPASGSADY NEKFEGRVMTTDTSTSTAYMELRSLRSDDTAVYYCARGGGGFAYWGQGTTLTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVF LFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMEALHNHYTQKSLSLSPGK
28	Tildrakizuma b LC	DIQMTQSPSSLSASVGDRVTITCRTSENIYSYLAWYQQKPGKAPKLLIYNAKTLAEGVPS RFSGSGSGTDFTLTISLQPEDFATYYCQHHYGIPFTFGQGTKEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSLSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
29	Etolizumab HC	EVQLVESGGGLVQPGGSLRLSCAASGFFITNNYWGVRQAPGKLEWVGYSISYSGSTSYN PSLKSRTTISRDTSKNTFYLMNSLRAEDTAVYYCARTGSSGYFDFWGQGTTLTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSV FLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMEALHNHYTQKSLSLSPG
30	Etolizumab LC	DIQMTQSPSSLSASVGDRVTITCRASESVDLLHWYQQKPGKAPKLLIKYASQSIGVPS RFSGSGSGTDFTLTISLQPEDFATYYCQQGNSLPNTFGQGTKEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSLSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
31	MEDI2070 VH-CDR1	SYGMH
32	MEDI2070 VH-CDR2	VIWYDGSNEYADSVKG
33	MEDI207- VH-CDR3	DRGYTSSWYPDAFDI
34	MEDI2070 VL-CDR1	TGSSSNTGAGYDVH
35	MEDI2070 VL-CDR2	GSGNRPS
36	MEDI2070 VL-CDR3	QSYDSSLGQV
37	LCN2 variant	DQCIDG
38	LCN2 variant	GNGQSG
39	CRP variant	YSIFSATKRQDNEIL
40	CRP variant	TVFSRMPPRDKTMRF
41	S100A8 variant	VAAHKKSHESHKE
42	S100A8 variant	WQPTKKAMKKATKSS
43	Antibody B VH	QVQLQESGPGLVKPSQTLSTCTVSGGSISGGYYWSWIRQHPGKLEWIGHIHYSGNTYYN PSLKSRTTISRDTSKNQFSLKLSSVTAADTAVYYCAKNRGFYGMVWGQGTITVTVSS
44	Antibody B	DIQMTQSPSSVSASVGDRVTITCRASQVISSWLAWYQQKPGKAPSLLIYAASSLQSGVPSRF

SEQ ID NO	Description	Sequence
	VL	SGSVSGTDFTLTISSLQPEDFATYYCQQANSFPFTFGPGTKVDFK
45	Antibody B VH-CDR1	SGGYYS
46	Antibody B VH-CDR2	HIHYSGNTYYNPSLKS
47	Antibody B VH-CDR3	NRGFYYGMDV
48	Antibody B VL-CDR1	RASQVISSWLA
49	Antibody B VL-CDR2	AASSLQS
50	Antibody B VL-CDR3	QQANSFPFT

[00317] All patents and publications referred to herein are expressly incorporated by reference in their entireties.

[00318] Aspects of the present disclosure can be further defined by reference to the following non-limiting examples, which describe in detail preparation of certain antibodies of the present disclosure and methods for using antibodies of the present disclosure. It will be apparent to those skilled in the art that many modifications, both to materials and methods, can be practiced without departing from the scope of the present disclosure.

[00319] It is to be appreciated that the Detailed Description section, and not the Summary and Abstract sections, is intended to be used to interpret the claims. The Summary and Abstract sections may set forth one or more but not all exemplary aspects of the present invention as contemplated by the inventor(s), and thus, are not intended to limit the present invention and the appended claims in any way.

[00320] The present invention has been described above with the aid of functional building blocks illustrating the implementation of specified functions and relationships thereof. The boundaries of these functional building blocks have been arbitrarily defined herein for the convenience of the description. Alternate boundaries can be defined so long as the specified functions and relationships thereof are appropriately performed.

EXAMPLES

[00321] The invention will be more fully understood by reference to the following examples which detail exemplary aspects of the invention.

Example 1

Phase 2a Clinical Study Protocol

[00322] A Phase 2a study was conducted to evaluate the efficacy and safety of multiple IV doses of MEDI2070 (700 mg) or placebo administered on Week 0 (Day 1) and Week 4 (Day 29) during an initial 12-week treatment period in subjects with moderate to severe CD who have failed or are intolerant to anti-TNF α therapy. The following clinical trial protocol was carried out in human patients. Results of the clinical trial are presented in Example 2.

I. Clinical Study Summary

[00323] The Phase 2a study evaluated the efficacy and safety of multiple IV doses of MEDI2070 (700 mg) or placebo administered on Week 0 (Day 1) and Week 4 (Day 29) during an initial 12-week treatment period in subjects with moderate to severe CD who failed or are intolerant to anti-TNF α therapy. A 100-week, open-label, treatment period was included to allow evaluation of the long-term safety of MEDI2070 (administered at 210 mg SC Q4W) and to provide information on PK and efficacy data.

[00324] The primary objective of this study was to evaluate the efficacy of MEDI2070 versus placebo to induce a clinical effect (defined as at least a 100-point reduction in CDAI from baseline) or remission (defined as CDAI < 150) at Week 8 in subjects with moderate to severe CD.

[00325] Secondary objectives of this study included evaluating: the efficacy of MEDI2070 versus placebo in achieving CDAI remission at Week 8; the effect of MEDI2070 versus placebo in achieving at least a CDAI 100-point reduction from baseline at Week 8; the effect of MEDI2070 versus placebo in achieving at least a CDAI 70-point reduction from baseline at Week 8; the effect of MEDI2070 versus placebo in achieving CDAI remission or at least a CDAI 100-point reduction from baseline at Week 12; the effect of MEDI2070 versus placebo on the change from baseline in CDAI at Week 8; the safety and tolerability of MEDI2070; and the PK and immunogenicity (IM) of MEDI2070.

[00326] Exploratory objectives of this study included evaluating: the effect of MEDI2070 on other measures of clinical effect including but not limited to CDAI response, change from baseline in CDAI at other timepoints, and sustained CDAI response; the effect of treatment on inflammatory markers in blood and stool; the predictive value of blood or fecal biomarkers with respect to subject response to MEDI2070; and the effect of MEDI2070 on Patient Reported Outcomes (PROs).

II. Study Design Overview

- [00327] This was a two-part Phase 2a study comprising a 12-week, double-blind, placebo-controlled, treatment period followed by a 100-week, open-label, treatment period to evaluate the short-term efficacy, and the short- and long-term safety of MEDI2070 in subjects with moderate to severe, active CD who failed or are intolerant to anti-TNF α therapy as determined by the investigator. Subjects were stratified based on the number of prior anti-TNF α agents that they have failed (1 vs > 1). Subjects at various centers worldwide were randomized in a 1:1 ratio to initially receive a fixed IV dose of MEDI2070 (700 mg) or placebo on Week 0 (Day 1) and Week 4 (Day 29) during the 12-week, double-blind, placebo-controlled, treatment period. At the completion of the double-blind, placebo-controlled, treatment period (Week 12), subjects had the option to enter a 100-week, open-label, treatment period where they received open-label MEDI2070 (210 mg SC) Q4W (Week 12 through Week 112) as described in FIG. 1.
- [00328] MEDI2070 or placebo was administered as an IV infusion over a period of at least 60 minutes via an infusion pump on Week 0 (Day 1) and Week 4 (Day 29). Subjects who completed the 12-week, double-blind, placebo-controlled, treatment period and entered the 100-week, open-label, treatment period received MEDI2070 at a fixed dose of 210 mg SC injection Q4W for 26 doses (through Week 112). The primary analysis of the study was conducted after the last subject in the study completed the 12-week, double-blind, placebo-controlled, treatment period or was withdrawn from the study prior to completing the 12-week, double-blind, placebo-controlled, treatment period.
- [00329] The doses of MEDI2070 in this study were 700 mg IV Q4W in the 12-week, double-blind, placebo-controlled, treatment period (Weeks 0 and 4) and 210 mg SC Q4W in the 100-week, open-label, treatment period (Week 12 to Week 112).
- [00330] Pharmacokinetic/PD modeling of MEDI2070 predicted a greater than 99% mean suppression of plasma IL23 throughout the duration of the study for both the 700 mg IV and 210 mg SC dosing regimens. Furthermore, (potency-corrected) serum concentrations of MEDI2070 at these dosing regimens were predicted to be higher than those of the anti-IL12/23p40 antibody ustekinumab shown to be efficacious in CD (Sandborn et al. Gastroenterol. 135:1130-41 (2008)). Administration of 700 mg IV was predicted to rapidly achieve steady-state target suppression.

[00331] Previous clinical data (Sandborn et al. *Gastroenterol.* 135:1130-41 (2008)) indicate that changes from placebo in the response parameters after administration of IV ustekinumab maximized between 6-8 weeks after start of ustekinumab administration; therefore, the proposed placebo-controlled, double-blind period of 12 weeks is sufficient to characterize the effect of MEDI2070 in this patient population. Regulatory guidance recommends assessing the primary endpoint for induction of effect between 4-8 weeks (or after 2 cycles of dosing), thus the assessment of the primary endpoint at Week 8 is appropriate. In addition, Week 12 was assessed to observe the potential extended time course of effect for MEDI2070.

[00332] All subjects received investigational product (700 mg MEDI2070 or placebo) by IV infusion over a minimum period of 60 minutes during the 12-week, double-blind, placebo-controlled, treatment period. MEDI2070 (700 mg) or placebo was delivered in 5.0% w/v dextrose in a volume of 100 mL over a minimum of 60 minutes using an infusion pump. Before and after each IV infusion, the IV access was flushed with 5% w/v dextrose.

[00333] MEDI2070 was administered by subcutaneous (SC) injection during the 100-week, open-label, treatment period. Each SC dose was administered to the subject's anterior abdominal wall by an experienced and qualified staff member. Each SC injection was no more than 1.0 mL in volume (i.e., 3×1.0 mL injections for the 210 mg SC dose). As the MEDI2070 dosage volume exceeds 1.0 mL, the dose was equally divided in 3 syringes and administered as multiple SC injections on alternating (left or right) sites on the subject's anterior abdominal wall with no more than approximately 30 seconds of time between each injection and at a distance of at least 2 cm apart.

III. Disease Evaluation and Methods

[00334] CDAI: The CDAI is the oldest and most widely used of several multi-item instruments that have been developed and is validated for use in clinical studies to measure disease activity in CD (Best et al. *Gastroenterology* 70:439-44 (1976); Sands et al. *N Engl J Med.* 350(9):876-85 (2004)). The CDAI measures the severity of active disease using symptom scores that are monitored over the previous week and includes patient-reported symptoms, physician-assessed signs, and laboratory markers. The CDAI score is calculated by summing weighted scores for subjective items (number of liquid or very soft stools, abdominal pain and general well-being) recorded by a diary during a 1-week period, and objective items (associated symptoms, taking antidiarrheal such as loperamide/opiates,

abdominal mass, hematocrit, daily morning temperature, and body weight). The CDAI scores range from 0 to 600, with higher scores indicating greater disease activity. Subjects with scores of < 150, 150 to 219, and 220 to 450 represent remission, mild disease, and moderate to severe disease, respectively; whereas subjects with scores of > 450 have very severe disease (Buxton et al. Value Health. 10:214-20 (2007)). The CDAI was calculated at the site in order to determine the eligibility for the study. For statistical analysis, CDAI for all visits was also calculated.

[00335] Patient Reported Outcomes: The study assessed patient reported outcomes (PROs) using the IBDQ. The IBDQ was completed by subjects using a paper questionnaire at study visits, scheduled at Weeks 0, 4, 8, and 12 and was administered before any other assessments.

[00336] Inflammatory Bowel Disease Questionnaire (IBDQ): The IBDQ is a validated, disease-specific PRO instrument that measures health-related quality of life in patients with IBD (Guyatt et al. Gastroenterology. 96:804-10 (1989)). The IBDQ covers the following dimensions: bowel symptoms (10 items), systemic symptoms (5 items), emotional function (12 items), and social function (5 items). Items are scored on a 7-point Likert scale, yielding a global score in the range 32 to 224 (with higher scores indicating better quality of life). The IBDQ has been frequently used in drug approval applications to assess treatment efficacy in IBD. The IBDQ was designed to be self-administered and completed in 5 minutes.

IV. Endpoints

[00337] The primary endpoint of the study was CDAI response at Week 8, defined by either a CDAI score of < 150 or a CDAI reduction from baseline of at least 100 points. Baseline was defined as the latest nonmissing observation prior to first administration of the investigational product.

[00338] Missing data was imputed by nonresponder imputation approach; i.e., any subject with missing information on primary endpoint was assumed as nonresponder. In addition, subjects with a clinically meaningful increase in steroid use were assumed to be a nonresponder for the primary analysis perspective.

[00339] For the primary endpoint, comparisons between treatment arms were based on the mITT population and were performed using a logistic regression model with treatment and stratification factor as covariate. The stratification factor for this study was defined by the

number of prior anti-TNF α agents a subject had received (1 vs > 1). The significance of treatment effect was tested using the two-sided test at $\alpha = 10\%$.

[00340] The following sensitivity analyses were performed: (1) A sensitivity analysis was performed by adjusting for baseline CDAI score and/or other baseline covariates by extending the model planned above for subjects in mITT population. (2) A mixed effect longitudinal logistic regression model was implemented on the observed responses. This logistic random-effect model includes a random intercept to account for the variability between subjects. Fixed categorical effects include stratification factor, treatment, visit, and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline score. (3) A sensitivity analysis was performed by adjusting for baseline CDAI score and/or other baseline covariates by extending the model planned above for subjects in the PP Population.

[00341] Secondary Endpoints included:

- 1) CDAI remission at Week 8, as defined by a CDAI score of < 150;
- 2) A reduction of at least 100 points from baseline in CDAI at Week 8;
- 3) A reduction of at least 70 points from baseline in CDAI at Week 8;
- 4) CDAI response (either remission defined by CDAI < 150 or a CDAI reduction from baseline of at least 100 points from baseline) at Week 12. Secondary endpoints 1, 2, 3, and 4 were analyzed in a similar way to the primary endpoint. In addition, a sensitivity analysis was performed by carrying forward the last response on or before the Week 8 visit to Week 12 for subjects who had increased steroid (defined as 5 mg/day prednisolone, or equivalent, or 3 mg/day budesonide).
- 5) Change from baseline CDAI at Week 8. Secondary endpoint 5 was analyzed by using the inverse probability weighting generalized estimating equations method adjusting for prior anti-TNF α use. Also a sensitivity analysis was performed using an ANCOVA model after missing data was imputed using the LOCF approach through the end of the double-blind, placebo-controlled, treatment period adjusting for prior anti-TNF α use.
- 6) To evaluate the safety and tolerability of MEDI2070, the safety and tolerability endpoints included AEs including SAEs, significant changes in laboratory values and vital signs. All safety-related endpoints for the 12-week, double-blind, placebo-controlled, treatment period were reported based on safety population using the actual treatment received. Subjects randomized to placebo with at least one dose of MEDI2070 were included

in the active arm; also the subjects randomized to the MEDI2070 arm without any active dose were included in the placebo arm. The Medical Dictionary for Regulatory Activities (MedDRA) was used to code all AEs. Treatment-emergent AEs were defined as any AE with onset on or after the administration of the first dose of investigational product up to and including 36 weeks post-last dose.

7) To evaluate the PK and immunogenicity (IM) of Multiple Doses of MEDI2070, descriptive statistics of serum MEDI2070 concentration data were provided by visit. Individual and mean serum concentration-time profiles of MEDI2070 were generated. For PK data analysis, time zero was defined as the beginning of infusion. The presence of anti-drug antibodies (ADAs) to MEDI2070 in serum was also assessed.

Example 2

Phase 2a Clinical Study Results

I. Study design and patients

[00342] The phase 2a study (clinicaltrials.gov identifier: NCT01714726) described in Example 1 included a 12-week, double-blind, placebo-controlled treatment period followed by a 100-week open-label treatment period to evaluate short-term efficacy and short- and long-term safety of MEDI2070 in patients with active moderate to severe Crohn's disease who failed prior anti-TNF- α therapy. Conducted at 60 centers worldwide, the study included adults aged 18 to 65 years diagnosed with ileal, ileo-colonic, or colonic Crohn's disease for at least 6 months.

[00343] Patients had to have moderate to severe active Crohn's disease (defined as a Crohn's Disease Activity Index [CDAI] score of 220–450), with evidence of active inflammation (baseline C-reactive protein [CRP] ≥ 5 mg/L, fecal calprotectin [FCP] ≥ 250 μ g/g, or endoscopic evidence of inflammation [photographic documentation of at least 3 nonanastomotic ulcerations, each >0.5 cm in diameter, or 10 aphthous ulcerations involving at least 10 cm of contiguous intestine] within 12 weeks before screening). Patients must have received at least one anti-TNF- α therapy at approved doses for Crohn's disease, with primary nonresponse (signs and symptoms of active disease, despite at least 1 induction regimen, including at least 2 doses of anti-TNF- α therapy at least 2 weeks apart) or secondary nonresponse (recurrence of symptoms of persistently active disease during

maintenance anti-TNF- α therapy following initial clinical benefit) or intolerance (including but not limited to infusion-related reaction, demyelination, congestive heart failure, or infection). Exclusion criteria included having an allogeneic bone marrow transplant or cell-based transplantation; short-bowel syndrome; obstructive stricture within 3 months of study; bowel surgery within 12 weeks of study; ileostomy or colostomy; a clinically significant concomitant disease; or prior treatment with a biologic agent targeting IL12 or IL23.

[00344] Washout of other prior therapies was required, including infliximab for 8 weeks before study, adalimumab or certolizumab for 10 weeks, natalizumab for 12 weeks; cyclosporine, mycophenolate mofetil, sirolimus, thalidomide, or tacrolimus for 4 weeks; intravenous or intramuscular corticosteroids for 2 weeks; or topical mesalamine or rectal corticosteroids for 2 weeks. Concomitant use of 5-aminosalicylates and glucocorticosteroids was permitted if doses were stable for at least 2 weeks before randomization and remained stable through week 8. Similarly, concomitant use of immunomodulators, *e.g.*, azathioprine, was permitted if the dose remained stable from 8 weeks before randomization through week 8. Use of oral antibiotics for Crohn's disease, probiotics, and antidiarrheals was allowed.

[00345] All patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and each site's local institutional review board approved the protocol.

II. Treatment

[00346] For the double-blind period, an interactive voice or web-based response system was used for randomization to treatment arms, assigning unique randomization codes to each patient. Randomization was stratified based on the number of prior failed anti-TNF- α agents (1 vs >1). Using blinded randomization with concealed allocation based on a permutation block algorithm, patients were randomized 1:1 within each stratum to receive MEDI2070 700 mg or placebo intravenously over 60 minutes at week 0 (day 1) and week 4 (day 29). Patients, investigators, and the sponsor were blinded to treatment until the last patient reached week 12, when the primary analysis was conducted. During the open-label period (weeks 12 through 112), all patients received MEDI2070 210 mg subcutaneously every 4 weeks (26 doses over 100 weeks).

III. Study Assessments

[00347] The primary outcome measure was the proportion of patients achieving clinical effect, defined as at least a 100-point CDAI score reduction from baseline or CDAI score less than 150 at week 8. Secondary measures included the proportion of patients achieving CDAI remission (defined as CDAI score <150) at week 8, at least a 100-point CDAI score reduction (CR100) from baseline at week 8, at least a 70-point CDAI score reduction (CR70) from baseline at week 8, clinical effect at week 12, CDAI remission at week 12, and the safety and tolerability of MEDI2070, including adverse events, serious adverse events, and significant changes in laboratory values and vital signs. Serum MEDI2070 concentrations and the presence of ADAs were evaluated at baseline, week 8, week 24, and end of study.

[00348] Exploratory outcome measures included inflammatory markers in the blood and stool (CRP and FCP), responses of other biomarkers and their predictive value for clinical effects, sustained clinical effect between weeks 8 and 24, and sustained CDAI remission assessed at weeks 8 and 24. Biomarker assessments included changes in IL22 serum levels (expressed in high levels in Crohn's disease patients and a marker of disease activity [Schmechel *et al.*, *Inflamm Bowel Dis*, 14:204-212 (2008)]) from baseline after treatment with MEDI2070 versus placebo at weeks 8 and 12; association of change from baseline in IL22 levels with clinical effect and CDAI remission after treatment with MEDI2070 versus placebo at weeks 8 and 12; and assessment of higher IL22 serum levels at baseline as a predictor of clinical effect and CDAI remission after treatment with MEDI2070 compared with placebo at weeks 8 and 12.

IV. Statistical analysis

[00349] Assuming a CDAI clinical effect rate of 20% in the placebo group, approximately 54 patients per treatment arm were required to provide 87% power to detect a 25% difference in CDAI clinical effect rates at week 8 between MEDI2070 700 mg and placebo, using a two-sided test at significance level of $\alpha=0.1$. Assuming an approximately 10% dropout rate per treatment arm adjustment, approximately 60 patients were to be randomized.

[00350] The modified intent-to-treat population included all randomized patients who received at least one dose of study treatment during the double-blind period. The safety population comprised patients who received any study treatment during the double-blind period. The per-protocol population included patients who received all treatment doses and

had no major protocol deviations. The open-label population included all patients who received at least 1 dose of MEDI2070 during the open-label period.

[00351] For the primary and secondary measures with binary outcomes, comparison between treatment arms was based on the modified intent-to-treat population, using a logistic regression model [Ge *et al.*, *Drug Inf J*, 45:481-493 (2011)], with treatment and stratification factor (number of prior anti-TNF- α agents of 1 vs >1) as covariates. The significance of the treatment effect was tested using the 2-sided test at $\alpha=10\%$. A sensitivity analysis was conducted by extending the planned logistic regression model to adjust for baseline CDAI score and/or other baseline covariates. Missing data for dichotomous end points were imputed using non-responder imputation. A patient imputed as a nonresponder before week 8 was considered a nonresponder for all subsequent visits. Additionally, patients with a clinically meaningful increase in steroid use were assumed to be nonresponders. Clinically meaningful increase in steroid dose was defined as an increase of at least 5 mg/day for at least 3 days of prednisone or equivalent, or an increase of at least 3 mg/day for at least 3 days of budesonide. Missing data for continuous measures were handled using the inverse probability weighting generalized estimating equations method, adjusting for prior anti-TNF- α agent use.

[00352] Pharmacokinetic data were summarized. Exploratory analyses were performed for patients in the open-label period. Efficacy data from the double-blind and open-label periods up to week 24 for these patients were combined and reported by treatment arms in the double-blind period. Change from baseline in CRP and FCP were analyzed using a mixed-effects repeated measures model, adjusting for prior anti-TNF- α use and baseline, for the open-label population. Comparisons between MEDI2070 210 mg at week 24 and MEDI2070 700 mg or placebo at week 12 were performed.

V. Patient Results

[00353] In total, 121 patients were randomized; 119 of these received double-blind treatment (FIG. 1). In the double-blind period, 52 of 59 (86.7%) and 52 of 60 (85.2%) patients completed week 12 in the MEDI2070 and placebo groups, respectively. Baseline patient characteristics generally were balanced between treatment groups (TABLE 1), except CDAI and CRP levels were numerically higher in the MEDI2070 group. Results from weeks 8, 12, and 24 are reported here; the study is ongoing for long-term follow-up.

TABLE 1. Baseline Characteristics and Demographics (modified intent-to-treat population).

Parameter	MEDI2070 (N=59)	Placebo (N=60)	Total (N=119)
Mean age, yr (SD)	34.9 (11.2)	38.1 (10.7)	36.5 (11.0)
Female, no. (%)	37 (62.7)	37 (61.7)	74 (62.2)
Mean weight, kg (SD)	70.4 (20.7)	71.9 (15.4)	71.2 (18.2)
Mean disease duration, yr (SD)	13.2 (9.4)	11.2 (8.5)	12.2 (9.0)
≥2 yr, %	96.6	90.0	93.3
Sites of disease, no. (%)			
Ileal only	14 (23.7)	18 (30.0)	32 (26.9)
Colonic only	16 (27.1)	18 (30.0)	34 (28.6)
Ileo-colonic	28 (47.5)	24 (40.0)	52 (43.7)
Other	1 (1.7)	0	1 (0.8)
Crohn's Disease Activity Index score			
Mean (SD)	325.0 (59.2)	312.4 (56.3)	318.6 (57.8)
Minimum, maximum	222, 440	221, 450	221, 450
Mean C-reactive protein, mg/L (SD)	29.8 (35.4)	21.1 (24.2)	25.4 (30.4)
Mean C-reactive protein ≥5 mg/L, no. (%)	46 (78.0)	39 (65.0)	85 (71.4)
Mean fecal calprotectin, µg/g (SD)*	536.7 (303.2)	616.9 (420.7)	578.2 (369.3)
Mean fecal calprotectin ≥250 µg/g, no. (%)	41 (73.2)	47 (78.3)	88 (75.9)
Prior anti-tumor necrosis factor-α agents, no. (%)			
1	18 (30.5)	19 (31.7)	37 (31.1)
2	35 (59.3)	35 (58.3)	70 (58.8)
≥3	6 (10.2)	6 (10.0)	12 (10.1)
Prior use of anti-tumor necrosis factor-α agents, no. (%)			
Infliximab	51 (86.4)	50 (83.3)	101 (84.9)
Adalimumab	45 (76.3)	45 (75.0)	90 (75.6)
Certolizumab	10 (16.9)	11 (18.3)	21 (17.6)

Parameter	MEDI2070 (N=59)	Placebo (N=60)	Total (N=119)
Reason for discontinuing prior anti-tumor necrosis factor- α agent, no. (%)			
Primary failure	23 (39.0)	23 (38.3)	46 (38.7)
Secondary failure	34 (57.6)	33 (55.0)	67 (56.3)
Intolerance	27 (45.8)	26 (43.3)	53 (44.5)
Other	7 (11.9)	11 (18.3)	18 (15.1)
Not applicable	0	2 (3.3)	2 (1.7)
5-aminosalicylate use at baseline, no. (%)	18 (30.5)	18 (30.0)	36 (30.3)
Corticosteroid use at baseline, no. (%)	24 (40.7)	24 (40.0)	48 (40.3)
Immunomodulators use at baseline, no. (%)	18 (30.5)	14 (23.3)	32 (26.9)
Prior surgery for Crohn's disease, no. (%)	29 (49.2)	26 (43.3)	55 (46.2)

*Three patients had missing fecal calprotectin assessments.

VI. Efficacy

(i) Week 8

[00354] For the primary outcome measure, the rate of clinical effect at week 8 was significantly higher in the MEDI2070 group versus the placebo group (49.2% vs. 26.7%, respectively; $P=0.01$; point estimate: 0.225 [90% confidence interval (CI): 0.083 to 0.368]; FIG. 2A). CDAI remission rates were 27.1% with MEDI2070 and 15.0% with placebo ($P=0.10$; point estimate: 0.122 [90% CI: 0.000 to 0.243]). CR70 rates were 52.5% and 46.7% in the MEDI2070 and placebo groups, respectively ($P=0.52$), and CR100 rates were 45.8% and 25.0% in the MEDI2070 and placebo groups, respectively ($P=0.02$).

[00355] A significantly greater proportion of patients receiving MEDI2070 achieved the composite end points of CDAI effect and 50% reduction in FCP or CRP versus baseline ($P<0.001$), and CDAI remission and 50% reduction in FCP or CRP versus baseline ($P=0.02$; FIG. 2B). MEDI2070 treatment also resulted in significantly greater reductions in FCP versus placebo (least squares mean change -153.5 vs. -49.7; least squares mean difference -105.6 [90% CI: -184.0 to -27.2]; $P=0.027$) and significantly reduced CRP levels (least squares mean change: -12.6 vs. 5.1 with placebo; least squares mean difference -17.6 [90% CI: -28.3 to -6.9]; $P=0.007$).

(ii) Week 12

[00356] At week 12, the rate of clinical effect was greater with MEDI2070 (37.3% vs 28.3%; $P=0.29$), as was the rate of CDAI remission (20.3% vs. 13.3%; $P=0.31$); however, the differences were not statistically significant. Rates of CR100 at week 12 were 37.3% with MEDI2070 and 28.3% with placebo ($P=0.288$). At week 12, significant reductions in FCP and CRP with MEDI2070 were maintained (FCP: least squares mean change -179.6 vs -55.1; least squares mean difference -124.6 [90% CI: -221.2 to -27.9]; $P=0.034$; CRP: least squares mean change: -13.4 vs -2.6 with placebo; least squares mean difference -10.8 [90% CI: -17.6 to -4.1]; $P=0.008$).

(iii) Week 24

[00357] Clinical effect and CDAI remission rates were maintained in the MEDI2070 group at 24 weeks. The proportion of patients receiving placebo then open-label MEDI2070 (placebo/MEDI2070 group) who achieved clinical effect and CDAI remission was similar to those receiving MEDI2070 700 mg then open-label MEDI2070 (MEDI2070/MEDI2070) at week 24 (FIG. 3A and 3B). Over the 24-week period, the MEDI2070/MEDI2070 group continued to achieve the composite end points of CDAI effect plus 50% reduction in FCP or CRP versus baseline, and CDAI remission plus 50% reduction in FCP or CRP versus baseline (TABLE 2). The proportion of patients in the placebo/MEDI2070 group achieving both composite end points at week 24 was similar to those in the MEDI2070/MEDI2070 group. In the MEDI2070/MEDI2070 group, changes from baseline in FCP and CRP levels were maintained between weeks 12 and 24; in the placebo/MEDI2070 group, decreases in FCP and CRP levels were observed between weeks 12 and 24.

TABLE 2. Composite End Points (weeks 8 through 24), Sustained Effect and Remission (open-label population), and Change from Baseline in Fecal Calprotectin and C-reactive Protein (mixed-effects model; open-label population).

Parameter, no. (%)	MEDI2070 700 mg/ MEDI2070 210 mg (N=52)	Placebo/ MEDI2070 210 mg (N=52)
Crohn's Disease Activity index effect and $\geq 50\%$ reduction in fecal calprotectin or C-reactive protein		

Parameter, no. (%)	MEDI2070 700 mg/ MEDI2070 210 mg (N=52)	Placebo/ MEDI2070 210 mg (N=52)
vs baseline (nonresponder imputation)		
Week 8	24 (46.2)	6 (11.5)
Week 12	22 (42.3)	5 (9.6)
Week 24	24 (46.2)	25 (48.1)
Crohn's Disease Activity index remission and $\geq 50\%$ reduction in fecal calprotectin or C-reactive protein vs. baseline (nonresponder imputation)		
Week 8	14 (26.9)	5 (9.6)
Week 12	12 (23.1)	4 (7.7)
Week 24	19 (36.5)	18 (34.6)
Sustained effect at weeks 8 and 24* (nonresponder imputation)	22 (42.3)	12 (23.1)
Sustained remission at weeks 8 and 24 [†] (nonresponder imputation)	12 (23.1)	6 (11.5)
Mean change in fecal calprotectin, ($\mu\text{g/g}$) [‡]		
Double-blind period (Week 12)	-186.5 (n=40)	-46.0 (n=41)
Open-label period (Week 24)	-252.3 (n=36)	-253.8 (n=39)
Difference at week 12 vs week 24 (90% CI)	-65.7 (-161.0 to 29.5)	-207.8 (-307.0 to -108.5)
P value	0.254	<0.001
Mean change in C reactive protein (mg/L) [‡]		
Double-blind period (Week 12)	-16.4 (n=51)	0.1 (n=52)
Open-label period (Week 24)	-18.2 (n=45)	-10.6 (n=49)
Difference at Week 12 vs Week 24 (90% CI)	-1.8 (-7.2 to 3.6)	-10.8 (-16.4 to -5.1)
P value	0.580	0.002

*Sustained effect is defined as achieving the criteria of effect at both week 8 and week 24.

Percentage calculated using number of patients in the open-label population.

[†]Sustained remission is defined as achieving the criteria of remission at both week 8 and week 24. Percentage calculated using the number of patients in the open-label population.

[‡]Mean and P value were obtained from a mixed-effects model with fixed terms for treatment group, visit, treatment by visit interaction, stratification factor of prior anti-tumor necrosis factor- α use, and baseline fecal calprotectin or C-reactive protein, and patients within treatment as random effect, assuming unstructured covariance structure.

VII. MEDI2070 Exposure-Response Relationship

[00358] At the 700-mg intravenous dose of MEDI2070, no definitive relationship between exposure and efficacy was established (data not shown). Serum MEDI2070 concentrations at the week 4 trough and at weeks 8 and 12 varied over a tenfold range and were not related to CDAI response or nonresponse at week 8 (data not shown). These findings are consistent with dosing at the plateau of the dose-response curve.

VIII. Biomarkers

[00359] Patients in the MEDI2070 group had greater reductions in serum IL22 levels versus those in the placebo/MEDI2070 group (FIG. 7). Baseline serum IL22 levels greater than or equal to the median value of 15.6 pg/mL were associated with an increased likelihood of clinical effect in the MEDI2070 group. Patients in the MEDI2070 group with baseline IL22 levels less than 15.6 pg/mL had a CR100 response rate similar to that in the placebo group (Figure 4). Clinical response was not a strong function of IL22 in the placebo group.

IX. Safety

(i) Week 12

[00360] At the end of the double-blind period, the proportion of patients with treatment-emergent adverse events was similar between the MEDI2070 and placebo groups (67.8% vs. 68.3%, respectively), as were the proportion of patients with grade 3 or greater adverse events (10.2% vs. 11.7%, respectively) and serious adverse events (8.5% vs. 8.3%, respectively). Treatment-related adverse events were observed in 13.6% of patients receiving MEDI2070 and 21.7% of patients receiving placebo; those observed in at least 5% of patients in either group are shown in TABLE 3. Serious adverse events occurred in five patients in the MEDI2070 group and five in the placebo group; events included Crohn's disease (three events in two patients), colonoscopy-associated colon perforation (n=1), pyrexia (n=1), and cellulitis (n=1) in the MEDI2070 group, and anemia (n=1), Crohn's disease (two events in

two patients), diarrhea (n=1), gastrointestinal hemorrhage (n=1), and abdominal abscess (n=1) in the placebo group.

TABLE 3. Treatment-Emergent Adverse Events in at Least 5% of Patients in Either Treatment Group (up to week 12; safety population)

Adverse Event, n (%)	MEDI2070 (N=59)	Placebo (N=60)
Headache	10 (16.9)	4 (6.7)
Nasopharyngitis	8 (13.6)	6 (10.0)
Abdominal pain	6 (10.2)	6 (10.0)
Crohn's disease	5 (8.5)	5 (8.3)
Vomiting	3 (5.1)	2 (3.3)
Arthralgia	3 (5.1)	2 (3.3)
Proctalgia	3 (5.0)	0
Dizziness	3 (5.0)	0
Pyrexia	2 (3.4)	4 (6.7)
Nausea	2 (3.4)	3 (5.0)
Diarrhea	0	5 (8.3)
Sinusitis	0	4 (6.7)
Insomnia	0	3 (5.0)
Cough	0	3 (5.0)

[00361] Infections that were serious or at least grade 3 in severity, or that required oral or parenteral antimicrobial therapy, occurred in four patients with four events in the MEDI2070 group, and in seven patients with 11 events in the placebo group. Treatment discontinuation attributable to treatment-emergent adverse events occurred in 8.5% of MEDI2070 patients (including gastrointestinal disorders [6.8%] and infection [1.7%]) and in 10.0% of placebo patients (including gastrointestinal disorders [6.7%], infection [1.7%], and eye disorder [1.7%]).

(ii) Week 24

[00362] At week 24, treatment-emergent adverse events were observed in 67.3% of patients in the MEDI2070 group and 65.4% of those in the placebo/MEDI2070 group, with treatment-related adverse events observed in 25.0% and 21.2% of patients, respectively. Treatment-emergent adverse events of at least grade 3 severity occurred in 13.5% of patients in the MEDI2070 group and 3.8% of patients in the placebo/MEDI2070 group; serious adverse events were observed in 15.4% and 7.7% of patients, respectively. Treatment discontinuation attributable to treatment-emergent adverse events occurred in 9.6% of MEDI2070 patients (including Crohn's disease flare [3.8%], anal fistula [1.9%], anemia and lymphopenia [1.9%], and anal abscess [1.9%]), and in 3.8% of placebo/MEDI2070 patients (including pelvic abscess [1.9%] and kidney stones [1.9%]). The number of infection events that were serious, at least grade 3 in severity, or required oral or parenteral antimicrobial therapy were equal in the MEDI2070 and placebo/MEDI2070 groups (13 events).

X. Immunogenicity

[00363] Antidrug antibodies were detected in two of 119 patients. One patient receiving MEDI2070 had antidrug antibodies at baseline, but not in subsequent assessments. The other patient, who received placebo during the double-blind period, had antidrug antibodies at week 24.

XI. Discussion

[00364] In patients with moderate to severe Crohn's disease who failed prior anti-TNF- α therapy, MEDI2070 resulted in a significantly greater rate of clinical effect, a composite of a 100-point reduction in CDAI and CDAI remission, at 8 weeks compared with placebo (49.2% vs. 26.7%, respectively; $P=0.01$), meeting the primary study end point. Clinical efficacy was consistent with the biologic effects observed with MEDI2070. Patients in the MEDI2070 group had greater decreases from baseline in FCP and CRP relative to placebo. The beneficial effects of MEDI2070 on FCP and CRP are remarkable given that this patient population was previously heavily treated with anti-TNF- α therapies; more than 65% of patients had received two or more prior anti-TNF- α agents.

[00365] At week 12, the rate of clinical effect was greater in the MEDI2070 group, as was the rate of CDAI remission; however, these differences were not significant. Significant reductions in FCP and CRP with MEDI2070 were maintained at week 12. At week 24, clinical effect, CDAI remission, and changes from baseline in levels of FCP and CRP were

maintained between weeks 12 and 24 in the MEDI2070 group. Among patients in the placebo/MEDI2070 group, the proportion achieving clinical effect and CDAI remission at week 24 was similar to those who received MEDI2070 in both periods, and significant decreases in FCP and CRP levels were observed between weeks 12 and 24. At the 700-mg intravenous dose of MEDI2070, no definitive relationship between exposure and efficacy was established. This finding is consistent with dosing at the plateau of the dose-response curve. A wider range of doses will be explored in future studies.

[00366] MEDI2070 was well tolerated, with rates of treatment-emergent adverse events, grade 3 or greater adverse events, serious adverse events, and discontinuations owing to treatment-emergent adverse events similar to those of placebo at 12 weeks. Rates of serious or severe infections were less than 10% in the MEDI2070 group at week 12. At week 24, overall rates of treatment-emergent adverse events were similar between the MEDI2070 and placebo/MEDI2070 groups; rates of grade 3 or greater adverse events and serious adverse events were numerically greater in the MEDI2070 group versus the placebo/MEDI2070 group (13.5% vs. 3.8% and 15.4% vs. 7.7%, respectively), as were rates of discontinuations attributable to treatment-emergent adverse events (9.6% vs. 3.8%, respectively). Rates of serious or severe infections were the same in both treatment groups at 24 weeks (13 events). One patient had antidrug antibodies at baseline; presumably, this was a false-positive result and was not detected on follow-up assessment.

[00367] Although specific inclusion criteria, primary end points, and timing of assessments vary, the results of our study suggest that the short-term CDAI remission rate achieved with MEDI2070 (27.1% at 8 weeks) generally compares favorably with those of other biologic therapies evaluated in patients with Crohn's disease who failed prior anti-TNF- α therapy. These include ustekinumab (26% [7/27] at 8 weeks) (Sandborn et al. *Gastroenterology* 135:1130-41 (2008)), vedolizumab (10.5% [n=105] at 6 weeks), (Sandborn et al. *N Engl J Med* 369:711-21 (2013)) and adalimumab (21% [34/159 with secondary nonresponse to infliximab] at 4 weeks) (Sandborn et al. *Ann Intern Med* 146:829-38 (2007)). The safety profile of MEDI2070 also compares favorably with other biologics available for patients with Crohn's disease. A recent meta-analysis of studies evaluating the dual IL23/IL12 inhibitors ustekinumab and briakinumab found an increased risk of major adverse cardiovascular events in psoriasis patients treated for 12 to 20 weeks [Tzellos et al., *J Eur Acad Dermatol*

Venereol, 27:1586-1587 (2013)]. No patients in our study experienced a major adverse cardiovascular event up to 24 weeks of follow-up. MEDI2070 is specific for IL23 and does not inhibit IL12; the clinical significance of this specificity is not known. However, follow-up for this study (104 weeks) is ongoing to determine longer-term efficacy and safety.

[00368] We evaluated serum IL22 levels at baseline and following MEDI2070 treatment. IL22, expressed at high levels in Crohn's disease, is an effector cytokine that supports mucosal barrier integrity and is an indicator of IL23 axis activity [Schmechel et al., *Inflamm Bowel Dis*,14:204-212 (2008)]. Serum IL22 levels were reduced in the MEDI2070 group compared with the placebo group. Additionally, baseline serum IL22 levels greater than or equal to 15.6 pg/mL were associated with an increased likelihood of clinical effect in the MEDI2070 group, whereas MEDI2070-treated patients with baseline IL22 levels less than 15.6 pg/mL had CR100 responses similar to those in the placebo group. FIG. 4. In contrast, in a study by Dige *et al.*, IL22 levels were not reduced in Crohn's disease patients effectively treated with adalimumab [Dige et al., *J Crohns Colitis*,7:248-255 (2013)]. This study is among the first to incorporate novel biomarkers to further the understanding of the pathogenesis and improve the treatment of Crohn's disease.

[00369] In conclusion, MEDI2070 treatment demonstrated consistently robust efficacy, with an acceptable safety profile in patients with Crohn's disease who failed prior anti-TNF- α therapies.

Example 3

Immunoassays for Detection and Quantification of IL23 Pathway Biomarkers IL22 and LCN2

[00370] IL22 and/or LCN2 can be detected and quantified according to the exemplary methods disclosed in this Example (Example 3). These methods were applied, for example, to obtain the experimental data presented in Example 4 (see below). The methods were also used to test samples for the phase 2a study presented in Examples 1 and 2.

3.1 IL22 ELISA immunoassay

[00371] IL22 levels were measured using a quantitative ELISA-based immunoassay. A mouse monoclonal antibody specific for human IL-22 was pre-coated onto a microplate (R&D Systems, Cat #D2200). One hundred microliters of assay diluent were first added to wells of

microplates followed by addition of 100 μ L of standards, controls and samples. The plates were incubated for 2 hours $\pm$ 15 minutes at room temperature to allow IL22 to bind to the capture antibody on the plates. Plates were then washed 5 times using 1X Wash buffer (1X PBS pH 7.4 / 0.05% Tween-20) to remove unbound materials and were further incubated with 200 μ L of the detection antibody (anti-IL22 antibody-HRP conjugate, (R&D Systems, Cat #D2200) for 2 hours $\pm$ 15 minutes at room temperature. After that, the plates were washed again and incubated with 150 μ L of TMB, a chromogenic HRP substrate (Neogen, Cat # 331176) for 20 minutes $\pm$ 3 minutes at room temperature in the dark. The enzyme reaction was stopped by the addition of 100 μ L of stop solution (1M HCL).

[00372] Within 30 minutes after stopping the reaction, plates were read on a SpectraMaxPlus 384 Microplate Spectrophotometer (Molecular Devices) to measure the optical density at 450 nm. The intensity of the color generated is directly proportional to the amount of bound IL22. The IL22 concentrations in samples and controls were interpolated from the standard curve of recombinant *E. coli*-derived IL22, which was run on each plate. The quadratic model was used for curve fitting. The assay was reproducible and precise. The quantifiable range was established to be 10 pg/mL- 800 pg/mL of IL-22 in 100% serum.

3.2 LCN2 ELISA immunoassay

[00373] A standard Meso Scale Discovery plate (MSD, Cat# L15XA) was coated with 1 μ g/mL of a rat-anti-human Lipocalin-2 antibody (R&D Systems, Cat# MAB17571), at 50 μ L/well at 2°C - 8°C overnight. The plate was washed three times with 200 μ L ELISA Wash Buffer (0.05% Tween-20/PBS) and blocked with 150 μ L/well of I-Block buffer (IBB) (0.5% Tween-20/0.2% I-Block Buffer/PBS) for at least 60 minutes on a plate shaker with gentle shaking. Reference standards, quality controls and negative control, prepared in IBB, and serum test samples, diluted to the minimum required dilution of 1:50 in IBB, were added to the plate at 30 μ L/well.

[00374] The assay plate was incubated for 2 hours at room temperature on a plate shaker with gentle shaking. Unbound analyte was removed by washing the plate. To detect bound analyte, 0.5 μ g/mL of a biotin-conjugated goat-anti-human Lipocalin-2 antibody (R&D Systems, Cat# BAF1757) was added at 30 μ L/well and the plate was incubated for an additional 60 minutes on a plate shaker with gentle shaking. Unbound detection antibody was removed by washing the plate. Streptavidin SULFO-TAGTM detection dye (MSD, Cat#

R32AD-1) was added to the plate at 0.5 µg/well and the plate was incubated for an additional 30 minutes covered to protect from light exposure. The plate was washed and 1X Read Buffer (MSD, Cat# R92TC-2) was added at 150 µL/well and the plate was read on a MSD Sector Imager within 20 minutes.

[00375] ECL (electrochemiluminescence) values for each plate were collected using the MSD Sector Imager. The ECL values for the reference standards were plotted with Softmax Pro GxP v6.4 software (Molecular Devices, Sunnyvale, CA) using 5-Parameter Logistic model of curve fitting. The concentrations of unknown samples were interpolated from the standard curves on the same assay plate. The Softmax-derived data was then imported into Microsoft Excel Software to generate data reports and graphs. The assay's dynamic range was established to be from 0.70 ng/ml to 1000.00 ng/mL adjusted to 100% serum.

Example 4

Identification of IL23 Pathway Biomarkers (IL22 and/or LCN2) As Predicted Biomarkers for Treatment of IL23-mediated Diseases with an anti-IL23 Antibody

[00376] IL23 is expressed primarily from activated dendritic cells and macrophages (see Gaffen et al (2014) Nature Revs Immunol 14: 585-600; Oppmann et al (2000) Immunity 13: 715-251) and acts directly on a variety of hematopoietic cell types including Th17, Th22, γδ T cells and innate lymphoid cells (ILCs) to induce cytokines including IL22, IL21, IL17A, IL17F, IL17A/F, TNF alpha and GM-CSF (*see, e.g.,* Gaffen et al (2014) Nature Revs Immunol 14: 585-600; Zheng et al (2007) Nature 445: 648-51; El-Behi et al (2011) Nature Immunol 12: 568-575). These effector and regulatory cytokines can in turn act on a variety of other cell types expressing the appropriate cognate receptors. IL23-induced IL22, for example, can stimulate IL22-receptor expressing epithelial cells and keratinocytes to secrete antimicrobial proteins such as LCN2 (Sonnenberg et al (2010) Adv Immunol 107: 1-29; Stallhofer et al (2015) Inflamm Bowel Dis 2015 Aug 7; Behnsen et al (2014) Immunity 40: 262-73).

[00377] In the Phase 2a study described in Examples 1 and 2, CD patients with elevated baseline serum IL22 or LCN2 levels of greater than or equal to 15.6 pg/mL or 215 ng/mL, respectively (as measured using the immunoassays described in Example 3), had an increased likelihood of clinical effect in the MEDI2070 group, whereas MEDI2070-treated

patients with baseline IL22 levels less than 15.6 pg/mL or 215 ng/mL, respectively, had CR100 responses similar to those in the placebo group. FIGs. 4 and 5. In particular, patients with baseline serum IL22 levels ≥ 15.6 pg/mL or patients with baseline serum LCN2 levels ≥ 215 ng/mL were observed to have statistically significant increased CDAI-100 responses when treated with MEDI2070 compared to placebo at week 8. FIGs. 4 and 5.

[00378] To further understand the relationship between baseline serum IL22 and/or LCN2 levels and response to treatment with MEDI2070, the set of baseline values of either IL22 or LCN2 across the entire study population was divided into 10 levels, or deciles, such that each of the 11 analyte cut-offs progressively segmented the study population into groups with 10% less of the total study population. The differential clinical response rate between MEDI2070 and placebo exposed subjects as a function of baseline IL22 and LCN2 serum levels at each decile cut-off is provided in FIGs. 6A-C and the individual IL22 and LCN2 serum decile values is summarized below in TABLE 4 (IL22) and TABLE 5 (LCN2). For example, as reported in TABLE 4, at the 4th decile, 40% of the total study population had a baseline IL-22 level of <12.7 pg/mL and 60% of the total study population had a baseline IL-22 level ≥ 12.7 pg/mL. The CDAI response rate at week 8 (as measured by the percentage (%) of subjects achieving a CDAI score <150 or a reduction in CDAI score of >100) in those subjects exposed to MEDI2070 and with baseline IL-22 levels ≥ 12.7 pg/mL, i.e. above the 4th decile, was 58.3%. 21 subjects exposed to MEDI2070 and with baseline IL22 levels above the 4th decile for the study population (12.7 pg/ml) were found to be CDAI responders at week 8. The function in R called 'quantiles' was used to determine decile values. The numbers of CDAI responder and non-responders in the MEDI2070 and placebo exposed groups, and the CDAI response rates at week 8 of the study in subjects with baseline IL22 or LCN2 values greater than or equal to each decile cut are also indicated in TABLES 4 and 5, and differences between treatment and placebo response rates for each decile cut is provided in FIG. 6A. Two additional measurements of clinical response – the difference between the percentage (%) of subjects treated with MEDI2070 versus those treated with placebo achieving a 100 point improvement in CDAI score at week 8 (FIG. 6B); and the difference between the percentage (%) of subjects treated with MEDI2070 versus those treated with placebo achieving a CDAI response (CDAI score <150 or a reduction in CDAI score of >100) + also achieving a $>50\%$ reduction in either FCP or CRP compared to baseline FCP or

CRP at week 8 (FIG. 6C) – as a function of baseline IL22 and LCN2 levels/deciles described in TABLES 4 or 5 were also performed.

[00379] As shown in FIGs. 6A-C and reported in TABLE 4 below, CD patients treated with MEDI2070 having increasingly higher levels of baseline IL22 achieved higher CDAI response rates at week 8 compared to placebo (as measured using any of the three different clinical response measurements shown in FIGs. 6A-C), illustrating that MEDI2070 induced better clinical responses in patients with high baseline IL22 serum levels. Notably, subjects with high levels of IL22 (including, *e.g.*, subjects with IL22 levels at the 5th, 6th or 7th deciles (0.5, 0.6 or 0.7 quantiles)) had greater clinical response rate differences from placebo (irrespective of which of the three different clinical response measurements was used) compared to the IL22 low subjects (including, *e.g.* subjects with IL22 levels at the 1st or 2nd deciles (0.1 or 0.2 quantiles)). *See* FIGs. 6A-C. These IL22 high subjects also had increased CDAI response rates compared to all comers treated with MEDI2070 (*see, e.g.*, FIG. 8).

[00380] Importantly, the CDAI response rates and CDAI remission rates observed in IL22 high subjects treated with MEDI2070 in the Phase 2a study are amongst the highest clinical response rates to biologics therapy for CD reported to date. For example, as shown in FIG. 8, the CDAI-100 response rate differential (defined as the difference in the percentage (%) of subjects achieving a CDAI-100 response between treatment and placebo) and/or CDAI remission rate differential (defined as the difference in the percentage (%) of subjects achieving a reduction in total CDAI score to below 150 points between treatment and placebo) achieved in patients having elevated baseline serum IL22 treated with MEDI2070 for 8 weeks were highly increased compared to the published CDAI-100 response and/or CDAI remission rates of patients treated with a number of other compounds currently approved or under development to treat CD including: Ustekinumab (response rates after 6 weeks or 8 weeks of treatment with a 6 mg/kg dose as reported in Figure 1 of Sandborn et al., *N Engl J Med.* 2012 Oct 18;367(16):1519-28.); Vedolizumab (response rates after 6 weeks or 10 weeks of treatment as reported in Figure 3 of Sands et. al., *Gastroenterology.* 2014 Sep;147(3):618-627); or Adalimumab (response rates after 4 weeks of treatment in patients who are secondary failures to infliximab as reported in Sandborn et. al, *Ann Intern Med.* 2007;146:829-838). For example, both the CDAI-100 response rate differential (“CDAI Response Delta vs. Placebo”) and the CDAI remission rate differential (“CDAI Remission

Delta vs. Placebo”) achieved in patients treated with MEDI2070 for 8 weeks who had a baseline CRP $\geq 5\text{mg/L}$; baseline IL-22 $\geq 11.3\text{pg/mL}$; baseline IL-22 $\geq 15.6\text{ pg/mL}$; or baseline IL-22 $\geq 11.3\text{ pg/mL}$ + CRP $\geq 5\text{mg/L}$ (as measured using the IL22 immunoassay described in Example 3) were greater than the reported CDAI-100 response rate differential and/or the CDAI remission rate differential for Ustekinumab, Vedolizumab and Adalimumab reported in FIG. 8. The overall clinical response and remission rates for all patients treated with MEDI2070 in the Phase 2a study, irrespective of biomarker status, was similar to the response rates of other molecules currently approved or under development. TABLE 6 summarizes the CDAI-100 response rate differential and the CDAI remission rate differential for each of the MEDI2070-treated subgroups plotted in FIG. 8. These results further underscore the surprising and unexpected predictive value of high or elevated IL22 serum levels (alone or in combination with other biomarkers disclosed herein) in identifying patients having an IL23-mediated disease or disorder responsive to treatment with an IL23 antagonist (including, *e.g.*, an anti-IL23 antibody or fragment thereof such as MEDI2070).

[00381] Similarly, as shown in FIGs. 6A-C and reported in TABLE 5, CD patients treated with MEDI2070 having increasingly higher levels of baseline LCN2 achieved higher clinical response rates (as measured using any of the three different clinical response measurements shown in FIGs. 6A-C) at week 8 compared to placebo, supporting that MEDI2070 induced better clinical responses in patients with high baseline LCN2 serum levels. Notably, LCN2 high subjects (including, *e.g.*, subjects with LCN2 levels at the 5th, 6th or 7th deciles (0.5, 0.6 or 0.7 quantiles)) had greater clinical response rate differences from placebo (irrespective of which of the three different clinical response measurements was used) compared to the LCN2 low subjects (including, *e.g.* subjects with LCN2 levels at the 1st or 2nd deciles (0.1 or 0.2 quantiles)). These results further demonstrate the surprising and unexpected predictive value of high or elevated LCN2 serum levels in identifying patients having an IL23-mediated disease or disorder responsive to treatment with an IL23 antagonist (including, *e.g.*, an anti-IL23 antibody or fragment thereof such as MEDI2070).

[00382] The relationship between increasing clinical response rates and increasing baseline biomarker levels was not always as evident in patients in the 8th, 9th or 10th deciles. At these IL22 or LCN2 levels too few, if any, patients treated with MEDI2070 or placebo were available for analysis. *See, e.g.*, FIGs. 6A-C; TABLES 4 and 5. However, given a larger

sample size, increased clinical response rates for patients identified as having IL22 or LCN2 levels at the 8th, 9th or 10th deciles are expected.

[00383] Taken together, these results support that high IL22 serum levels and/or high LCN2 serum levels (including, *e.g.*, the median baseline IL22 and/or LCN2 serum levels identified in the study or serum IL22 levels between 7.9 pg/mL and 31.4 pg/mL and/or serum LCN2 levels between 142.8 ng/mL and 261.1 ng/mL) can be used to identify a patient having an IL23-mediated disease or disorder suitable for treatment with an IL23 antagonist (including, *e.g.*, an anti-IL23 antibody or fragment thereof such as MEDI2070).

TABLE 4. Subject counts and CDAI Response Rate at Week 8 by Decile Baseline IL22 Levels.

Decile	Baseline IL-22 (pg/mL)	MEDI2070 responders (# subjects)	MEDI2070 Non-responders (# subjects)	Placebo responders (# subjects)	Placebo Non-responders (# subjects)	MEDI2070 CDAI Response rate (W8)	Placebo CDAI Response rate (W8)
0	1	28	28	16	44	0.5000	0.2667
1	1	28	28	16	44	0.5000	0.2667
2	7.9	25	22	10	36	0.5319	0.2174
3	11.3	24	18	9	30	0.5714	0.2308
4	12.7	21	15	9	25	0.5833	0.2647
5	15.6	20	10	7	21	0.6667	0.2500
6	19.6	18	8	5	16	0.6923	0.2381
7	23.1	14	5	5	11	0.7368	0.3125
8	31.4	9	5	3	7	0.6429	0.3000
9	46.8	3	4	2	3	0.4286	0.4000
10	711	0	1	0	0		

TABLE 5. Subject counts and CDAI Response Rate at Week 8 by Decile Baseline LCN2 Levels.

Decile	Baseline LCN2 (ng/mL)	MEDI2070 Responders (# subjects)	MEDI2070 Non-responders (# subjects)	Placebo Responders (# subjects)	Placebo Non-responders (# subjects)	MEDI2070 CDAI Response rate (W8)	Placebo CDAI response rate (W8)
0	77.7	28	22	15	35	0.5600	0.3000
1	142.8	27	19	13	31	0.5870	0.2955
2	163.6	23	16	12	29	0.5897	0.2927
3	184.3	21	14	12	23	0.6000	0.3429
4	201.3	20	14	6	20	0.5882	0.2308
5	214.6	18	12	4	16	0.6000	0.2000
6	233.4	16	8	3	13	0.6667	0.1875
7	261.1	14	6	3	7	0.7000	0.3000

Decile	Baseline LCN2 (ng/mL)	MEDI2070 Responders (# subjects)	MEDI2070 Non-responders (# subjects)	Placebo Responders (# subjects)	Placebo Non-responders (# subjects)	MEDI2070 CDAI Response rate (W8)	Placebo CDAI response rate (W8)
8	294.8	10	4	2	4	0.7143	0.3333
9	326.6	5	2	1	2	0.7143	0.3333
10	434.0	0	0	1	0		

TABLE 6. CDAI-100 response rate differential (defined as the difference in the percentage (%) of subjects achieving a CDAI-100 response between treatment and placebo) and CDAI remission rate differential (defined as the difference in the percentage (%) of subjects achieving a total CDAI score of below 150 points between treatment and placebo) for various subgroups.

population	N	MEDI2070 CDAI Response Rate Minus Placebo CDAI Response Rate at Week 8	MEDI2070 CDAI Remission Rate Minus Placebo CDAI Remission Rate at Week 8
mITT	N=119	20.8%	12.2%
IL22 >= 11.3 pg/mL	N=81	31.5%	18.3%
IL22 >= 15.6 pg/mL	N=58	38.2%	29.2%
CRP >= 5	N=85	30.8%	19.8%
CRP >= 5 + IL22 >= 11.3 pg/mL	N=62	44.4%	26.9%

[00384] As noted previously, IL23-induced IL22 induces cells to secrete LCN2. Thus, the observation that baseline serum levels of two separate IL23 pathway members (i.e. elevated IL22 or LCN2) each were predictive of patient clinical response to MEDI2070 (e.g. CDAI-100 Response Rate at week 8) strongly suggests that other IL23 pathway biomarkers may also predict an increased likelihood of clinical effect in response to treatment with MEDI2070. Accordingly, to the extent that serum baseline levels of IL22 and/or LCN2 or any other IL23 pathway analyte (including, e.g., CCL20, IL17F, IL17A/F, IL23R, IL12B, IL6, IL21, TNF, CCR6, CCL22, IL1R1, IFN- γ , S100A12, DEFB-2, DEFB-4, IL1, SERPINB3, PI3/Elafin, LL37, ROR γ , ROR γ T, IL26, S100A7, DEFB103B, or GM-CSF) reflects increased IL23 axis activity, a patient determined to have increased IL23 pathway activity (as determined by measuring one or more IL23 pathway biomarkers) may be more likely to benefit from treatment with an IL23 antagonist (including, e.g., an anti-IL23 antibody or an antigen-binding fragment thereof such as MEDI2070).

[00385] While the present invention has been described in terms of specific aspects, it is understood that variations and modifications will occur to those skilled in the art. Accordingly, only such limitations as appear in the claims should be placed on the invention.

[00386] The breadth and scope of the present invention should not be limited by any of the above-described exemplary aspects, but should be defined only in accordance with the following claims and their equivalents.

[00387] The foregoing description of the specific aspects will so fully reveal the general nature of the invention that others can, by applying knowledge within the skill of the art, readily modify and/or adapt for various applications such specific aspects, without undue experimentation, without departing from the general concept of the present invention. Therefore, such adaptations and modifications are intended to be within the meaning and range of equivalents of the disclosed aspects, based on the teaching and guidance presented herein. It is to be understood that the phraseology or terminology herein is for the purpose of description and not of limitation, such that the terminology or phraseology of the present specification is to be interpreted by the skilled artisan in light of the teachings and guidance.

[00388] This application claims the benefit of the filing date of U.S. Provisional Application No. 62/220,062 filed on September 17, 2015, which is incorporated by reference in its entirety herein.

CLAIMS

What is claimed is:

1. A method of treating an interleukin-23 (IL23)-mediated disease in a patient, comprising administering an IL23 antagonist to a patient if the patient is determined to have (i) a higher or increased level of interleukin-22 (IL22) and/or (ii) a higher or increased level of lipocalin 2 (LCN2) in one or more samples taken from the patient compared to a predetermined IL22 and/or LCN2 threshold level, or compared to a IL22 and/or LCN2 level in one or more control samples.

2. A method of treating a patient having an IL23-mediated disease comprising suspending or not initiating the administration of an IL23 antagonist to a patient if the patient is determined to have (i) a lower or decreased level of interleukin-22 (IL22) and/or (ii) a lower or decreased level of lipocalin 2 (LCN2) in one or more samples taken from the patient compared to a predetermined IL22 and/or LCN2 threshold level, or compared to a IL22 and/or LCN2 level in one or more control samples.

3. A method of treating an interleukin-23 (IL23)-mediated disease in a patient, wherein the patient failed, was non-responsive or intolerant to treatment with an anti-TNF agent comprising administering an IL23 antagonist to the patient if the patient is determined to have (i) a higher or increased level of interleukin-22 (IL22) and/or (ii) a higher or increased level of lipocalin 2 (LCN2) in one or more samples taken from the patient compared to a predetermined IL22 and/or LCN2 threshold level, or compared to a IL22 and/or LCN2 level in one or more control samples.

4. A method of determining whether to treat a patient having an IL23-mediated disease with an IL-23 antagonist, comprising determining to treat the patient if the patient is determined to have (i) a higher or increased level of interleukin-22 (IL22) and/or (ii) a higher or increased level of lipocalin 2 (LCN2) in one or more samples taken from the patient compared to a predetermined IL22 and/or LCN2 threshold level, or compared to a IL22 and/or LCN2 level in one or more control samples.

5. A method of selecting a patient diagnosed with an IL23-mediated disease as a candidate for treatment with an IL23 antagonist, comprising selecting the patient for treatment if the patient is determined to have (i) a higher or increased level of interleukin-22 (IL22) and/or (ii) a higher or increased level of lipocalin 2 (LCN2) in one or more samples taken from the patient compared to a predetermined IL22 and/or LCN2 threshold level, or compared to a IL22 and/or LCN2 level in one or more control samples.

6. The method according to any one of claims 1 to 5, further comprising measuring the level of IL22 and/or LCN2 in one or more of the samples obtained from the patient or instructing a clinical laboratory or healthcare provider to measure the level of IL22 and/or LCN2 in the sample and/or submitting the one or more samples obtained from the patient to a clinical laboratory or healthcare provider to measure the level of IL22 and/or LCN2 in the sample.

7. The method according to any one of claims 1 to 6, further comprising determining the level of IL22 and/or LCN2 in the one or more samples obtained from the patient.

8. The method according to any one of claims 1 to 7 further comprising advising a healthcare provider to administer an IL23 antagonist to the patient if the patient is determined to have (i) a higher or increased level of IL22 and/or (ii) a higher or increased level of LCN2 in one or more of the samples compared to a predetermined IL22 and/or LCN2 threshold level, or compared to a IL22 and/or LCN2 level in one or more control samples, or to suspend or deny the administration of an IL23 antagonist to the patient if the patient is determined to have (i) a lower or decreased level of IL22 and/or (ii) a lower or decreased level of LCN2 in one or more of the samples compared to a predetermined IL22 and/or LCN2 threshold level, or compared to a IL22 and/or LCN2 level in one or more control samples

9. A method of measuring the efficacy or pharmacodynamics of an IL23 antagonist in a patient diagnosed with an IL23-mediated disease, comprising:

- (a) measuring the level of IL22 and/or LCN2 in a first sample taken from the patient;
- (b) administering an IL23 antagonist; and

(c) measuring the level of IL22 and/or LCN2 in a second sample taken from the patient, wherein a reduction in the level of IL22 and/or LCN2 in the second sample compared to the patient's level IL22 and/or LCN2 in the first sample indicates that the patient is responding to treatment.

10. The method according to claim 9, wherein the second sample is taken 1, 2, 4, 8, 12, or 28 weeks, or at intervening times, after administering the IL23 antagonist.

11. The method according to any one of claims 1 to 10, wherein the IL23 antagonist is an anti-IL23 antibody or antigen-binding fragment thereof.

12. The method of claim 11, wherein the anti-IL23 antibody or antigen-binding fragment thereof binds to the p19 subunit of IL23 (SEQ ID NO: 13), to the p40 subunit of IL23 (SEQ ID NO: 14), or both.

13. The method according to any one of claims 11 or 12, wherein the anti-IL23 antibody or antigen-binding fragment thereof comprises ustekinumab, briakinumab, guselkumab, BI-655066, tildrakinumab, LY-3074828, or an antigen-binding fragment thereof.

14. The method according to claim 11, wherein the anti-IL23 antibody or antigen-binding fragment thereof comprises (i) a variable region (VH) comprising or consisting of SEQ ID NO: 5 and/or a light chain variable region (VL) comprising or consisting of SEQ ID NO: 6, or (ii) a variable region (VH) comprising or consisting of SEQ ID NO: 43 and/or a light chain variable region (VL) comprising or consisting of SEQ ID NO: 44.

15. The method according to claim 11, wherein the anti-IL23 antibody or antigen-binding fragment thereof comprises at least one complementarity determining region selected from SEQ ID NOS: 31-36 or SEQ ID NOS: 45-50.

16. The method according to any one of claims 14 or 15, wherein the antibody is administered at a fixed dose.

17. The method according to claim 16, wherein the fixed dose is between 10 and 1000 mg/dose.

18. The method according to claim 16, wherein the fixed dose is about 210 mg/dose or about 700 mg/dose.

19. The method according to any one of claims 1 to 18 wherein the patient has been treated before, during, after, or alternatively to the administration of an IL23 antagonist or anti-IL23 antibody or antigen-binding fragment with one or more additional therapies for the treatment of the IL23-mediated disease or disorder.

20. The method according to any one of claims 1 to 19, wherein the one or more samples taken from the patient and/or the one or more control samples are one or more selected from the group consisting of: whole blood, blood serum, plasma, saliva, sputum, bronchoalveolar lavage fluid, cerebrospinal fluid, pleural fluid, pericardial fluid, ascites, synovial fluid, epithelial cells, urine, stool, skin, tissue biopsy, or a combination thereof.

21. The method according to any one of claims 1 to 20, wherein the one or more control samples are (i) a sample or samples obtained from normal healthy individuals; (ii) a sample or samples obtained from patients with a non-IL23-mediated disease; or (iii) a combination thereof.

22. The method according to any one of claims 1 to 21, wherein the patient's level of IL22 and/or LCN2 is measured in an immunoassay.

23. The method according to any one of claims 1 to 22, further comprising determining the level of one or more IL23 Pathway Biomarkers selected from the group consisting of CCL20, IL17F, IL17A/F, IL23R, IL12B, IL6, IL21, TNF, CCR6, CCL22, IL1R1, IFN- γ , S100A12, DEFB-2, DEFB-4, IL1, SERPINB3, PI3/Elafin, LL37, ROR γ , ROR γ T, IL26, S100A7, DEFB103B, and GM-CSF.

24. The method according to any one of claims 1 to 23, wherein the predetermined threshold level of IL22 and/or LCN2 is selected from the group consisting of:

- (a) about the mean level of IL22 and/or LCN2;
- (b) about the median level of IL22 and/or LCN2; and
- (c) about the 1st, 2nd, 3rd, 4th, 5th, 6th, 7th, 8th, or 9th decile baseline level of IL22 and/or LCN2 as described in TABLES 4 or 5;

as measured in the serum using an immunoassay from a plurality of normal healthy patients, patients with a non-IL23-mediated disease, and/or patients with an IL23-mediated disease.

25. The method according to any one of claims 1 to 24, wherein the IL23-mediated disease or disorder is a pulmonary disease, an inflammatory bowel disease, a chronic inflammatory skin disease, an inflammatory disease, an autoimmune disease, a neurodegenerative disease, an infection, or a cancer.

26. The method according to any one of claims 1 to 25, wherein the IL23-mediated disease or disorder is selected from the group consisting of: asthma, IPF, COPD, Crohn's disease, ulcerative colitis (UC), celiac disease, atopic dermatitis, allergic contact dermatitis, eczema, psoriasis, alopecia areata, palmoplantar pustulosis, psoriatic arthritis, ankylosing spondylitis, arthritis, rheumatoid arthritis (RA), a rheumatic disorder, ANCA vasculitis, Behcet's disease, autoimmune thyroiditis, type 1 diabetes, multiple sclerosis (MS), Sjogren's syndrome (SS), systemic lupus erythematosus (SLE), Alzheimer's disease, mycobacterial disease, leishmaniasis, a fungal infection, a viral infection, gastric cancer, colorectal cancer, esophageal cancer, leukemia, hepatitis B virus (HBV)-related hepatocellular carcinoma, breast cancer, lung cancer, and nasopharyngeal cancer.

27. The method according to claim 25, wherein the inflammatory bowel disease is Crohn's disease, UC or Celiac Disease.

28. The method according to claim 27, wherein the patient is determined to have a level of CRP $\geq 5\text{mg/L}$ and/or a level of FCP $\geq 250\text{ }\mu\text{g/g}$, a level of FCP $\geq 200\text{ }\mu\text{g/g}$, a level of FCP $\geq 150\text{ }\mu\text{g/g}$, a level of FCP $\geq 100\text{ }\mu\text{g/g}$, or a level of FCP at least about $100\text{ }\mu\text{g/g}$ to at least about $250\text{ }\mu\text{g/g}$ in one or more samples taken from the patient.

29. The method according to any one of claims 1 to 28, wherein

(a) the predetermined IL22 threshold level is at least about 7.9 pg/mL to at least about 31.4 pg/mL as measured using an immunoassay; and/or

(b) the predetermined LCN2 threshold level is at least about 143 ng/mL to at least about 261 ng/mL as measured using an immunoassay.

30. The method according to claim 29, wherein

(a) the predetermined IL22 threshold level is about 15.6 pg/mL as measured using an immunoassay; and/or

(b) the predetermined LCN2 threshold level is about 215 ng/mL as measured using an immunoassay.

31. The method according to any one of claims 27 to 30, wherein administration of the IL23 antagonist or anti-IL23 antibody or antigen-binding fragment thereof results in a Crohn's Disease Activity Index (CDAI) response score reduction of at least 100 points and/or a reduction in the total CDAI score to below 150 points after first administering the anti-IL23 antibody or antigen-binding fragment thereof.

32. The method according to claim 31, wherein the CDAI response score reduction of at least 100 points or reduction in the total CDAI score to below 150 points occurs within 1, 2, 4, 8, 12, 16 or 24 weeks or later after first administering the IL23 antagonist or anti-IL23 antibody or antigen-binding fragment thereof.

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Subject Disposition

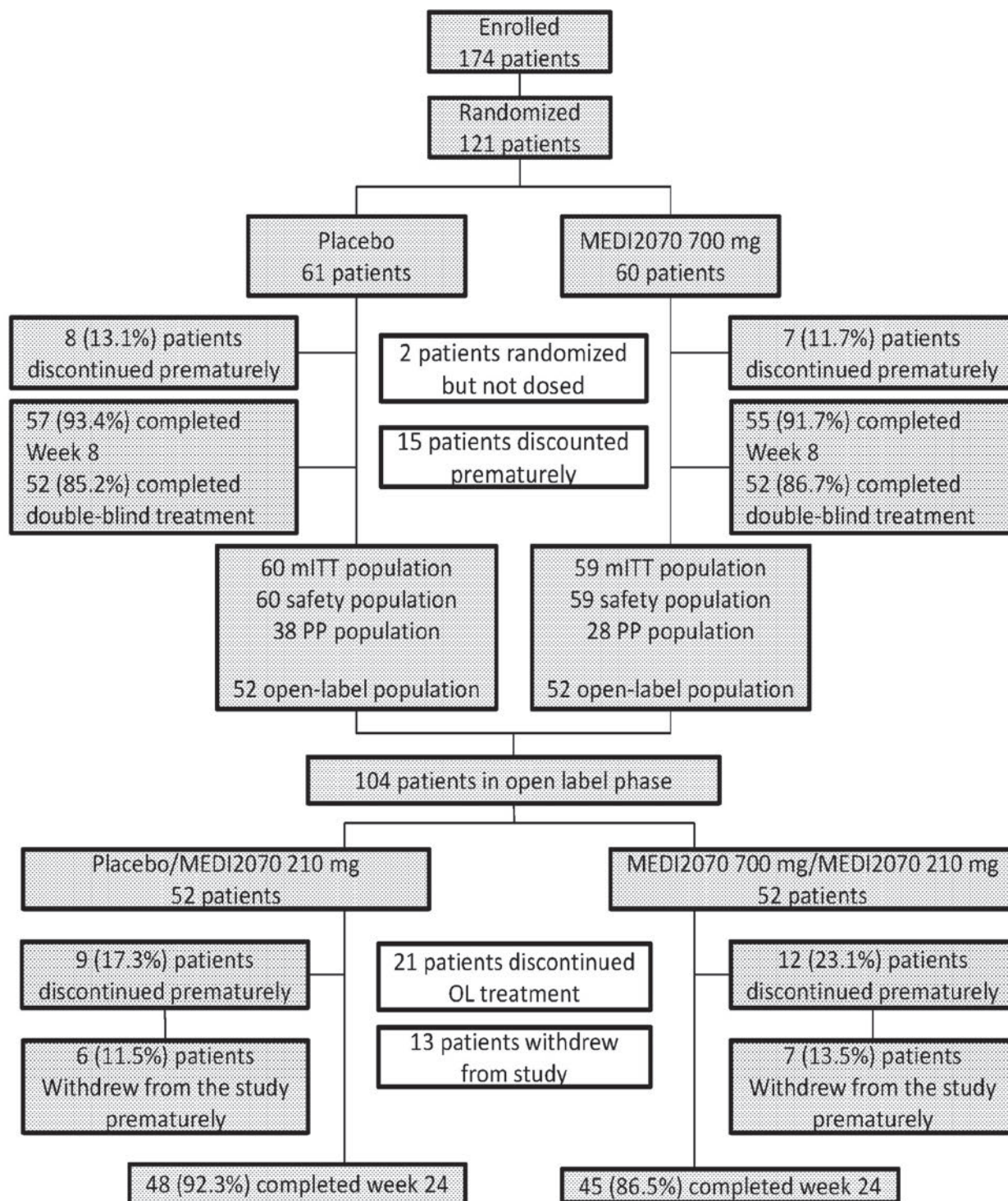


FIG. 1