(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 November 2022 (24.11.2022)

WIPO | PCT

(10) International Publication Number
WO 2022/243937 A1

(51) International Patent Classification:
A61K 39/395 (2006.01) *A61P 1/04* (2006.01)
A61P 1/00 (2006.01) *C07K 16/24* (2006.01)

(21) International Application Number:
PCT/IB2022/054701

(22) International Filing Date:
19 May 2022 (19.05.2022)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/191,076 20 May 2021 (20.05.2021) US

(71) Applicant: **JANSSEN BIOTECH, INC.** [US/US]; 800/850 Ridgeview Drive, Horsham, Pennsylvania 19044 (US).

(72) Inventors: **GERMINARO, Matthew**; 1400 McKean Road, Spring House, Pennsylvania 19477 (US). **O'BRIEN, Christopher**; 110 Chinaberry Drive, Lafayette Hill, Pennsylvania 19444 (US). **PERRIGOUE, Jacqueline**; 1400 McKean Road, Spring House, Pennsylvania 19477 (US). **VETTER, Marion**; 1400 McKean Road, Spring House, Pennsylvania 19477 (US).

(74) Agent: **SHIRTZ, Joseph F.** et al.; Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, New Jersey 08933 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,

(54) Title: METHOD OF TREATING INFLAMMATORY BOWEL DISEASE WITH A COMBINATION THERAPY OF ANTIBODIES TO IL-23 AND TNF ALPHA

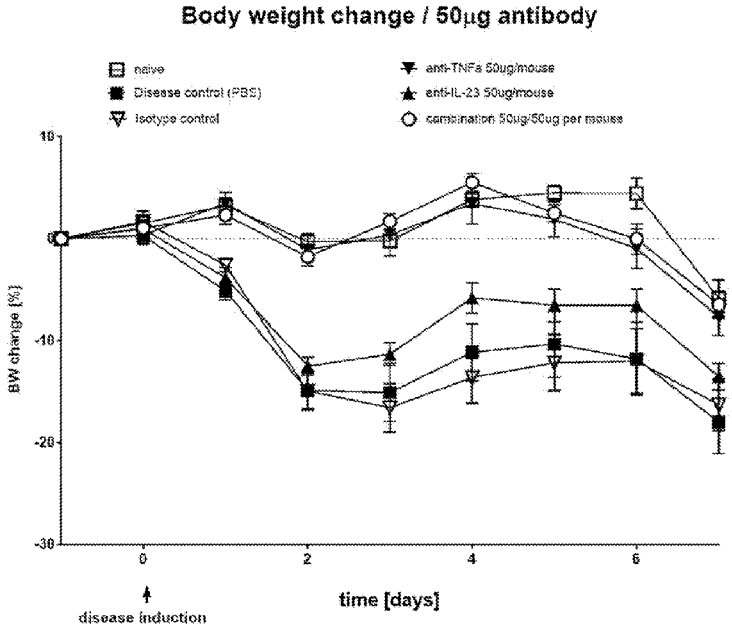


FIG. 1A

(57) Abstract: A method of treating inflammatory bowel disorders, such as ulcerative colitis, comprises administering an IL-23 inhibitor, such as an anti-IL-23p19 antibody (e.g., guselkumab) and a TNFα inhibitor, such as an anti-TNFα antibody (e.g., golimumab).

[Continued on next page]

WO 2022/243937 A1

EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
— *with sequence listing part of description (Rule 5.2(a))*
— *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

METHOD OF TREATING INFLAMMATORY BOWEL DISEASE WITH A COMBINATION THERAPY OF ANTIBODIES TO IL-23 AND TNF ALPHA

REFERENCE TO SEQUENCE LISTING SUBMITTED ELECTRONICALLY

[0001] This application contains a sequence listing, which is submitted electronically via EFSWeb as an ASCII formatted sequence listing with a file name "JBI6562WOPCT1_SEQLIST.txt", creation date of 27 April 2022 and having a size of 18 kb. The sequence listing submitted via EFSWeb is part of the specification and is herein incorporated by reference in its entirety

BACKGROUND OF THE INVENTION

[0002] Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are characterized by idiopathic intestinal inflammation, disruption of the epithelial barrier, and microbial dysbiosis. While the use of biologic agents, such as anti-TNFα antibody therapies, has revolutionized the clinical management of IBD, many patients do not achieve a clinical response with induction therapy and biologic therapies used as monotherapies have short term remission rates <20%.

[0003] The role of IL-23 in promoting intestinal inflammation has been demonstrated in several mouse models where attenuated colitis was exhibited in mice treated with neutralizing anti-IL-23p19 antibodies or in mice with a genetic deletion of the p19 subunit of IL-23. Genome-wide association studies (GWAS) have identified polymorphisms in the IL-23 receptor gene (IL23R) associated with both risk and protection for IBD. In patients with moderate to severe Crohn's disease, two anti-IL-23 agents, risankizumab (BI 655066) and brazikumab (MEDI2070, AMG-139), have recently reported Phase 2 results demonstrating efficacy. While there may be a role for anti-IL-23 therapies in the treatment of IBD, it is anticipated that a population of patients may not fully respond to IL-23 alone as observed with anti-TNFα therapies.

[0004] There is a need for improved treatment of IBD, particularly of patients that do not respond to therapies based on either an anti-TNFα antibody or an anti-IL-23 antibody alone.

SUMMARY OF THE INVENTION

[0005] Provided herein is a method of treating an inflammatory disease in a patient, the method comprising: a) administering a first co-therapeutically effective and clinically safe amount of an IL-23 inhibitor; and b) administering a second co-therapeutically effective and clinically safe amount of a TNFα inhibitor, wherein the method is effective to treat the inflammatory disease and the patient shows a clinical response.

[0006] In one embodiment of the method, the inflammatory disease is an inflammatory bowel disease (IBD) and the patient shows a clinical response based on a clinical endpoint selected from the group consisting of Mayo score, partial Mayo score, Ulcerative Colitis Endoscopic Index of Severity (UCEIS), the markers CRP and/or fecal calprotectin and patient-reported outcome and symptom measures.

[0007] In one embodiment of the method, the IL-23 inhibitor comprises an anti-IL-23p19 antibody or antigen-binding fragment thereof and the TNFα inhibitor comprises an anti-TNFα antibody or antigen-binding fragment thereof.

[0008] In one embodiment of the method, the IBD is Crohn's disease (CD).

[0009] In one embodiment of the method, the IBD is ulcerative colitis (UC) or indeterminate colitis.

[0010] In one embodiment of the method, the IBD is moderately to severely active UC.

[0011] In one embodiment of the method, the patient was previously treated with a TNFα inhibitor alone and wherein the UC did not undergo remission after the previous treatment.

[0012] In one embodiment of the method, the patient was previously treated with an IL-23 inhibitor alone and wherein the UC did not undergo remission after the previous treatment.

[0013] In one embodiment of the method, the anti-IL-23p19 antibody or antigen-binding fragment thereof comprises: a) heavy chain complementarity determining region (CDR) amino acid sequences of SEQ ID NOs: 1-3 and light chain CDR amino acid sequences of SEQ ID NOs: 4-6; b) heavy chain variable region amino acid sequence of SEQ ID NO: 7 and light chain variable region amino acid sequence of SEQ ID NO: 8; or c) heavy chain amino acid sequence of SEQ ID NO: 9 and a light chain amino acid sequence of SEQ ID NO: 10.

[0014] In one embodiment of the method, the anti-TNFα antibody or antigen-binding fragment thereof comprises: a) heavy chain CDR amino acid sequences of SEQ ID NOs: 11-13 and light chain CDR amino acid sequences of SEQ ID NOs: 14-16; b) heavy chain variable region amino

acid sequence of SEQ ID NO: 17 and light chain variable region amino acid sequence of SEQ ID NO: 18; or c) a heavy chain amino acid sequence of SEQ ID NO: 19 and light chain amino acid sequence of SEQ ID NO: 20.

[0015] In one embodiment of the method, the anti-IL-23p19 antibody or antigen-binding fragment thereof comprises: a) heavy chain CDR amino acid sequences of SEQ ID NOs: 1-3 and light chain CDR amino acid sequences of SEQ ID NOs: 4-6; b) heavy chain variable region amino acid sequence of SEQ ID NO: 7 and light chain variable region amino acid sequence of SEQ ID NO: 8; or c) heavy chain amino acid sequence of SEQ ID NO: 9 and light chain amino acid sequence of SEQ ID NO: 10, and the anti-TNFα antibody or antigen-binding fragment thereof comprises: a) heavy chain CDR amino acid sequences of SEQ ID NOs: 11-13 and light chain CDR amino acid sequences of SEQ ID NOs: 14-16; b) heavy chain variable region amino acid sequence of SEQ ID NO: 17 and light chain variable region amino acid sequence of SEQ ID NO: 18; or c) heavy chain amino acid sequence of SEQ ID NO: 19 and light chain amino acid sequence of SEQ ID NO: 20.

[0016] In one embodiment of the method, the IL-23 inhibitor comprises an anti-IL-23 antibody selected from the group consisting of guselkumab, risanakizumab, tildrakizumab and mirakizumab and the TNFα inhibitor is selected from the group consisting of golimumab, adalimumab, infliximab, certolizumab pegol and etanercept.

[0017] Further provided herein is a method of treating UC in a patient, the method comprising: a) administering a first co-therapeutically effective amount of an anti-IL-23p19 antibody comprising (i) heavy chain CDR amino acid sequences of SEQ ID NOs: 1-3 and light chain CDR amino acid sequences of SEQ ID NOs: 4-6, (ii) heavy chain variable region amino acid sequence of SEQ ID NO: 7 and the light chain variable region amino acid sequence of SEQ ID NO: 8, or (iii) the heavy chain amino acid sequence of SEQ ID NO: 9 and the light chain amino acid sequence of SEQ ID NO:10; and b) administering a second co-therapeutically effective amount of an anti-TNFα antibody comprising (i) heavy chain CDR amino acid sequences of SEQ ID NOs: 11-13 and light chain CDR amino acid sequences of SEQ ID NOs: 14-16, (ii) heavy chain variable region amino acid sequence of SEQ ID NO: 17 and the light chain variable region amino acid sequence of SEQ ID NO: 18, or (iii) heavy chain amino acid sequence of SEQ ID NO: 19 and the light chain amino acid sequence of SEQ ID NO: 20, wherein the method is effective and clinically safe to treat UC and the patient shows a clinical response based on a clinical endpoint selected from the

group consisting of Mayo score, partial Mayo score, UCEIS, the markers CRP and/or fecal calprotectin and patient-reported outcome and symptom measures.

[0018] In one embodiment of the method, the anti-TNFα antibody and the anti-IL-23p19 antibody are administered in a ratio of from 1:2 to 2:1 (w/w).

[0019] In one embodiment of the method, the anti-TNFα antibody and the anti-IL-23p19 antibody are administered in a ratio of from 15:1 to 400:1 (w/w).

[0020] In one embodiment of the method, the anti-IL-23p19 antibody and the anti-TNFα antibody are administered simultaneously.

[0021] In one embodiment of the method, the anti-IL-23p19 antibody and the anti-TNFα antibody are administered sequentially.

[0022] In one embodiment of the method, the anti-IL-23p19 antibody and the anti-TNFα antibody are administered within one day of one another.

[0023] In one embodiment of the method, the anti-IL-23p19 antibody is administered in an initial intravenous dose of 200 mg, intravenous doses of 200 mg at weeks 4 and 8 and subsequent subcutaneous doses of 100 mg every 8 weeks and the anti-TNFα antibody is administered in an initial subcutaneous dose of 200 mg and subsequent subcutaneous doses of 100 mg at weeks 2, 6 and 10.

[0024] In one embodiment of the method, the patient shows a clinical remission based on a clinical endpoint selected from the group consisting of Mayo score, partial Mayo score, UCEIS, the markers CRP and/or fecal calprotectin and patient-reported outcome and symptom measures.

[0025] In one embodiment of the method, the clinical endpoint is measured about 12 weeks or about 38 weeks after initial treatment.

[0026] In one embodiment of the method, the clinical endpoint is based on the Mayo Score.

[0027] Yet further provided herein is a method of reducing inflammation of the colon in a patient with IBD, the method comprising: a) administering a first co-therapeutically effective amount of an anti-IL-23p19 antibody or antigen-binding fragment thereof; and b) administering a second co-therapeutically effective amount of an anti-TNFα antibody or antigen-binding fragment thereof, wherein the method is effective and clinically safe to reduce inflammation of the colon of the patient to a level comparable to the colon of a normal subject.

[0028] In one embodiment of the method, the inflammation is very minimal or normal in a tissue sample from the colon of the patient after administration of the anti-IL-23p19 antibody or antigen-binding fragment thereof and the anti-TNFα antibody or antigen-binding fragment thereof.

[0029] In one embodiment of the method, gland loss is very minimal or normal in a tissue sample from the colon of the patient after administration of the anti-IL-23p19 antibody or antigen-binding fragment thereof and the anti-TNFα antibody or antigen-binding fragment thereof.

[0030] In one embodiment of the method, erosion is very minimal or normal in a tissue sample from the colon of the patient after administration of the anti-IL-23p19 antibody or antigen-binding fragment thereof and the anti-TNFα antibody or antigen-binding fragment thereof.

[0031] In one embodiment of the method, mucosal thickness and hyperplasia are independently very minimal or normal in a tissue sample from the colon of the patient after administration of the anti-IL-23p19 antibody or antigen-binding fragment thereof and the anti-TNFα antibody or antigen-binding fragment thereof.

[0032] In one embodiment of the method, after administration of the anti-IL-23p19 antibody or antigen-binding fragment thereof and the anti-TNFα antibody or antigen-binding fragment thereof, histopathology of the colon is identical to that of normal tissue.

[0033] In one embodiment of the method, the anti-IL-23p19 antibody or antigen-binding fragment thereof comprises: a) heavy chain CDR amino acid sequences of SEQ ID NOs: 1-3 and light chain CDR amino acid sequences of SEQ ID NOs: 4-6; b) heavy chain variable region amino acid sequence of SEQ ID NO: 7 and light chain variable region amino acid sequence of SEQ ID NO: 8; or c) heavy chain amino acid sequence of SEQ ID NO: 9 and light chain amino acid sequence of SEQ ID NO: 10; and the anti-TNFα antibody or antigen-binding fragment thereof comprises d) heavy chain CDR amino acid sequences of SEQ ID NOs: 11-13 and light chain CDR amino acid sequences of SEQ ID NOs: 14-16; e) heavy chain variable region amino acid sequence of SEQ ID NO: 17 and light chain variable region amino acid sequence of SEQ ID NO: 18; or f) heavy chain amino acid sequence of SEQ ID NO: 19 and light chain amino acid sequence of SEQ ID NO: 20.

[0034] In one embodiment of the method, the anti-TNFα antibody or antigen-binding fragment thereof and the anti-IL-23p19 antibody or antigen-binding fragment thereof are administered in a ratio of from 1:2 to 2:1 (w/w).

[0035] In one embodiment of the method, the anti-TNFα antibody or antigen-binding fragment thereof and the anti-IL-23p19 antibody or antigen-binding fragment thereof are administered in a ratio of from 15:1 to 400:1 (w/w).

[0036] In one embodiment of the method, the a) anti-IL-23p19 antibody or antigen-binding fragment thereof and the b) anti-TNFα antibody or antigen-binding fragment thereof are administered simultaneously.

[0037] In one embodiment of the method, the a) anti-IL-23p19 antibody or antigen-binding fragment thereof and the b) anti-TNFα antibody or antigen-binding fragment thereof are administered sequentially.

[0038] In one embodiment of the method, the a) anti-IL-23p19 antibody or antigen-binding fragment thereof and the b) anti-TNFα antibody or antigen-binding fragment thereof are administered within one day of one another.

[0039] Yet further provided herein is a method of treating IBD in a patient and reducing weight loss in the patient, the method comprising a) administering a first co-therapeutically and weight reducing effective and clinically safe amount of an anti-IL-23p19 antibody or antigen-binding fragment thereof; and b) administering a second co-therapeutically and weight reducing effective and clinically safe amount of an anti-TNFα antibody or antigen-binding fragment thereof.

[0040] In one embodiment of the method, the anti-TNFα antibody or antigen-binding fragment thereof and the anti-IL-23p19 antibody or antigen-binding fragment thereof are administered in a ratio of from 1:2 to 2:1 (w/w)

[0041] In one embodiment of the method, the anti-TNFα antibody or antigen-binding fragment thereof and the anti-IL-23p19 antibody or antigen-binding fragment thereof are administered in a ratio of from 15:1 to 400:1 (w/w).

[0042] In one embodiment of the method, the a) anti-IL-23p19 antibody or antigen-binding fragment thereof and the b) anti-TNFα antibody or antigen-binding fragment thereof are administered simultaneously.

[0043] In one embodiment of the method, the a) anti-IL-23p19 antibody or antigen-binding fragment thereof and the b) anti-TNFα antibody or antigen-binding fragment thereof are administered sequentially.

[0044] In one embodiment of the method, the a) anti-IL-23p19 antibody or antigen-binding fragment thereof and the b) anti-TNFα antibody or antigen-binding fragment thereof are administered within one day of one another.

[0045] In one embodiment of the method, the anti-IL-23p19 antibody or antigen-binding fragment thereof comprises: a) heavy chain CDR amino acid sequences of SEQ ID NOs: 1-3 and light chain CDR amino acid sequences of SEQ ID NOs: 4-6; b) heavy chain variable region amino acid sequence of SEQ ID NO: 7 and light chain variable region amino acid sequence of SEQ ID NO: 8; or c) heavy chain amino acid sequence of SEQ ID NO: 9 and light chain amino acid sequence of SEQ ID NO: 10; and the anti-TNFα antibody or antigen-binding fragment thereof comprises a) heavy chain CDR amino acid sequences of SEQ ID NOs: 11-13 and light chain CDR amino acid sequences of SEQ ID NOs: 14-16; b) heavy chain variable region amino acid sequence of SEQ ID NO: 17 and light chain variable region amino acid sequence of SEQ ID NO: 18; or c) heavy chain amino acid sequence of SEQ ID NO: 19 and light chain amino acid sequence of SEQ ID NO: 20.

[0046] Yet further provided herein is a method of treating moderately to severely active UC in a human patient, the method comprising: a) administering 0.0005 to 0.002 mg/kg of an anti-IL-23p19 antibody or an antigen-binding fragment thereof comprising the sequences of (i) heavy chain CDR amino acid sequences of SEQ ID NOs:1-3 and light chain CDR amino acid sequences of SEQ ID NOs: 4-6; (ii) heavy chain variable region amino acid sequence of SEQ ID NO: 7 and light chain variable region amino acid sequence of SEQ ID NO: 8; or (iii) heavy chain amino acid sequence of SEQ ID NO: 9 and light chain amino acid sequence of SEQ ID NO: 10; and b) administering 0.020 to 0.125 mg/kg of an anti-TNFα antibody or an antigen-binding fragment thereof comprising the sequences of (i) heavy chain CDR amino acid sequences of SEQ ID NOs: 11-13 and the light chain CDR amino acid sequences of SEQ ID NOs: 14-16; (ii) heavy chain variable region amino acid sequence of SEQ ID NO: 17 and light chain variable region amino acid sequence of SEQ ID NO: 18; or (iii) heavy chain amino acid sequence of SEQ ID NO: 19 and light chain amino acid sequence of SEQ ID NO: 20.

[0047] In one embodiment of the method, the method is effective and clinically safe in treating the UC.

[0048] In one embodiment of the method, the patient shows a clinical remission based on a clinical endpoint selected from the group consisting of Mayo score, partial Mayo score, UCEIS, the markers CRP and/or fecal calprotectin and patient-reported outcome and symptom measures.

[0049] In one embodiment of the method, the anti-IL-23p19 antibody or antigen-binding fragment thereof is in an aqueous solution in a pharmaceutical composition at 100 mg/mL; 7.9% (w/v) sucrose; 4.0 mM Histidine; 6.9 mM L-Histidine monohydrochloride monohydrate; 0.053% (w/v) Polysorbate 80 of the composition, and the anti-TNFα antibody or antigen-binding fragment thereof is in an aqueous solution in a pharmaceutical composition at 100 mg/mL; 4.1% (w/v) sorbitol; 5.6 mM L-Histidine and L-Histidine monohydrochloride monohydrate; 0.015% (w/v) Polysorbate 80 of the composition.

[0050] Yet further provided herein is a pharmaceutical product comprising a composition of: a) an anti-IL-23 inhibitor and b) an anti-TNFα inhibitor for use in combination therapy to treat an inflammatory disorder, wherein a first co-therapeutically effective and clinically safe amount of the IL-23 inhibitor and a second co-therapeutically effective and clinically safe amount of the TNFα inhibitor are administered to a patient and the patient shows a clinical response.

[0051] In one embodiment of the pharmaceutical product, the anti-IL-23 inhibitor is an anti-IL-23p19 antibody or antigen-binding fragment thereof and the anti-TNFα inhibitor is an anti-TNFα antibody or antigen-binding fragment thereof and the inflammatory disorder is an IBD.

[0052] In one embodiment of the pharmaceutical product, the IBD is UC, the anti-IL-23p19 antibody is guselkumab and the anti-TNFα antibody is golimumab.

[0053] Yet further provided herein is a method of treating UC in a patient, the method comprising a combination therapy phase followed by a monotherapy phase, wherein, i) the combination therapy phase comprises a) administering a first co-therapeutically effective and clinically safe amount of an anti-IL-23p19 antibody or antigen-binding fragment thereof and b) administering a second co-therapeutically effective and clinically safe amount of an anti-TNFα antibody or antigen-binding fragment thereof, and ii) the monotherapy phase comprises administering a therapeutically effective and clinically safe amount of the anti-IL-23p19 antibody or antigen-binding fragment thereof.

[0054] In one embodiment of the method, the anti-IL-23p19 antibody or antigen-binding fragment thereof comprises: a) heavy chain CDR amino acid sequences of SEQ ID NOs: 1-3 and light chain CDR amino acid sequences of SEQ ID NOs: 4-6; b) heavy chain variable region amino acid sequence of SEQ ID NO: 7 and light chain variable region amino acid sequence of SEQ ID NO: 8; or c) heavy chain amino acid sequence of SEQ ID NO: 9 and light chain amino acid sequence of SEQ ID NO: 10.

[0055] In one embodiment of the method, the anti-TNFα antibody or antigen-binding fragment thereof comprises: a) heavy chain CDR amino acid sequences of SEQ ID NOs: 11-13 and light chain CDR amino acid sequences of SEQ ID NOs: 14-16; b) heavy chain variable region amino acid sequence of SEQ ID NO: 17 and light chain variable region amino acid sequence of SEQ ID NO: 18; or c) heavy chain amino acid sequence of SEQ ID NO: 19 and light chain amino acid sequence of SEQ ID NO: 20

[0056] In one embodiment of the method, the anti-IL-23p19 antibody or antigen-binding fragment thereof comprises: a) heavy chain CDR amino acid sequences of SEQ ID NOs: 1-3 and light chain CDR amino acid sequences of SEQ ID NOS: 4-6; b) heavy chain variable region amino acid sequence of SEQ ID NO: 7 and light chain variable region amino acid sequence of SEQ ID NO: 8; or c) heavy chain amino acid sequence of SEQ ID NO: 9 and light chain amino acid sequence of SEQ ID NO: 10, and the anti-TNFα antibody or antigen-binding fragment thereof comprises: a) heavy chain CDR amino acid sequences of SEQ ID NOs: 11-13 and light chain CDR amino acid sequences of SEQ ID NOs: 14-16; b) heavy chain variable region amino acid sequence of SEQ ID NO: 17 and light chain variable region amino acid sequence of SEQ ID NO: 18; or c) heavy chain amino acid sequence of SEQ ID NO: 19 and light chain amino acid sequence of SEQ ID NO:20.

[0057] In one embodiment of the method, the anti-IL-23p19 antibody or antigen-binding fragment thereof is guselkumab and the anti-TNFα antibody or antigen-binding fragment thereof is golimumab.

[0058] In one embodiment of the method, during the combination therapy phase, the anti-TNFα antibody or antigen-binding fragment thereof and the anti-IL-23p19 antibody or antigen-binding fragment thereof are administered in a ratio of from 1:2 to 2:1 (w/w).

[0059] In one embodiment of the method, during the combination therapy phase, the anti-TNFα antibody or antigen-binding fragment thereof and the anti-IL-23p19 antibody or antigen-binding fragment thereof are administered in a ratio of from 15:1 to 400:1 (w/w).

[0060] In one embodiment of the method, during the combination therapy phase, the anti-IL-23p19 antibody or antigen-binding fragment thereof and the anti-TNFα antibody or antigen-binding fragment thereof are administered simultaneously.

[0061] In one embodiment of the method, during the combination therapy phase, the anti-IL-23p19 antibody or antigen-binding fragment thereof and the anti-TNFα antibody or antigen-binding fragment thereof are administered sequentially.

[0062] In one embodiment of the method, during the combination therapy phase, the anti-IL-23p19 antibody or antigen-binding fragment thereof and the anti-TNFα antibody or antigen-binding fragment thereof are administered within one day of one another.

[0063] In one embodiment of the method, the duration of the combination therapy phase is 12 weeks.

[0064] In one embodiment of the method, during the combination therapy phase, the anti-IL-23p19 antibody or antigen-binding fragment thereof is administered in an initial intravenous dose of 200 mg and intravenous doses of 200 mg at weeks 4 and 8 and the anti-TNFα antibody or antigen-binding fragment thereof is administered in an initial subcutaneous dose of 200 mg and subsequent subcutaneous doses of 100 mg at weeks 2, 6 and 10, and during the monotherapy phase, the anti-IL-23p19 antibody or antigen-binding fragment thereof is administered subcutaneously 100 mg every 8 weeks.

[0065] In one embodiment of the method, the patient shows a clinical response based on a clinical endpoint selected from the group consisting of Mayo score, partial Mayo score, UCEIS, the markers CRP and/or fecal calprotectin and patient-reported outcome and symptom measures, wherein the clinical response is measured about 12 weeks after initial treatment and/or about 38 weeks after initial treatment.

[0066] Yet further provided herein is a method of treating ulcerative colitis in a patient, the method comprising administering a therapeutically effective and clinically safe amount of an anti-IL-23p19 antibody or antigen-binding fragment thereof.

[0067] In one embodiment of the method, the anti-IL-23p19 antibody or antigen-binding fragment thereof comprises: a) heavy chain CDR amino acid sequences of SEQ ID NOs: 1-3 and

light chain CDR amino acid sequences of SEQ ID NOs: 4-6; b) heavy chain variable region amino acid sequence of SEQ ID NO: 7 and light chain variable region amino acid sequence of SEQ ID NO: 8; or c) heavy chain amino acid sequence of SEQ ID NO: 9 and light chain amino acid sequence of SEQ ID NO: 10.

[0068] In one embodiment of the method, the anti-IL-23p19 antibody or antigen-binding fragment thereof is guselkumab.

[0069] In one embodiment of the method, the anti-IL-23p19 antibody or antigen-binding fragment thereof is administered in an initial dose of 200 mg, 600 mg or 1200 mg and a dose of 100 mg 2 weeks after the initial dose, 6 weeks after the initial dose, 10 weeks after the initial dose and every 4 or 8 weeks after the dose at 10 weeks.

[0070] In one embodiment of the method, the patient shows a clinical response based on a clinical endpoint selected from the group consisting of Mayo score, partial Mayo score, UCEIS, the markers CRP and/or fecal calprotectin and patient-reported outcome and symptom measures.

BRIEF DESCRIPTION OF DRAWINGS

[0071] Fig. 1A and Fig. 1B show the results of a body weight loss analysis performed on mice after low dose (Fig. 1A at 50 µg) and high dose (Fig. 1B at 500 µg) anti-TNFα and anti-IL-23p19 antibody treatment alone or in combination. Each line represents the group mean with error bars for standard error (n=9 antibody treatment; n=5 PBS control; n=3 naïve control) and is shown as percent change from day -1 (dotted line). Some error bars are within the size of the symbol and are not depicted. Disease was induced by administration of anti-CD40 antibody (BioXCell, Cat. No. BE0016-2, Agonist CD40 Ab clone FGK4.55, lot# 5345/0515).

[0072] Fig. 2A and Fig. 2B show the results of a histopathology study performed on the colon of mice treated with low dose (Fig. 2A at 50 µg/mouse) anti-TNFα and/or anti-IL-23p19 antibody and high dose (Fig. 2B at 500 µg/mouse) anti-TNFα and/or anti-IL-23p19 antibody, respectively. Disease was induced by administration of anti-CD40 antibody.

[0073] Fig. 3A shows humanized treatment signatures of anti-TNFα or anti-IL-23p19 monotherapy from the anti-CD40 model of murine colitis projected onto the Crohn's Evaluation of Response to Ustekinumab Anti-Interleukin-12/23 for Induction (CERTIFI) human IBD gene expression network. Fig. 3A shows the overlap between genes present in the anti-TNFα and

anti-IL-23p19 subnetworks as illustrated by a Venn diagram. Fig. 3B illustrates the largest connected component of the shared anti-TNFα and anti-IL-23p19 subnetworks.

[0074] Fig. 4A, Fig. 4B, Fig. 4C and Fig. 4D show the results of a body weight loss analysis performed on female $RAG2^{-/-}$ mice dosed ip with isotype control antibody (Fig. 4A), or anti-IL-23p19 antibody (Fig. 4B) at 50, 15, 5, 1.5. 0.5, 0.15 μg/mouse, or an anti-TNFα antibody (Fig. 4C) at 150 and 15 μg/mouse. Disease was induced by administration of anti-CD40 antibody. As shown in Fig. 4D, statistics were generated comparing each group to the isotype control.

[0075] Fig. 5A, Fig. 5B and Fig. 5C show the results of a histopathology study performed on the colon of female $RAG2^{-/-}$ mice dosed ip with isotype control antibody (Fig. 5A), anti-IL-23p19 antibody at 50, 15, 5, 1.5. 0.5, 0.15 μg/mouse (Fig. 5B), or an anti-TNFα antibody at 150 and 15 μg/mouse (Fig. 5C). Disease was induced by administration of anti-CD40 antibody.

[0076] Fig. 6A, Fig. 6B, Fig. 6C and Fig. 6D show the results of a body weight loss analysis performed on mice dosed with control antibody (Fig. 6A), 500 μg/mouse anti-TNFα antibody alone (Fig. 6B), 1.5, 5, or 25 μg/mouse anti-IL-23p19 antibody alone (Fig. 6C), or a combination of 500 μg/mouse anti-TNFα antibody with 1.5, 5, or 25 μg/mouse anti-IL-23p19 antibody (Fig. 6D). Disease was induced by administration of anti-CD40 antibody. Fig. 6E shows a compilation of the data from the different groups.

[0077] Fig. 7A, Fig. 7B and Fig. 7C show the results of a histopathology study performed on the colon of mice dosed with 500 μg/mouse anti-TNFα antibody alone, mouse anti-IL-23p19 antibody alone, or a combination of 500 μg/mouse anti-TNF antibody with mouse anti-IL-23p19 antibody at an anti-IL-23p19 antibody concentration of: 1.5 μg (Fig. 7A), 5 μg (Fig. 7B), or 25 μg (Fig. 7C). Disease was induced by administration of anti-CD40 antibody.

[0078] Fig. 8 shows the results of a network analysis based on humanized colonic gene expression signatures of anti-TNFα (500 μg) or high dose anti-IL-23p19 (25 μg) monotherapies that were intersected with a gene expression signature from the combination therapy (500 μg anti-TNFα with 1.5 μg anti-IL-23p19). The analysis was performed to determine whether the molecular response to anti-TNFα and low dose anti-IL-23p19 antibody combination treatment was additive or unique compared with either therapy alone. A unique subnetwork was identified of about 200 genes; the subnetwork was enriched in fibroblasts and extracellular matrix organization, cell types and pathways involved in wound repair and mucosal healing.

DETAILED DESCRIPTION OF THE INVENTION

[0079] Definitions:

[0080] Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

[0081] As used herein, including the appended claims, the singular forms of words such as "a," "an," and "the," include their corresponding plural references unless the context clearly dictates otherwise.

[0082] "About" means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system. Unless explicitly stated otherwise within the Examples or elsewhere in the Specification in the context of a particular assay, result or embodiment, "about" means within one standard deviation per the practice in the art, or a range of up to 5%, whichever is larger.

[0083] "Administration" and "treatment," as it applies to an animal, human, experimental subject, cell, tissue, organ, or biological fluid, refers to contact of an exogenous pharmaceutical, therapeutic, diagnostic agent, or composition to the animal, human, subject, cell, tissue, organ, or biological fluid. "Administration" and "treatment" can refer, e.g., to therapeutic, pharmacokinetic, diagnostic, research, and experimental methods. Treatment of a cell encompasses contact of a reagent to the cell, as well as contact of a reagent to a fluid, where the fluid is in contact with the cell. "Administration" and "treatment" also means in vitro and ex vivo treatments, e.g., of a cell, by a reagent, diagnostic, binding composition, or by another cell.

[0084] "Treatment," as it applies to a human, veterinary, or research subject, refers to therapeutic treatment, prophylactic or preventative measures, to research and diagnostic applications. "Treatment" as it applies to a human, veterinary, or research subject, or cell, tissue, or organ, encompasses contact of an agent with animal subject, a cell, tissue, physiological compartment, or physiological fluid. "Treatment of a cell" also encompasses situations where the agent contacts a target, such as IL-23 receptor, e.g., in the fluid phase or colloidal phase, but also situations where the agonist or antagonist does not contact the cell or the receptor.

[0085] "Treat" or "treating" may also refer to administration of a therapeutic agent, such as a composition described herein, internally or externally to a patient in need of the therapeutic agent. Typically, the agent is administered in an amount effective to prevent or alleviate one or more disease symptoms, or one or more adverse effects of treatment with a different therapeutic agent, whether by preventing the development of, inducing the regression of, or inhibiting the progression of such symptom(s) or adverse effect(s) by any clinically measurable degree. The amount of a therapeutic agent that is effective to alleviate any particular disease symptom or adverse effect (also referred to as the "therapeutically effective amount") may vary according to factors such as the disease state, age, and weight of the patient, the ability of the therapeutic agent to elicit a desired response in the patient, the overall health of the patient, the method, route and dose of administration, and the severity of side effects.

[0086] An "inhibitor," as used herein, is any agent that reduces the activity of a targeted molecule. Specifically, an antagonist of IL-23 or TNFα is an agent that reduces the biological activity of IL-23 or TNFα, for example by blocking binding of IL-23 or TNFα to its receptor or otherwise reducing its activity (e.g. as measured in a bioassay).

[0087] As used herein, an "anti-IL-23 specific antibody," "anti-IL-23 antibody," "antibody portion," or "antibody fragment" and/or "antibody variant" and the like include any protein or peptide containing molecule that comprises at least a portion of an immunoglobulin molecule, such as but not limited to, at least one complementarity determining region (CDR) of a heavy or light chain or a ligand binding portion thereof, a heavy chain or light chain variable region, a heavy chain or light chain constant region, a framework region, or any portion thereof, or at least one portion of an IL-23 receptor or binding protein, which can be incorporated into an antibody of the present invention. Such antibody optionally further affects a specific ligand, such as but not limited to, where such antibody modulates, decreases, increases, antagonizes, agonizes, mitigates, alleviates, blocks, inhibits, abrogates and/or interferes with at least one IL-23 activity or binding, or with IL-23 receptor activity or binding, in vitro, in situ and/or in vivo. As a nonlimiting example, a suitable anti-IL-23 antibody, specified portion or variant of the present invention can bind at least one IL-23 molecule, or specified portions, variants or domains thereof. A suitable anti-IL-23 antibody, specified portion, or variant can also optionally affect at least one of IL-23 activity or function, such as but not limited to, RNA, DNA or protein synthesis,

IL-23 release, IL-23 receptor signaling, membrane IL-23 cleavage, IL-23 activity, IL-23 production and/or synthesis.

[0088] The term "antibody" is further intended to encompass antibodies, digestion fragments, specified portions and variants thereof, including antibody mimetics or comprising portions of antibodies that mimic the structure and/or function of an antibody or specified fragment or portion thereof, including single chain antibodies and fragments thereof. Functional fragments include antigen-binding fragments that bind to a mammalian IL-23. For example, antibody fragments capable of binding to IL-23 or portions thereof, include, but are not limited to, Fab (e.g., by papain digestion), Fab' (e.g., by pepsin digestion and partial reduction) and F(ab')2 (e.g., by pepsin digestion), facb (e.g., by plasmin digestion), pFc' (e.g., by pepsin or plasmin digestion), Fd (e.g., by pepsin digestion, partial reduction and reaggregation), Fv or scFv (e.g., by molecular biology techniques) fragments.

[0089] Such fragments can be produced by enzymatic cleavage, synthetic or recombinant techniques, as known in the art and/or as described herein. Antibodies can also be produced in a variety of truncated forms using antibody genes in which one or more stop codons have been introduced upstream of the natural stop site. For example, a combination gene encoding a F(ab')2 heavy chain portion can be designed to include DNA sequences encoding the CH1 domain and/or hinge region of the heavy chain. The various portions of antibodies can be joined together chemically by conventional techniques, or can be prepared as a contiguous protein using genetic engineering techniques.

[0090] "Humanized antibody" refers to an antibody in which the antigen binding sites are derived from non-human species and the variable region frameworks are derived from human immunoglobulin sequences. Humanized antibody may include substitutions in the framework so that the framework may not be an exact copy of expressed human immunoglobulin or human immunoglobulin germline gene sequences.

[0091] "Human antibody" refers to an antibody having heavy and light chain variable regions in which both the framework and the antigen binding site are derived from sequences of human origin. If the antibody contains a constant region or a portion of the constant region, the constant region also is derived from sequences of human origin.

[0092] "Subject" or "patient" as used interchangeably includes any human or nonhuman animal "Nonhuman animal" includes all vertebrates, e.g., mammals and non-mammals, such as nonhuman primates, sheep, dogs, cats, horses, cows, chickens, amphibians, reptiles, etc.

[0093] "Tumor necrosis factor," "TNF" or "TNFα" refers to the well-known human tumor necrosis factor-α (TNFα), a multifunctional pro-inflammatory cytokine. TNFα triggers pro-inflammatory pathways that result in tissue injury, such as degradation of cartilage and bone, induction of adhesion molecules, induction of pro-coagulant activity on vascular endothelial cells, an increase in the adherence of neutrophils and lymphocytes, and stimulation of the release of platelet activating factor from macrophages, neutrophils and vascular endothelial cells.

[0094] TNFα is found as a soluble protein as well as a precursor form called transmembrane TNFα that is expressed as a cell surface type II polypeptide. Transmembrane TNFα is processed by metalloproteinases such as TNFα-converting enzyme (TACE) between residues Ala76 and Va177, resulting in the release of the soluble form of TNFα of 157 amino acid residues. Soluble TNFα is a homotrimer of 17-kDa cleaved monomers. Transmembrane TNFα also exists as a homotrimer of 26-kD uncleaved monomers.

[0095] In a first aspect is provided a method of treating an inflammatory bowel disease (IBD) in a subject. The method comprises administering a first co-therapeutically effective amount of an IL-23 inhibitor and administering a second co-therapeutically effective amount of a TNFα inhibitor. The method is effective to treat the inflammatory bowel disease, and the first and second co-therapeutically effective amounts are the same or different.

[0096] The combination of an IL-23 inhibitor (e.g., an anti-IL-23 antibody or antigen-binding fragment thereof) and a TNFα inhibitor (e.g., an anti-TNFα antibody or antigen-binding fragment thereof) may provide a systemic impact as well as a local impact on the bowel or colon. The combination may provide a greater systemic impact than by treatment with either an IL-23 inhibitor (e.g., an anti-IL-23 antibody or antigen-binding fragment thereof) or a TNFα inhibitor (e.g., an anti-TNFα antibody or antigen-binding fragment thereof) alone. The combination can provide for superior anti-inflammatory activity in treating IBD in a human. An anti-IL-23 antibody (e.g., an anti-IL-23p19 antibody that binds the p19 subunit of IL-23) can be highly efficacious in blocking the development of IBD (e.g., colitis and Crohn's disease), but not in blocking anti-CD40-induced body weight loss, while an anti-TNFα antibody can provide

substantial protection against anti-CD40-induced body weight loss with some degree of protection against IBD. Each antibody, and the combination, may provide for a differential effect on local versus systemic inflammation.

[0097] In one embodiment, the IL-23 inhibitor used herein is selected from anti-IL-23 antibodies or antigen-binding fragments thereof, which include, without limitation, guselkumab, risanakizumab, tildrakizumab and mirakizumab. In one embodiment, the IL-23 inhibitor is selected from any of the anti-IL-23p19 antibodies and antigen-binding fragments thereof described in U.S. Patent No. 7,491,391 and U.S. Patent Application Publication No. 2018/0094052, the entire disclosure of which are incorporated herein by reference.

[0098] In one embodiment, the anti-IL-23p19 antibody or an antigen-binding fragment thereof comprises complementarity determining region (CDR) sequences of: (i) heavy chain CDR amino acid sequences of SEQ ID NO: 1 (HCDR1), SEQ ID NO: 2 (HCDR2), and SEQ ID NO: 3 (HCDR3); and (ii) light chain CDR amino acid sequences of SEQ ID NO: 4 (LCDR1), SEQ ID NO: 5 (LCDR2), and SEQ ID NO: 6 (LCDR3). In one embodiment, the anti-IL-23p19 antibody or an antigen-binding fragment thereof comprises a heavy chain variable region amino acid sequence of SEQ ID NO: 7 and a light chain variable region amino acid sequence of SEQ ID NO: 8. In one embodiment, the anti-IL-23p19 antibody or an antigen-binding fragment thereof comprises a heavy chain amino acid sequence of SEQ ID NO: 9 and a light chain amino acid sequence of SEQ ID NO: 10.

[0099] Table 1: Anti-IL-23p19 Antibody Sequences:

SEQ ID NO:	Description	Sequence
1	HCDR1	NYWIG
2	HCDR2	IIDPSNSYTR YSPSFQG
3	HCDR3	WYYKPFDV
4	LCDR1	TGSSSNIGSG YDVH
5	LCDR2	GNSKRPS
6	LCDR3	ASWTDGLSLV V
7	VH	EVQLVQSGAE VKKPGESLKI SCKGSGYSFS NYWIGWVRQM PGKGLEWMGI IDPSNSYTRY SPSFQGQVTI SADKSISTAY LQWSSLKASD TAMYYCARWY YKPFDVWGQG TLVTVSS
8	VL	QSVLTQPPSV SGAPGQRVTI SCTGSSSNIG SGYDVHWYQQ LPGTAPKLLI YGNSKRPSGV PDRFSGSKSG TSASLAITGL QSEDEADYYC ASWTDGLSLV VFGGGTKLTV L
9	Heavy Chain	EVQLVQSGAE VKKPGESLKI SCKGSGYSFS NYWIGWVRQM PGKGLEWMGI IDPSNSYTRY SPSFQGQVTI SADKSISTAY LQWSSLKASD TAMYYCARWY YKPFDVWGQG TLVTVSSAST

		KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTQTYIC NVNHKPSNTK VDKKVEPKSC DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT LPPSRDELTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK
10	Light Chain	QSVLTQPPSV SGAPGQRVTI SCTGSSSNIG SGYDVHWYQQ LPGTAPKLLI YGNSKRPSGV PDRFSGSKSG TSASLAITGL QSEDEADYYC ASWTDGLSLV VFGGGTKLTV LGQPKAAPSV TLFPPSSEEL QANKATLVCL ISDFYPGAVT VAWKADSSPV KAGVETTTPS KQSNNKYAAS SYLSLTPEQW KSHRSYSCQV THEGSTVEKT VAPTECS

[0100] In one embodiment, the IL-23 inhibitor used herein is guselkumab (an anti-IL-23p19 antibody marketed by Janssen Biotech, Inc. under the tradename TREMFYA®).

[0101] In one embodiment, the TNFα inhibitor used herein is selected from golimumab, adalimumab, infliximab, certolizumab pegol, and etanercept. In one embodiment, the TNFα inhibitor is selected from the anti-TNFα antibodies and antigen-binding fragments thereof described in U.S. Patent No. 7,250,165 and U.S. Patent Application Publication No. 2017/0218092, the entire disclosure of which are incorporated herein by reference.

[0102] In one embodiment, the TNFα inhibitor used herein is an anti-TNFα antibody or an antigen-binding fragment thereof comprising CDR sequences of: (i) heavy chain CDR amino acid sequences of SEQ ID NO: 11 (HCDR1), SEQ ID NO: 12 (HCDR2), and SEQ ID NO: 13 (HCDR3); and (ii) light chain CDR amino acid sequences of SEQ ID NO: 14 (LCDR1), SEQ ID NO: 15 (LCDRL), and SEQ ID NO: 16 (LCDR3). In one embodiment, the TNF-α inhibitor used herein is an anti-TNF-α antibody or an antigen-binding fragment thereof comprising a heavy chain variable region amino acid sequence of SEQ ID NO: 17 and a light chain variable region amino acid sequence of SEQ ID NO: 18. In one embodiment, the TNF-α inhibitor used herein is an anti-TNF-α antibody or an antigen-binding fragment thereof comprising a heavy chain amino acid sequence of SEQ ID NO: 19 and a light chain amino acid sequence of SEQ ID NO: 20.

[0103] Table 2: Anti-TNFα Antibody Sequences:

SEQ ID NO:	Description	Sequence

11	HCDR1	SYAMH
12	HCDR2	FMSYDGSNKK YADSVKG
13	HCDR3	DRGIAAGGNY YYYGMDV
14	LCDR1	RASQSVYSYL A
15	LCDR2	DASNRAT
16	LCDR3	QQRSNWPPFT
17	VH	QVQLVESGGG VVQPGRSLRL SCAASGFIFS SYAMHWVRQA PGNGLEWVAF MSYDGSNKKY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARDR GIAAGGNYYY YGMDVWGQGT TVTVSS
18	VL	EIVLTQSPAT LSLSPGERAT LSCRASQSVY SYLAWYQQKP GQAPRLLIYD ASNRATGIPA RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ RSNWPPFTFG PGTKVDIKRT V
19	Heavy Chain	QVQLVESGGG VVQPGRSLRL SCAASGFIFS SYAMHWVRQA PGNGLEWVAF MSYDGSNKKY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARDR GIAAGGNYYY YGMDVWGQGT TVTVSSASTK GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKKVEPKSCD KTHTCPPCPA PELLGGPSVF LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG QPREPQVYTL PPSRDELTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGK
20	Light Chain	EIVLTQSPAT LSLSPGERAT LSCRASQSVY SYLAWYQQKP GQAPRLLIYD ASNRATGIPA RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ RSNWPPFTFG PGTKVDIKRT VAAPSVFIFP PSDEQLKSGT ASVVCLLNNF YPREAKVQWK VDNALQSGNS QESVTEQDSK DSTYSLSSTL TLSKADYEKH KVYACEVTHQ GLSSPVTKSF NRGEC

[0104] In one embodiment, the TNF-α inhibitor used herein is golimumab (an anti-TNF-α antibody marketed by Janssen Biotech, Inc. under the tradename SIMPONI®).

[0105] Various host animals may be used to produce anti-TNFα antibodies. For example, Balb/c mice may be used to generate mouse anti-human TNFα antibodies. The antibodies made in Balb/c mice and other non-human animals may be humanized using various technologies to generate more human-like sequences.

[0106] Anti-IL-23 antibodies can optionally be characterized by high affinity binding to IL-23 and, optionally, having low toxicity. Anti-TNFα antibodies can optionally be characterized by high affinity binding to TNFα and, optionally, having low toxicity. In particular, an antibody,

specified fragment or variant of the antibody may be used in where the individual components, such as the variable region, constant region and framework, individually and/or collectively, optionally and preferably possess low immunogenicity. Low or acceptable immunogenicity and/or high affinity, as well as other suitable properties, can contribute to the therapeutic results achieved. "Low immunogenicity" is defined herein as raising significant HAHA, HACA or HAMA responses in less than about 75%, or preferably less than about 50% of the patients treated and/or raising low titers in the patient treated (less than about 300, preferably less than about 100 measured with a double antigen enzyme immunoassay) (Elliott et al., Lancet 344:1125-1127 (1994), entirely incorporated herein by reference). For the anti-IL-23 antibodies, "low immunogenicity" can also be defined as the incidence of titrable levels of antibodies to the anti-IL-23 antibody in patients treated with anti-IL-23 antibody as occurring in less than 25% of patients treated, preferably, in less than 10% of patients treated with the recommended dose for the recommended course of therapy during the treatment period. For the anti-TNFα antibodies, "low immunogenicity" can also be defined as the incidence of titratable levels of antibodies to the anti-TNFα antibody in patients treated with anti-TNFα antibody as occurring in less than 25% of patients treated, preferably, in less than 10% of patients treated with the recommended dose for the recommended course of therapy during the treatment period.

[0107] At least one anti-IL-23 antibody and anti-TNFα antibody used in the methods described herein can be produced by a cell line, a mixed cell line, an immortalized cell or clonal population of immortalized cells, as well known in the art. See, e.g., Ausubel, et al., ed., Current Protocols in Molecular Biology, John Wiley & Sons, Inc., NY (1987-2001); Sambrook, et al., Molecular Cloning: A Laboratory Manual, 2nd Edition, Cold Spring Harbor, N.Y. (1989); Harlow and Lane, Antibodies, a Laboratory Manual, Cold Spring Harbor, N.Y. (1989); Colligan, et al., eds., Current Protocols in Immunology, John Wiley & Sons, Inc., NY (1994-2001); Colligan et al., Current Protocols in Protein Science, John Wiley & Sons, NY (1997-2001), each entirely incorporated herein by reference herein.

[0108] An anti-IL-23 antibody and/or an anti-TNFα antibody can also be generated by immunization of a transgenic animal (e.g., mouse, rat, hamster, non-human primate, and the like) capable of producing a repertoire of human antibodies, as described herein and/or as known in the art. Cells that produce a human anti-IL-23 antibody can be isolated from such animals and immortalized using suitable methods, such as the methods described herein.

[0109] The anti-IL-23 antibodies used in the methods described herein can also be prepared using at least one anti-IL-23 antibody encoding nucleic acid to provide transgenic animals or mammals, such as goats, cows, horses, sheep, rabbits, and the like, that produce such antibodies in their milk. The anti-TNFα antibodies used in the methods described herein can also be prepared using at least one anti-TNFα antibody encoding nucleic acid to provide transgenic animals or mammals, such as goats, cows, horses, sheep, rabbits, and the like, that produce such antibodies in their milk. Such animals can be provided using known methods. See, e.g., but not limited to, U.S. Patent Nos. 5,827,690; 5,849,992; 4,873,316; 5,849,992; 5,994,616; 5,565,362; 5,304,489, and the like, each of which is entirely incorporated herein by reference.

[0110] The anti-IL-23 antibodies can bind human IL-23 with a wide range of affinities (KD). In a preferred embodiment, a human mAb can optionally bind human IL-23 with high affinity. For example, a human mAb can bind human IL-23 with a KD equal to or less than about 10^{-7} M, such as but not limited to, 0.1-9.9 (or any range or value therein) X 10^{-7}, 10^{-8}, 10^{-9}, 10^{-10}, 10^{-11}, 10^{-12}, 10^{-13} or any range or value therein.

[0111] The anti-TNFα antibodies can bind human TNFα with a wide range of affinities (KD). In a preferred embodiment, a human mAb can optionally bind human TNFα with high affinity. For example, a human mAb can bind human TNFα with a KD equal to or less than about 10^{-7} M, such as but not limited to, 0.1-9.9 (or any range or value therein) X 10^{-7}, 10^{-8}, 10^{-9}, 10^{-10}, 10^{-11}, 10^{-12}, 10^{-13} or any range or value therein.

[0112] The anti-IL-23 antibodies may be an IgG1, IgG2, IgG3 or IgG4 isotype. The anti-TNFα antibodies may be an IgG1, IgG2, IgG3 or IgG4 isotype.

[0113] Without wishing to be bound by theory, the benefits of combining an anti-IL-23 antibody with an anti-TNFα antibody can arise from distinct gene expression changes induced by each antibody. As described in the Example 1 and at least in Fig. 2A and Fig. 2B, at doses where each antibody provided similar protection against colonic inflammation (Fig. 2, 50 µg anti-IL-23p19 and 500 µg anti-TNFα), distinct intestinal gene expression changes were observed in mice when blocking IL-23p19 compared to blocking TNFα. These gene expression changes may apply to human disease as well. Integration of 'humanized' murine anti-TNFα and anti-IL-23p19 gene signatures with a human intestinal biopsy gene network can allow for focus only on genes that were expressed and varied in human intestinal tissues. Additional context for the potential molecular impact of each antibody on human IBD can be obtained by generating treatment

subnetworks that included genes one step removed in the network (i.e. strongly correlated) from genes within each signature. Individual anti-TNFα and anti-IL-23 subnetworks show unique single antibody gene signatures, allowing for insight into the biology targeted by both mechanisms.

[0114] Effectiveness of treatment according to the methods described herein can be determined, for example, by assessing the degree of weight loss, nutrient absorption, and histopathological studies of tissue samples. Histopathological studies can include measurement of one or more of submucosal edema, inflammation, gland loss, erosion, mucosal thickness, and hyperplasia.

[0115] Submucosal edema can be quantified by measuring thickness from the muscularis mucosa to the internal border of the outer muscle layer (e.g., in a nontangential area thought to best represent the severity of this change). Inflammation scoring can reflect the extent of macrophage, lymphocyte, and neutrophil infiltration into the colon. Gland loss of the crypt epithelium and remaining gland epithelium can be quantitated by assessing the percentage of the mucosa affected. Erosion reflects a loss of surface epithelium and can be scored by assessing the percentage of mucosa that is affected (e.g., by mucosal hemorrhage). Mucosal thickness can be assessed by measuring a non-tangential area of the section that best represents the overall mucosal thickness. Increased thickness reflects gland elongation and mucosal hyperplasia.

[0116] An overall histopathology score can be derived from measurements of one or more of submucosal edema, inflammation, gland loss, erosion, mucosal thickness, and hyperplasia. An exemplary scoring system for mice is described in Example 1. A similar system can be used for human and other mammalian subjects.

[0117] In some embodiments, the inflammatory bowel disease is colitis, e.g., ulcerative colitis. Colitis can involve irritation, swelling and other signs of inflammation of the colon. Sores and ulcers are present in ulcerative colitis.

[0118] In some embodiments, the inflammatory bowel disease is Crohn's disease. Crohn's disease may be confined to the colon, but may also be present in other tissues such as the small intestine. Crohn's disease can involve inflammation of the colon and small intestine. There may even be inflammation of the mouth, anus, skin, eyes, joints, and/or liver.

[0119] In some embodiments, the subject was previously treated with a TNFα inhibitor alone and the inflammatory bowel disease did not undergo remission after the previous treatment. In some embodiments, the subject was previously treated with an IL-23 inhibitor alone and the inflammatory bowel disease did not undergo remission after the previous treatment. The methods described herein may be beneficial for subjects who did not respond to monotherapy treatments with either TNFα inhibitor (e.g., an anti-TNFα antibody) or IL-23 inhibitor (e.g., an anti-IL-23 antibody). Based on results described herein showing substantial improvement in histopathology of the colon when administering both an anti-TNFα antibody and an anti-IL-23 antibody (as compared to either antibody alone), subjects may respond much better to the combination of a TNFα inhibitor (e.g., an anti-TNFα antibody) and an IL-23 inhibitor (e.g., an anti-IL-23 antibody).

[0120] In various embodiments, the IL-23 inhibitor comprises an anti-IL-23 antibody or an antigen-binding fragment thereof. In some embodiments, the anti-IL-23 antibody or antigen-binding fragment comprises an anti-IL-23p19 antibody or an antigen-binding fragment thereof, which can bind to the p19 subunit of IL-23. In some embodiments, the anti-IL-23 antibody comprises a human antibody or a humanized antibody. In some embodiments, the anti-IL-23 antibody comprises a human antibody or a humanized antibody.

[0121] In various embodiments, the TNFα inhibitor comprises an anti-TNFα antibody or an antigen-binding fragment thereof. In some embodiments, the anti-TNFα antibody comprises a human antibody or a humanized antibody.

[0122] Anti-IL-23 antibodies and/or anti-TNFα antibodies can also be humanized or prepared as human antibodies engineered with retention of high affinity for the antigen and other favorable biological properties. Humanized (or human) antibodies can be optionally prepared by a process of analysis of the parental sequences and various conceptual humanized products using three-dimensional models of the parental and humanized sequences. Three-dimensional immunoglobulin models are commonly available and are familiar to those skilled in the art. Computer programs are available which illustrate and display probable three-dimensional conformational structures of selected candidate immunoglobulin sequences. Inspection of these displays permits analysis of the likely role of the residues in the functioning of the candidate immunoglobulin sequence, i.e., the analysis of residues that influence the ability of the candidate immunoglobulin to bind its antigen. In this way, framework (FR) residues can be

selected and combined from the consensus and import sequences so that the desired antibody characteristic, such as increased affinity for the target antigen(s), is achieved.

[0123] Humanization or engineering of antibodies of the present invention can be performed using any known method, such as but not limited to those described in, Winter (Jones et al., Nature 321:522 (1986); Riechmann et al., Nature 332:323 (1988); Verhoeyen et al., Science 239:1534 (1988)); Sims et al., J. Immunol. 151: 2296 (1993); Chothia and Lesk, J. Mol. Biol. 196:901 (1987); Carter et al., Proc. Natl. Acad. Sci. U.S.A. 89:4285 (1992); Presta et al., J. Immunol. 151:2623 (1993); and U.S. Patent Numbers: 5,723,323; 5,976,862; 5,824,514; 5,817,483; 5,814,476; 5,763,192; 5,723,323; 5,766,886; 5,714,352; 6,204,023; 6,180,370; 5,693,762; 5,530,101; 5,585,089; 5,225,539; and 4,816,567, each entirely incorporated herein by reference.

[0124] In another aspect is provided a method of reducing inflammation of the colon in a subject who has inflammatory bowel disease. The method comprises administering a first co-inflammation reducing effective amount of an IL-23 inhibitor and administering a second co-inflammation reducing effective amount of a TNFα inhibitor. The method is effective to reduce inflammation of the colon of the subject to a level comparable to the colon of a normal patient.

[0125] The first and second co-inflammation reducing effective amounts are the same or different.

[0126] Prevention or reduction of inflammation can be measured by histopathological analysis, degree of weight loss, and degree of inflammation.

[0127] In some embodiments, in a histopathology study of a tissue sample from the colon of the subject after administration of the IL-23 inhibitor and the TNFα inhibitor, the inflammation score is very minimal or normal. Very minimal inflammation may reflect the presence of just one or two small foci, with mononuclear inflammatory cells (MNIC) likely background mucosal lymphoid aggregates.

[0128] In some embodiments, in a histopathology study of a tissue sample from the colon of the subject after administration of the IL-23 inhibitor and the TNFα inhibitor, the gland loss score is very minimal or normal. Very minimal gland loss may involve only one or two small focal areas of gland loss.

[0129] In some embodiments, in a histopathology study of a tissue sample from the colon of the subject after administration of the IL-23 inhibitor and the TNFα inhibitor, the erosion score is

very minimal or normal. Very minimal erosion may involve only one or two small focal areas of mucosal erosion.

[0130] In some embodiments, in a histopathology study of a tissue sample from the colon of the subject after administration of the IL-23 inhibitor and the TNFα inhibitor, the mucosal thickness and hyperplasia score are independently very minimal or normal. Very minimal mucosal thickness may involve less than a 25% increase in mucosal thickness as compared to the thickness of normal mucosal tissue.

[0131] In some embodiments, after administration of the IL-23 inhibitor and the TNFα inhibitor, the histopathology of the colon is about identical (or identical) to that of normal tissue.

[0132] The histopathology can be assessed by measuring one or more of submucosal edema, inflammation, gland loss, erosion, mucosal thickness, and hyperplasia. Any or all of these parameters may be measured and scored. An exemplary scoring system is described in Example 1.

[0133] In various embodiments, the IL-23 inhibitor is an anti-IL-23p19 antibody or an antigen-binding fragment thereof. Exemplary anti-IL-23p19 antibodies and antigen-binding fragments thereof are described in U.S. Patent No. 7,491,391 and U.S. Patent Application Publication No. 2018/0094052, both of which are incorporated by reference herein in its entirety. In various embodiments, the TNFα inhibitor is an anti-TNFα antibody or an antigen binding fragment thereof. Exemplary ant-TNFα antibodies and antigen-binding fragments thereof are described in U.S. Patent No. 7,250,165 and U.S. Patent Application Publication No. 2017/0218092, both of which are incorporated by reference herein by its entirety.

[0134] In some embodiments, the anti-TNFα antibody and the anti-IL-23 antibody (e.g., an anti-IL-23p19 antibody) are administered in a ratio of from 1:2 to 2:1 (w/w). The ratio may be calculated from the dosage of one antibody in a patient in mg/kg and the dosage of the other antibody in the same patient in mg/kg. In some embodiments, the anti-TNFα antibody and the anti-IL-23p19 antibody are administered in a ratio of from 15:1 to 400:1 (w/w). The ratio may be calculated from the dosage of one antibody in a patient in mg/kg and the dosage of the other antibody in the same patient in mg/kg.

[0135] Administration to a subject (e.g., human patient) of anti-TNFα antibody and an anti-IL-23 antibody (e.g., an anit-IL-23p19 antibody) in a ratio of from 1:2 to 2:1 (w/w) can provide for enhanced treatment of IBD (e.g., colitis and Crohn's disease) in the subject. In some

embodiments, the ratio of anti-TNFα antibody to anti-IL-23 antibody is from 1:2 to 1:1.8 (w/w). In some embodiments, the ratio of anti-TNFα antibody to anti-IL-23 antibody is from 1:1.9 to 1:1.7 (w/w). In some embodiments, the ratio of anti-TNFα antibody to anti-IL-23 antibody is from 1:1.8 to 1:1.6 (w/w). In some embodiments, the ratio of anti-TNFα antibody to anti-IL-23 antibody is from 1:1.7 to 1:1.5 (w/w). In some embodiments, the ratio of anti-TNFα antibody to anti-IL-23 antibody is from 1:1.6 to 1:1.4 (w/w). In some embodiments, the ratio of anti-TNFα antibody to anti-IL-23 antibody is from 1:1.5 to 1:1.3 (w/w). In some embodiments, the ratio of anti-TNFα antibody to anti-IL-23 antibody is from 1:1.4 to 1:1.2 (w/w). In some embodiments, the ratio of anti-TNFα antibody to anti-IL-23 antibody is from 1:1.3 to 1:1.1 (w/w). In some embodiments, the ratio of anti-TNFα antibody to anti-IL-23 antibody is from 1:1.2 to 1:1 (w/w). In some embodiments, the ratio of anti-TNFα antibody to anti-IL-23 antibody is from 1:1.1 to 1.1:1 (w/w). In some embodiments, the ratio of anti-TNFα antibody to anti-IL-23 antibody is from 1:1 to 1.2:1 (w/w). In some embodiments, the ratio of anti-TNFα antibody to anti-IL-23 antibody is from 1.1:1 to 1.3:1 (w/w). In some embodiments, the ratio of anti-TNFα antibody to anti-IL-23 antibody is from 1.2:1 to 1.4:1 (w/w). In some embodiments, the ratio of anti-TNFα antibody to anti-IL-23 antibody is from 1.3:1 to 1.5:1 (w/w). In some embodiments, the ratio of anti-TNFα antibody to anti-IL-23 antibody is from 1.4:1 to 1.6:1 (w/w). In some embodiments, the ratio of anti-TNFα antibody to anti-IL-23 antibody is from 1.5:1 to 1.7:1 (w/w). In some embodiments, the ratio of anti-TNFα antibody to anti-IL-23 antibody is from 1.6:1 to 1.8:1 (w/w). In some embodiments, the ratio of anti-TNFα antibody to anti-IL-23 antibody is from 1.7:1 to 1.9:1 (w/w). In some embodiments, the ratio of anti-TNFα antibody to anti-IL-23 antibody is from 1.8:1 to 2:1 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is about 1:2, 1:1.8, 1:1.5, 1:1.2, 1:1, 1.2:1, 1.5:1, 1.8:1 or 2:1 (w/w).

[0136] A minimally active dose of an anti-IL-23 antibody (e.g., an anti-IL-23p19 antibody) can be administered to the subject (e.g., human patient) with a larger dose of anti-TNFα antibody to prevent development of inflammatory bowel disease (e.g., colitis and Crohn's disease). The ratio of the minimally active dose of anti-IL-23 to the ratio of the larger dose of anti-TNFα antibody can range from 1:400 to 1:15 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:400 to 1:350 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:370 to 1:320 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:350 to 1:300

(w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:300 to 1:250 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:280 to 1:230 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:250 to 1:200 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:220 to 1:170 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:170 to 1:120 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:150 to 1:100 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:120 to 1:80 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:100 to 1:60 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:80 to 1:40 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:60 to 1:30 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:50 to 1:25 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:40 to 1:20 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:35 to 1:15 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is about 1:400, 1:300, 1:200, 1:150, 1:100, 1:75, 1:50, 1:25, or 1:15 (w/w).

[0137] In some embodiments, the anti-TNFα antibody and the anti-IL-23 antibody (e.g., an anti-IL-23p19 antibody) are administered in a ratio of from 15:1 to 400:1 (w/w). In some embodiments, the a) anti-IL-23 antibody or the antigen-binding fragment thereof and the b) anti-TNFα antibody or the antigen-binding fragment thereof are administered simultaneously. In some embodiments, the a) anti-IL-23 antibody or the antigen-binding fragment thereof and the b) anti-TNFα antibody or the antigen-binding fragment thereof are administered sequentially. The a) anti-IL-23 antibody or the antigen-binding fragment thereof and the b) anti-TNFα antibody or the antigen-binding fragment thereof may be administered within one hour, two hours, three hours, six hours, 12 hours, one day, two days, three days, or four days of one another.

[0138] In some embodiments, the combination of the a) anti-IL-23 antibody (e.g., an anti-IL-23p19 antibody) or the antigen-binding fragment thereof and the b) anti-TNFα antibody or the antigen-binding fragment is effective to treat a subject who was previously treated with an anti-TNFα antibody alone without significant remission of the inflammatory bowel disease. In some

embodiments, the combination of the a) anti-IL-23 antibody or the antigen-binding fragment thereof and the b) anti-TNFα antibody or the antigen-binding fragment is effective to treat a subject who was previously treated with an anti-IL-23 antibody alone without significant remission of the inflammatory bowel disease.

[0139] In another aspect is provided a method of treating inflammatory bowel disease in a human subject. The method comprises: (a) administering 0.0005 to 0.002 mg/kg (based on the body mass of the human subject) of an anti-IL-23 antibody (e.g., an anti-IL-23p19 antibody) or an antigen-binding fragment thereof; and (b) administering 0.020 to 0.125 mg/kg (based on the body mass of the human subject) of an anti-TNFα antibody or an antigen-binding fragment thereof. In various embodiments, the method is effective to treat the inflammatory bowel disease. In some embodiments, the inflammatory bowel disease is colitis. In some embodiments, the inflammatory bowel disease is Crohn's disease. In some embodiments, the method is effective to inhibit weight loss (e.g., weight loss associated with the inflammatory bowel disease.) The (a) anti-IL-23 antibody or the antigen-binding fragment thereof and the (b) anti-TNFα antibody or the antigen-binding fragment thereof may be administered simultaneously, sequentially, or within one day of one another.

[0140] In various embodiments, administration to a subject (e.g., human patient) of 0.020 to 0.125 mg/kg anti-TNFα antibody and 0.020 to 0.125 mg/kg of an anti-IL-23 antibody (e.g., an anti-IL-23p19 antibody) can provide for enhanced treatment of IBD (e.g., colitis and Crohn's disease) in the subject. Initial results from evaluating the combination of 50 μg each anti-TNFα and anti-IL-23 in mice suggest that the combination provides enhanced protection against colitis versus single treatments at the same dose. See Example 1. In some embodiments, 0.020 to 0.040 mg/kg anti-TNFα antibody and 0.020 to 0.040 mg/kg of an anti-IL-23 antibody are administered to a human subject. In some embodiments, 0.030 to 0.050 mg/kg anti-TNFα antibody and 0.030 to 0.050 mg/kg of an anti-IL-23 antibody are administered to a human subject. In some embodiments, 0.040 to 0.060 mg/kg anti-TNFα antibody and 0.040 to 0.060 mg/kg of an anti-IL-23 antibody are administered to a human subject. In some embodiments, 0.050 to 0.070 mg/kg anti-TNFα antibody and 0.050 to 0.070 mg/kg of an anti-IL-23 antibody are administered to a human subject. In some embodiments, 0.060 to 0.080 mg/kg anti-TNFα antibody and 0.060 to 0.080 mg/kg of an anti-IL-23 antibody are administered to a human subject. In some embodiments, 0.070 to 0.090 mg/kg anti-TNFα antibody and 0.070 to 0.090

mg/kg of an anti-IL-23 antibody are administered to a human subject. In some embodiments, 0.080 to 0.100 mg/kg anti-TNFα antibody and 0.080 to 0.100 mg/kg of an anti-IL-23 antibody are administered to a human subject. In some embodiments, 0.090 to 0.110 mg/kg anti-TNFα antibody and 0.090 to 0.110 mg/kg of an anti-IL-23 antibody are administered to a human subject. In some embodiments, 0.100 to 0.125 mg/kg anti-TNFα antibody and 0.100 to 0.125 mg/kg of an anti-IL-23 antibody are administered to a human subject.

[0141] In various embodiments, the anti-IL-23 antibody (e.g., the anti-IL-23p19 antibody) is administered to the subject (e.g., human patient) daily, every two days, every three days, every four days, every five days, every six days, or once every week. In various embodiments, the anti-TNFα antibody is administered to the subject (e.g., human patient) daily, every two days, every three days, every four days, every five days, every six days, or once every week. In some embodiments, both the anti-IL-23 antibody and the anti-TNFα antibody are administered daily, every two days, every three days, every four days, every five days, every six days, or once every week.

[0142] The anti-IL-23 antibody (e.g., the anti-IL-23p19 antibody) and the anti-TNFα antibody can be administered conjointly to the subject (e.g., human patient). Alternatively, the anti-IL-23 antibody and the anti-TNFα antibody can be administered separately to the subject. If administered separately, the antibodies may be administered within three hours, six hours, twelve hours, one day, two days, three days, or four days of one another.

[0143] In some embodiments, the combination of the a) anti-IL-23 antibody (e.g., anti-IL-23p19 antibody) or the antigen-binding fragment thereof and the b) anti-TNFα antibody or the antigen-binding fragment is effective to treat a subject who was previously treated with an anti-TNFα antibody alone without significant remission of the inflammatory bowel disease. In some embodiments, the combination of the a) anti-IL-23 antibody or the antigen-binding fragment thereof and the b) anti-TNFα antibody or the antigen-binding fragment is effective to treat a subject who was previously treated with an anti-IL-23 antibody alone without significant remission of the inflammatory bowel disease.

[0144] In another aspect, a minimally active dose of an anti-IL-23 antibody (e.g., an anti-IL-23p19 antibody) can be administered with a larger dose of anti-TNFα antibody to prevent relapse of inflammatory bowel disease (e.g., ulcerative colitis, indeterminate colitis and/or Crohn's disease) when the subject is in remission from inflammatory bowel disease. The ratio of

the minimally active dose of anti-IL-23 antibody to the ratio of the larger dose of anti-TNFα antibody can range from 1:400 to 1:15 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:400 to 1:350 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:370 to 1:320 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:350 to 1:300 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:300 to 1:250 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:280 to 1:230 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:250 to 1:200 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:220 to 1:170 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:170 to 1:120 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:150 to 1:100 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:120 to 1:80 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:100 to 1:60 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:80 to 1:40 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:60 to 1:30 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:50 to 1:25 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:40 to 1:20 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is from 1:35 to 1:15 (w/w). In some embodiments, the ratio of anti-IL-23 antibody to anti-TNFα antibody is about 1:400, 1:300, 1:200, 1:150, 1:100, 1:75, 1:50, 1:25, or 1:15 (w/w).

[0145] In various embodiments, the anti-IL-23 antibody (e.g., anti-IL-23p19 antibody) is administered daily, every two days, every three days, every four days, every five days, every six days, or once every week. In various embodiments, the anti-TNFα antibody is administered daily, every two days, every three days, every four days, every five days, every six days, or once every week. In some embodiments, both the anti-IL-23 antibody and the anti-TNFα antibody are administered daily, every two days, every three days, every four days, every five days, every six days, or once every week.

[0146] The anti-IL-23 antibody (e.g., anti-IL-23p19 antibody) and the anti-TNFα antibody can be administered conjointly. Alternatively, the anti-IL-23 antibody and the anti-TNFα antibody can be administered separately.

[0147] Combining anti-TNFα antibody (500 μg/mouse) treatment with minimally active doses of anti-IL-23 antibody (e.g., anti-IL-23p19 antibody) can provide superior efficacy in preventing development of colitis when compared to either single antibody treatment at these doses. See, e.g., Example 5. An analysis of colonic gene signatures of this combination therapy versus anti-TNFα or anti-IL-23 monotherapy identified a unique set of genes modulated by combination therapy enriched in fibroblasts and extracellular matrix organization, cell types and pathways involved in wound repair. This novel finding indicates that a combination treatment of antibodies against TNFα and IL-23 can provide for superior efficacy in treating colitis and inflammatory bowel syndrome. Further, a combination treatment of antibodies against TNFα and IL-23 may have synergistic effects due to modulation of specific gene networks implicated in mucosal healing.

[0148] The data in Example 5 demonstrates that combination treatment with antibodies against TNFα and IL-23 (e.g., subunit p19 of IL-23) can provide superior protection against colitis, as compared to treatment with either antibody as monotherapy. The colitis may be acute colitis. Without wishing to be bound by theory, transcriptomics and gene network analyses identified both overlapping and distinct molecular effects for each monotherapy and revealed a unique set of genes influenced by the combination treatment that are implicated in wound repair processes. Taken together, these findings suggest that combination therapy with anti-TNFα and anti-IL-23 antibodies can provide a synergistic impact on alleviating intestinal inflammation. The synergistic impact may arise through the targeting of common inflammatory pathways. The synergistic impact may arise from treatment of distinct cell types implicated in IBD pathogenesis with an impact on genes involved in tissue restoration.

[0149] In some embodiments, the combination of the a) anti-IL-23 antibody (e.g., anti-IL-23 antibody) or the antigen-binding fragment thereof and the b) anti-TNFα antibody or the antigen-binding fragment is effective to treat a subject who was previously treated with an anti-TNFα antibody alone without significant remission of the inflammatory bowel disease. In some embodiments, the combination of the a) anti-IL-23 antibody or the antigen-binding fragment thereof and the b) anti-TNFα antibody or the antigen-binding fragment is effective to treat a

subject who was previously treated with an anti-IL-23 antibody alone without significant remission of the inflammatory bowel disease.

[0150] Formulations:

[0151] Each of the anti-TNFα and anti-IL-23 (e.g., anti-IL-23p19) antibodies may be present in stable formulations. The stable formulations may comprise a phosphate buffer with saline or a chosen salt, as well as preserved solutions and formulations containing a preservative as well as multi-use preserved formulations suitable for pharmaceutical or veterinary use, comprising an anti-IL-23 (e.g., anti-IL-23p19) antibody and/or anti-TNFα antibody in a pharmaceutically acceptable formulation.

[0152] Preserved formulations may contain at least one known preservative or optionally selected from the group consisting of at least one phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, phenylmercuric nitrite, phenoxyethanol, formaldehyde, chlorobutanol, magnesium chloride (e.g., hexahydrate), alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, polymers, or mixtures thereof in an aqueous diluent. Any suitable concentration or mixture can be used, such as about 0.0015%, or any range, value, or fraction therein. Non-limiting examples include, without preservative, about 0.1-2% m-cresol (e.g., 0.2, 0.3. 0.4, 0.5, 0.9, 1.0%), about 0.1-3% benzyl alcohol (e.g., 0.5, 0.9, 1.1, 1.5, 1.9, 2.0, 2.5%), about 0.001-0.5% thimerosal (e.g., 0.005, 0.01), about 0.001-2.0% phenol (e.g., 0.05, 0.25, 0.28, 0.5, 0.9, 1.0%), 0.0005-1.0% alkylparaben(s) (e.g., 0.00075, 0.0009, 0.001, 0.002, 0.005, 0.0075, 0.009, 0.01, 0.02, 0.05, 0.075, 0.09, 0.1, 0.2, 0.3, 0.5, 0.75, 0.9, 1.0%), and the like.

[0153] The aqueous diluent may further comprise a pharmaceutically acceptable preservative. Preferred preservatives include those selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof. The concentration of preservative used in the formulation is a concentration sufficient to yield an anti-microbial effect. Such concentrations are dependent on the preservative selected and are readily determined by the skilled artisan.

[0154] Other excipients, e.g., isotonicity agents, buffers, antioxidants, and preservative enhancers, can be added to the diluent. An isotonicity agent, such as glycerin, is commonly used at known concentrations. A physiologically tolerated buffer is preferably added to provide

improved pH control. The formulations can cover a wide range of pHs, such as from about pH 4 to about pH 10, and preferred ranges from about pH 5 to about pH 9, and a most preferred range of about 6.0 to about 8.0. Preferably, the formulations of the present invention have a pH between about 6.8 and about 7.8. Preferred buffers include phosphate buffers, most preferably, sodium phosphate, particularly, phosphate buffered saline (PBS).

[0155] Other additives, such as a pharmaceutically acceptable solubilizers like Tween 20 (polyoxyethylene (20) sorbitan monolaurate), Tween 40 (polyoxyethylene (20) sorbitan monopalmitate), Tween 80 (polyoxyethylene (20) sorbitan monooleate), Pluronic F68 (polyoxyethylene polyoxypropylene block copolymers), and PEG (polyethylene glycol) or nonionic surfactants, such as polysorbate 20 or 80 or poloxamer 184 or 188, Pluronic® polyls, other block co-polymers, and chelators, such as EDTA and EGTA, can be added to the formulations or compositions to reduce aggregation. These additives may be useful if a pump or plastic container is used to administer the formulation. The presence of pharmaceutically acceptable surfactant can reduce any propensity for an antibody to aggregate.

[0156] The formulations of the present invention can be prepared by a process that comprises mixing at least one anti-IL-23 antibody or anti-TNFα antibody with a selected buffer. The buffer can be a phosphate buffer containing saline or a chosen salt. Mixing the at least one anti-IL-23 antibody and buffer in an aqueous diluent is carried out using conventional dissolution and mixing procedures. To prepare a suitable formulation, for example, a measured amount of at least one antibody in water or buffer is combined with the desired buffering agent in water in quantities sufficient to provide the protein and buffer at the desired concentrations. Variations of this process would be recognized by one of ordinary skill in the art. For example, the order the components are added, whether additional additives are used, the temperature and pH at which the formulation is prepared, are all factors that can be optimized for the concentration and means of administration used.

[0157] Stable or preserved formulations comprising one or both of anti-IL-23 antibody (e.g., anti-IL-23p19 antibody) and anti-TNFα antibody can be provided to patients as clear solutions or as dual vials comprising a vial of lyophilized at least one antibody that is reconstituted with a second vial containing a preservative or buffer and excipients in an aqueous diluent. Either a single solution vial or dual vial requiring reconstitution can be reused multiple times and can

suffice for a single or multiple cycles of patient treatment and thus provides a more convenient treatment regimen than currently available.

[0158] For parenteral administration, the anti-IL-23 antibody (e.g., anti-IL-23p19 antibody) or anti-TNFα antibody can be formulated as a solution, suspension, emulsion, particle, powder, or lyophilized powder in association, or separately provided, with a pharmaceutically acceptable parenteral vehicle. Examples of such vehicles are water, saline, Ringer's solution, dextrose solution, and about 1-10% human serum albumin. Liposomes and nonaqueous vehicles, such as fixed oils, can also be used. The vehicle or lyophilized powder can contain additives that maintain isotonicity (e.g., sodium chloride, mannitol) and chemical stability (e.g., buffers and preservatives). The formulation is sterilized by known or suitable techniques.

[0159] Suitable pharmaceutical carriers are described in the most recent edition of Remington's Pharmaceutical Sciences, A. Osol, a standard reference text in this field.

[0160] Many known and developed modes can be used according to the present invention for administering pharmaceutically effective amounts of at least one anti-IL-23 antibody (e.g., anti-IL-23p19 antibody) or anti-TNFα antibody. While pulmonary administration is used in the following description, other modes of administration can be used according to the present invention with suitable results. Anti-IL-23 and anti-TNFα antibodies of the present invention can be delivered in a carrier, as a solution, emulsion, colloid, or suspension, or as a dry powder, using any of a variety of devices and methods suitable for administration by inhalation or other modes described here within or known in the art.

[0161] Formulations for parenteral administration may comprise a common excipient. Exemplary common excipients include, but are not limited to, sterile water or saline, polyalkylene glycols, such as polyethylene glycol, oils of vegetable origin, hydrogenated naphthalenes and the like. Aqueous or oily suspensions for injection can be prepared by using an appropriate emulsifier or humidifier and a suspending agent, according to known methods. Agents for injection can be a non-toxic, non-orally administrable diluting agent, such as aqueous solution, a sterile injectable solution or suspension in a solvent. As the usable vehicle or solvent, water, Ringer's solution, isotonic saline, etc. are allowed; as an ordinary solvent or suspending solvent, sterile involatile oil can be used. For these purposes, any kind of involatile oil and fatty acid can be used, including natural or synthetic or semisynthetic fatty oils or fatty acids; natural or synthetic or semisynthtetic mono- or di- or tri-glycerides.

[0162] Formulations for oral administration may include the co-administration of adjuvants (e.g., resorcinols and nonionic surfactants, such as polyoxyethylene oleyl ether and nhexadecylpolyethylene ether) to increase artificially the permeability of the intestinal walls, as well as the co-administration of enzymatic inhibitors (e.g., pancreatic trypsin inhibitors, diisopropylfluorophosphate (DFF) and trasylol) to inhibit enzymatic degradation. Formulations for delivery of hydrophilic agents including proteins and antibodies and a combination of at least two surfactants intended for oral, buccal, mucosal, nasal, pulmonary, vaginal transmembrane, or rectal administration are taught in U.S. Patent No. 6,309,663. The active constituent compound of the solid-type dosage form for oral administration can be mixed with at least one additive, including sucrose, lactose, cellulose, mannitol, trehalose, raffinose, maltitol, dextran, starches, agar, arginates, chitins, chitosans, pectins, gum tragacanth, gum arabic, gelatin, collagen, casein, albumin, synthetic or semisynthetic polymer, and glyceride. These dosage forms can also contain other type(s) of additives, e.g., inactive diluting agent, lubricant, such as magnesium stearate, paraben, preserving agent, such as sorbic acid, ascorbic acid, α-tocopherol, antioxidant such as cysteine, disintegrator, binder, thickener, buffering agent, sweetening agent, flavoring agent, perfuming agent, etc.

[0163] It can be desirable to deliver the compounds of the present invention to the subject over prolonged periods of time, for example, for periods of one week to one year from a single administration. Various slow release, depot or implant dosage forms can be utilized. For example, a dosage form can contain a pharmaceutically acceptable non-toxic salt of the compounds that has a low degree of solubility in body fluids, for example, (a) an acid addition salt with a polybasic acid, such as phosphoric acid, sulfuric acid, citric acid, tartaric acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalene mono- or di-sulfonic acids, polygalacturonic acid, and the like; (b) a salt with a polyvalent metal cation, such as zinc, calcium, bismuth, barium, magnesium, aluminum, copper, cobalt, nickel, cadmium and the like, or with an organic cation formed from e.g., N,N'-dibenzyl-ethylenediamine or ethylenediamine; or (c) combinations of (a) and (b), e.g., a zinc tannate salt. Additionally, the compounds of the present invention or, preferably, a relatively insoluble salt, such as those just described, can be formulated in a gel, for example, an aluminum monostearate gel with, e.g., sesame oil, suitable for injection. Particularly preferred salts are zinc salts, zinc tannate salts, pamoate salts, and the like.

[0164] Examples

[0165] The present invention is also described and demonstrated by way of the following examples. However, the use of these and other examples anywhere in the specification is illustrative only and in no way limits the scope and meaning of the invention or of any exemplified term. Likewise, the invention is not limited to any particular preferred embodiments described here. Indeed, many modifications and variations of the invention may be apparent to those skilled in the art upon reading this specification, and such variations can be made without departing from the invention in spirit or in scope. The invention is therefore to be limited only by the terms of the appended claims along with the full scope of equivalents to which those claims are entitled.

[0166] Example 1: Dose range determination for single treatments with antibody against TNFα or IL-23p19 and combination studies in the CD40 antibody-induced colitis model

[0167] Three separate studies were conducted. In all three studies, animals were randomized by weight, assigned to treatment groups and labeled by a specific number from 1-10 for each group. Vehicle (PBS) and mAb treatments were administered as a single intraperitoneal (ip) injection one day before (day -1) disease was induced by injecting 0.2 mg CD40 agonist antibody in 0.2 ml PBS per animal ip (day 0).

[0168] Naïve control mice were not treated and were kept in a separate cage until termination at day 7. Observations for clinical signs of disease were conducted daily. Body weights were measured and recorded daily from day -1 until termination at day 7. At study termination (day 7), the animals were euthanized by CO_2 overdose and colon tissues removed and processed accordingly for histological analysis.

[0169] Following euthanasia, the colon, defined as the intestinal segment between cecum and rectum, was excised and flushed with ice cold PBS to remove fecal content. One centimeter of the proximal colon was placed in histology cassettes and submerged into a fixative solution (10% Neutral Buffered Formalin, NBF). After 24 hours the cassettes were removed from the fixative and transferred to 70% ethanol and stored refrigerated until processing. The remaining colon tissue was divided into three equal parts; the first third snap frozen in liquid nitrogen for PK analysis, the second third snap frozen in liquid nitrogen for cytokine analysis, and the last third (distal, close to rectum) stored in 1 ml RNAlater (AmbionTM) on ice until all animals had been

euthanized and tissues removed accordingly and then frozen for RNA extraction and gene expression analysis. All frozen samples were stored at -80°C until further processing.

[0170] In all three studies, animals were randomized by weight, assigned to treatment groups and labeled by a specific number from 1-10 for each group. Vehicle (PBS) and mAb treatments were administered as a single intraperitoneal (ip) injection one day before (day -1) disease was induced by injecting 0.2 mg CD40 agonist antibody in 0.2 ml PBS per animal ip (day 0). Naïve control mice were not treated and were kept in a separate cage until termination at day 7.

[0171] Observations for clinical signs of disease were conducted daily. Body weights were measured and recorded daily from day -1 until termination at day 7. The animals were euthanized at day 7 by CO_2 overdose and colon tissues removed and processed accordingly for histological analysis.

[0172] In the first study, anti-TNFα or anti-IL-23p19 mAbs were evaluated in a CD40 colitis model. These antibodies were evaluated individually at doses of 500 µg or 50 µg per mouse, or in combination (i.e., 500 µg + 500 µg/mouse each or 50 + 50 µg/mouse each). The protocol is summarized in Table 3 below.

[0173] Table 3: Evaluation of single antibody treatment against TNFα and IL-23p19 versus combination (at equal high and low doses) in the CD40 colitis model

Test article	Route	Dose	Number of animals
Naïve		None	3
Vehicle (PBS)	ip	10 ml/kg, day -1	5
CNTO 6601	ip	1000 µg/mouse, day -1	9
CNTO 5048	ip	50 µg/mouse, day -1	9
CNTO 5048	ip	500 µg/mouse, day -1	9
CNTO 3723	ip	50 µg/mouse, day -1	9
CNTO 3723	ip	500 µg/mouse, day -1	9
CNTO 3723 + CNTO 5048	ip	50 + 50 µg/mouse, day -1	10
CNTO 3723 + CNTO 5048	ip	500 + 500 µg/mouse, day -1	10

[0174] CNTO 3723 is a murine anti-IL-23p19 monoclonal antibody (neutralizing IL-23p19 mAb). CNTO 5048 is a murine anti-TNFα monoclonal antibody (neutralizing TNFα mAb). CNTO 6601 refers to the isotype control used throughout the experiments. CNTO 6601 does not specifically bind to either TNFα or IL-23p19.

[0175] Anti-inflammatory activity of anti-TNFα and anti-IL-23p19 antibody treatment, alone or in combination, was assessed in the anti-CD40 antibody induced colitis model. Ligation of the co-stimulatory receptor CD40 via an agonist antibody causes an acute innate systemic and colonic inflammatory response in lymphopenic (T and B cell-deficient) $RAG2^{-/-}$ mice where the inflammatory response in the colon peaks around day 7, followed by resolution. IL-23 drives local colonic inflammation in this model.

[0176] While the expression of TNFα controls manifestations of systemic disease (e.g., body weight loss), TNFα has only modest effects on colitis development. (1) The inventors sought to investigate the distinct molecular impact of anti-TNFα versus anti-IL-23p19 antibody treatment on intestinal gene expression and determine whether combination treatment of anti-TNFα and anti-IL-23p19 exhibited enhanced efficacy over either monotherapy. At day -1, $RAG2^{-/-}$ mice were dosed once ip with 0.5 mg or 0.05 mg anti-TNFα antibody (CNTO5048), 0.5 mg or 0.05 mg anti-IL-23p19 antibody (CNTO3732), a combination of both antibodies (0.5 mg or 0.05 mg each), 1.0 mg isotype control antibody (CNTO6601), or 10 ml/kg PBS. (The $RAG2^{-/-}$ mice used in all examples herein are 8-10 week old female mice sourced from Taconic Farms.) One day later, at 10 day 0, all animals were challenged ip with anti-CD40 antibody (0.2 mg) to induce inflammation.

[0177] Body weight loss analysis was performed after low dose (50 μg) and high dose (500 μg) antibody treatment. Body weight was monitored from day -1, when the mice were injected with antibody or PBS, until termination on day 7.

[0178] The data are shown in Fig. 1A and Fig. 1B. Each line represents the group mean with error bars for standard error (n=9 antibody treatment; n=5 PBS control; n=3 naïve control) and is shown as percent change from day -1 (dotted line). Some error bars are within the size of the symbol and are not depicted. Fig. 1A shows the low dose (50 μg/mouse) and Fig. 1B shows the high dose antibody treatment (500 μg/mouse). Statistical significance of differences in body weight loss between antibody treatment groups and the isotype control group as comparator were analyzed by 2-way ANOVA with Dunnett's multiple comparison test and P-values for each time point are shown in the table. P-values indicating significance are highlighted in bold/italic.

[0179] The CD40 mAb-induced colitis model is characterized by a biphasic weight loss with an initial rapid body weight loss within 24-48 hours after the CD40-agonist antibody dosing followed by recovery and a second weight loss phase at days 5-7. Single treatment with anti-IL-

23p19 antibody (0.5 mg and 0.05 mg) did not protect mice from the initial rapid body weight loss but promoted a faster recovery after day 2 with an overall dose-dependent partial protection against body weight loss during the second phase of the disease, as shown in Fig. 1A and Fig. 1B.

[0180] In contrast, single treatments with anti-TNFα antibody (0.5 mg and 0.05 mg) completely protected mice from body weight loss during the entire duration of the study for both doses. Similar to the single antibody treatments against TNFα, the combination treatment resulted in complete protection from body weight loss at both doses (Fig. 1A and Fig. 1B). No adverse effects were observed for the low-dose or high-dose combination treatments of anti-TNFα/IL-23p19.

[0181] At termination (day 7), colon histopathology scores were determined for low and high dose antibody treatment groups. The proximal colon sections were stained with H&E and examined for histopathological changes by a blinded pathologist using a severity score from 0-20 according to the following protocol.

[0182] For proximal colons, two (2) pieces were cut and embedded in paraffin. Sections (5 µm) were cut and stained with hematoxylin & eosin (H&E). The two colon segments from each animal were evaluated for histopathology individually and average values per animal were used in group analysis. For each H&E stained section, submucosal edema was quantitated by measuring the thickness from the muscularis mucosa to the internal border of the outer muscle layer in a nontangential area thought to best represent the severity of this change.

[0183] The Inflammation Score reflected the extent of macrophage, lymphocyte, and neutrophil (PMN) infiltrate. A severity score was assigned according to the following criteria:

0 = Normal;

0.5 = Very Minimal; one or two small foci, mononuclear inflammatory cells (MNIC) likely background mucosal lymphoid aggregates. However, if aggregates are Peyer's patches, then they are not scored as abnormal

1 = Minimal, larger focal area with MNIC and neutrophils or minimal diffuse, no separation of glands, may be mostly in areas of submucosal edema or mesentery

2 = Mild, diffuse mild, or multifocal affecting 11–25% of mucosa with minor focal or multifocal gland separation, no separation in most areas

3 = Moderate, 26–50% of mucosa affected with minimal to mild focal or multifocal separation of glands by inflammatory cell infiltrate, milder in remaining areas of mucosa with some areas having no gland separation by inflammation

4 = Marked, 51–75% of mucosa affected with mild to moderate separation of glands by inflammatory cell infiltrate, minimal to mild in remaining areas of mucosa but all glands have some separation by infiltrate

5 = Severe, 76–100% of mucosa affected with moderate to marked areas of gland separation by inflammatory cell infiltrate, mild to moderate in remaining areas of mucosa

[0184] A gland loss score was determined. Crypt epithelial and remaining gland epithelial loss is scored based on the approximate percent of the mucosa that was affected as follows:

0 = None

0.5 = Very Minimal, 1 or 2 small focal areas of gland loss or mucosal erosion

1 = Minimal, 1–10% of the mucosa affected

2 = Mild, 11–25% of the mucosa affected

3 = Moderate, 26–50% of the mucosa affected

4 = Marked, 51–75% of the mucosa affected

5 = Severe, 76–100% of the mucosa affected

[0185] An erosion score was determined. The loss of surface epithelium was scored based on the approximate percent of the mucosa that was affected as follows. This is generally associated with mucosal hemorrhage (reflective of the bleeding seen clinically and at necropsy):

0 = None

0.5 = Very Minimal, 1 or 2 small focal areas of gland loss or mucosal erosion

1 = Minimal, 1–10% of the mucosa affected

2 = Mild, 11–25% of the mucosa affected

3 = Moderate, 26–50% of the mucosa affected

4 = Marked, 51–75% of the mucosa affected

5 = Severe, 76–100% of the mucosa affected

[0186] A mucosal thickness and hyperplasia score was determined. Mucosal thickness was measured in a non-tangential area of the section that best represents the overall mucosal

thickness. This parameter is indicative of gland elongation and mucosal hyperplasia. A hyperplasia score is derived from the measurement as follows:

0 = ≤200 µm = normal

0.5 = 201–250 µm = very minimal

1 = 251–350 µm = minimal

2 = 351–450 µm = mild

3 = 451–550 µm = moderate

4 = 551–650 µm = marked

5 = >650 µm = severe

[0187] The histopathology score is a sum of inflammation, gland loss, erosion, and hyperplasia scores. The range is from 0 to 20. The histopathology scores are shown in Fig. 2A and Fig. 2B. In these figures, each bar represents the group mean with standard error. No histopathological findings were observed in naïve animals. Fig. 2A shows the results for low dose antibody (50 µg/mouse). Fig. 2B depicts the results for the high dose treatment group (500 µg/mouse). Differences between treatment groups and respective vehicle and isotype controls were analyzed for significance by One-way ANOVA and Sidak's multiple comparisons test.

[0188] In the proximal colon, treatment with isotype antibody (1000 µg/mouse) showed a trend toward reduced histopathology when compared to the disease control (PBS), but this did not reach statistical significance. Monotreatment with anti-TNFα antibody significantly reduced colon inflammation at the high dose (500 µg, Fig. 2B) when compared to isotype control, but not at the low dose (50 µg, Fig. 2A).

[0189] A single dose of anti-IL-23p19 antibody was highly efficacious at the high dose (500 µg, Fig. 2B), completely preventing the development of colitis. At the low dose (50 µg, Fig. 2A), the monotreatment significantly reduced histopathology compared to the isotype group but did not completely prevent colitis. The high dose combination of both antibodies (500 µg anti-TNFα + 500 µg anti-IL-23p19/mouse, Fig. 2B) completely prevented colitis in the disease model, similar to the high dose of a single anti-IL-23p19 treatment.

[0190] The low dose combination treatment (50 µg anti-TNFα + 50 µg anti-IL-23p19/mouse, Fig. 2A) was significantly more efficacious than the single anti-TNFα treatment and showed a trend for improved protection compared to monotreatment against IL-23p19, indicating potential superior efficacy for the combination.

[0191] Example 2: Anti-TNFα and anti-IL-23p19 treatments impact unique genes in the intestine

[0192] The anti-TNFα and anti-IL-23p19 treatments show differential effects on readouts of systemic and local inflammation. In this example, an assessment was made whether the treatments of Example 1 above had distinct molecular effects on intestinal gene expression. To generate intestinal gene signatures, mRNA was isolated from the distal colon and submitted for microarray analysis.

[0193] For RNA extraction, tissue samples were thawed on ice and transferred into new tubes containing 900 µl of Qiazol (Qiagen) and one metal bead, followed by lysis using the TissueLyser II for disruption and homogenization of the tissue by running it 1min at a frequency of 30 S^{-1}. 180 µl of chloroform were added to each sample, vortexed for 30 seconds, incubated for two minutes at room temperature, and centrifuged at 14,000 rpm for 15 minutes at 4°C to separate the mix into an organic and an aqueous phase. 150 µl of the aqueous phase was used for RNA extraction using the RNeasy 96 well plate kit (Qiagen) including an on-column DNase digestion step all according to the manufacturer's protocols. Quality and quantity of the isolated RNA was determined by Nanodrop at a Nanodrop 8000 instrument (ThermoScientific) and by LabChip GX (DNA 5K/RNA/CZE Chip for use with GXTouch/GXII Touch HT) on Caliper instrument (Life Science) according to the manufacturer's protocols. For Caliper analysis the colon RNA aliquots were diluted 1:4 with molecular grade water.

[0194] The following exclusion criteria were used to determine which samples would be accepted for gene expression analysis by microarray. Nanodrop absorbance 260/280 (protein amount to nucleic acid) should be >1.8. Nanodrop absorbance 260/230 (salt amount to nucleic acid) should be close to 2. If nanodrop absorbance 260/230 was less than 1.5, then repurification was performed. Caliper RIN (RNA integrity number) should be 5-10. If less than 5, the accuracy of microarray analysis may be affected. RNA was shipped to BioStorage Technologies (Indianapolis, IN) for microarray analysis.

[0195] Differential gene expression analysis was performed by comparing the effect of anti-TNFα or anti-IL-23p19 to that of isotype control treatment. Because treatment with either the 50 µg anti-IL-23p19 or 500 µg anti-TNFα doses resulted in similar levels of reduction in histological inflammation (Fig. 2), the inventors chose these colonic gene expression signatures

for further evaluation to mitigate potential confounding effects of differential cellular infiltrates gene expression.

[0196] Murine gene signatures for each treatment were evaluated for overlap and enrichment in biological pathways (Enrichr: http://amp.pharm.mssm.edu/Enrichr/). The overlap of the individual gene signatures generated from anti-TNFα or anti-IL-23p19 treatment was relatively small, with only 11% of genes shared between the signatures, and did not show any specific pathway enrichment. The gene signature for anti-TNFα treatment (267 genes, FDR < 0.05, FC >1.2) was enriched in metabolic pathways and cytokine-cytokine receptor interactions while the anti-IL-23p19 gene signature (765 genes, FDR < 0.05, FC > 1.2) was enriched in circadian rhythm and p53 signaling.

[0197] Example 3: Anti-TNFα and anti-IL-23p19 single antibody treatments impact overlapping and distinct portions of human IBD networks

[0198] In collaboration with the Mount Sinai School of Medicine (New York, NY), a predictive Bayesian network model was generated for integrating transcriptional and genetic data derived from intestinal biopsy samples from the Crohn's disease CERTIFI clinical trial (847 IBD biopsies, 28 non-IBD control biopsies; 7,796 gene nodes). This type of molecular integrative network provides a data-driven framework for studying gene-gene interactions in the context of disease. To translate the anti-TNFα and anti-IL-23p19 monotherapy gene signatures generated in murine colitis models to clinical disease, murine gene signatures were integrated with a human IBD patient gene network. As stated above, the 50 µg anti-IL-23p19 and 500 µg anti-TNFα doses were selected for evaluation based on their similar impact on histological inflammation.

[0199] To bridge the murine model data to the human IBD network, a 'humanized' version of each treatment gene signature was first generated by mapping the murine genes to their human orthologues (767 genes for anti-IL-23p19 and 274 genes for anti-TNFα). The murine genes were mapped to their human orthologs using NCBI HomoloGene (https://www.ncbi.nlm.nih.gov/homologene) database (Build 68, 04/14/2014). Each NCBI Gene Id for each murine gene profiled was matched to all corresponding human members of the same cluster of putative orthologs.

[0200] A database term was considered significant if its one-sided Fisher's Exact test E-value (Bonferroni corrected p-value) was less than 0.05.

[0201] A hypergeometric test was performed in Excel (HYPGEOM.DIST function) to determine the enrichment of IBD GWAS loci genes in gene subnetworks. The gene list used for IBD GWAS loci enrichment was derived from Jostins et al, Nature 2012(8) and Liu et al, Nature Genetics 2015(9).

[0202] Using these humanized gene signatures, the enrichment analysis of the individual treatment signatures was extended to human pathways. The gene signature for anti-TNFα treatment was enriched in cellular response to stress and lipids, reactive oxygen species metabolism, inflammatory response genes and genes upregulated in patient biopsies. The anti-IL-23p19 treatment signature was enriched in cellular metabolism, regulation of proliferation and genes down-regulated in IBD patient biopsies.

[0203] Next, these humanized gene signatures were mapped onto the CERTIFI Bayesian network and generated treatment subnetworks using a web-based network visualization tool. Gene lists were generated as tab delimited text files and imported. Gene lists were applied to the T26 Pan-Intestine Bayesian Network (CERTIFI network(7)) and genes within the network and their first neighbors (genes within 1 step of a selected gene, either incoming or outgoing) were used to create a subnetwork.

[0204] These treatment subnetworks contain genes modified by anti-TNFα or anti-IL-23p19 treatment in the mouse model that are reflected in human IBD tissue and their immediate neighboring genes in the network. Thus, enrichment analysis of these subnetworks may provide insights into the biological pathways targeted by each therapeutic in the context of human disease tissue.

[0205] Fig. 3A and Fig. 3B show humanized treatment signatures of anti-TNFα or anti-IL-23p19 monotherapy from the anti-CD40 model of murine colitis projected onto the CERTIFI human IBD gene expression network. First neighbors of genes within the human IBD network were extracted to produce treatment subnetworks. The overlap between genes present in the anti-TNFα and anti-IL-23p19 subnetworks is illustrated by the Venn diagram in the center. The largest connected component of the shared subnetwork of anti-TNFα and anti-IL-23p19 is shown in Fig. 3B.

[0206] While no specific biology was enriched in analysis of the intersection of the original gene signatures, focused analysis of the largest connected component of the network neighborhood shared by both anti-TNFα and anti-IL-23p19 revealed enrichment in genes dysregulated in IBD

patient tissues as well as IBD GWAS loci genes, suggesting that efficacy of these distinct mechanisms could be mediated, in part, through targeting of shared core inflammatory pathways. The intersection of these two therapeutic subnetworks was significantly enriched in IBD GWAS loci genes (p = 0.001) and genes up-regulated in IBD patient tissue (multiple signatures; top signature E-value 7.25e-27) (Fig. 3). The unique portion of the anti-TNF subnetwork was highly enriched in neutrophil and $CD11b^{+}$ macrophage gene signatures (E-values 8.28e-10 and 30 2.41e-06, respectively) while the unique portion of the anti-IL-23p19 subnetwork was highly enriched for colonic epithelial cells (E-value 1.27e-32), consistent with the role of IL-23 in promoting the expression of cytokines, such as IL-17A and IL-22, that impact epithelial cell biology. The relative enrichment in myeloid cells and epithelial cells in the anti-TNFα and anti-IL-23p19 unique regions of the network, respectively, raised an additional hypothesis that combination therapy with both antibodies could provide benefit by targeting distinct cell types involved in IBD pathogenesis. Remarkably similar results were observed when performing the same type of network analyses using gene signatures derived from anti-TNFα or anti-IL-23p19 therapeutic treatments in an orthogonal murine model of intestinal inflammation, the T cell transfer model of colitis. Taken together, these network analyses suggest that the anti-TNFα and anti-IL-23p19 mechanisms of action are distinct, but converge on the molecular drivers of intestinal inflammation.

[0207] Example 4: Expanded dose range analysis for anti-TNFα and anti-IL-23p19 antibody treatments in anti-CD40 antibody induced colitis

[0208] To enable further evaluation of the effects of combination therapy, an extended dose response study in the CD40-antibody induced colitis model was conducted to determine the minimal effective dose for each antibody. One day before disease induction with anti-CD40 agonistic antibody, female $RAG2^{-/-}$ mice were dosed ip with anti-IL-23p19 antibody (CNTO 3723 at 50, 15, 5, 1.5. 0.5, 0.15 µg/mouse), anti-TNFα antibody (CNTO 5048 at 150 and 15 µg/mouse) or isotype control (50 µg/mouse). The protocol is summarized in Table 4 below.

[0209] Table 4: Evaluation of lower dose range for single antibody against TNFα and IL-23p19 in the CD40 colitis model

Test article	Route	Dose	Number of animals
Naïve		None	5
Vehicle (PBS)	ip	10 ml/kg, day -1	5

CNTO 6601	ip	50 µg/mouse, day -1	10
CNTO 3723	ip	50 µg/mouse, day -1	10
CNTO 3723	ip	15 µg/mouse, day -1	10
CNTO 3723	ip	5 µg/mouse, day -1	10
CNTO 3723	ip	1.5 µg/mouse, day -1	10
CNTO 3723	ip	0.5 µg/mouse, day -1	10
CNTO 3723	ip	0.15 µg/mouse, day -1	10
CNTO 5048	ip	150 µg/mouse, day -1	10
CNTO 5048	ip	15 µg/mouse, day -1	10

[0210] Body weight was monitored from day -1, when the mice were injected with antibody or PBS, until termination on day 7. The data is shown in Fig. 4A, Fig. 4B, Fig. 4C and Fig. 4D. Each line represents the group mean with standard error (n=10 antibody treatment; n=5 PBS control; n=3 naïve control) and is shown as percent change from day -1 (dotted line). The significance of differences to the isotype control group was analyzed for each treatment group by 2-way ANOVA with Dunnett's multiple comparison test and the resulting p-values for each study day are shown in the table. P-values indicating significant differences are highlighted in bold/italic.

[0211] A partially significant increase in body weight loss was observed in the isotype control group when compared to vehicle control. Treatment with anti-IL-23p19 antibody showed partial dose-dependent protection against body weight loss starting at day 2 at the two highest doses (15, 50 µg/mouse). Only at the lowest dose of anti-IL-23p19 antibody (0.15 µg/mouse), no protection from body weight loss was observed, as shown in Fig. 4B. Treatment with anti-TNFα antibody completely protected against the body weight loss at the higher dose (150 µg/mouse), but at the lower dose (15 µg/mouse), only a partial protection was noted. See Figure 4C.

[0212] A histopathology analysis of the proximal colon was performed as follows, after single antibody treatments for dose range determination. At termination (day 7), proximal colon sections were removed, flushed, fixed and then stained with H&E. The stained samples were examined for histopathological changes by a blinded pathologist using a severity score from 0-20 using the protocol in Example 1 above. The data is shown in Fig. 5A, Fig. 5B and Fig. 5C. No histopathological findings were observed in naïve animals. Differences between antibody

treatment groups and respective isotype controls were analyzed for significance by a one-way ANOVA-Sidak's multiple comparisons test. The line depicts the group median.

[0213] Colon histopathology demonstrated dose-dependent protection from colitis by anti-IL-23p19 antibody treatment, as shown in Figure 5B. At the 50 µg/mouse dose, anti-IL-23p19 antibody treatment provided near complete protection. Partial protection was detected at antibody doses of 15 µg and 5 µg, and no protection was observed at doses of 1.5 µg and lower. In contrast, no significant treatment effects were detected for the two dose levels of anti-TNFα antibody (150, 15 µg) on colon histopathology. See Figure 5C. These results confirm that blocking IL-23 signaling is highly efficacious against colitis in this model. Inhibition of TNFα, although efficacious against systemic inflammation (as measured by the amelioration of body weight loss), only offers moderate protection against colitis in this model.

[0214] Example 5: Determination of anti-inflammatory activity of a combination of fixed dose anti-TNFα antibody and varying doses of anti-IL-23p19 antibody in the CD40 colitis model

[0215] A combination study was performed in the CD40 colitis model using a fixed dose of anti-TNFα antibody (500 µg/mouse) in combination with varying doses of anti-IL-23p19 antibody (1.5, 5, 25 µg/mouse). Corresponding single doses of anti-IL-23p19 antibody were also included. The protocol is summarized in Table 5 below.

[0216] Table 5: Evaluation of single high dose TNFα antibody treatment and low doses of IL-23p19 alone versus in combination in the CD40 colitis model

Test article	Route	Dose	Number of animals
Naïve		None	5
Vehicle (PBS)	ip	10 ml/kg, day -1	10
CNTO 6601	ip	525 µg/mouse, day -1	10
CNTO 5048	ip	500 µg/mouse, day -1	10
CNTO 3723	ip	1.5 µg/mouse, day -1	10
CNTO 3723	ip	5 µg/mouse, day -1	10
CNTO 3723	ip	25 µg/mouse, day -1	10
CNTO 3723 + CNTO 5048	ip	1.5+500 µg/mouse, day -1	10
CNTO 3723 + CNTO 5048	ip	5+500 µg/mouse, day -1	10
CNTO 3723 + CNTO 5048	ip	25+500 µg/mouse, day -1	10

[0217] An assay of body weight loss after single and combination treatment with high dose anti-TNFα and low dose anti-IL-23p19 antibody was undertaken as follows.

[0218] Body weight was monitored from day -1, when the mice were injected with antibody (isotype control: 525 µg; anti-TNFα: 500 µg; anti-IL-23p19: 25, 5, 1.5 µg) or PBS (10 ml/kg), until termination on day 7. The data are shown in Figure 6. Each line represents the group mean (n=10 antibody treatment and vehicle; n=5 naïve control) and is shown as percent change from day -1 (dotted line). The significance of differences to isotype control group was analyzed by for each treatment group by 2-way ANOVA with Dunnett's multiple comparison test. P-values for each study day are shown in the table and highlighted in bold/italic if they indicate significance.

[0219] Consistent with previous studies, high dose anti-TNFα antibody completely protected against body weight loss, as shown in Figure 6B. In contrast, monotreatment with anti-IL-23p19 antibody, at all doses, provided partial protection from body weight loss, particularly during the late phase of anti-CD40 antibody induced disease. See Figure 6C. The combination of anti-TNFα antibody and anti-IL-23p19 antibody provided no additional detectable benefit on inhibition of weight loss as compared to the monotherapy (Figure 6D). Without wishing to be bound by theory, this effect may be due to the robust efficacy of monotherapy of anti-TNFα antibody on this parameter.

[0220] Histopathology analysis for proximal colon was performed after single and combination antibody treatments with high dose anti-TNFα and low dose anti-IL-23p19 antibody. At termination (day 7), proximal colon tissue samples were removed, flushed, fixed and then stained with H&E and examined for histopathological changes by a blinded pathologist using a severity score from 0-20, as described in Example 1 above. The data are shown in Fig. 7A, Fig. 7B and Fig. 7C. No histopathological findings were observed in naïve animals. Differences between antibody treatment groups and respective isotype controls were analyzed for significance by One-way ANOVA-Sidak's multiple comparisons test. The line depicts the group median.

[0221] As shown in Fig. 7A, Fig. 7B, and Fig. 7C, anti-TNFα antibody (500 µg/mouse) did not offer significant protection against colon histopathology as compared to the isotype control. The anti-IL-23p19 antibody (1.5, 5 and 25 µg/mouse) treatment demonstrated dose-dependent protection from colitis, with no protection seen at the lowest dose (1.5 µg/mouse). Partial protection from colitis was observed with the two higher doses (5 and 25 µg/mouse).

[0222] Due to the low amount of antibody used for anti-IL-23p19, the statistical significance for the single anti-IL-23p19 treatments were calculated against the vehicle control, but not against

the high dose (525 μg/mouse) isotype control. All combination treatments showed significant protection from colon inflammation compared with single anti-TNFα treatment. See Fig. 7A, Fig. 7B and Fig. 7C. Of note, in the case of the lowest combination dose evaluated (500 μg/mouse TNFα + 1.5 μg/mouse anti-IL-23p19), both monotherapy treatments failed to provide any protection from colonic histopathology but showed significant improvement in histopathology when given in combination. See Figure 7A. It was unexpected that the relatively small amount of anti-IL-23p19 antibody in combination with anti-TNFα antibody (e.g., as a ratio of 1:333 (w/w)) provided such a substantial improvement in colon histopathology. It was also unexpected that the colon histopathology score observed in the group receiving 500 μg/mouse TNFα + 1.5 μg/mouse anti-IL-23p19 is not statistically different from that observed in the isotype control group. These results indicate that a combination treatment of fixed high dose TNFα mAb and a sub-optimal low dose of IL-23p19 provides superior protection compared to the monotherapies against the two cytokines.

[0223] Example 6: Combination anti-TNFα and anti-IL-23p19 treatment impacts a unique subnetwork enriched in wound healing pathways

[0224] The molecular impact of combination therapy with anti-TNFα and anti-IL-23p19 antibodies versus monotherapy was determined. Humanized colonic gene expression signatures of anti-TNFα (500 μg) or high dose anti-IL-23p19 (25 μg) monotherapies were intersected with a gene expression signature from the combination therapy (500 μg anti-TNFα/1.5 μg anti-IL-23p19) to determine whether the molecular response to anti-TNFα and low dose anti-IL-23p19 antibody combination treatment was additive or unique compared with either therapy alone.

[0225] The 25 μg dose of anti-IL-23p19 treatment was selected for comparison so as to compare the effect of combination treatment of anti-TNFα with a sub-optimal dose of anti-IL-23p19 to that of a monotherapy dose of anti-IL-23p19 that had efficacy in the model.

[0226] As in Study 1, humanized colonic gene signatures were generated for each single and combination therapy treatment group for evaluating signature overlap, generating treatment subnetworks and performing enrichment analyses. The data is shown in Figure 8, left panel. Two hundred twenty genes were found to be uniquely differentially-regulated after combination therapy (500 μg anti-TNFα/1.5 μg anti-IL-23p19) versus either monotherapy (500 μg anti-TNFα or 25 μg anti-IL-23p19). These genes were projected onto the CERTIFI intestinal

Bayesian network. The largest connected component of the resulting induced 1-step subnetwork was subjected to enrichment analysis, with results shown in Figure 8, right panel. A network analysis of these 220 genes identified a unique subnetwork (shown in Figure 8) for the combination treatment that was enriched in fibroblasts and extracellular matrix organization, cell types and pathways involved in wound repair and mucosal healing. Thus, anti-TNFα and anti-IL-23p19 therapies may provide added benefit when used in combination by targeting both shared and unique disease relevant pathways.

[0227] Example 7: Clinical Study of anti-TNFα and anti-IL-23p19 treatment in UC

[0228] A Phase 2a Randomized, Double-blind, Active-controlled, Parallel-group, Multicenter, Proof-of-concept Clinical Study to Evaluate the Efficacy and Safety of Combination Therapy With Guselkumab and Golimumab in Participants With Moderately to Severely Active Ulcerative Colitis

[0229] Guselkumab (TREMFYA®) is a fully human immunoglobulin G1 lambda monoclonal antibody (mAb) that binds to the p19 subunit of human interleukin (IL)-23 with high specificity and affinity. The binding of guselkumab to IL-23 blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor, inhibiting IL-23-specific intracellular signaling and subsequent activation and cytokine production. Guselkumab is currently approved in the United States, European Union, Canada, and several other countries for the treatment of moderate to severe plaque psoriasis. In addition, guselkumab is also being evaluated in psoriatic arthritis (PsA) and Crohn's disease globally.

[0230] Golimumab (SIMPONI®) is a fully human anti-tumor necrosis factor alpha (TNFα) mAb that binds to TNFα with high affinity. This interaction prevents the binding of TNFα to its receptors, thereby inhibiting the biological activity of TNFα. Golimumab is approved for treatment of moderately to severely active ulcerative colitis (UC) in over 90 countries worldwide. Additionally, golimumab is approved for 1 or more of the following indications around the world: rheumatoid arthritis (RA), PsA, ankylosing spondylitis (AS), nonradiographic axial spondyloarthritis (nr-Axial SpA), and polyarticular juvenile idiopathic arthritis (pJIA).

[0231] OBJECTIVES AND ENDPOINTS

[0232] This study will consist of 2 distinct phases: a 12-week combination comparison phase followed by a 26-week monotherapy phase.

[0233] Objectives

[0234] Primary Objectives

[0235] Combination Comparison Phase

- To evaluate the clinical efficacy of combination therapy with guselkumab and golimumab in participants with moderately to severely active UC.
- To evaluate the safety of combination therapy with guselkumab and golimumab in participants with moderately to severely active UC.

[0236] Secondary Objectives

[0237] Combination Comparison Phase

- To evaluate the effect of combination therapy with guselkumab and golimumab on endoscopic improvement.
- To evaluate the impact of combination therapy with guselkumab and golimumab on disease specific health-related quality of life (HRQOL), including fatigue.
- To evaluate the efficacy of combination therapy with guselkumab and golimumab by negative response signature status at baseline.
- To evaluate the pharmacokinetics (PK), immunogenicity, and pharmacodynamics (PD) of combination therapy with guselkumab and golimumab, including changes in C-reactive protein (CRP), fecal calprotectin, and other PD biomarkers.

[0238] Monotherapy Phase

- To evaluate the clinical efficacy of combination therapy followed by guselkumab monotherapy.
- To evaluate the safety of combination therapy followed by guselkumab monotherapy.
- To evaluate the effect of combination therapy followed by guselkumab monotherapy on endoscopic improvement.
- To evaluate the impact of combination therapy followed by guselkumab monotherapy on disease-specific HRQOL, including fatigue.
- To evaluate the efficacy of combination therapy followed by guselkumab monotherapy by negative response signature status at baseline.
- To evaluate the PK, immunogenicity, and PD of combination therapy followed by guselkumab monotherapy, including changes in CRP, fecal calprotectin, and other PD biomarkers.

[0239] Exploratory Objectives

- To explore the effect of combination therapy on patient-reported outcome (PRO) instruments (e.g., Bristol Stool Form Scale [BSFS] and Patient's Global Impression of Change [PGIC] of Severity of UC).

[0240] Endpoints

[0241] Primary Endpoint

- Clinical response at Week 12, defined as a decrease from baseline in the Mayo score ≥30% and ≥3 points with either a decrease in rectal bleeding subscore (RBS) ≥1 or a RBS of 0 or 1.

[0242] Major Secondary Endpoint

- Clinical remission at Week 12, defined as a Mayo score ≤ 2 with no individual subscore >1.

Note: Other remission definitions may be considered and will be fully described in the Statistical Analysis Plan (SAP).

[0243] Hypothesis

[0244] Combination therapy with guselkumab and golimumab will result in a rate of clinical response at Week 12 that is superior to both monotherapy arms.

[0245] OVERALL DESIGN

[0246] This is a Phase 2a, randomized, double-blind, active-controlled, parallel-group, multicenter, interventional proof-of-concept (POC) clinical study designed to evaluate the efficacy and safety of combination therapy with guselkumab and golimumab in adults with moderately to severely active UC. The target population is men or women 18 to 65 years old with moderately to severely active UC, as defined by a Mayo score of 6 to 12, inclusive, at baseline, including an endoscopy subscore ≥2 as obtained during the central review of the video endoscopy. Participants must be naïve to TNF antagonists and have failed or not tolerated conventional therapy with oral or intravenous (IV) corticosteroids or immunomodulators (6-mercaptopurine [6-MP] or azathioprine [AZA]).

[0247] Immunomodulators (6-MP, AZA, and methotrexate [MTX]) must be discontinued for at least 2 weeks before the first dose of study intervention. For participants who are receiving oral corticosteroids at baseline, the investigator must begin tapering the daily dose of corticosteroids at Week 6. All participants will be evaluated for clinical worsening of UC throughout the study.

In general, doses of concomitant therapies for UC should remain stable through Week 38 (except for oral corticosteroid tapering beginning at Week 6), and concomitant therapies for UC should not be initiated unless considered medically necessary by the investigator. Initiation of prohibited therapies will result in discontinuation of study intervention.

[0248] Endoscopy with central read is planned for screening/baseline, Week 12, and Week 38. Consenting participants will have an additional endoscopy at Week 4, which will also be assessed by a central reader. Efficacy, PK and PD parameters, biomarkers, and safety will be assessed according to the Schedule of Activities (SoA). A pharmacogenomic blood sample will be collected from participants who consent to this component of the protocol (where local regulations permit). Participation in pharmacogenomic research is optional.

[0249] An interim analysis is planned to inform future clinical development. Database locks (DBLs) are planned at Weeks 12 and 38, and a final DBL is planned after all participants complete the safety follow-up visit. An independent Data Monitoring Committee (DMC) will be commissioned for this study.

[0250] NUMBER OF PARTICIPANTS

[0251] A target of 210 participants will be enrolled in this study with 70 participants planned per intervention group.

[0252] INTERVENTION GROUPS AND DURATION

[0253] This study will consist of 2 distinct phases: a 12-week combination comparison phase followed by a 26-week monotherapy phase. At Week 0, a target of 210 participants will be randomized in a 1:1:1 ratio to either combination therapy with guselkumab and golimumab, guselkumab monotherapy, or golimumab monotherapy, stratified by the concomitant use of corticosteroids at baseline (Y/N). Participants randomized to combination therapy will receive guselkumab monotherapy after Week 12. Participants randomized to a monotherapy group will continue on their originally randomized monotherapy after Week 12. The combination therapy arm will employ the same dose regimens of guselkumab and golimumab being used in the respective monotherapy intervention groups to facilitate scientific interpretation of the results. The following is a description of the 3 intervention groups:

- Combination therapy: guselkumab 200 mg IV and golimumab 200 mg subcutaneous (SC) at Week 0; golimumab 100 mg SC at Weeks 2, 6, and 10; guselkumab 200 mg IV at Weeks 4 and 8 followed by guselkumab 100 mg SC q8w

- Guselkumab monotherapy: guselkumab 200 mg IV at Weeks 0, 4, and 8 followed by guselkumab 100 mg SC q8w
- Golimumab monotherapy: golimumab 200 mg SC injection at Week 0, followed by golimumab 100 mg at Week 2 and then golimumab 100 mg every 4 weeks (q4w)

[0254] In addition, placebo administrations (IV or SC) will be given, as appropriate, to maintain the blind throughout the duration of the study.

[0255] Overall participant duration will be up to 58 weeks total (screening: up to 8 weeks; treatment duration: 38 weeks [12 weeks for the combination comparison phase; 26 weeks for the monotherapy phase]; safety follow-up: approximately 16 weeks after the last administration of study intervention at Week 34). The end of the study will be defined as when the last participant completes his or her final safety follow-up visit.

[0256] EFFICACY EVALUATIONS (endpoints)

[0257] Efficacy evaluations will include the following:

- Mayo score and Partial Mayo score
- Ulcerative Colitis Endoscopic Index of Severity (UCEIS)
- Inflammatory PD markers including CRP and fecal calprotectin
- Patient-reported outcome measures to assess HRQOL outcomes and fatigue (ie, Inflammatory Bowel Disease Questionnaire [IBDQ], Patient-Reported Outcomes Measurement Information System [PROMIS]-29, and PROMIS Fatigue 7-item Short Form [7a])
- Exploratory patient-reported symptom measures including BSFS and PGIC of Severity of UC

[0258] OTHER EFFICACY EVALUATIONS (endpoints)

- Efficacy evaluations will include the following:

[0259] Combination Comparison Phase (i.e., through Week 12)

- Endoscopic healing at Week 12 (Mayo endoscopic subscore of 0 or 1).
- Normalization of endoscopic appearance of the mucosa (Mayo endoscopic subscore of 0).
- Histologic healing at Week 12.
- Mucosal healing at Week 12 (Composite Mayo endoscopic healing and histologic healing).

- Change from baseline in the total score of the Inflammatory Bowel Disease Questionnaire (IBDQ) at Weeks 6 and 12.
- A >20-point improvement in the IBDQ score at Weeks 6 and 12.
- Change from baseline in the 7 domains and the abdominal pain numerical rating scale of Patient-Reported Outcomes Measurement Information System (PROMIS)-29 at Weeks 6 and 12.
- Fatigue response at Weeks 6 and 12 (based on the PROMIS Fatigue Short Form 7a; to be defined in the SAP).
- Clinical response, clinical remission, and endoscopic healing at Week 12 by negative response signature status at baseline.
- Change from baseline in the Mayo score at Week 12.
- Change from baseline in the partial Mayo score through Week 12.
- Change from baseline in CRP through Week 12.
- Change from baseline in fecal calprotectin concentration through Week 12.
- Normalization of CRP concentration at Week 12 among participants with abnormal CRP concentration at baseline.
- Normalization of fecal calprotectin concentration at Week 12 among participants with abnormal fecal calprotectin concentration at baseline.
- Ulcerative Colitis Endoscopic Index of Severity (UCEIS) score at Weeks 0 and 12 by the level of Mayo endoscopy score at the corresponding visit.
- Change from baseline in the UCEIS score at Week 12.
- UCEIS score ≤4 at Week 12.
- UC-related emergency department visits, hospitalizations, and surgeries through Week 12.

[0260] Monotherapy Phase (i.e., after Week 12)

- Clinical remission at Week 38.
- Clinical response at Week 38.
- Maintenance of clinical response at Week 38 among participants who achieved clinical response at Week 12.
- Endoscopic healing at Week 38.
- Normalization of endoscopic appearance of the mucosa at Week 38.

- Histologic healing at Week 38.
- Mucosal healing at Week 38.
- Clinical remission and not receiving concomitant corticosteroids at Week 38.
- Maintenance of clinical remission at Week 38 among participants who achieved clinical remission at Week 12.
- Change from baseline in the total score of the IBDQ at Weeks 24 and 38.
- A >20-point improvement in the IBDQ score at Weeks 24 and 38.
- Change from baseline in the 7 domains and the abdominal pain numerical rating scale of PROMIS-29 at Weeks 24 and 38.
- Fatigue response at Weeks 24 and 38.
- Clinical response, clinical remission, and endoscopic healing at Week 38 by negative response signature status at baseline.
- Change from baseline in the Mayo score at Week 38.
- Change from baseline in the partial Mayo score through Week 38.
- Change from baseline in CRP through Week 38.
- Change from baseline in fecal calprotectin concentration through Week 38.
- Normalization of CRP concentration at Week 38 among participants with abnormal CRP concentration at baseline.
- Normalization of fecal calprotectin concentration at Week 38 among participants with abnormal fecal calprotectin concentration at baseline.
- UCEIS score at Week 38 by the level of Mayo endoscopy score at Week 38.
- Change from baseline in the UCEIS score at Week 38.
- UCEIS score ≤4 at Week 38.
- UC-related emergency department visits, hospitalizations, and surgeries through Week 38.

[0261] Exploratory Endpoints

- BSFS score over time.
- The distribution of the PGIC of Severity of UC over time.

[0262] PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS

[0263] Serum samples will be analyzed to determine concentrations of guselkumab and golimumab and detection of anti-guselkumab and anti-golimumab antibodies, respectively,

using validated, specific, and sensitive immunoassay methods by or under the supervision of the sponsor.

[0264] PHARMACODYNAMIC AND BIOMARKER EVALUATIONS

[0265] Biomarker assessments will be made to examine the biologic response to treatment and to identify biomarkers that are relevant to guselkumab and/or golimumab in the treatment of UC. Assessments will include the evaluation of relevant biomarkers in serum, stool, whole blood, and mucosal biopsy samples (RNA [ribonucleic acid], histology, and single cell isolation).

[0266] PHARMACOGENOMIC (DNA) EVALUATIONS

[0267] A pharmacogenomic whole blood sample of approximately 5 mL will be collected (where local regulations permit) for genetic analyses as specified in the SoA. Only participants who sign the consent form to participate in the genetic assessment will have whole blood deoxyribonucleic acid (DNA) samples collected. Participation in the pharmacogenomic sub-study is optional.

[0268] SAFETY EVALUATIONS

[0269] Safety evaluations conducted at each study visit will include the assessment of adverse events (AEs, at the visit and those occurring between evaluation visits), a tuberculosis (TB) evaluation and other infection assessment, clinical laboratory blood tests (hematology and chemistry), vital signs, suicidality assessment, concomitant medication review, observations for injection-site reactions, AEs temporally associated with infusion, and/or hypersensitivity reactions.

[0270] STATISTICAL METHODS

[0271] Sample Size Determination

[0272] A sample size of 210 participants (70 per intervention group) was determined by the power to detect a significant difference in the proportion of participants in clinical response at Week 12 (primary endpoint) between the combination therapy and both monotherapies using a 1-sided chisquare test with 0.1 significance level for each comparison. The study is sized such that the combination therapy has approximately 80% power based on simulations to achieve both comparisons to monotherapy for the primary endpoint. The proportion of participants in clinical response at Week 12 is assumed to be 75% for the combination therapy, which is based on the additive effect from both monotherapies (20% improvement from each monotherapy relative to a historical placebo response of 35%).

[0273] Efficacy Analyses

[0274] All randomized participants who receive at least 1 dose of study intervention will be included in the efficacy analyses. Participants will be analyzed according to the treatment group to which they were randomized regardless of the treatment they received.

[0275] For testing of the primary endpoint, the efficacy of combination therapy versus each monotherapy will be compared. For both statistical comparisons of the primary endpoint, a Cochran-Mantel-Haenszel (CMH) chi-square test stratified by concomitant use of corticosteroids at baseline (Y/N) will be used. The testing will be done simultaneously at the 1-sided 0.1 level of significance for each comparison. The study will be considered positive if the combination therapy group is significantly different from both monotherapy groups for the primary endpoint.

[0276] If both tests of the primary endpoint are positive, a CMH chi-square test (1-sided) stratified by concomitant use of corticosteroids at baseline (Y/N) will be used to compare the efficacy of the combination therapy to each monotherapy for the major secondary endpoint. The testing will be done simultaneously at the 1-sided 0.1 level of significance for each comparison.

[0277] Analyses for other efficacy endpoints will be performed with no adjustments made for multiple comparisons and nominal p-values will be provided.

[0278] Safety Analyses

[0279] Safety data, including but not limited to, AEs, serious adverse events (SAEs), infections, serious infections, changes in laboratory assessments, and changes in vital signs will be summarized. Treatment-emergent AEs will be summarized by treatment group and Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms.

[0280] Other Analyses

[0281] Pharmacokinetic Analyses

[0282] Serum guselkumab and golimumab concentrations over time will be summarized for each treatment group over time using descriptive statistics.

[0283] Population PK modeling may be conducted when appropriate. If these population PK analyses are conducted, the results of these analyses will be presented in a separate report.

[0284] Immunogenicity Analyses

[0285] The incidence of antibodies to guselkumab and to golimumab will be summarized for all participants who receive at least 1 dose of guselkumab or golimumab and have appropriate

samples for detection of antibodies to guselkumab and to golimumab (i.e., participants with at least 1 sample obtained after their first dose of guselkumab or golimumab, respectively).

[0286] Pharmacokinetic/Pharmacodynamic Analyses

[0287] The relationship between serum concentrations of guselkumab and golimumab and the efficacy measures and/or relevant biomarker(s) may be explored graphically when appropriate. Additional analysis may be conducted if deemed necessary.

[0288] Biomarkers Analyses

[0289] Changes in serum protein analytes, fecal biomarkers, and biopsy and whole blood RNA obtained over time will be summarized by treatment group. Associations between baseline levels and changes from baseline in select markers and response to treatment will be explored. Biomarker analyses will be summarized in a separate technical report.

[0290] Pharmacogenomic Analyses

[0291] Genetic (DNA) analyses will be conducted only in participants who sign the consent form to participate in the pharmacogenomic sub-study. These analyses are considered exploratory and will be summarized in a separate technical report.

[0292] Clinical Results

[0293] The study population included 214 randomized participants with moderate-severely active UC (~70 per group). The study population comprises participants who are TNF-naïve and have failed or not tolerated conventional therapy with oral or intravenous (IV) corticosteroids or immunomodulators (6-MP or AZA). The study comprise 12 weeks of combination induction, followed by 26 weeks of monotherapy maintenance. The combination induction doses of guselkumab (GUS) 200 mg IV at Weeks 0, 4, and 8 and golimumab (GOL) 200 mg subcutaneous (SC) at Weeks 0, followed by 100 mg SC at Weeks 2, 6, and 10. Following combination induction, GUS monotherapy is administered as 100 mg SC q8. The same dose regimens as above are used for GUS and GOL monotherapy arms, respectively.

[0294] Primary and Major Secondary Endpoints

[0295] The primary endpoint of clinical response at Week 12 is defined as a decrease from baseline in the Mayo score >30% and >3 points, with either a decrease in rectal bleeding subscore (RBS) >1 or RBS of 0 or 1. A major secondary endpoint was clinical remission at Week 12, defined as a Mayo score <2, with no individual subscore > 1. Other efficacy endpoints included (select endpoints with available data noted): (i) endoscopic healing at Week 12 (Mayo

endoscopic subscore of 0 or 1), (ii) normalization of endoscopic appearance of the mucosa (Mayo endoscopic subscore of 0), (iii) change from baseline in Mayo score at Week 12, (iv) change from baseline partial Mayo score through Week 12, (v) change from baseline in CRP through Week 12, (vi) change from baseline in fecal calprotectin through Week 12, and normalization of CRP at Week 12 among participants with abnormal CRP concentrations at baseline (same for fecal calprotectin).

[0296] Mayo score is incorporated into various definitions of clinical response and remission and is calculated as the sum of 4 subscores (stool frequency, rectal bleeding [RBS], endoscopy, and the Physician's Global Assessment). Clinical response is defined as a decrease from baseline in the Mayo score >30% and >3 points, with a decrease from baseline in the rectal bleeding subscore (RBS) of >1 or a RBS of 0 or 1. Clinical remission is defined as a Mayo score < 2, with no individual subscore > 1. Clinical remission (Health Authority definition) is defined as a stool frequency subscore of 0 or 1, RBS of 0, and an endoscopy subscore of 0 or 1 with no friability present on endoscopy, where the stool frequency subscore has not increased from baseline. Symptomatic remission is defined as a stool frequency subscore of 0 or 1 and a RBS of 0. Endoscopic healing (i.e., improvement in the endoscopic appearance of the mucosa) is defined as an endoscopy subscore of 0 or 1. Endoscopic healing will be evaluated based on the presence of friability when an endoscopy subscore of 1 is observed.

[0297] Conclusions

[0298] The 12-week, 24-week, and 38-week data is shown in Tables 6-25 below. This data suggests that combination therapy is superior to either monotherapy. The rates of clinical remission by Health Authority definition (more stringent) and endoscopic healing at Week 12 were nearly double with combination therapy than that observed with either monotherapy. Rapid improvement in multiple parameters was seen with combination therapy. In addition, for the combination therapy arm, even after the 26 weeks of maintenance period when guselkumab alone was administered, the rates of clinical remission and endoscopic healing maintained higher than either monotherapy arm. In the context of other currently available advanced therapies in similar biologic-naïve populations, combination therapy confers a numerically higher rate of clinical remission following induction (with numerous caveats re: comparing across studies). At the point of analysis, combination therapy has an acceptable safety profile.

[0299] Table 6 – Summary of Demographics at Baseline; Primary Analysis Set

	Golimumab Monotherapy	Guselkumab Monotherapy	Combination Therapy	Total
N, Primary Analysis Set	72	71	71	214
Mean age (SD), years	38.1 (10.47)	39.1 (13.67)	37.8 (11.69)	38.4 (11.96)
Sex, n (%)				
Female	30 (41.7%)	31 (43.7%)	37 (52.1%)	98 (45.8%)
Male	42 (58.3%)	40 (56.3%)	34 (47.9%)	116 (54.2%)
Race, White, n (%)	67 (93.1%)	71 (100.0%)	70 (98.6%)	208 (97.2%)
Ethnicity, Not Hispanic or Latino, n (%)	68 (94.4%)	65 (91.5%)	66 (93.0%)	199 (93.0%)
Region [a] n (%)				
Eastern Europe [a]	61 (84.7%)	58 (81.7%)	60 (84.5%)	179 (83.6%)
Latin America	4 (5.6%)	6 (8.5%)	7 (9.9%)	17 (7.9%)
Rest of World	7 (9.7%)	7 (9.9%)	4 (5.6%)	18 (8.4%)
Mean weight (SD), kg	73.9 (17.11)	69.6 (16.72)	69.8 (18.79)	71.1 (17.59)
Mean BMI (SD), kg/m^2	25.0 (5.07)	23.5 (4.71)	23.5 (5.05)	24.0 (4.97)
[a] Eastern Europe: Poland, Russia, Ukraine; Latin America: Argentina, Mexico, Brazil; Rest of World: United States, Germany, Australia				

[0300] Table 7 – Summary of UC Disease Characteristics at Baseline (Mayo Score); Primary Analysis Set

	Golimumab Monotherapy	Guselkumab Monotherapy	Combination Therapy	Total
N	72	71	71	214
UC Duration, years (mean [SD])	4.7 (4.48)	5.4 (5.70)	4.6 (4.61)	4.9 (4.95)
Mayo Score (0-12) (mean [SD])	8.7 (1.44)	8.9 (1.33)	8.8 (1.37)	8.8 (1.38)
Partial Mayo Score (0-9) (mean [SD])	6.2 (1.24)	6.3 (1.21)	6.2 (1.13)	6.2 (1.19)
Severity of UC Disease, n (%)				
Moderately Active (6 ≤ Mayo Score ≤ 10)	63 (87.5%)	64 (90.1%%)	62 (87.3%)	189 (88.3%)
Severely Active (Mayo Score > 10)	9 (12.5%)	7 (9.9%)	9 (12.7%)	25 (11.7%)
Mayo Endoscopy Subscore (0-3), n (%)				
Subscore of 2 (moderate)	35 (48.6%)	24 (33.8%)	28 (39.4%)	87 (40.7%)
Subscore of 3 (severe)	37 (51.4%)	47 (66.2%)	43 (60.6%)	127 (59.3%)

Mayo Stool Frequency Subscore (0-3), n (%)				
Subscore of 1	12 (16.7%)	7 (9.9%)	8 (11.3%)	27 (12.6%)
Subscore of 2	27 (37.5%)	31 (43.7%)	24 (33.8%)	82 (38.3%)
Subscore of 3	33 (45.8%)	33 (46.4%)	39 (54.9%)	105 (49.1%)

[0301] Table 8 – Number of Participants in Clinical Response at Week 12 (Primary Endpoint); Primary Analysis Set

	Golimumab Monotherapy	Guselkumab Monotherapy	Combination Therapy
N	72	71	71
Participants in clinical response [a,b,c]	44 (61.1%)	53 (74.6%)	59 (83.1%)
Adjusted treatment difference (80% 2-sided CI) [d]	22.1 (12.9, 31.3)	8.5 (-0.2, 17.1)	
p-value [e]	0.003	0.215	

[a] Clinical response is defined as a decrease from baseline in the Mayo score ≥30% and ≥3 points with either decrease from baseline in the rectal bleeding subscore (RBS) of ≥1 or a RBS of 0 or 1.
[b] Participants who had an intercurrent event (had an ostomy or colectomy (partial or total), discontinued study intervention due to lack of therapeutic effect or due to an AE of worsening of UC, had a protocol-prohibited change in concomitant UC medication(s), discontinued study intervention for reasons other than lack of efficacy or an AE of worsening of UC, death) prior to the Week 12 visit were considered to not have achieved clinical response at Week 12.
[c] After accounting for intercurrent events, participants who are missing any or all of the Mayo subscores at Week 12 will be considered to not have achieved clinical response at Week 12.
[d] The confidence intervals for the treatment difference in the proportion of participants achieving clinical response between combination therapy versus each monotherapy were based on the Wald statistic.
[e] The p-values were based on the 1-sided Cochran-Mantel-Haenszel (CMH) test, stratified by concomitant use of corticosteroids at baseline (Yes/No).

[0302] Table 9 - Number of Participants in Clinical Remission at Week 12; Primary Analysis Set

	Golimumab Monotherapy	Guselkumab Monotherapy	Combination Therapy
N	72	71	71
Participants in clinical remission [a,b,c]	16 (22.2%)	15 (21.1%)	26 (36.6%)
Adjusted treatment difference (80% 2-sided CI) [d]	14.5 (4.9, 24.0)	15.5 (6.0, 25.0)	
p-value [e]	0.058	0.041	

[a] Clinical remission is defined as the Mayo score ≤ 2 with no individual subscore >1.
[b] Participants who had an intercurrent event (had an ostomy or colectomy (partial or total), discontinued study intervention due to lack of therapeutic effect or due to an AE of worsening of UC, had a protocol-prohibited change in concomitant UC medication(s), discontinued study intervention for reasons other than lack of efficacy or an AE of worsening of UC, death) prior to the Week 12 visit were considered to not have achieved clinical remission at Week 12.
[c] After accounting for intercurrent events, participants who are missing any or all of the Mayo subscores will be considered to not have achieved clinical remission at Week 12.
[d] The confidence intervals for the treatment difference in the proportion of participants achieving clinical remission between combination therapy versus each monotherapy were based on the Wald statistic.
[e] The p-values were based on the 1-sided Cochran-Mantel-Haenszel (CMH) test, stratified by concomitant use of corticosteroids at baseline (Yes/No).

[0303] Table 10 – Number of Participants With Endoscopic Healing at Week 12; Primary Analysis Set

	Golimumab Monotherapy	Guselkumab Monotherapy	Combination Therapy
N	72	71	71
Participants with endoscopic healing [a,b,c]	18 (25.0%)	21 (29.6%)	35 (49.3%)
Adjusted treatment difference (80% 2-sided CI) [d]	24.4 (14.5, 34.3)	19.7 (9.6, 29.9)	
p-value [e]	0.003	0.016	

[a] Endoscopic healing is defined as an endoscopy subscore of 0 or 1.
[b] Participants who had an intercurrent event (had an ostomy or colectomy (partial or total), discontinued study intervention due to lack of therapeutic effect or due to an AE of worsening of UC, had a protocol-prohibited change in concomitant UC medication(s), discontinued study intervention for reasons other than lack of efficacy or an AE of worsening of UC, death) prior to the Week 12 visit were considered to not have achieved endoscopic healing at Week 12.
[c] After accounting for intercurrent events, participants who had a missing endoscopy subscore at Week 12 were considered to not have achieved endoscopic healing at Week 12.
[d] The confidence intervals for the treatment difference in the proportion of participants achieving endoscopic healing between combination therapy versus each monotherapy were based on the Wald statistic.
[e] The p-values were based on the 1-sided Cochran-Mantel-Haenszel (CMH) test, stratified by concomitant use of corticosteroids at baseline (Yes/No).

[0304] Table 11 - Number of Participants in Modified Mayo Response at Week 12; Primary Analysis Set

	Golimumab Monotherapy	Guselkumab Monotherapy	Combination Therapy
N [a]	42	43	41
Participants with modified Mayo response [b,c,d]	24 (57.1%)	28 (65.1%)	33 (80.5%)
Adjusted treatment difference (80% 2-sided CI) [e]	23.1 (10.8, 35.4)	15.4 (3.1, 27.6)	
p-value [f]	0.023	0.119	

[a] Interim data from a subset of participants.
[b] The modified Mayo response is defined as a decrease from baseline in the modified Mayo score of ≥2 and ≥30%, plus a decrease in rectal bleeding subscore of ≥1 or an absolute rectal bleeding subscore of ≤1. The modified Mayo score, which is the Mayo score without the PGA subscore, is calculated as the sum of the stool frequency, rectal bleeding, and endoscopy subscores, and may range from 0 to 9.
[c] Participants who had an intercurrent event (had an ostomy or colectomy (partial or total), discontinued study intervention due to lack of therapeutic effect or due to an AE of worsening of UC, had a protocol-prohibited change in concomitant UC medication(s), discontinued study intervention for reasons other than lack of efficacy or an AE of worsening of UC, death) prior to the Week 12 visit were considered to not have achieved modified Mayo response at Week 12.
[d] After accounting for intercurrent events, participants who are missing any or all of the Mayo subscores that compromise the modified Mayo score (i.e., stool frequency, rectal bleeding, and endoscopy subscores) will be considered to not have achieved modified Mayo response at Week 12.
[e] The confidence intervals for the treatment difference in the proportion of participants achieving modified Mayo response between combination therapy versus each monotherapy were based on the Wald statistic.
[f] The p-values were based on the 1-sided Cochran-Mantel-Haenszel (CMH) test, stratified by concomitant use of corticosteroids at baseline (Yes/No).

[0305] Table 12 – Number of Participants in Clinical Remission by Health Authority Definition at Week 12; Primary Analysis Set

	Golimumab Monotherapy	Guselkumab Monotherapy	Combination Therapy
N	72	71	71
Participants in clinical remission by Health Authority definition [a,b,c]	18 (25.0%)	17 (23.9%)	33 (46.5%)
Adjusted treatment difference (80% 2-sided CI) [d]	21.6 (11.7, 31.4)	22.5 (12.7, 32.4)	
p-value [e]	0.007	0.005	

[a] Clinical remission by Health Authority definition is defined as a stool frequency subscore of 0 or 1, rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on the endoscopy, where the stool frequency subscore has not increased from baseline.
[b] Participants who had an intercurrent event (had an ostomy or colectomy (partial or total), discontinued study intervention due to lack of therapeutic effect or due to an AE of worsening of UC, had a protocol-prohibited change in concomitant UC medication(s), discontinued study intervention for reasons other than lack of efficacy or an AE of worsening of UC, death) prior to the Week 12 visit were considered to not have achieved clinical remission by Health Authority definition at Week 12.
[c] After accounting for intercurrent events, participants who are missing any or all of the components of the clinical remission by Health Authority definition at Week 12 will be considered to not have achieved clinical remission by Health Authority definition at Week 12.
[d] The confidence intervals for the treatment difference in the proportion of participants achieving clinical remission by Health Authority definition between combination therapy versus each monotherapy were based on the Wald statistic.
[e] The p-values were based on the 1-sided Cochran-Mantel-Haenszel (CMH) test, stratified by concomitant use of corticosteroids at baseline (Yes/No).

[0306] Table 13 - Overall Summary of Treatment-Emergent Adverse Events Through Week 12; Primary Analysis Set

	Golimumab Monotherapy	Guselkumab Monotherapy	Combination Therapy
N, Primary Analysis Set	72	71	71
Avg duration of follow up (weeks)	12.0	12.1	12.4
Avg exposure (number of administrations)[a]	5.8	5.8	5.9
Participants with ≥1, n (%)			
Adverse events (AEs)	38 (52.8%)	31 (43.7%)	29 (40.8%)
Serious AEs (SAEs)	1 (1.4%)	2 (2.8%)	1 (1.4%)
AEs leading to discontinuation of study intervention	3 (4.2%)	1 (1.4%)	2 (2.8%)
Infection	16 (22.2%)	10 (14.1%)	10 (14.1%)
Serious infection [b]	0	0	1 (1.4%)
AEs leading to death	0	0	0
One or more AEs associated with COVID-19 infection	0	0	1 (1.4%)

Key: AE = adverse event, Avg = average
Note: Participants are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 21.1.
[a] Average number of visits study intervention received.
[b] Infection as assessed by the investigator.

[0307] Table 14 – Summary of Treatment-Emergent Adverse Events Through Week 12 by MedDRA System-Organ Class and Preferred Term; Primary Analysis Set

	Golimumab Monotherapy	Guselkumab Monotherapy	Combination Therapy
Analysis Set[a]: Primary Analysis Set	42	43	41
Avg duration of follow up (weeks)	12.1	12.1	12.2
Avg exposure (number of administrations)[b]	6.0	6.0	6.0
Participants with 1 or more AEs	21 (50.0%)	22 (51.2%)	14 (34.1%)
MedDRA System-Organ Class/Preferred Term			
Infections and infestations	10 (23.8%)	9 (20.9%)	5 (12.2%)
Nasopharyngitis	3 (7.1%)	2 (4.7%)	2 (4.9%)
Fungal skin infection	0	0	1 (2.4%)
Influenza	1 (2.4%)	1 (2.3%)	1 (2.4%)
Pharyngitis	0	0	1 (2.4%)
Rash pustular	0	0	1 (2.4%)
Sepsis	0	0	1 (2.4%)
Upper respiratory tract infection	2 (4.8%)	3 (7.0%)	1 (2.4%)
Amoebiasis	1 (2.4%)	0	0
Bronchitis	1 (2.4%)	0	0
Herpes zoster	1 (2.4%)	0	0
Impetigo	0	1 (2.3%)	0
Respiratory tract infection	0	1 (2.3%)	0
Rhinitis	1 (2.4%)	0	0
Tracheitis	0	2 (4.7%)	0
Blood and lymphatic system disorders	5 (11.9%)	7 (16.3%)	4 (9.8%)
Anaemia	3 (7.1%)	4 (9.3%)	2 (4.9%)
Iron deficiency anaemia	0	0	1 (2.4%)

Leukopenia	1 (2.4%)	2 (4.7%)	1 (2.4%)
Neutropenia	0	4 (9.3%)	1 (2.4%)
Lymphopenia	2 (4.8%)	0	0
Gastrointestinal disorders	5 (11.9%)	6 (14.0%)	4 (9.8%)
Colitis ulcerative	5 (11.9%)	1 (2.3%)	2 (4.9%)
Abdominal pain	0	0	1 (2.4%)
Abdominal pain upper	0	1 (2.3%)	1 (2.4%)
Gingival bleeding	0	0	1 (2.4%)
Haemorrhoids	0	0	1 (2.4%)
Nausea	0	1 (2.3%)	1 (2.4%)
Vomiting	0	1 (2.3%)	1 (2.4%)
Dental caries	0	1 (2.3%)	0
Dyspepsia	0	1 (2.3%)	0
Hypoaesthesia oral	0	1 (2.3%)	0
Small intestinal obstruction	0	1 (2.3%)	0
General disorders and administration site conditions	2 (4.8%)	1 (2.3%)	2 (4.9%)
Injection site erythema	0	0	1 (2.4%)
Non-cardiac chest pain	0	0	1 (2.4%)
Fatigue	1 (2.4%)	0	0
Injection site swelling	0	1 (2.3%)	0
Pyrexia	1 (2.4%)	0	0
Nervous system disorders	2 (4.8%)	4 (9.3%)	2 (4.9%)
Headache	1 (2.4%)	1 (2.3%)	1 (2.4%)
Presyncope	0	0	1 (2.4%)
Dizziness	0	1 (2.3%)	0
Dysgeusia	0	1 (2.3%)	0
Somnolence	1 (2.4%)	1 (2.3%)	0
Skin and subcutaneous tissue disorders	0	0	2 (4.9%)
Dermatitis allergic	0	0	1 (2.4%)
Pyoderma gangrenosum	0	0	1 (2.4%)
Endocrine disorders	0	0	1 (2.4%)
Adrenal insufficiency	0	0	1 (2.4%)
Immune system disorders	0	1 (2.3%)	1 (2.4%)
Seasonal allergy	0	0	1 (2.4%)
Drug hypersensitivity	0	1 (2.3%)	0
Musculoskeletal and connective tissue disorders	2 (4.8%)	2 (4.7%)	1 (2.4%)
Arthralgia	1 (2.4%)	0	1 (2.4%)
Back pain	0	1 (2.3%)	0
Bone pain	1 (2.4%)	0	0
Muscle spasms	0	1 (2.3%)	0
Myalgia	1 (2.4%)	0	0

Osteoarthritis	1 (2.4%)	0	0
Psychiatric disorders	0	0	1 (2.4%)
Nightmare	0	0	1 (2.4%)
Reproductive system and breast disorders	0	0	1 (2.4%)
Endometriosis	0	0	1 (2.4%)
Cardiac disorders	0	1 (2.3%)	0
Atrial fibrillation	0	1 (2.3%)	0
Eye disorders	0	1 (2.3%)	0
Ocular hyperaemia	0	1 (2.3%)	0
Hepatobiliary disorders	1 (2.4%)	0	0
Cholangitis sclerosing	1 (2.4%)	0	0
Injury, poisoning and procedural complications	1 (2.4%)	1 (2.3%)	0
Contusion	0	1 (2.3%)	0
Head injury	1 (2.4%)	0	0
Investigations	1 (2.4%)	4 (9.3%)	0
Alanine aminotransferase increased	1 (2.4%)	0	0
Aspartate aminotransferase increased	1 (2.4%)	0	0
Blood alkaline phosphatase increased	0	1 (2.3%)	0
Blood pressure increased	0	1 (2.3%)	0
Hepatic enzyme increased	0	1 (2.3%)	0
Transaminases increased	0	1 (2.3%)	0
Metabolism and nutrition disorders	0	1 (2.3%)	0
Hypophosphataemia	0	1 (2.3%)	0
Respiratory, thoracic and mediastinal disorders	1 (2.4%)	1 (2.3%)	0
Cough	1 (2.4%)	0	0
Oropharyngeal pain	0	1 (2.3%)	0

Key: AE = adverse event, Avg = average
Note: Participants are counted only once for any given event, regardless of the number of times they actually experienced the event.
Adverse events are coded using MedDRA Version 21.1.
[a] Interim data from a subset of participants.
[b] Average number of visits study intervention received.

[0308] Table 15 - Number of Participants With Treatment-Emergent Adverse events Leading To Discontinuation of Study Intervention Through Week 12 by MedDRA System-Organ Class and Preferred Term; Primary Analysis Set

	Golimumab Monotherapy	Guselkumab Monotherapy	Combination Therapy
Analysis Set[a]: Primary Analysis Set	42	43	41
Avg duration of follow up (weeks)	12.1	12.1	12.2
Avg exposure (number of administrations)[b]	6.0	6.0	6.0
Participants with treatment-emergent adverse events leading to discontinuation of study intervention	2 (4.8%)	1 (2.3%)	2 (4.9%)
MedDRA System-Organ Class/Preferred Term			
Gastrointestinal disorders	2 (4.8%)	1 (2.3%)	2 (4.9%)
Colitis ulcerative	2 (4.8%)	0	2 (4.9%)
Small intestinal obstruction	0	1 (2.3%)	0

Key: Avg = average
Note: Participants are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 21.1.
[a] Interim data from a subset of participants.
[b] Average number of visits study intervention received.

[0309] Table 16 – Number of Participants With 1 or More Treatment-Emergent Serious Infections Through Week 12 by MedDRA System-Organ Class and Preferred Term; Primary Analysis Set

	Golimumab Monotherapy	Guselkumab Monotherapy	Combination Therapy
Analysis Set[a]: Primary Analysis Set	42	43	41

Avg duration of follow up (weeks)	12.1	12.1	12.2
Avg exposure (number of administrations)[b]	6.0	6.0	6.0
Participants with 1 or more AEs of serious infection [c]	0	0	1 (2.4%)
MedDRA System-Organ Class/Preferred Term			
Infections and infestations	0	0	1 (2.4%)
Influenza	0	0	1 (2.4%)
Sepsis	0	0	1 (2.4%)

Key: Avg = average
Note: Participants are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 21.1.
[a] Interim data from a subset of participants.
[b] Average number of visits study intervention received.
[c] Serious infection as assessed by the investigator.

[0310] Table 17 – Overall Summary of Treatment-Emergent Adverse Events Through Week 24; Full Analysis Set

	Golimumab Monotherapy	Guselkumab Monotherapy	Combination Therapy [d]
Analysis Set[a]: Full Analysis Set	55	55	58
Avg duration of follow up (weeks)	19.3	19.6	18.5
Avg exposure (number of administrations)[b]	8.9	9.1	8.4
Participants with 1 or more AEs	31 (56.4%)	29 (52.7%)	28 (48.3%)
Participants with 1 or more serious AEs	2 (3.6%)	2 (3.6%)	2 (3.4%)

Participants with 1 or more AEs leading to discontinuation of study intervention	3 (5.5%)	1 (1.8%)	5 (8.6%)
Participants with 1 or more AEs of infection [c]	15 (27.3%)	12 (21.8%)	11 (19.0%)
Participants with 1 or more AEs of serious infection [c]	0	0	2 (3.4%)

Key: AE = adverse event, Avg = average
Note: Participants are counted only once for any given event, regardless of the number of times they actually experienced the event.
Adverse events are coded using MedDRA Version 21.1.
[a] Interim data from a subset of participants.
[b] Average number of visits study intervention received.
[c] Infection as assessed by the investigator.
[d] Participants in the combination therapy group switched to guselkumab monotherapy beginning at Week 12.

[0311] Table 18 - Number of Participants With Treatment-Emergent Adverse Events Leading to Discontinuation of Study Intervention Through Week 24 by MedDRA System-Organ Class and Preferred Term; Full Analysis Set

	Golimumab Monotherapy	Guselkumab Monotherapy	Combination Therapy [c]
Analysis Set[a]: Full Analysis Set	55	55	58
Avg duration of follow up (weeks)	19.3	19.6	18.5
Avg exposure (number of administrations)[b]	8.9	9.1	8.4
Participants with treatment-emergent adverse events leading to discontinuation of study intervention	3 (5.5%)	1 (1.8%)	5 (8.6%)
MedDRA System-Organ Class/Preferred Term			

Gastrointestinal disorders	2 (3.6%)	1 (1.8%)	3 (5.2%)
Colitis ulcerative	2 (3.6%)	0	3 (5.2%)
Small intestinal obstruction	0	1 (1.8%)	0
Infections and infestations	0	0	2 (3.4%)
Cytomegalovirus colitis	0	0	1 (1.7%)
Extrapulmonary tuberculosis	0	0	1 (1.7%)
Respiratory, thoracic and mediastinal disorders	1 (1.8%)	0	0
Pulmonary embolism	1 (1.8%)	0	0

Key: Avg = average
Note: Participants are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 21.1.
[a] Interim data from a subset of participants.
[b] Average number of visits study intervention received.
[c] Participants in the combination therapy group switched to guselkumab monotherapy beginning at Week 12.

[0312] Table 19 - Number of Participants With Treatment-Emergent Serious Adverse Events Through Week 24 by MedDRA System-Organ Class and Preferred Term; Full Analysis Set

	Golimumab Monotherapy	Guselkumab Monotherapy	Combination Therapy [c]
Analysis Set[a]: Full Analysis Set	55	55	58
Avg duration of follow up (weeks)	19.3	19.6	18.5
Avg exposure (number of administrations)[b]	8.9	9.1	8.4
Participants with 1 or more treatment-emergent serious adverse events	2 (3.6%)	2 (3.6%)	2 (3.4%)
MedDRA System-Organ Class/Preferred Term			
Infections and infestations	0	0	2 (3.4%)

Extrapulmonary tuberculosis	0	0	1 (1.7%)
Influenza	0	0	1 (1.7%)
Sepsis	0	0	1 (1.7%)
Respiratory, thoracic and mediastinal disorders	1 (1.8%)	0	1 (1.7%)
Pulmonary embolism	1 (1.8%)	0	1 (1.7%)
Cardiac disorders	0	1 (1.8%)	0
Atrial fibrillation	0	1 (1.8%)	0
Gastrointestinal disorders	1 (1.8%)	1 (1.8%)	0
Colitis ulcerative	1 (1.8%)	0	0
Small intestinal obstruction	0	1 (1.8%)	0

Key: Avg = average
Note: Participants are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 21.1.
[a] Interim data from a subset of participants.
[b] Average number of visits study intervention received.
[c] Participants in the combination therapy group switched to guselkumab monotherapy beginning at Week 12.

[0313] Table 20 - Number of Participants With 1 or More Treatment-Emergent Serious Infections Through Week 24 by MedDRA System-Organ Class and Preferred Term; Full Analysis Set

	Golimumab Monotherapy	Guselkumab Monotherapy	Combination Therapy [d]
Analysis Set[a]: Full Analysis Set	55	55	58
Avg duration of follow up (weeks)	19.3	19.6	18.5
Avg exposure (number of administrations)[b]	8.9	9.1	8.4
Participants with 1 or more AEs of serious infection [c]	0	0	2 (3.4%)

MedDRA System-Organ Class/Preferred Term			
Infections and infestations	0	0	2 (3.4%)
Extrapulmonary tuberculosis	0	0	1 (1.7%)
Influenza	0	0	1 (1.7%)
Sepsis	0	0	1 (1.7%)

Key: Avg = average
Note: Participants are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 21.1.
[a] Interim data from a subset of participants.
[b] Average number of visits study intervention received.
[c] Infection as assessed by the investigator.
[d] Participants in the combination therapy group switched to guselkumab monotherapy beginning at Week 12.

[0314] Table 21 – Number of Participants With Endoscopic Healing at Week 38

	Golimumab Monotherapy	Guselkumab Monotherapy	Combination Therapy [e]
N	58	57	58
Participants with endoscopic healing [a,b,c]	13 (22.4%)	16 (28.1%)	26 (44.8%)
80% 2-sided CI [d]	15.4, 29.4	20.4, 35.7	36.5, 53.2

[a] Endoscopic healing is defined as an endoscopy subscore of 0 or 1.
[b] Participants who had an intercurrent event (had an ostomy or colectomy (partial or total), discontinued study intervention due to lack of therapeutic effect or due to an AE of worsening of UC, had a protocol-prohibited change in concomitant UC medication(s), discontinued study intervention for reasons other than lack of efficacy or an AE of worsening of UC, death) prior to the Week 12 visit were considered to not have achieved endoscopic healing at Week 12.
[c] After accounting for intercurrent events, participants who had a missing endoscopy subscore at Week 12 were considered to not have achieved endoscopic healing at Week 12.
[d] The confidence intervals (CIs) were based on the Wald statistic..
[e] Participants in the combination therapy group switched to guselkumab monotherapy beginning at Week 12.

[0315] Table 22 – Number of Participants in Clinical Remission at Week 38[a]

	Golimumab Monotherapy	Guselkumab Monotherapy	Combination Therapy [f]
N	58	57	58
Participants in clinical remission [b,c,d]	14 (24.1%)	15 (26.3%)	23 (39.7%)
80% 2-sided CI [e]	16.9, 31.3	18.8, 33.8	31.4, 47.9

[a] Missing Data Non-responder Imputation: after applying the ICE rules, participants who had a missing clinical remission status were considered to not have achieved clinical remission.
[b] Clinical remission is defined as the Mayo score ≤ 2 with no individual subscore >1.
[c] Participants who had an intercurrent event (had an ostomy or colectomy (partial or total), discontinued study intervention due to lack of therapeutic effect or due to an AE of worsening of UC, had a protocol-prohibited change in concomitant UC medication(s), discontinued study intervention for reasons other than lack of efficacy or an AE of worsening of UC, death) prior to the Week 12 visit were considered to not have achieved clinical remission at Week 12.
[d] After accounting for intercurrent events, participants who are missing any or all of the Mayo subscores will be considered to not have achieved clinical remission at Week 12.
[e] The confidence intervals for the treatment difference in the proportion of participants achieving clinical remission between combination therapy versus each monotherapy were based on the Wald statistic.
[f] Participants in the combination therapy group switched to guselkumab monotherapy beginning at Week 12.

[0316] Table 23 – Number of Participants in Clinical Remission by Health Authority Definition at Week 38[a]

	Golimumab Monotherapy	Guselkumab Monotherapy	Combination Therapy [f]
N	58	57	58
Participants in clinical remission by Health Authority definition [b,c,d]	13 (22.4%)	15 (26.3%)	25 (43.1%)
80% 2-sided CI [e]	15.4, 29.4	18.8, 33.8	34.8, 51.4

[a] Missing Data Non-responder Imputation: after applying the ICE rules, participants who had a missing clinical remission status were considered to not have achieved clinical remission.
[b] Clinical remission by Health Authority definition is defined as a stool frequency subscore of 0 or 1, rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on the endoscopy, where the stool frequency subscore has not increased from baseline.
[c] Participants who had an intercurrent event (had an ostomy or colectomy (partial or total), discontinued study intervention due to lack of therapeutic effect or due to an AE of worsening of UC, had a protocol-prohibited change in concomitant UC medication(s), discontinued study intervention for reasons other than lack of efficacy or an AE of worsening of UC, death) prior to the Week 12 visit were considered to not have achieved clinical remission by Health Authority definition at Week 12.
[d] After accounting for intercurrent events, participants who are missing any or all of the components of the clinical remission by Health Authority definition at Week 12 will be considered to not have achieved clinical remission by Health Authority definition at Week 12.
[e] The confidence intervals for the treatment difference in the proportion of participants achieving clinical remission by Health Authority definition between combination therapy versus each monotherapy were based on the Wald statistic.
[f] Participants in the combination therapy group switched to guselkumab monotherapy beginning at Week 12.

[0317] Table 24 – Summary of Treatment-emergent AEs Through Week 38 (Monotherapy Phase)

	Golimumab Monotherapy	Guselkumab Monotherapy	Combination Therapy [d]
Number of patients	72	71	71
Avg duration of follow-up (weeks)	40.9	42.2	43.1
Avg exposure (number of administrations)[a]	12.5	13.1	13.2
Participants with ≥1, n (%)			
Adverse event (AEs)	50 (69.4%)	41 (57.7%)	44 (62.0%)
Serious adverse event (SAEs)	4 (5.6%)	4 (5.6%)	4 (5.6%)
AEs leading to discontinuation of study intervention	4 (5.6%)	1 (1.4%)	7 (9.9%)
Infection[b]	22 (30.6%)	17 (23.9%)	21 (29.6%)
Serious infection[b]	2 (2.8%)	2 (2.8%)	2 (2.8%)

AEs leading to death[c]	0	1 (1.4%)	1 (1.4%)
Associated with COVID-19 infection	2 (2.8%)	3 (4.2%)	2 (2.8%)

[a] Average number of visits study intervention received.
[b] Infection as assessed by the investigator.
[c] AEs leading to death are based on the AE outcome of Fatal.
[d] Participants in the combination therapy group switched to guselkumab monotherapy beginning at Week 12.

[0318] Table 25 – Treatment-emergent Serious AEs Through Week 38

	Golimumab Monotherapy	Guselkumab Monotherapy	Combination Therapy [e]
Number of patients	72	71	71
Avg duration of follow-up (weeks)	40.9	42.2	43.1
Patients with ≥1 treatment-emergent SAEs, n (%)	4 (5.6%)	4 (5.6%)	4 (5.6%)
Infections and infestations	2 (2.8%)	2 (2.8%)	2 (2.8%)
Influenza	0	0	1 (1.4%)[a]
Sepsis	0	0	1 (1.4%)[a]
Tuberculosis of intrathoracic lymph nodes	0	0	1 (1.4%)[b]
Bronchitis	0	1 (1.4%)[c]	0
COVID-19	0	1 (1.4%) [d]	0
COVID-19 pneumonia	1 (1.4%)	0	0
Chronic sinusitis	1 (1.4%)	0	0
Gastrointestinal disorders	1 (1.4%)	2 (2.8%)	0
Colitis ulcerative	1 (1.4%)	0	0
Gastrointestinal hemorrhage	0	1 (1.4%)[c]	0
Small intestinal obstruction	0	1 (1.4%)	0

Respiratory, thoracic and mediastinal disorders	1 (1.4%)	0	1 (1.4%)
Pulmonary embolism	1 (1.4%)	0	1 (1.4%)[b]
Cardiac disorders	0	1 (1.4%)	0
Atrial fibrillation	0	1 (1.4%)	0
Neoplasm benign, malignant and unspecified (including cysts and polyps)	0	1 (1.4%)	0
Adenocarcinoma of colon	0	1 (1.4%) [d]	0
Metabolism and nutrition disorders	1 (1.4%)	0	0
Dehydration	1 (1.4%)	0	0
Injury, poisoning and procedural complications	0	0	1 (1.4%)
Poisoning	0	0	1 (1.4%)

Key: AE = adverse event, Avg = average
[a] Subject ID 100180; [b] Subject ID 100170; [c] Subject ID 100147; [d] Subject ID 100109.
[e] Participants in the combination therapy group switched to guselkumab monotherapy beginning at Week 12.

[0319] The present application describes a number of examples and embodiments of the invention. Nevertheless, it must be borne in mind that various modifications of the described examples and embodiments can be developed, while not departing from the scope and the essence of the invention in principle. With this in mind, other embodiments are included in the scope of the items listed below. At that, all the numerical ranges described herein include all the sub ranges contained therein, as well as any individual values within the scope of these ranges. All publications, patents and patent applications mentioned in this description are hereby incorporated by reference.

[0320] The invention can be described with reference to the following numbered embodiments:

[0321] 1. An IL-23 inhibitor and a TNFα inhibitor for use in the treatment of an inflammatory disease in a patient, wherein the inhibitors are in co-therapeutically effective and clinically safe amounts and the patient shows a clinical response.

[0322] 2. An IL-23 inhibitor and a TNFα inhibitor for use according to embodiment 1, wherein the inflammatory disease is an inflammatory bowel disease (IBD) and the patient shows a clinical response based on a clinical endpoint selected from the group consisting of Mayo score, partial Mayo score, Ulcerative Colitis Endoscopic Index of Severity (UCEIS), the markers CRP and/or fecal calprotectin and patient-reported outcome and symptom measures.

[0323] 3. An IL-23 inhibitor and a TNFα inhibitor for use according to any one of the preceding embodiments, wherein the IL-23 inhibitor comprises an anti-IL-23p19 antibody or antigen-binding fragment thereof and the TNFα inhibitor comprises an anti-TNFα antibody or antigen-binding fragment thereof.

[0324] 4. An IL-23 inhibitor and a TNFα inhibitor for use according to any one of the preceding embodiments, wherein the IBD is Crohn's disease.

[0325] 5. An IL-23 inhibitor and a TNFα inhibitor for use according to any one of the preceding embodiments, wherein the IBD is ulcerative colitis (UC) or indeterminate colitis.

[0326] 6. An IL-23 inhibitor and a TNFα inhibitor for use according to any one of the preceding embodiments, wherein the inflammatory bowel disease is moderately to severely active UC.

[0327] 7. An IL-23 inhibitor and a TNFα inhibitor for use according to any one of the preceding embodiments, wherein the patient was previously treated with a TNFα inhibitor alone and wherein the UC did not undergo remission after the previous treatment.

[0328] 8. An IL-23 inhibitor and a TNFα inhibitor for use according to any one of the preceding embodiments, wherein the patient was previously treated with an IL-23 inhibitor alone and wherein the UC did not undergo remission after the previous treatment.

[0329] 9. An IL-23 inhibitor and a TNFα inhibitor for use according to any one of the preceding embodiments, wherein the anti-IL-23p19 antibody comprises: a) heavy chain complementarity determining region (CDR) amino acid sequences of SEQ ID NOs: 1-3 and light chain CDR amino acid sequences of SEQ ID NOs: 4-6; b) heavy chain variable region amino acid sequence of SEQ ID NO: 7 and light chain variable region amino acid sequence of SEQ ID NO: 8; or c) heavy chain amino acid sequence of SEQ ID NO: 9 and light chain amino acid sequence of SEQ ID NO: 10.

[0330] 10. An IL-23 inhibitor and a TNFα inhibitor for use according to any one of the preceding embodiments, wherein the anti-TNFα antibody comprises: a) heavy chain CDR amino acid sequences of SEQ ID NOs: 11-13 and light chain CDR amino acid sequences of SEQ ID NOs: 14-16; b) heavy chain variable region amino acid sequence of SEQ ID NO: 17 and light chain variable

region amino acid sequence of SEQ ID NO: 18; or c) heavy chain amino acid sequence of SEQ ID NO: 19 and light chain amino acid sequence of SEQ ID NO: 20.

[0331] 11. An IL-23 inhibitor and a TNFα inhibitor for use according to any one of the preceding embodiments, wherein the anti-IL-23p19 antibody comprises: a) heavy chain CDR amino acid sequences of SEQ ID NOs: 1-3 and light chain CDR amino acid sequences of SEQ ID NOs: 4-6; b) heavy chain variable region amino acid sequence of SEQ ID NO: 7 and light chain variable region amino acid sequence of SEQ ID NO: 8; or c) heavy chain amino acid sequence of SEQ ID NO: 9 and light chain amino acid sequence of SEQ ID NO: 10, and the anti-TNFα antibody comprises: a) heavy chain CDR amino acid sequences of SEQ ID NOs: 11-13 and light chain CDR amino acid sequences of SEQ ID NOs: 14-16; b) heavy chain variable region amino acid sequence of SEQ ID NO: 17 and light chain variable region amino acid sequence of SEQ ID NO: 18; or c) heavy chain amino acid sequence of SEQ ID NO: 19 and light chain amino acid sequence of SEQ ID NO: 20.

[0332] 12. An anti-IL-23p19 antibody and an anti-TNFα antibody for use in the treatment of UC in a patient, wherein the anti-IL-23p19 antibody comprises (i) heavy chain CDR amino acid sequences of SEQ ID NOs: 1-3 and light chain CDR amino acid sequences of SEQ ID NOs: 4-6, (ii) heavy chain variable region amino acid sequence of SEQ ID NO: 7 and light chain variable region amino acid sequence of SEQ ID NO: 8, or (iii) heavy chain amino acid sequence of SEQ ID NO: 9 and light chain amino acid sequence of SEQ ID NO: 10; and the anti-TNFα antibody comprises (i) heavy chain CDR amino acid sequences of SEQ ID NOs: 11-13 and light chain CDR amino acid sequences of SEQ ID NOs: 14-16, (ii) heavy chain variable region amino acid sequence of SEQ ID NO: 17 and light chain variable region amino acid sequence of SEQ ID NO: 18, or (iii) heavy chain amino acid sequence of SEQ ID NO: 19 and light chain amino acid sequence of SEQ ID NO: 20, wherein the antibodies are in co-therapeutically effective and clinically safe amounts and the use is effective to treat ulcerative colitis and the patient shows a clinical response based on a clinical endpoint selected from the group consisting of Mayo score, partial Mayo score, UCEIS, the markers CRP and/or fecal calprotectin and patient-reported outcome and symptom measures.

[0333] 13. An anti-IL-23p19 antibody and an anti-TNFα antibody for use according to embodiment 12, wherein the anti-TNFα antibody and the anti-IL-23p19 antibody are administered in a ratio of from 1:2 to 2:1 (w/w).

[0334] 14. An anti-IL-23p19 antibody and an anti-TNFα antibody for use according to embodiment 12 or 13, wherein the anti-TNFα antibody and the anti-IL-23p19 antibody are administered in a ratio of from 15:1 to 400:1 (w/w).

[0335] 15. An anti-IL-23p19 antibody and an anti-TNFα antibody for use according to any of embodiments 12-14, wherein the anti-IL-23p19 antibody and the anti-TNFα antibody are administered simultaneously.

[0336] 16. An anti-IL-23p19 antibody and an anti-TNFα antibody for use according to any of embodiments 12-14, wherein the anti-IL-23p19 antibody and the anti-TNFα antibody are administered sequentially.

[0337] 17. An anti-IL-23p19 antibody and an anti-TNFα antibody for use according to any of embodiments 12-14 and 16, wherein the anti-IL-23p19 antibody and the anti-TNFα antibody are administered within one day of one another.

[0338] 18. An anti-IL-23p19 antibody and an anti-TNFα antibody for use according to any of embodiments 12-17, wherein the anti-IL-23p19 antibody is administered in an initial intravenous dose of 200 mg, intravenous doses of 200 mg at weeks 4 and 8 and subsequent subcutaneous doses of 100 mg every 8 weeks and the anti-TNFα antibody is administered in an initial subcutaneous dose of 200 mg and subsequent subcutaneous doses of 100 mg at weeks 2, 6 and 10.

[0339] 19. An anti-IL-23p19 antibody and an anti-TNFα antibody for use according to any of embodiments 12-18, wherein the patient shows a clinical remission based on a clinical endpoint selected from the group consisting of Mayo score, partial Mayo score, UCEIS, the markers CRP and/or fecal calprotectin and patient-reported outcome and symptom measures.

[0340] 20. An anti-IL-23p19 antibody and an anti-TNFα antibody for use according to embodiment 19, wherein the clinical endpoint is measured about 12 weeks or about 38 weeks after initial treatment.

[0341] 21. An anti-IL-23p19 antibody and an anti-TNFα antibody for use according to embodiment 19 or 20, wherein the clinical endpoint is based on the Mayo Score.

[0342] 22. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use in reducing inflammation of the colon in a patient with IBD, wherein the antibodies are in co-therapeutically effective and clinically safe

amounts and the use is effective to reduce inflammation of the colon of the patient to a level comparable to the colon of a normal subject.

[0343] 23. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to embodiment 22, wherein the inflammation is very minimal or normal in a tissue sample from the colon of the patient after administration of the anti-IL-23 antibody or antigen-binding fragment thereof and the anti-TNFα antibody or antigen-binding fragment thereof.

[0344] 24. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to embodiment 22, wherein gland loss is very minimal or normal in a tissue sample from the colon of the subject after administration of the anti-IL-23 antibody or antigen-binding fragment thereof and the anti-TNFα antibody or antigen-binding fragment thereof.

[0345] 25. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to embodiment 22, wherein erosion is very minimal or normal in a tissue sample from the colon of the subject after administration of the anti-IL-23 antibody or antigen-binding fragment thereof and the anti-TNFα antibody or antigen-binding fragment thereof.

[0346] 26. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to embodiment 22, wherein mucosal thickness and hyperplasia are independently very minimal or normal in a tissue sample from the colon of the subject after administration of the anti-IL-23 antibody or antigen-binding fragment thereof and the anti-TNFα antibody or antigen-binding fragment thereof.

[0347] 27. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to embodiment 22, wherein after administration of the anti-IL-23 antibody or antigen-binding fragment thereof and the anti-TNFα antibody or antigen-binding fragment thereof, histopathology of the colon is identical to that of normal tissue.

[0348] 28. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to any of embodiments 22-27, wherein the anti-IL-23 antibody or antigen-binding fragment thereof comprises: a) heavy chain CDR amino acid sequences of SEQ ID NOs: 1-3 and light chain CDR amino acid sequences of SEQ

ID NOs: 4-6; b) heavy chain variable region amino acid sequence of SEQ ID NO: 7 and light chain variable region amino acid sequence of SEQID NO: 8; or c) heavy chain amino acid sequence of SEQ ID NO: 9 and light chain amino acid sequence of SEQ ID NO: 10; and the anti-TNFα antibody or antigen-binding fragment thereof comprises d) heavy chain CDR amino acid sequences of SEQ ID NOs: 11-13 and light chain CDR amino acid sequences of SEQ ID NOs: 14-16; e) heavy chain variable region amino acid sequence of SEQ ID NO: 17 and light chain variable region amino acid sequence of SEQ ID NO: 18; or f) the heavy chain amino acid sequence of SEQ ID NO: 19 and the light chain amino acid sequence of SEQ ID NO: 20.

[0349] 29. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to any of embodiments 22-28, wherein the anti-TNFα antibody or antigen-binding fragment thereof and the anti-IL-23 antibody or antigen-binding fragment thereof are administered in a ratio of from 1:2 to 2:1 (w/w).

[0350] 30. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to any of embodiments 22-28, wherein the anti-TNFα antibody or antigen-binding fragment thereof and the anti-IL-23 antibody or antigen-binding fragment thereof are administered in a ratio of from 15:1 to 400:1 (w/w).

[0351] 31. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to any of embodiments 22-30, wherein the a) anti-IL-23 antibody or antigen-binding fragment thereof and the b) anti-TNFα antibody or antigen-binding fragment thereof are administered simultaneously.

[0352] 32. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to any of embodiments 22-30, wherein the a) anti-IL-23 antibody or antigen-binding fragment thereof and the b) anti-TNFα antibody or antigen-binding fragment thereof are administered sequentially.

[0353] 33. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to any of embodiments 22-30, wherein the a) anti-IL-23 antibody or antigen-binding fragment thereof and the b) anti-TNFα antibody or antigen-binding fragment thereof are administered within one day of one another.

[0354] 34. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use in treating IBD in a patient and reducing weight loss in the patient and being clinically safe.

[0355] 35. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to embodiment 34, wherein the anti-TNFα antibody or antigen-binding fragment thereof and the anti-IL-23 antibody or antigen-binding fragment thereof are administered in a ratio of from 1:2 to 2:1 (w/w).

[0356] 36. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to embodiment 34, wherein the anti-TNFα antibody or antigen-binding fragment thereof and the anti-IL-23 antibody or antigen-binding fragment thereof are administered in a ratio of from 15:1 to 400:1 (w/w).

[0357] 37. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to any of embodiments 34-37, wherein the a) anti-IL-23 antibody or antigen-binding fragment thereof and the b) anti-TNFα antibody or antigen-binding fragment thereof are administered simultaneously.

[0358] 38. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to any of embodiments 34-37, wherein the a) anti-IL-23 antibody or antigen-binding fragment thereof and the b) anti-TNFα antibody or antigen-binding fragment thereof are administered sequentially.

[0359] 39. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to any of embodiments 34-36, and 38, wherein the a) anti-IL-23 antibody or antigen-binding fragment thereof and the b) anti-TNFα antibody or antigen-binding fragment thereof are administered within one day of one another.

[0360] 40. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to any of embodiments 34-39, wherein the anti-IL-23 antibody or antigen-binding fragment thereof comprises: a) heavy chain CDR amino acid sequences of SEQ ID NOs: 1-3 and light chain CDR amino acid sequences of SEQ ID NOs: 4-6; b) heavy chain variable region amino acid sequence of SEQ ID NO: 7 and light chain variable region amino acid sequence of SEQ ID NO: 8; or c) heavy chain amino acid sequence of SEQ ID NO: 9 and light chain amino acid sequence of SEQ ID NO: 10; and the anti-TNFα antibody or antigen-binding fragment thereof comprises d) heavy chain CDR amino acid sequences of SEQ ID NOs: 11-13 and light chain CDR amino acid sequences of SEQ ID NOs: 14-16; e) heavy chain variable region amino acid sequence of SEQ ID NO: 17 and light chain variable region amino acid

sequence of SEQ ID NO: 18; or f) heavy chain amino acid sequence of SEQ ID NO: 19 and light chain amino acid sequence of SEQ ID NO: 20.

[0361] 41. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use in treating moderately to severely active US in a human patient, wherein the anti-IL-23 antibody or antigen-binding fragment thereof is administered at 0.0005 to 0.002 mg/kg and comprises the sequences of (i) heavy chain CDR amino acid sequences of SEQ ID NOs: 1-3 and light chain CDR amino acid sequences of SEQ ID NOs: 4-6; (ii) heavy chain variable region amino acid sequence of SEQ ID NO: 7 and light chain variable region amino acid sequence of SEQ ID NO: 8; or (iii) heavy chain amino acid sequence of SEQ ID NO: 9 and light chain amino acid sequence of SEQ ID NO: 10 and the anti-TNFα antibody or antigen-binding fragment thereof is administered at 0.020 to 0.125 mg/kg and comprises the sequences of (iv) heavy chain CDR amino acid sequences of SEQ ID NOs: 11-13 and light chain CDR amino acid sequences of SEQ ID NOs: 14-16; (v) heavy chain variable region amino acid sequence of SEQ ID NO: 17 and light chain variable region amino acid sequence of SEQ ID NO: 18; or (vi) heavy chain amino acid sequence of SEQ ID NO: 19 and light chain amino acid sequence of SEQ ID NO: 20.

[0362] 42. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to embodiment 41, wherein the use is effective and clinically safe to treat the UC.

[0363] 43. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to embodiment 41 or 42, wherein the patient shows a clinical remission based on a clinical endpoint selected from the group consisting of Mayo score, partial Mayo score, UCEIS, the markers CRP and/or fecal calprotectin and patient-reported outcome and symptom measures.

[0364] 44. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to any of embodiments 41-43, wherein the anti-IL-23 antibody or antigen-binding fragment thereof is in an aqueous solution in a pharmaceutical composition at 100 mg/mL; 7.9% (w/v) sucrose; 4.0 mM Histidine; 6.9 mM L-Histidine monohydrochloride monohydrate; 0.053% (w/v) Polysorbate 80 of the composition, and the anti-TNFα antibody or antigen-binding fragment thereof is in an aqueous solution in a

pharmaceutical composition at 100 mg/mL; 4.1% (w/v) sorbitol; 5.6 mM L-Histidine and L-Histidine monohydrochloride monohydrate; 0.015% (w/v) Polysorbate 80 of the composition.

[0365] 45. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use in treating UC in a patient, wherein a first co-therapeutically effective and clinically safe amount of the anti-IL-23 antibody or antigen-binding fragment thereof and a second co-therapeutically effective and clinically safe amount of the anti-TNFα antibody or antigen-binding fragment thereof are administered during a combination therapy phase, which is followed by the administration of a therapeutically effective and clinically safe amount of the anti-IL-23 antibody or antigen-binding fragment thereof during a monotherapy phase and wherein the patient is a responder to therapy measured about 38 weeks after initial treatment.

[0366] 46. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to embodiment 45, wherein the anti-IL-23 antibody or antigen-binding fragment thereof comprises: a) heavy chain CDR amino acid sequences of SEQ ID NOs: 1-3 and light chain CDR amino acid sequences of SEQ ID NOs: 4-6; b) heavy chain variable region amino acid sequence of SEQ ID NO: 7 and light chain variable region amino acid sequence of SEQ ID NO: 8; or c) heavy chain amino acid sequence of SEQ ID NO: 9 and light chain amino acid sequence of SEQ ID NO: 10.

[0367] 47. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to embodiment 45 or 46, wherein the anti-TNFα antibody or antigen-binding fragment thereof comprises: a) heavy chain CDR amino acid sequences of SEQ ID NOs: 11-13 and light chain CDR amino acid sequences of SEQ ID NOs: 14-16; b) heavy chain variable region amino acid sequence of SEQ ID NO: 17 and light chain variable region amino acid sequence of SEQ ID NO: 18; or c) heavy chain amino acid sequence of SEQ ID NO: 19 and light chain amino acid sequence of SEQ ID NO:20.

[0368] 48. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to any of embodiments 45-47, wherein the anti-IL-23 antibody or antigen-binding fragment thereof comprises: a) heavy chain CDR amino acid sequences of SEQ ID NOs: 1-3 and light chain CDR amino acid sequences of SEQ ID NOs: 4-6; b) heavy chain variable region amino acid sequence of SEQ ID NO: 7 and light chain variable region amino acid sequence of SEQ ID NO: 8; or c) heavy chain amino acid sequence of

SEQ ID NO: 9 and light chain amino acid sequence of SEQ ID NO: 10, and the anti-TNFα antibody or antigen-binding fragment thereof comprises: a) heavy chain CDR amino acid sequences of SEQ ID NOs: 11-13 and light chain CDR amino acid sequences of SEQ ID NOs: 14-16; b) heavy chain variable region amino acid sequence of SEQ ID NO: 17 and light chain variable region amino acid sequence of SEQ ID NO: 18; or c) heavy chain amino acid sequence of SEQ ID NO: 19 and light chain amino acid sequence of SEQ ID NO: 20.

[0369] 49. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to any of embodiments 45-48, wherein the anti-IL-23 antibody or antigen-binding fragment thereof is guselkumab and the anti-TNFα antibody or antigen-binding fragment thereof is golimumab.

[0370] 50. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to any of embodiments 45-49, wherein during the combination therapy phase, the anti-TNFα antibody or antigen-binding fragment thereof and the anti-IL-23 antibody or antigen-binding fragment thereof are administered in a ratio of from 1:2 to 2:1 (w/w).

[0371] 51. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to any of embodiments 45-49, wherein during the combination therapy phase, the anti-TNFα antibody or antigen-binding fragment thereof and the anti-IL-23 antibody or antigen-binding fragment thereof are administered in a ratio of from 15:1 to 400:1 (w/w).

[0372] 52. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to any of embodiments 45-51, wherein during the combination therapy phase, the anti-IL-23 antibody or antigen-binding fragment thereof and the anti-TNFα antibody or antigen-binding fragment thereof are administered simultaneously.

[0373] 53. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to any of embodiments 45-51, wherein during the combination therapy phase, the anti-IL-23 antibody or antigen-binding fragment thereof and the anti-TNFα antibody or antigen-binding fragment thereof are administered sequentially.

[0374] 54. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to any of embodiments 45-51 and 53, wherein during the combination therapy phase, the anti-IL-23 antibody or antigen-binding fragment thereof and the anti-TNFα antibody or antigen-binding fragment thereof are administered within one day of one another.

[0375] 55. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to any of embodiments 45-54, wherein the duration of the combination therapy phase is 12 weeks.

[0376] 56. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to any of embodiments 45-55, wherein during the combination therapy phase, the anti-IL-23 antibody or antigen-binding fragment thereof is administered in an initial intravenous dose of 200 mg and intravenous doses of 200 mg at weeks 4 and 8 and the anti-TNFα antibody or antigen-binding fragment thereof is administered in an initial subcutaneous dose of 200 mg and subsequent subcutaneous doses of 100 mg at weeks 2, 6 and 10, and during the monotherapy phase, the anti-IL-23 antibody is administered subcutaneously 100 mg every 8 weeks.

[0377] 57. An anti-IL-23 antibody or antigen-binding fragment thereof and an anti-TNFα antibody or antigen-binding fragment thereof for use according to any of embodiments 45-56, wherein the patient shows a clinical response based on a clinical endpoint selected from the group consisting of Mayo score, partial Mayo score, UCEIS, the markers CRP and/or fecal calprotectin and patient-reported outcome and symptom measures, wherein the clinical response is measured about 38 weeks after initial treatment.

[0378] 58. An anti-IL-23 antibody or antigen-binding fragment thereof for use in treating UC in a patient, wherein a therapeutically effective and clinically safe amount of the anti-IL-23 antibody or antigen-binding fragment thereof is administered.

[0379] 59. An anti-IL-23 antibody or antigen-binding fragment thereof for use according to embodiment 58, wherein the anti-IL-23 antibody or antigen-binding fragment thereof comprises: a) heavy chain CDR amino acid sequences of SEQ ID NOs: 1-3 and light chain CDR amino acid sequences of SEQ ID NOs: 4-6; b) heavy chain variable region amino acid sequence of SEQ ID NO: 7 and light chain variable region amino acid sequence of SEQ ID NO: 8; or c) heavy

chain amino acid sequence of SEQ ID NO: 9 and light chain amino acid sequence of SEQ ID NO: 10.

[0380] 60. An anti-IL-23 antibody or antigen-binding fragment thereof for use according to embodiment 59, wherein the anti-IL-23 antibody or antigen-binding fragment thereof is guselkumab.

[0381] 61. An anti-IL-23 antibody or antigen-binding fragment thereof for use according to any of embodiments 58-60, wherein the anti-IL-23 antibody or antigen-binding fragment thereof is administered in an initial dose of 200 mg, 600 mg or 1200 mg and a dose of 100 mg 2 weeks after the initial dose, 6 weeks after the initial dose, 10 weeks after the initial dose and every 4 or 8 weeks after the dose at 10 weeks.

[0382] 62. An anti-IL-23 antibody or antigen-binding fragment thereof for use according to any of embodiments 58-61, wherein the patient shows a clinical response based on a clinical endpoint selected from the group consisting of Mayo score, partial Mayo score, UCEIS, the markers CRP and/or fecal calprotectin and patient reported outcome and symptom measures.

Claims

1. A method of treating an inflammatory bowel disease (IBD) in a patient, the method comprising: a) administering a first co-therapeutically effective and clinically safe amount of an IL-23 inhibitor; and b) administering a second co-therapeutically effective and clinically safe amount of a TNFα inhibitor, wherein the method is effective to treat the IBD and the patient shows a clinical response based on a clinical endpoint selected from the group consisting of Mayo score, partial Mayo score, Ulcerative Colitis Endoscopic Index of Severity (UCEIS), the markers CRP and/or fecal calprotectin and patient-reported outcome and symptom measures, and wherein the clinical endpoint is measured about 38 weeks after initial treatment.
2. The method of claim 1, wherein the IL-23 inhibitor comprises an anti-IL-23p19 antibody or antigen-binding fragment thereof and the TNFα inhibitor comprises an anti-TNFα antibody or antigen-binding fragment thereof.
3. The method of claim 1 or 2, wherein the IBD is Crohn's disease (CD).
4. The method of claim 1 or 2, wherein the IBD is ulcerative colitis (UC) or indeterminate colitis.
5. The method of claim 4, wherein the IBD is moderately to severely active UC.
6. The method of claim 5, wherein the patient was previously treated with a TNFα inhibitor alone and wherein the UC did not undergo remission after the previous treatment.
7. The method of claim 5, wherein the patient was previously treated with an IL-23 inhibitor alone and wherein the UC did not undergo remission after the previous treatment.
8. The method of any of claims 2-7, wherein the anti-IL-23p19 antibody or antigen-binding fragment thereof comprises: a) heavy chain complementarity determining region (CDR) amino acid sequences of SEQ ID NOs: 1-3 and light chain CDR amino acid sequences of SEQ ID NOs: 4-6; b) heavy chain variable region amino acid sequence of SEQ ID NO: 7 and light chain variable region amino acid sequence of SEQ ID NO: 8; or c) heavy chain amino acid sequence of SEQ ID NO: 9 and a light chain amino acid sequence of SEQ ID NO: 10.
9. The method of any of claims 2-8, wherein the anti-TNFα antibody or antigen-binding fragment thereof comprises: a) heavy chain CDR amino acid sequences of SEQ ID NOs: 11-13 and light chain CDR amino acid sequences of SEQ ID NOs: 14-16; b) heavy chain variable region amino acid sequence of SEQ ID NO: 17 and light chain variable region amino acid sequence of SEQ ID NO: 18; or c) a heavy chain amino acid sequence of SEQ ID NO: 19 and light chain amino acid sequence of SEQ ID NO: 20.

10. The method of any of claims 2-7, wherein the anti-IL-23p19 antibody or antigen-binding fragment thereof comprises: a) heavy chain CDR amino acid sequences of SEQ ID NOs: 1-3 and light chain CDR amino acid sequences of SEQ ID NOs: 4-6; b) heavy chain variable region amino acid sequence of SEQ ID NO: 7 and light chain variable region amino acid sequence of SEQ ID NO: 8; or c) heavy chain amino acid sequence of SEQ ID NO: 9 and light chain amino acid sequence of SEQ ID NO: 10, and the anti-TNFα antibody or antigen-binding fragment thereof comprises: a) heavy chain CDR amino acid sequences of SEQ ID NOs: 11-13 and light chain CDR amino acid sequences of SEQ ID NOs: 14-16; b) heavy chain variable region amino acid sequence of SEQ ID NO: 17 and light chain variable region amino acid sequence of SEQ ID NO: 18; or c) heavy chain amino acid sequence of SEQ ID NO: 19 and light chain amino acid sequence of SEQ ID NO: 20.
11. The method of any of claims 1-7, wherein the IL-23 inhibitor comprises an anti-IL-23 antibody selected from the group consisting of guselkumab, risanakizumab, tildrakizumab and mirakizumab and the TNFα inhibitor is selected from the group consisting of golimumab, adalimumab, infliximab, certolizumab pegol and etanercept.
12. A method of treating UC in a patient, the method comprising: a) administering a first co-therapeutically effective amount of an anti-IL-23p19 antibody comprising (i) heavy chain CDR amino acid sequences of SEQ ID NOs: 1-3 and light chain CDR amino acid sequences of SEQ ID NOs: 4-6, (ii) heavy chain variable region amino acid sequence of SEQ ID NO: 7 and the light chain variable region amino acid sequence of SEQ ID NO: 8, or (iii) the heavy chain amino acid sequence of SEQ ID NO: 9 and the light chain amino acid sequence of SEQ ID NO:10; and b) administering a second co-therapeutically effective amount of an anti-TNFα antibody comprising (i) heavy chain CDR amino acid sequences of SEQ ID NOs: 11-13 and light chain CDR amino acid sequences of SEQ ID NOs: 14-16, (ii) heavy chain variable region amino acid sequence of SEQ ID NO: 17 and the light chain variable region amino acid sequence of SEQ ID NO: 18, or (iii) heavy chain amino acid sequence of SEQ ID NO: 19 and the light chain amino acid sequence of SEQ ID NO: 20, wherein the method is effective and clinically safe to treat UC and the patient shows a clinical response based on a clinical endpoint selected from the group consisting of Mayo score, partial Mayo score, UCEIS, the markers CRP and/or fecal calprotectin and patient-reported outcome and symptom measures, and wherein the clinical endpoint is measured about 38 weeks after initial treatment.

13. The method of claim 12, wherein the anti-TNFα antibody and the anti-IL-23p19 antibody are administered in a ratio of from 1:2 to 2:1 (w/w).
14. The method of claim 12, wherein the anti-TNFα antibody and the anti-IL-23p19 antibody are administered in a ratio of from 15:1 to 400:1 (w/w).
15. The method of any of claims 12-14, wherein the anti-IL-23p19 antibody and the anti-TNFα antibody are administered simultaneously.
16. The method of any of claims 12-14, wherein the anti-IL-23p19 antibody and the anti-TNFα antibody are administered sequentially.
17. The method of any of claims 12-14 and 16, wherein the anti-IL-23p19 antibody and the anti-TNFα antibody are administered within one day of one another.
18. The method of any of claims 12-14, wherein the anti-IL-23p19 antibody is administered in an initial intravenous dose of 200 mg, intravenous doses of 200 mg at weeks 4 and 8 and subsequent subcutaneous doses of 100 mg every 8 weeks and the anti-TNFα antibody is administered in an initial subcutaneous dose of 200 mg and subsequent subcutaneous doses of 100 mg at weeks 2, 6 and 10.
19. The method of any of claims 12-18, wherein the clinical endpoint is based on the Mayo Score.
20. A method of reducing inflammation of the colon in a patient with IBD, the method comprising: a) administering a first co-therapeutically effective amount of an anti-IL-23p19 antibody or antigen-binding fragment thereof; and b) administering a second co-therapeutically effective amount of an anti-TNFα antibody or antigen-binding fragment thereof, wherein the method is effective and clinically safe to reduce inflammation of the colon of the patient to a level comparable to the colon of a normal subject measured about 38 weeks after initial treatment.
21. The method of claim 20, wherein the inflammation is very minimal or normal in a tissue sample from the colon of the patient after administration of the anti-IL-23p19 antibody or antigen-binding fragment thereof and the anti-TNFα antibody or antigen-binding fragment thereof.
22. The method of claim 20 or 21, wherein gland loss is very minimal or normal in a tissue sample from the colon of the patient after administration of the anti-IL-23p19 antibody or antigen-binding fragment thereof and the anti-TNFα antibody or antigen-binding fragment thereof.
23. The method of any of claims 20-22, wherein erosion is very minimal or normal in a tissue sample from the colon of the patient after administration of the anti-IL-23p19 antibody or antigen-binding fragment thereof and the anti-TNFα antibody or antigen-binding fragment thereof.

24. The method of any of claim 20-23, wherein mucosal thickness and hyperplasia are independently very minimal or normal in a tissue sample from the colon of the patient after administration of the anti-IL-23p19 antibody or antigen-binding fragment thereof and the anti-TNFα antibody or antigen-binding fragment thereof.
25. The method of any of claims 20-24, wherein after administration of the anti-IL-23p19 antibody or antigen-binding fragment thereof and the anti-TNFα antibody or antigen-binding fragment thereof, histopathology of the colon is identical to that of normal tissue.
26. The method of any of claims 20-25, wherein the anti-IL-23p19 antibody or antigen-binding fragment thereof comprises: a) heavy chain CDR amino acid sequences of SEQ ID NOs: 1-3 and light chain CDR amino acid sequences of SEQ ID NOs: 4-6; b) heavy chain variable region amino acid sequence of SEQ ID NO: 7 and light chain variable region amino acid sequence of SEQ ID NO: 8; or c) heavy chain amino acid sequence of SEQ ID NO: 9 and light chain amino acid sequence of SEQ ID NO: 10; and the anti-TNFα antibody or antigen-binding fragment thereof comprises d) heavy chain CDR amino acid sequences of SEQ ID NOs: 11-13 and light chain CDR amino acid sequences of SEQ ID NOs: 14-16; e) heavy chain variable region amino acid sequence of SEQ ID NO: 17 and light chain variable region amino acid sequence of SEQ ID NO: 18; or f) heavy chain amino acid sequence of SEQ ID NO: 19 and light chain amino acid sequence of SEQ ID NO: 20.
27. The method of any of claims 20-26, wherein the anti-TNFα antibody or antigen-binding fragment thereof and the anti-IL-23p19 antibody or antigen-binding fragment thereof are administered in a ratio of from 1:2 to 2:1 (w/w).
28. The method of any of claims 20-26, wherein the anti-TNFα antibody or antigen-binding fragment thereof and the anti-IL-23p19 antibody or antigen-binding fragment thereof are administered in a ratio of from 15:1 to 400:1 (w/w).
29. The method of any of claims 20-28, wherein the a) anti-IL-23p19 antibody or antigen-binding fragment thereof and the b) anti-TNFα antibody or antigen-binding fragment thereof are administered simultaneously.
30. The method of any of claims 20-28, wherein the a) anti-IL-23p19 antibody or antigen-binding fragment thereof and the b) anti-TNFα antibody or antigen-binding fragment thereof are administered sequentially.

31. The method of any of claims 20-28 and 30, wherein the a) anti-IL-23p19 antibody or antigen-binding fragment thereof and the b) anti-TNFα antibody or antigen-binding fragment thereof are administered within one day of one another.
32. A method of treating IBD in a patient and reducing weight loss in the patient, the method comprising a) administering a first co-therapeutically and weight reducing effective and clinically safe amount of an anti-IL-23p19 antibody or antigen-binding fragment thereof; and b) administering a second co-therapeutically and weight reducing effective and clinically safe amount of an anti-TNFα antibody or antigen-binding fragment thereof.
33. The method of claim 32, wherein the anti-TNFα antibody or antigen-binding fragment thereof and the anti-IL-23p19 antibody or antigen-binding fragment thereof are administered in a ratio of from 1:2 to 2:1 (w/w).
34. The method of claim 32, wherein the anti-TNFα antibody or antigen-binding fragment thereof and the anti-IL-23p19 antibody or antigen-binding fragment thereof are administered in a ratio of from 15:1 to 400:1 (w/w).
35. The method of any of claims 32-34, wherein the a) anti-IL-23p19 antibody or antigen-binding fragment thereof and the b) anti-TNFα antibody or antigen-binding fragment thereof are administered simultaneously.
36. The method of any of claims 32-34, wherein the a) anti-IL-23p19 antibody or antigen-binding fragment thereof and the b) anti-TNFα antibody or antigen-binding fragment thereof are administered sequentially.
37. The method of any claims 32-34 and 36, wherein the a) anti-IL-23p19 antibody or antigen-binding fragment thereof and the b) anti-TNFα antibody or antigen-binding fragment thereof are administered within one day of one another.
38. The method of any of claims 32-37, wherein the anti-IL-23p19 antibody or antigen-binding fragment thereof comprises: a) heavy chain CDR amino acid sequences of SEQ ID NOs: 1-3 and light chain CDR amino acid sequences of SEQ ID NOs: 4-6; b) heavy chain variable region amino acid sequence of SEQ ID NO: 7 and light chain variable region amino acid sequence of SEQ ID NO: 8; or c) heavy chain amino acid sequence of SEQ ID NO: 9 and light chain amino acid sequence of SEQ ID NO: 10; and the anti-TNFα antibody or antigen-binding fragment thereof comprises a) heavy chain CDR amino acid sequences of SEQ ID NOs: 11-13 and light chain CDR amino acid sequences of SEQ ID NOs: 14-16; b) heavy chain variable region amino acid sequence

of SEQ ID NO: 17 and light chain variable region amino acid sequence of SEQ ID NO: 18; or c) heavy chain amino acid sequence of SEQ ID NO: 19 and light chain amino acid sequence of SEQ ID NO: 20.

39. A method of treating moderately to severely active UC in a human patient, the method comprising: a) administering 0.0005 to 0.002 mg/kg of an anti-IL-23p19 antibody or an antigen-binding fragment thereof comprising the sequences of (i) heavy chain CDR amino acid sequences of SEQ ID NOs:1-3 and light chain CDR amino acid sequences of SEQ ID NOs: 4-6; (ii) heavy chain variable region amino acid sequence of SEQ ID NO: 7 and light chain variable region amino acid sequence of SEQ ID NO: 8; or (iii) heavy chain amino acid sequence of SEQ ID NO: 9 and light chain amino acid sequence of SEQ ID NO: 10 and b) administering 0.020 to 0.125 mg/kg of an anti-TNFα antibody or an antigen-binding fragment thereof comprising the sequences of (i) heavy chain CDR amino acid sequences of SEQ ID NOs: 11-13 and the light chain CDR amino acid sequences of SEQ ID NOs: 14-16; (ii) heavy chain variable region amino acid sequence of SEQ ID NO: 17 and light chain variable region amino acid sequence of SEQ ID NO: 18; or (iii) heavy chain amino acid sequence of SEQ ID NO: 19 and light chain amino acid sequence of SEQ ID NO: 20, wherein the method is effective and clinically safe in treating the UC and the patient shows a clinical response based on a clinical endpoint selected from the group consisting of Mayo score, partial Mayo score, Ulcerative Colitis Endoscopic Index of Severity (UCEIS), the markers CRP and/or fecal calprotectin and patient-reported outcome and symptom measures, and wherein the clinical endpoint is measured about 38 weeks after initial treatment.
40. The method of any of claims 39, wherein the anti-IL-23p19 antibody or antigen-binding fragment thereof is in an aqueous solution in a pharmaceutical composition at 100 mg/mL; 7.9% (w/v) sucrose; 4.0 mM Histidine; 6.9 mM L-Histidine monohydrochloride monohydrate; 0.053% (w/v) Polysorbate 80 of the composition, and the anti-TNFα antibody or antigen-binding fragment thereof is in an aqueous solution in a pharmaceutical composition at 100 mg/mL; 4.1% (w/v) sorbitol; 5.6 mM L-Histidine and L-Histidine monohydrochloride monohydrate; 0.015% (w/v) Polysorbate 80 of the composition.
41. A pharmaceutical product comprising a composition of: a) an anti-IL-23 inhibitor and b) an anti-TNFα inhibitor for use in combination therapy to treat an inflammatory disorder, wherein a first co-therapeutically effective and clinically safe amount of the IL-23 inhibitor and a second co-therapeutically effective and clinically safe amount of the TNFα inhibitor are administered to a

patient having IBD and the patient shows a clinical response based on a clinical endpoint selected from the group consisting of Mayo score, partial Mayo score, Ulcerative Colitis Endoscopic Index of Severity (UCEIS), the markers CRP and/or fecal calprotectin and patient-reported outcome and symptom measures, and wherein the clinical endpoint is measured about 38 weeks after initial treatment.

42. The product of claim 41, wherein the anti-IL-23 inhibitor is an anti-IL-23p19 antibody or antigen-binding fragment thereof and the anti-TNFα inhibitor is an anti-TNFα antibody or antigen-binding fragment thereof.
43. The product of claim 41 or 42, wherein the IBD is UC, the anti-IL-23p19 antibody is guselkumab and the anti-TNFα antibody is golimumab.
44. A method of treating UC in a patient, the method comprising a combination therapy phase followed by a monotherapy phase, wherein, i) the combination therapy phase comprises a) administering a first co-therapeutically effective and clinically safe amount of an anti-IL-23p19 antibody or antigen-binding fragment thereof and b) administering a second co-therapeutically effective and clinically safe amount of an anti-TNFα antibody or antigen-binding fragment thereof, and ii) the monotherapy phase comprises administering a therapeutically effective and clinically safe amount of the anti-IL-23p19 antibody or antigen-binding fragment thereof and wherein the patient is a responder to therapy measured about 38 weeks after initial treatment.
45. The method of claim 44, wherein the anti-IL-23p19 antibody or antigen-binding fragment thereof comprises: a) heavy chain CDR amino acid sequences of SEQ ID NOs: 1-3 and light chain CDR amino acid sequences of SEQ ID NOs: 4-6; b) heavy chain variable region amino acid sequence of SEQ ID NO: 7 and light chain variable region amino acid sequence of SEQ ID NO: 8; or c) heavy chain amino acid sequence of SEQ ID NO: 9 and light chain amino acid sequence of SEQ ID NO: 10.
46. The method of claim 44 or 45, wherein the anti-TNFα antibody or antigen-binding fragment thereof comprises: a) heavy chain CDR amino acid sequences of SEQ ID NOs: 11-13 and light chain CDR amino acid sequences of SEQ ID NOs: 14-16; b) heavy chain variable region amino acid sequence of SEQ ID NO: 17 and light chain variable region amino acid sequence of SEQ ID NO: 18; or c) heavy chain amino acid sequence of SEQ ID NO: 19 and light chain amino acid sequence of SEQ ID NO: 20

47. The method of claim 44, wherein the anti-IL-23p19 antibody or antigen-binding fragment thereof comprises: a) heavy chain CDR amino acid sequences of SEQ ID NOs: 1-3 and light chain CDR amino acid sequences of SEQ ID NOS: 4-6; b) heavy chain variable region amino acid sequence of SEQ ID NO: 7 and light chain variable region amino acid sequence of SEQ ID NO: 8; or c) heavy chain amino acid sequence of SEQ ID NO: 9 and light chain amino acid sequence of SEQ ID NO: 10, and the anti-TNFα antibody or antigen-binding fragment thereof comprises: a) heavy chain CDR amino acid sequences of SEQ ID NOs: 11-13 and light chain CDR amino acid sequences of SEQ ID NOs: 14-16; b) heavy chain variable region amino acid sequence of SEQ ID NO: 17 and light chain variable region amino acid sequence of SEQ ID NO: 18; or c) heavy chain amino acid sequence of SEQ ID NO: 19 and light chain amino acid sequence of SEQ ID NO:20.
48. The method of claim 44, wherein the anti-IL-23p19 antibody or antigen-binding fragment thereof is guselkumab and the anti-TNFα antibody or antigen-binding fragment thereof is golimumab.
49. The method of any of claims 44-48, wherein during the combination therapy phase, the anti-TNFα antibody or antigen-binding fragment thereof and the anti-IL-23p19 antibody or antigen-binding fragment thereof are administered in a ratio of from 1:2 to 2:1 (w/w).
50. The method of any of claims 44-48, wherein during the combination therapy phase, the anti-TNFα antibody or antigen-binding fragment thereof and the anti-IL-23p19 antibody or antigen-binding fragment thereof are administered in a ratio of from 15:1 to 400:1 (w/w).
51. The method of any of claims 44-50, wherein during the combination therapy phase, the anti-IL-23p19 antibody or antigen-binding fragment thereof and the anti-TNFα antibody or antigen-binding fragment thereof are administered simultaneously.
52. The method of any of claims 44-50, wherein during the combination therapy phase, the anti-IL-23p19 antibody or antigen-binding fragment thereof and the anti-TNFα antibody or antigen-binding fragment thereof are administered sequentially.
53. The method of any of claims 44-50 and 52, wherein during the combination therapy phase, the anti-IL-23p19 antibody or antigen-binding fragment thereof and the anti-TNFα antibody or antigen-binding fragment thereof are administered within one day of one another.
54. The method of any of claims 44-53, wherein the duration of the combination therapy phase is 12 weeks.

55. The method of any of claims 44-54, wherein during the combination therapy phase, the anti-IL-23p19 antibody or antigen-binding fragment thereof is administered in an initial intravenous dose of 200 mg and intravenous doses of 200 mg at weeks 4 and 8 and the anti-TNFα antibody or antigen-binding fragment thereof is administered in an initial subcutaneous dose of 200 mg and subsequent subcutaneous doses of 100 mg at weeks 2, 6 and 10, and during the monotherapy phase, the anti-IL-23p19 antibody or antigen-binding fragment thereof is administered subcutaneously 100 mg every 8 weeks.
56. The method of any of claims 44-55, wherein the patient shows a clinical response based on a clinical endpoint selected from the group consisting of Mayo score, partial Mayo score, UCEIS, the markers CRP and/or fecal calprotectin and patient-reported outcome and symptom measures, wherein the clinical response is measured about 38 weeks after initial treatment.
57. A method of treating ulcerative colitis in a patient, the method comprising administering a therapeutically effective and clinically safe amount of an anti-IL-23p19 antibody or antigen-binding fragment thereof, wherein the patient shows a clinical response based on a clinical endpoint selected from the group consisting of Mayo score, partial Mayo score, UCEIS, the markers CRP and/or fecal calprotectin and patient-reported outcome and symptom measures.
58. The method of claim 57, wherein the anti-IL-23p19 antibody or antigen-binding fragment thereof comprises: a) heavy chain CDR amino acid sequences of SEQ ID NOs: 1-3 and light chain CDR amino acid sequences of SEQ ID NOs: 4-6; b) heavy chain variable region amino acid sequence of SEQ ID NO: 7 and light chain variable region amino acid sequence of SEQ ID NO: 8; or c) heavy chain amino acid sequence of SEQ ID NO: 9 and light chain amino acid sequence of SEQ ID NO: 10.
59. The method of claim 57 or 58, wherein the anti-IL-23p19 antibody or antigen-binding fragment thereof is guselkumab.
60. The method of any of claims 57-59, wherein the anti-IL-23p19 antibody or antigen-binding fragment thereof is administered in an initial dose of 200 mg, 600 mg or 1200 mg and a dose of 100 mg 2 weeks after the initial dose, 6 weeks after the initial dose, 10 weeks after the initial dose and every 4 or 8 weeks after the dose at 10 weeks.

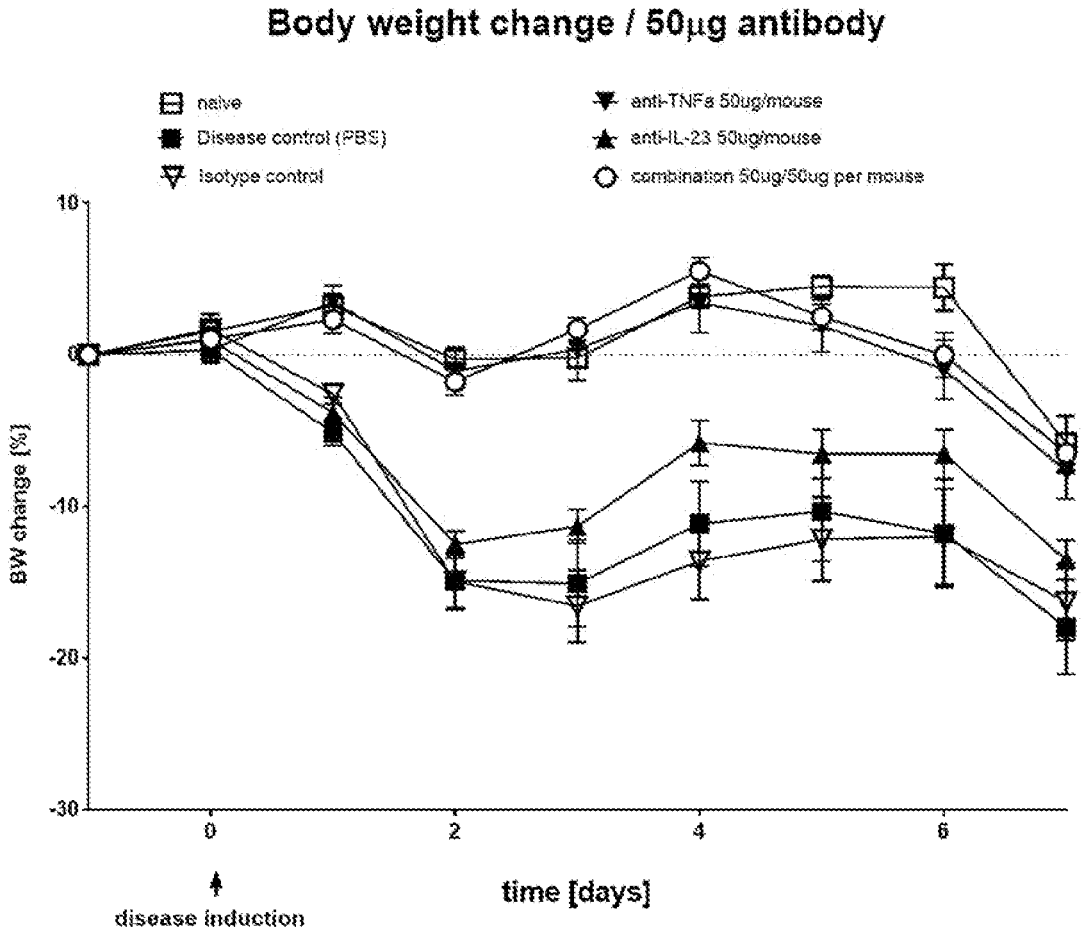
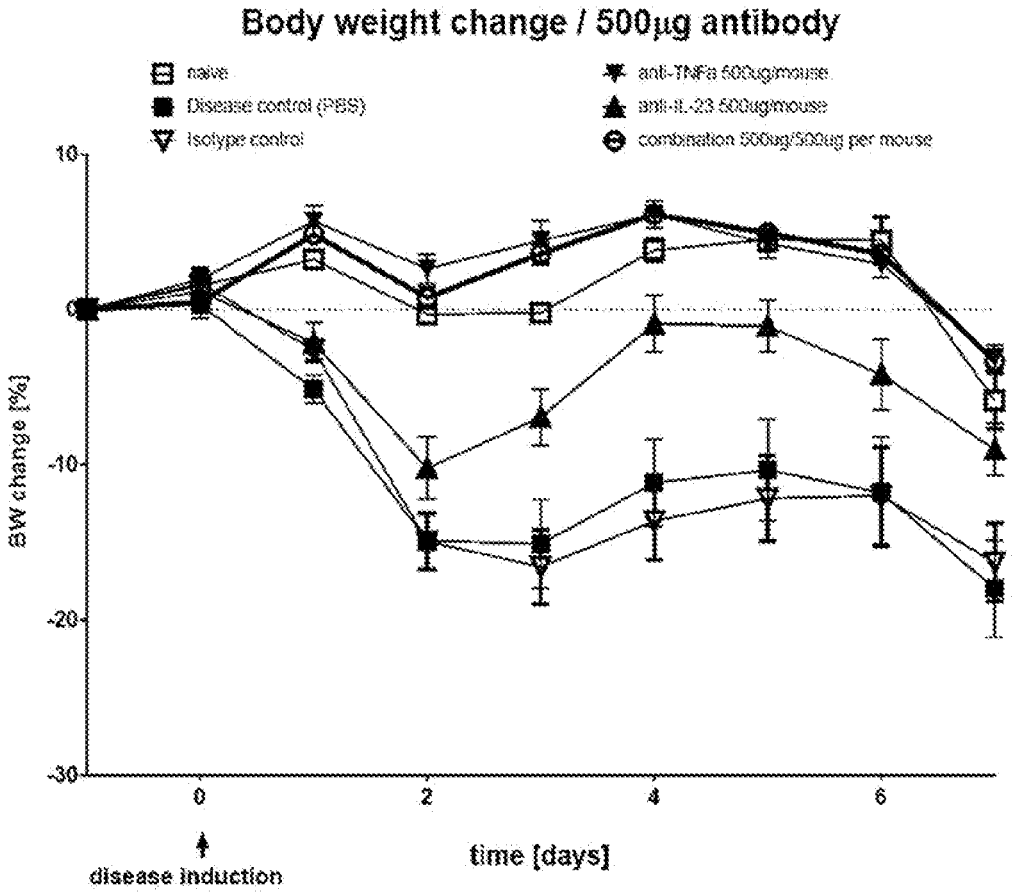

Body weight change / 50µg antibody
naive
Disease control (PBS)
isotype control
anti-TNFa 50ug/mouse
anti-IL-23 50ug/mouse
combination 50ug/50ug per mouse
10
0
-10
-20
-30
BW change [%]
0
2
4
6
time [days]
disease induction

FIG. 1A



mab treatment	Day -1	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
50µg aTNFα	0.999	0.957	*0.008*	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0001*
500µg aTNFα	0.999	0.9998	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0001*
50µg aIL-23	0.999	0.9979	0.6242	0.6242	*0.0302*	*0.0003*	*0.0158*	*0.0219*	0.5024
500µg aIL-23	0.999	0.9996	0.0633	0.0633	*0.0001*	*0.0001*	*0.0001*	*0.0005*	*0.0009*
50µg aTNFα + aIL-23	0.999	0.9995	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0001*
500µg aTNFα + aIL-23	0.999	0.9694	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0001*

FIG. 1B

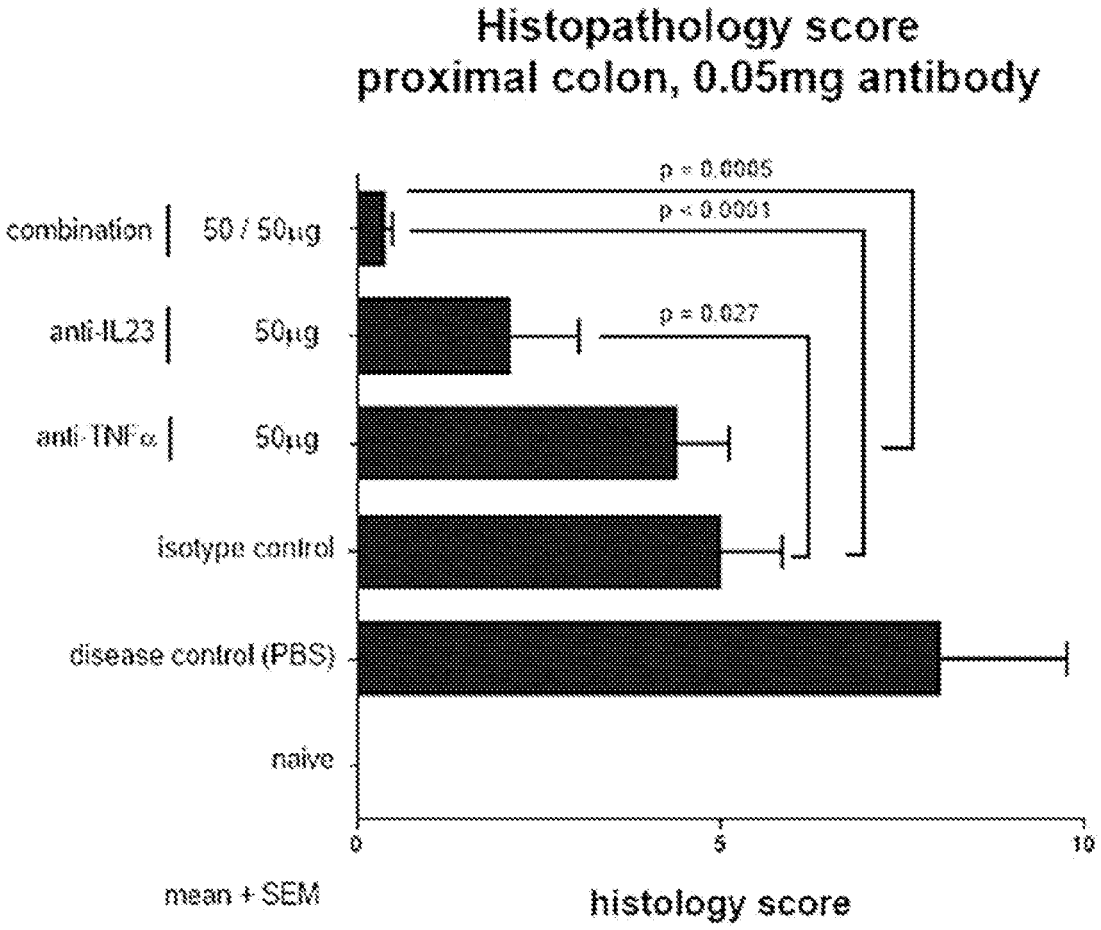

Histopathology score
proximal colon, 0.05mg antibody
p = 0.0085
p = 0.0001
p = 0.027
combination
50 / 50µg
anti-IL23
50µg
anti-TNFα
50µg
isotype control
disease control (PBS)
naive
0
5
10
mean + SEM
histology score

FIG. 2A

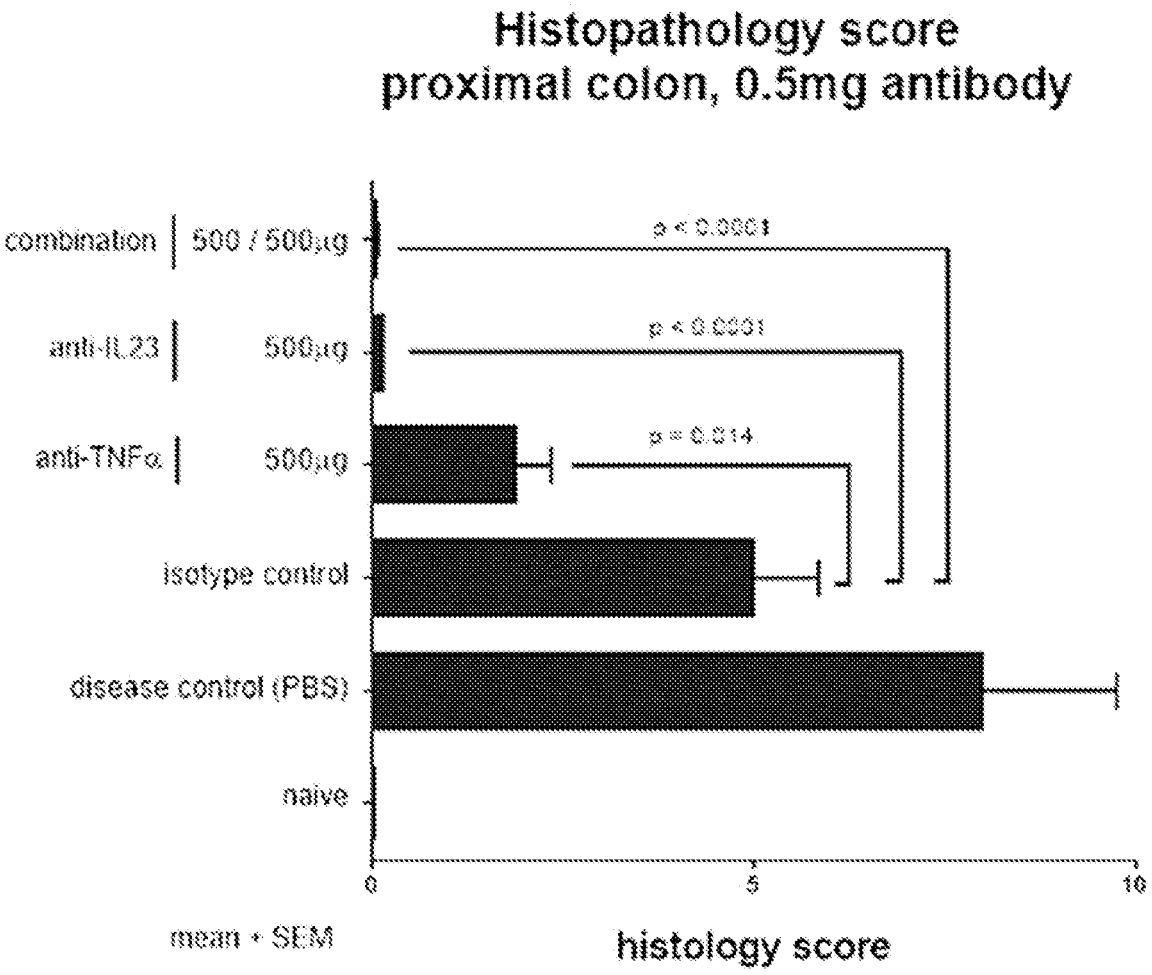

Histopathology score
proximal colon, 0.5mg antibody
combination
500 / 500µg
anti-IL23
500µg
anti-TNFα
500µg
isotype control
disease control (PBS)
naive
p < 0.0001
p < 0.0001
p = 0.014
0
5
10
mean + SEM
histology score

FIG. 2B

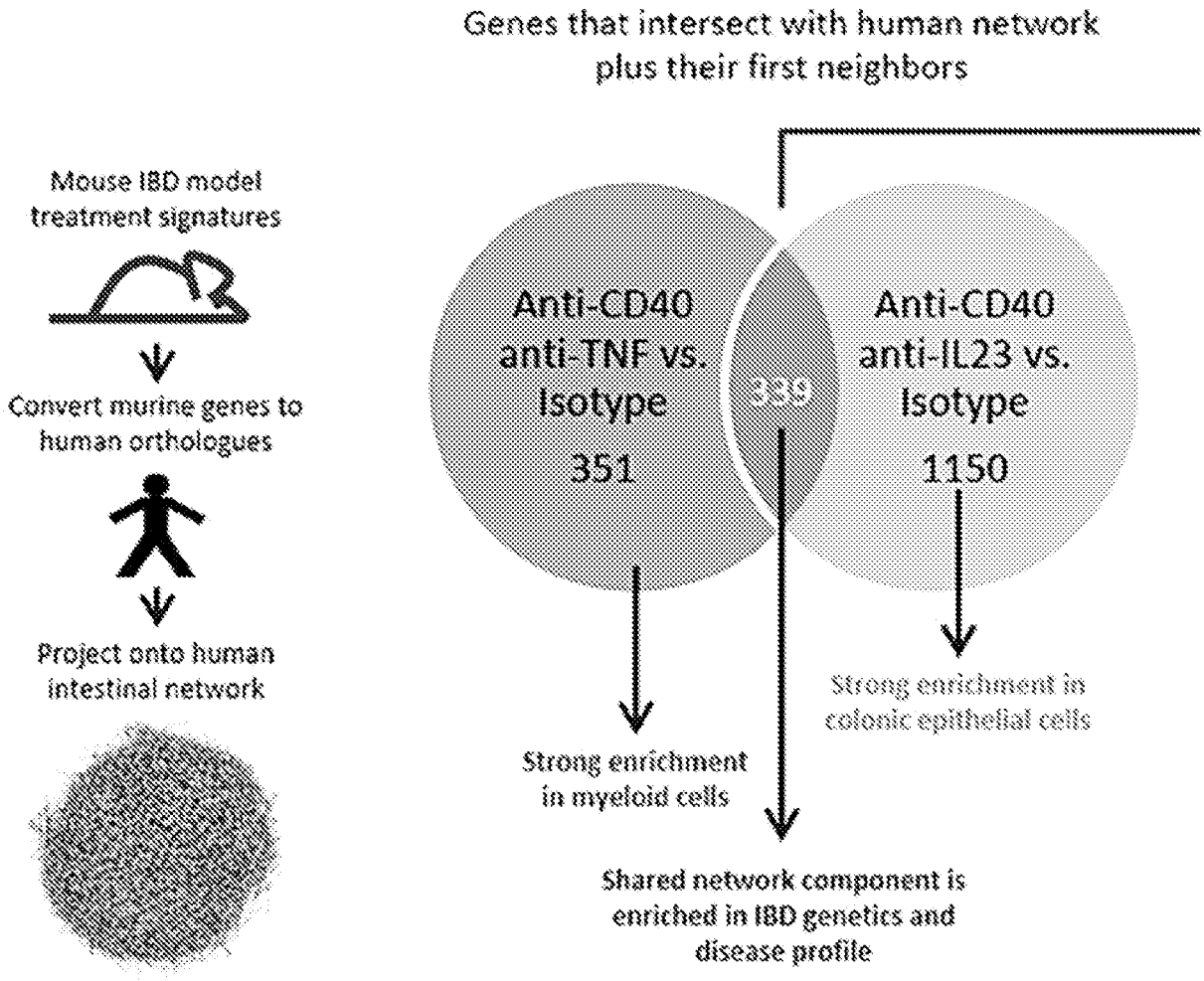

Mouse IBD model treatment signatures
Convert murine genes to human orthologues
Project onto human intestinal network
Genes that intersect with human network plus their first neighbors
Anti-CD40 anti-TNF vs. Isotype
351
338
Anti-CD40 anti-IL23 vs. Isotype
1150
Strong enrichment in myeloid cells
Strong enrichment in colonic epithelial cells
Shared network component is enriched in IBD genetics and disease profile

FIG. 3A

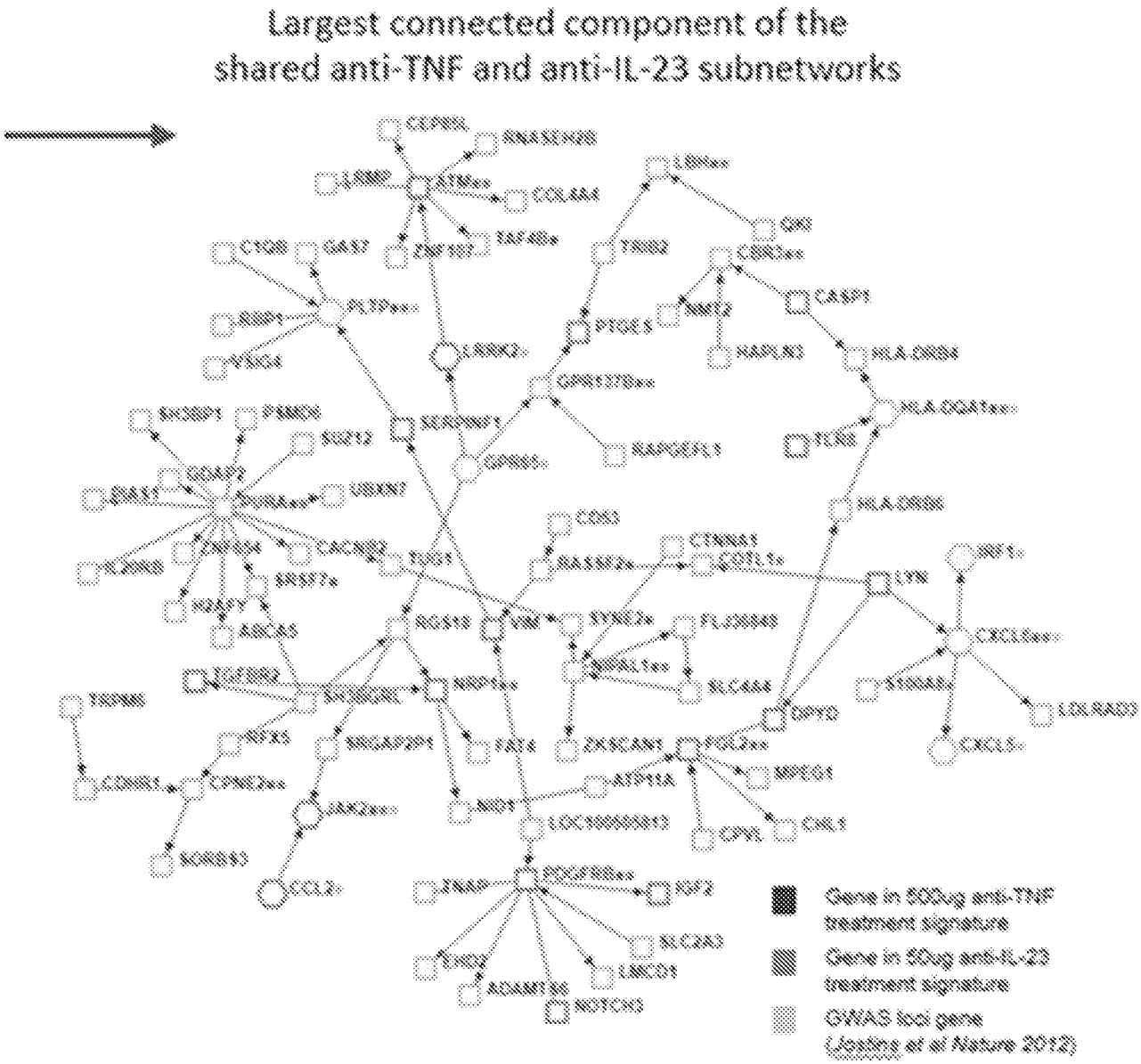

Largest connected component of the
shared anti-TNF and anti-IL-23 subnetworks
Gene in 502ug anti-TNF
treatment signature
Gene in 50ug anti-IL-23
treatment signature
GWAS loci gene
Jostins et al Nature 2012

FIG. 3B

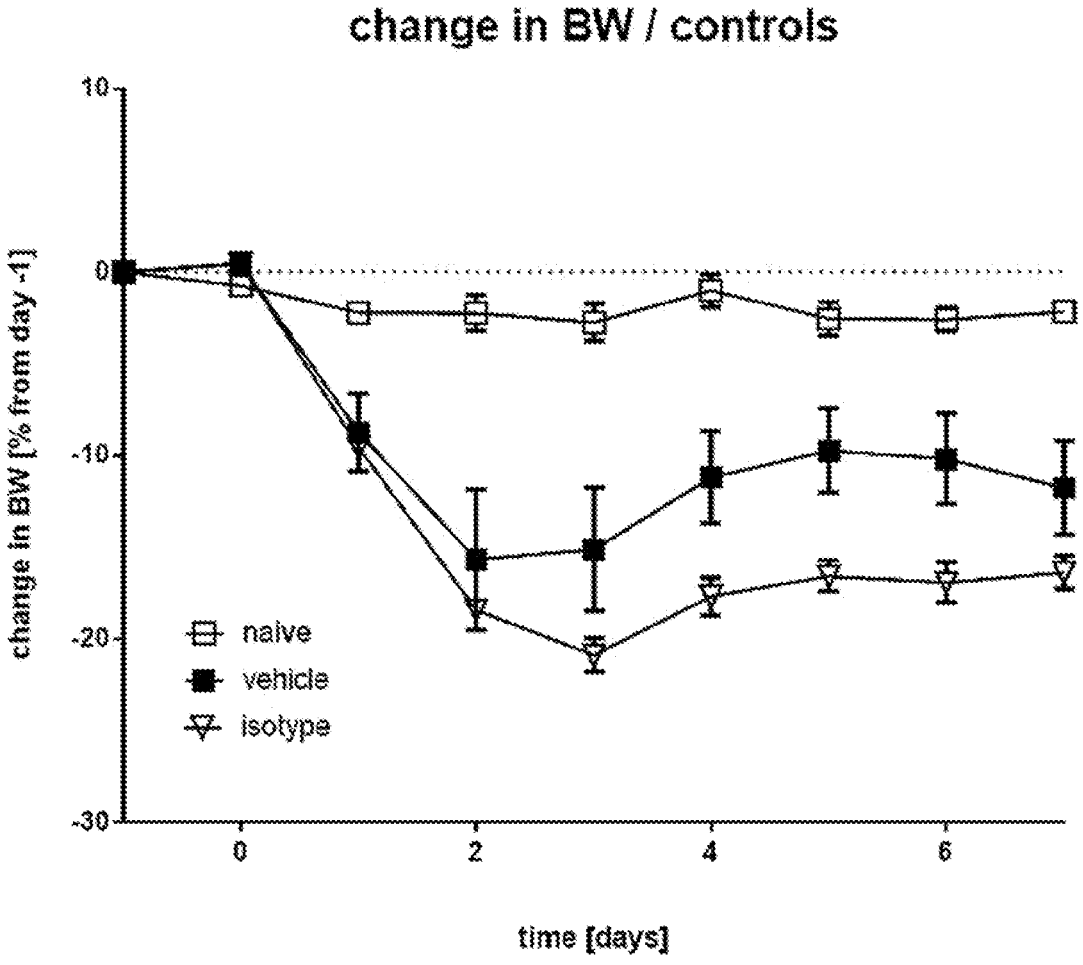

change in BW / controls
change in BW [% from day -1]
10
0
-10
-20
-30
0
2
4
6
time [days]
naive
vehicle
isotype

FIG. 4A

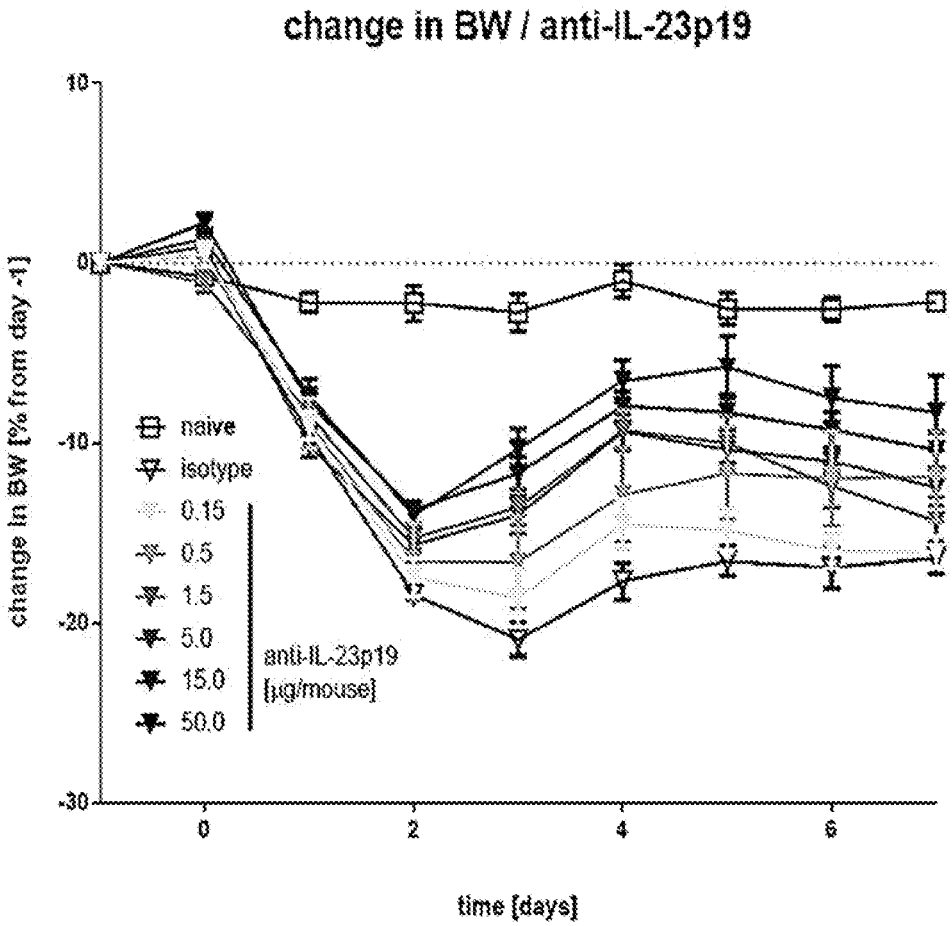

change in BW / anti-IL-23p19
change in BW [% from day -1]
10
0
-10
-20
-30
0
2
4
6
time [days]
naive
isotype
0.15
0.5
1.5
5.0
15.0
50.0
anti-IL-23p19
[µg/mouse]

FIG. 4B

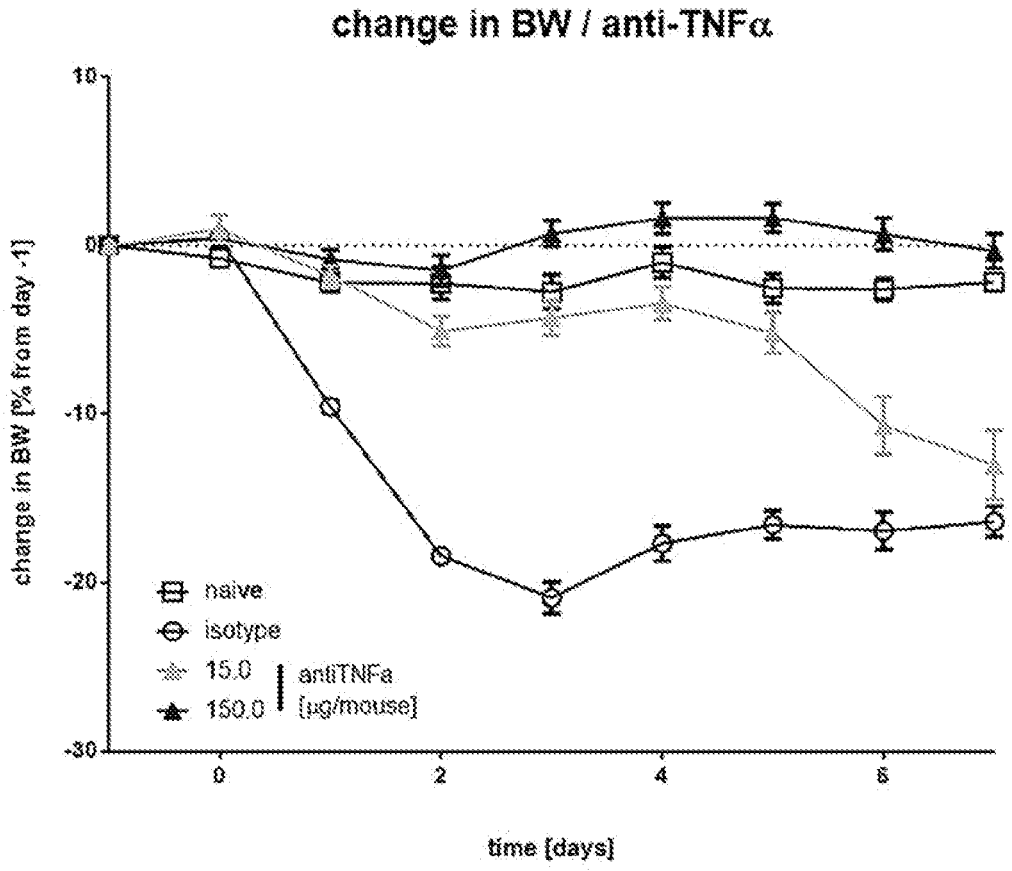

change in BW / anti-TNFα
change in BW [% from day -1]
10
0
-10
-20
-30
0
2
4
6
time [days]
naive
isotype
15.0
150.0
antiTNFa
[µg/mouse]

FIG. 4C

mab treatment	Day -1	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
vehicle	0.9999	0.9999	0.9994	0.6627	*0.0286*	*0.0094*	*0.0053*	*0.0061*	0.1302
0.15mg aIL-23	0.9999	0.9999	0.9995	0.9962	0.6460	0.2901	0.8859	0.9965	0.9997
0.5µg aIL-23	0.9999	0.9999	0.9994	0.8608	0.0733	*0.0315*	*0.0262*	*0.0240*	*0.0488*
1.5µg aIL-23	0.9999	0.9295	0.9894	0.2940	*0.0001*	*0.0001*	*0.0005*	*0.0400*	0.7572
5.0µg aIL-23	0.9999	0.9996	0.9995	0.2940	*0.0002*	*0.0001*	*0.0013*	*0.0025*	0.1064
15µg aIL-23	0.9999	0.9968	0.6920	*0.0497*	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0001*
50µg aIL-23	0.9999	0.8692	0.8394	*0.0294*	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0021*
15µg aTNFα	0.9999	0.9996	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0012*	0.2255
150µg aTNFα	0.9999	0.9999	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0001*

FIG. 4D

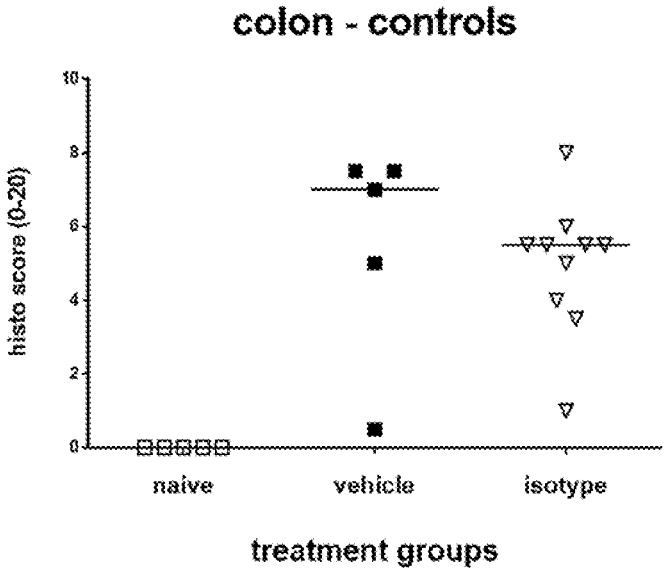

colon - controls
histo score (0-20)
0
2
4
6
8
10
naive
vehicle
isotype
treatment groups

FIG. 5A

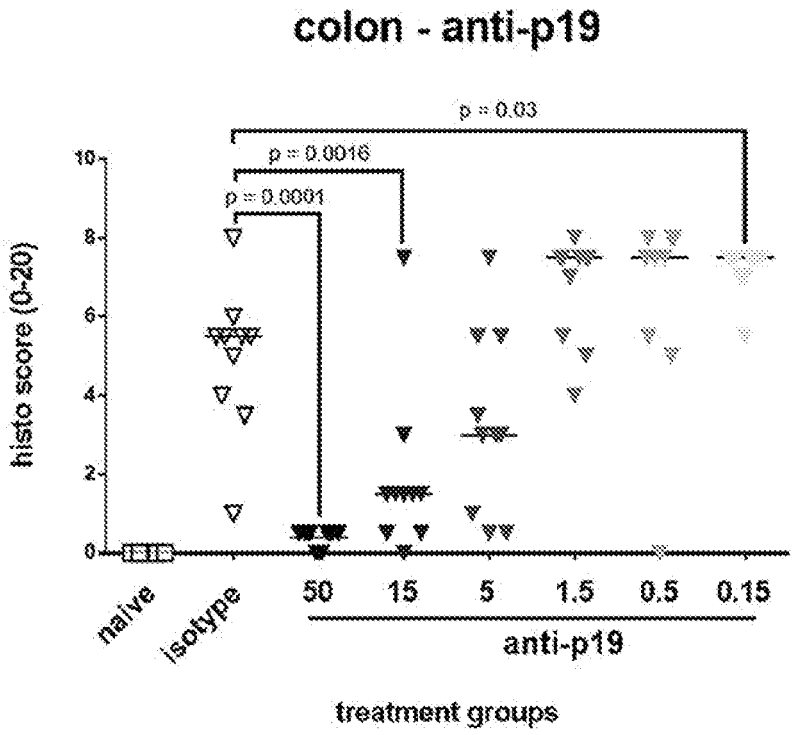

colon - anti-p19
p = 0.03
p = 0.0016
p = 0.0001
histo score (0-20)
0
2
4
6
8
10
naive
isotype
50
15
5
1.5
0.5
0.15
anti-p19
treatment groups

FIG. 5B

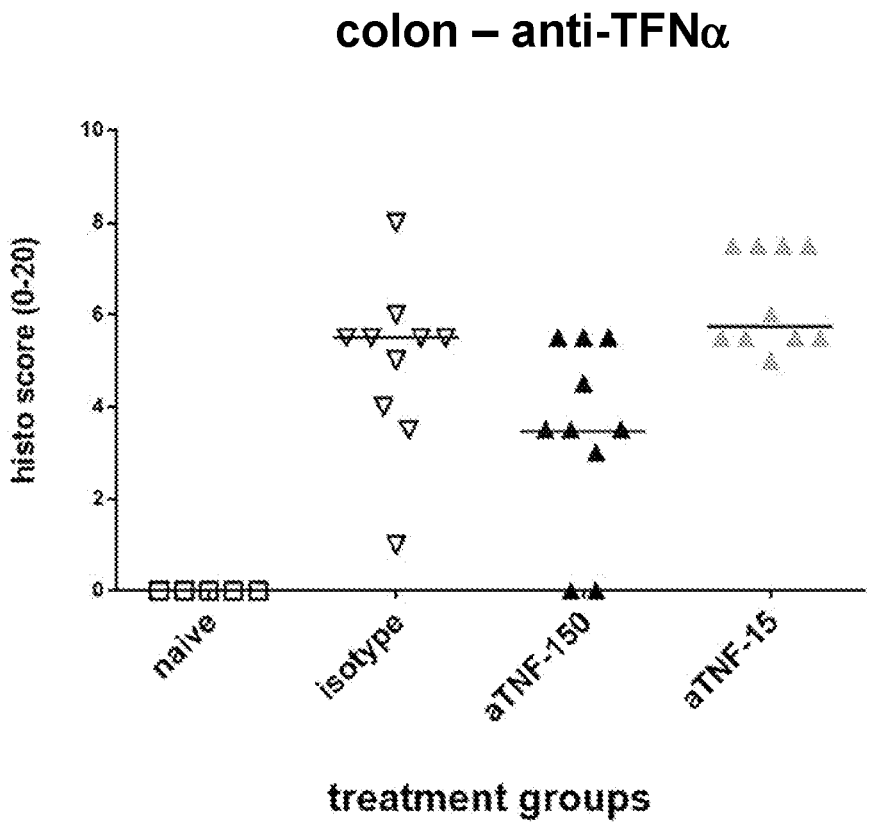

colon – anti-TFNα
histo score (0-20)
10
8
6
4
2
0
naive
isotype
aTNF-150
aTNF-15
treatment groups

FIG. 5C

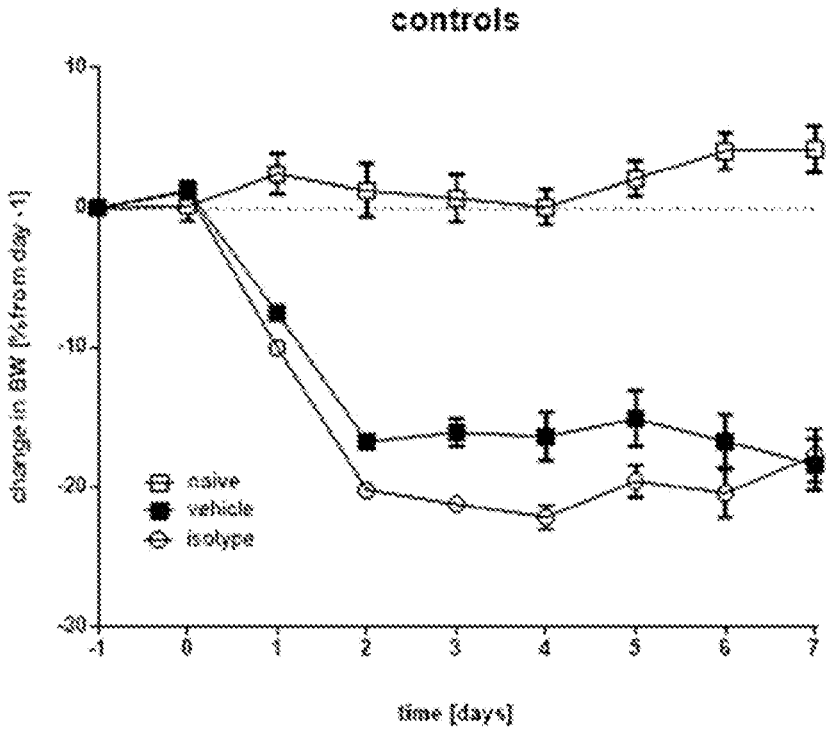

controls
change in BW (%from day -1)
time [days]
naive
vehicle
isotype

FIG. 6A

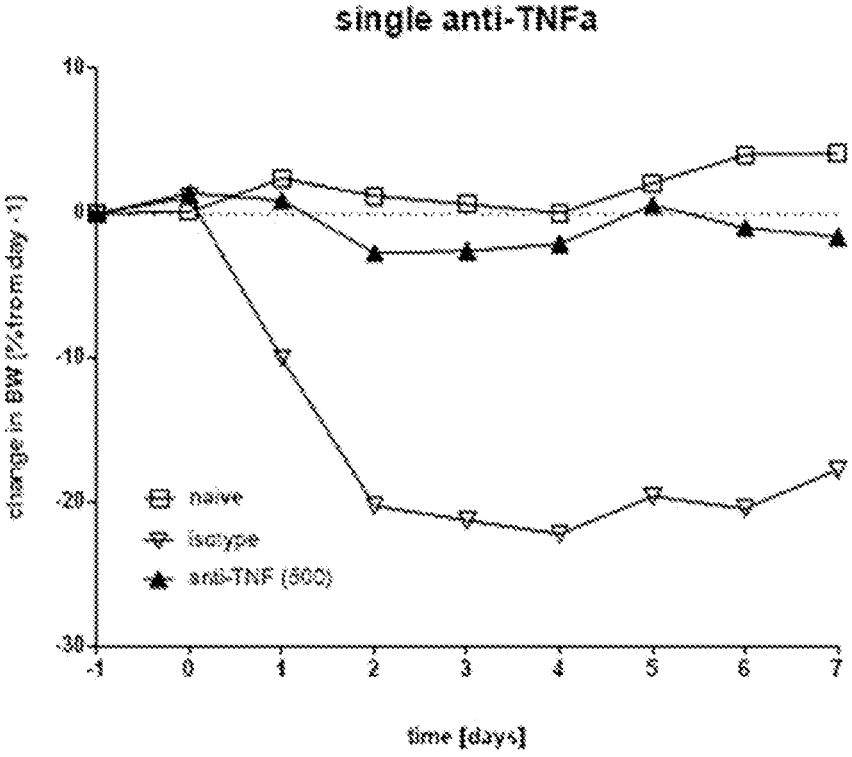

single anti-TNFa
change in BW (%from day -1)
time [days]
naive
isotype
anti-TNF (SOC)

FIG. 6B

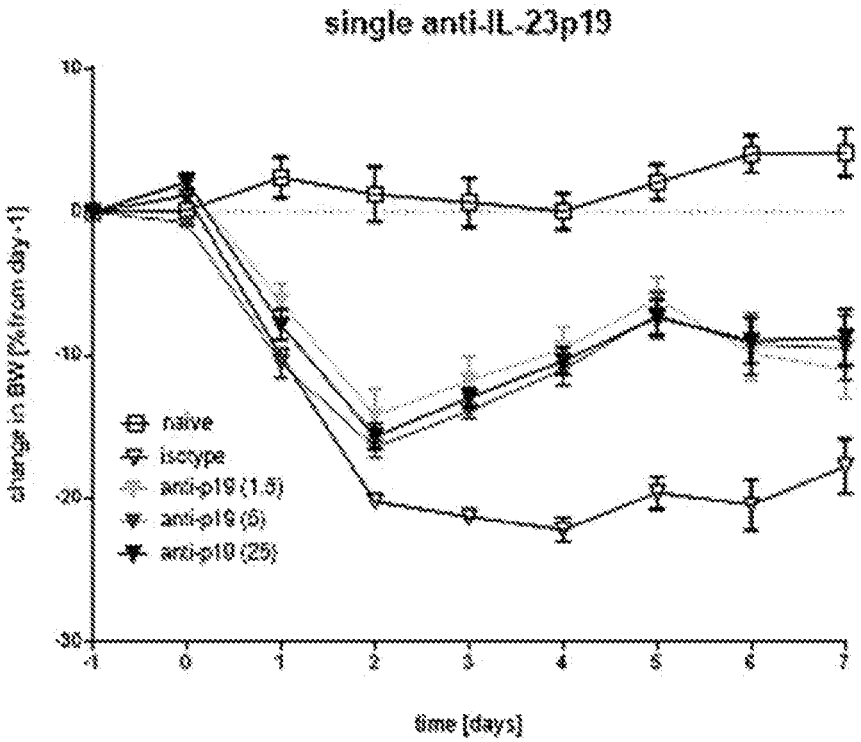

single anti-IL-23p19
naive
isotype
anti-p19 (1.5)
anti-p19 (5)
anti-p19 (25)
time [days]

FIG. 6C

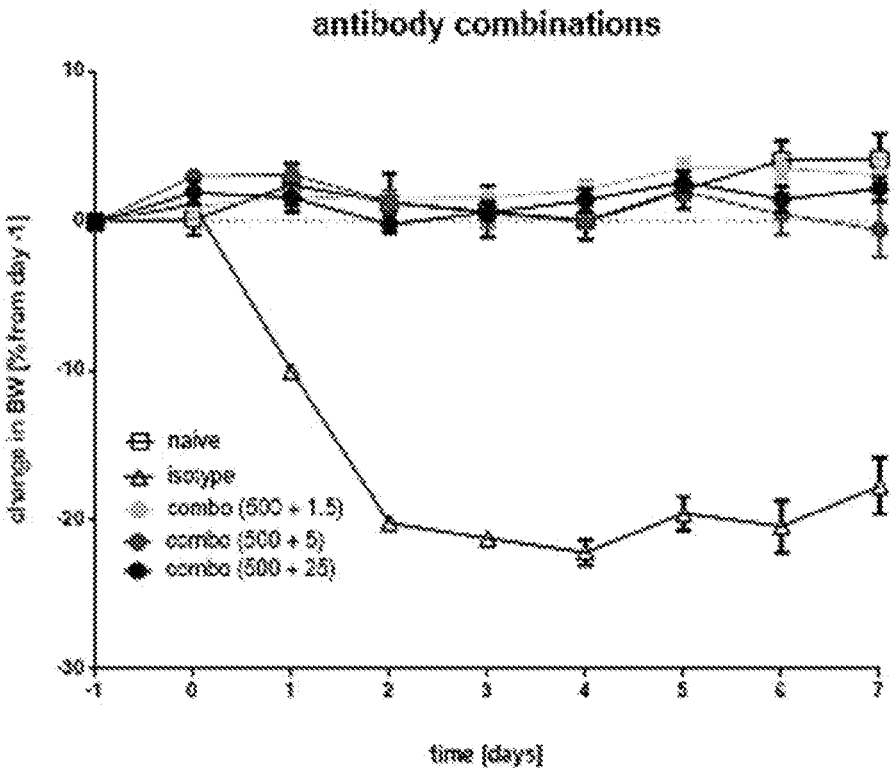

antibody combinations
naive
isotype
combo (500 + 1.5)
combo (500 + 5)
combo (500 + 25)
time [days]

FIG. 6D

	time [days]						time [days]		
mab treatment	Day -1	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
PBS	0.9999	0.9999	0.5354	0.1833	*0.0129*	*0.0034*	*0.0427*	0.1373	0.9394
500µg aTNF α	0.9999	0.9997	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0001*
1.5µg aIL-23	0.9999	0.9998	0.1213	*0.0021*	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0004*
5µg aIL-23	0.9999	0.8039	0.9996	0.1182	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0009*
25µg aIL-23	0.9999	0.9998	0.6811	*0.0368*	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0001*
500µg aTNF α + 1.5µg aIL-23	0.9999	0.9999	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0001*
500µg aTNF α + 5µg aIL-23	0.9999	0.8292	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0001*
500µg aTNF α + 25µg aIL-	0.9999	0.9977	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.0001*

FIG. 6E

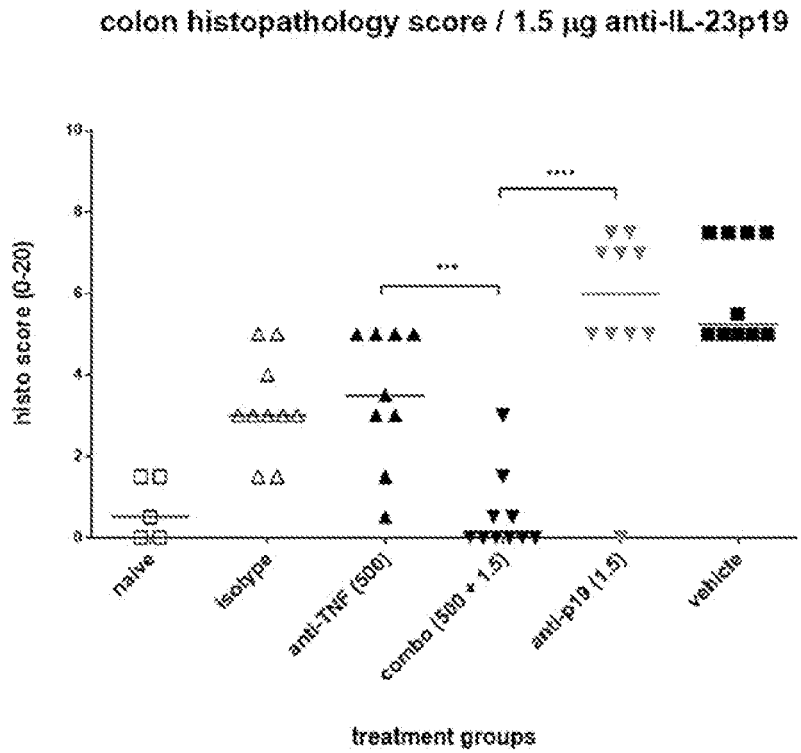

colon histopathology score / 1.5 µg anti-IL-23p19
histo score (0-20)
0
2
4
6
8
10
****
***
naive
isotype
anti-TNF (500)
combo (500 + 1.5)
anti-p19 (1.5)
vehicle
treatment groups

FIG. 7A

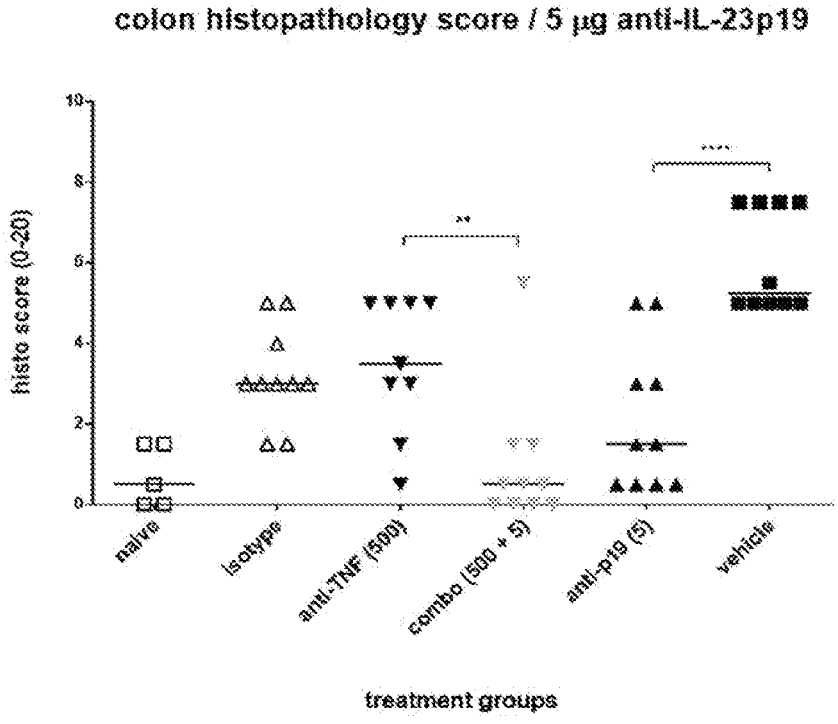

colon histopathology score / 5 µg anti-IL-23p19
histo score (0-20)
0
2
4
6
8
10
****
**
naive
isotype
anti-TNF (500)
combo (500 + 5)
anti-p19 (5)
vehicle
treatment groups

FIG. 7B

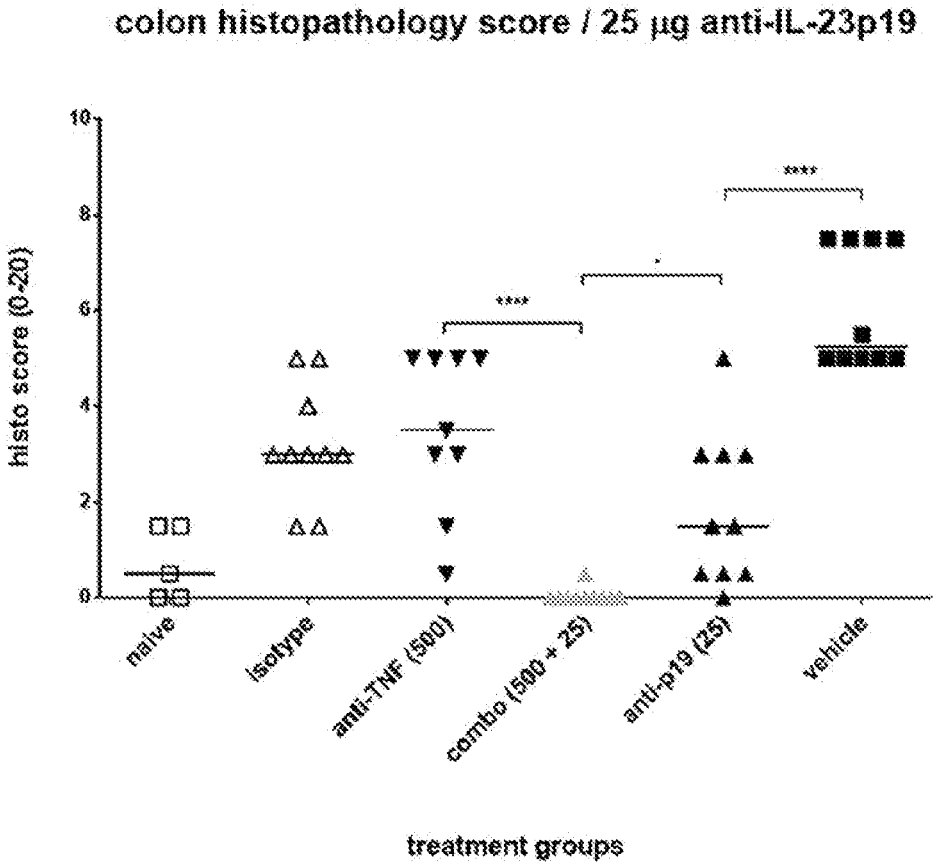

colon histopathology score / 25 µg anti-IL-23p19
histo score (0-20)
0
2
4
6
8
10
****
*
****
naive
isotype
anti-TNF (500)
combo (500 + 25)
anti-p19 (25)
vehicle
treatment groups

FIG. 7C

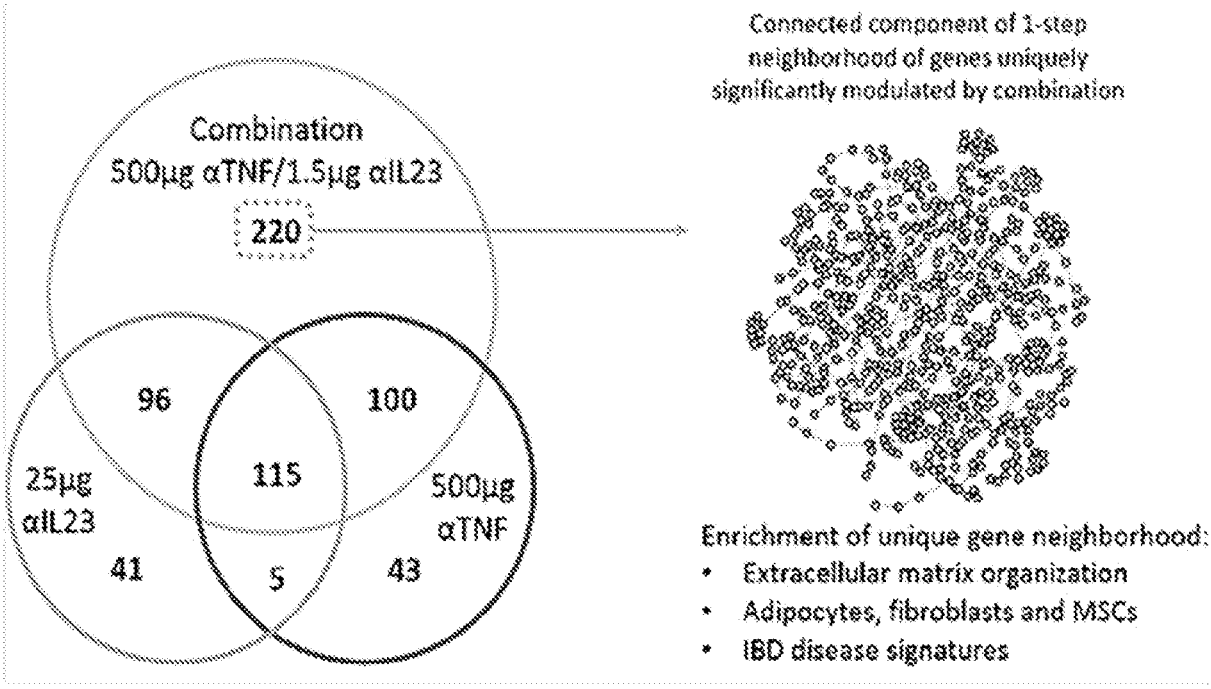

Combination
500µg αTNF/1.5µg αIL23
220
96
100
115
25µg
αIL23
500µg
αTNF
41
5
43
Connected component of 1-step neighborhood of genes uniquely significantly modulated by combination
Enrichment of unique gene neighborhood:
• Extracellular matrix organization
• Adipocytes, fibroblasts and MSCs
• IBD disease signatures

FIG. 8

SEQUENCE LISTING

<110> JANSSEN BIOTECH, INC.

<120> METHOD OF TREATING INFLAMMATORY BOWEL DISEASE WITH A COMBINATION THERAPY OF ANTIBODIES TO IL-23 AND TNF ALPHA

<130> JBI6562WOPCT1

<140> TO BE ASSIGNED
<141> 2022-05-20

<150> US 63/191076
<151> 2021-05-20

<160> 20

<170> PatentIn version 3.5

<210> 1
<211> 5
<212> PRT
<213> Homo sapiens

<400> 1

Asn Tyr Trp Ile Gly
1 5

<210> 2
<211> 17
<212> PRT
<213> Homo sapiens

<400> 2

Ile Ile Asp Pro Ser Asn Ser Tyr Thr Arg Tyr Ser Pro Ser Phe Gln
1 5 10 15

Gly

<210> 3
<211> 8
<212> PRT
<213> Homo sapiens

<400> 3

Trp Tyr Tyr Lys Pro Phe Asp Val
1 5

<210> 4
<211> 14
<212> PRT
<213> Homo sapiens

<400> 4

Thr Gly Ser Ser Ser Asn Ile Gly Ser Gly Tyr Asp Val His
1 5 10

<210> 5
<211> 7
<212> PRT
<213> Homo sapiens

<400> 5

Gly Asn Ser Lys Arg Pro Ser
1 5

<210> 6
<211> 11
<212> PRT
<213> Homo sapiens

<400> 6

Ala Ser Trp Thr Asp Gly Leu Ser Leu Val Val
1 5 10

<210> 7
<211> 117
<212> PRT
<213> Homo sapiens

<400> 7

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

```
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Ser Asn Tyr
            20                  25                  30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45

Gly Ile Ile Asp Pro Ser Asn Ser Tyr Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg Trp Tyr Tyr Lys Pro Phe Asp Val Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
        115
```

<210> 8
<211> 111
<212> PRT
<213> Homo sapiens

<400> 8

```
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ser Gly
            20                  25                  30

Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45

Leu Ile Tyr Gly Asn Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60
```

```
Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65                  70                  75                  80


Gln Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ser Trp Thr Asp Gly
                85                  90                  95


Leu Ser Leu Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110


<210>  9
<211>  447
<212>  PRT
<213>  Homo sapiens

<400>  9

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1               5                   10                  15


Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Ser Asn Tyr
            20                  25                  30


Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45


Gly Ile Ile Asp Pro Ser Asn Ser Tyr Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60


Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80


Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95


Ala Arg Trp Tyr Tyr Lys Pro Phe Asp Val Trp Gly Gln Gly Thr Leu
            100                 105                 110


Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125
```

```
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
    210                 215                 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320
```

```
Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335


Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350


Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365


Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380


Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400


Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415


Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430


His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210>  10
<211>  217
<212>  PRT
<213>  Homo sapiens

<400>  10

Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1               5                   10                  15


Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ser Gly
            20                  25                  30


Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45
```

```
Leu Ile Tyr Gly Asn Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65                  70                  75                  80

Gln Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ser Trp Thr Asp Gly
                85                  90                  95

Leu Ser Leu Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
        115                 120                 125

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
    130                 135                 140

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145                 150                 155                 160

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
                165                 170                 175

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
            180                 185                 190

His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
        195                 200                 205

Lys Thr Val Ala Pro Thr Glu Cys Ser
    210                 215
```

<210> 11
<211> 5
<212> PRT
<213> Homo sapiens

<400> 11

Ser Tyr Ala Met His
1 5

<210> 12
<211> 17
<212> PRT
<213> Homo sapiens

<400> 12

Phe Met Ser Tyr Asp Gly Ser Asn Lys Lys Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 13
<211> 17
<212> PRT
<213> Homo sapiens

<400> 13

Asp Arg Gly Ile Ala Ala Gly Gly Asn Tyr Tyr Tyr Tyr Gly Met Asp
1 5 10 15

Val

<210> 14
<211> 11
<212> PRT
<213> Homo sapiens

<400> 14

Arg Ala Ser Gln Ser Val Tyr Ser Tyr Leu Ala
1 5 10

<210> 15
<211> 7
<212> PRT

<213> Homo sapiens

<400> 15

Asp Ala Ser Asn Arg Ala Thr
1   5

<210> 16
<211> 10
<212> PRT
<213> Homo sapiens

<400> 16

Gln Gln Arg Ser Asn Trp Pro Pro Phe Thr
1   5   10

<210> 17
<211> 126
<212> PRT
<213> Homo sapiens

<400> 17

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Ser Ser Tyr
            20   25   30

Ala Met His Trp Val Arg Gln Ala Pro Gly Asn Gly Leu Glu Trp Val
        35   40   45

Ala Phe Met Ser Tyr Asp Gly Ser Asn Lys Lys Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

```
Ala Arg Asp Arg Gly Ile Ala Ala Gly Gly Asn Tyr Tyr Tyr Tyr Gly
            100                 105                 110


Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120                 125


<210>  18
<211>  111
<212>  PRT
<213>  Homo sapiens

<400>  18

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Tyr Ser Tyr
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45


Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80


Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
                85                  90                  95


Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg Thr Val
            100                 105                 110


<210>  19
<211>  456
<212>  PRT
<213>  Homo sapiens

<400>  19
```

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Ser Ser Tyr
            20                  25                  30

Ala Met His Trp Val Arg Gln Ala Pro Gly Asn Gly Leu Glu Trp Val
        35                  40                  45

Ala Phe Met Ser Tyr Asp Gly Ser Asn Lys Lys Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Arg Gly Ile Ala Ala Gly Gly Asn Tyr Tyr Tyr Tyr Gly
            100                 105                 110

Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser
        115                 120                 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
    130                 135                 140

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
145                 150                 155                 160

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
                165                 170                 175

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
            180                 185                 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
        195                 200                 205
```

```
Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
    210                 215                 220

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
225                 230                 235                 240

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
                245                 250                 255

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
            260                 265                 270

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
        275                 280                 285

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
    290                 295                 300

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
305                 310                 315                 320

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
                325                 330                 335

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
            340                 345                 350

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
        355                 360                 365

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
    370                 375                 380

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
385                 390                 395                 400
```

```
Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
                405                 410                 415


Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
            420                 425                 430


Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
        435                 440                 445


Ser Leu Ser Leu Ser Pro Gly Lys
    450                 455
```

<210> 20
<211> 215
<212> PRT
<213> Homo sapiens

<400> 20

```
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Tyr Ser Tyr
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45


Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80


Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
                85                  90                  95


Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg Thr Val Ala
            100                 105                 110
```

```
Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
        115                 120                 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
                165                 170                 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
            180                 185                 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
        195                 200                 205

Ser Phe Asn Arg Gly Glu Cys
    210                 215
```