

[0011] Disclosed herein is an IL-23 blockade that provides a mechanism to inhibit the inflammation and reduce clinical symptoms associated with Crohn's disease (CD). The IL-23 blockade specifically inhibits IL-23 and does not inhibit IL-12, *i.e.*, results in minimal (less than 1% IL-12 inhibition) or no inhibition of IL-12 activity following administration of brazikumab. In some **embodimentexample**s, the IL-23 blockade specifically inhibits IL-23 and there is no inhibition of IL-12. Specifically targeting IL-23 with brazikumab is expected to offer a better benefit:risk profile compared with IL-12/23 antibodies.

[0012] Current treatment options for patients with moderately to severely active CD is usually guided by severity of disease, location, and presence of additional concomitant conditions and clinical complications such as extraintestinal manifestations and malabsorption. The therapeutic options currently available include 'conventional treatments,' which include antibiotics, CS, immunomodulators (azathioprine, 6-mercaptopurine, and methotrexate), and biologic treatments such as TNF α antagonists, integrin antagonists, and IL-12 and IL-23 antagonists.

[0012a] In one aspect, the present disclosure provides a use of an anti-IL-23 antibody in the manufacture of a medicament for treating Crohn's disease in a subject in need thereof, wherein the anti-IL-23 antibody is to be administered intravenously to the subject followed by subcutaneous administration of the anti-IL-23 antibody to the subject.

[0012b] In another aspect, the present disclosure provides a method of selecting a subject amenable to treatment of Crohn's disease comprising

- (a) measuring the level of IL-22 in a biological sample obtained from the subject;
- (b) comparing the level of IL-22 in the sample to the level of IL-22 in a control; and
- (c) selecting the subject as amenable to treatment of Crohn's disease if the level of IL-22 is higher in the sample than in the control.

[0012c] In another aspect, the present disclosure provides a method of identifying a subject as a member of a patient sub-population amenable to treatment for Crohn's disease comprising

- (a) measuring the level of IL-22 in a biological sample obtained from the subject;
- (b) comparing the level of IL-22 in the sample to the level of IL-22 in a control; and
- (c) identifying the subject as a member of the patient sub-population amenable to treatment for Crohn's disease if the level of IL-22 in the subject's sample is higher than in the control.

[0013] In one aspectexample, the disclosure provides a method of treating Crohn's disease in a subject in need thereof comprising intravenous administration of an anti-IL-23 antibody to the subject followed by subcutaneous administration of the anti-IL-23 antibody to the subject. In some embodimentexamples, a biological sample of the subject has an IL-22 level of at least 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 pg/ml, such as wherein the IL-22 level is at least 9 pg/ml or wherein the IL-22 level is at least 50 pg/ml. In some embodimentexamples, the subject receives a plurality of intravenous administrations of the anti-IL-23 antibody, a plurality of subcutaneous administrations of the anti-IL-23 antibody, or both. In some embodimentexamples, intravenous administrations are delivered within 4 weeks of initiating treatment. In some embodimentexamples, intravenous administrations are delivered on days 1, 29 and 57 of treatment. In some embodimentexamples, subcutaneous administrations are delivered at least 12 weeks after initiating treatment. In some embodimentexamples, the subcutaneous administrations are delivered on about day 85 and about every 4 weeks thereafter. In some embodimentexamples, the subcutaneous administrations are delivered on day 85 and about every 4 weeks thereafter, such as wherein the subcutaneous administrations are delivered on day 85 and every 4 weeks thereafter.

[0014] This aspectexample of the disclosure also provides some embodimentexamples wherein the anti-IL-23 antibody is administered in an amount and at an interval of: (a) 720-1440 mg on or about days 1, 29, and 57 delivered intravenously, followed by (b) about 240 mg delivered subcutaneously on or about day 85 and about every 4 weeks thereafter through at least week 48. In some

embodimentexamples, the anti-IL-23 antibody has: (a) a heavy chain variable region comprising Complementarity Determining Regions (CDRs) with the following amino acid sequences: (i) CDR1: SYGMH (SEQ ID NO:3), (ii) CDR2: VIWYDGSNEYADSVKGR (SEQ ID NO:4), and (iii) CDR3: DRGYTSSWYPDAFDI (SEQ ID NO:5); and (b) a light chain variable region comprising CDRs with the following amino acid sequences: (i) CDR1: TGSSSNTGAGYDVH (SEQ ID NO:6), (ii) CDR2: GSGNRPS (SEQ ID NO:7), and (iii) CDR3: QSYDSSLGWW (SEQ ID NO:8). The brazikumab heavy- and light-chain variable region amino acid sequences are presented in Figure 2. In some embodimentexamples, the anti-IL-23 antibody is Brazikumab. In some embodimentexamples, 720-1440 mg of Brazikumab is administered on days 1, 29, and 57. In some embodimentexamples, Brazikumab is administered intravenously on days 1, 29, and 57. In some embodimentexamples, 1440 mg of Brazikumab is administered intravenously on days 1, 29 and 57. In some embodimentexamples, 720 mg of Brazikumab is administered intravenously on days 1, 29 and 57. In some embodimentexamples, 240 mg of Brazikumab is administered subcutaneously on or about day 85 and about every 4 weeks thereafter through at least week 48, e.g., wherein 240 mg of Brazikumab is administered subcutaneously on day 85 and about every 4 weeks thereafter through at least week 48, such as by administering 240 mg of Brazikumab subcutaneously on day 85 and every 4 weeks thereafter through at least week 48. In some embodimentexamples, 240 mg of Brazikumab is administered subcutaneously on day 85 and every 4 weeks thereafter through week 48-52. In some embodimentexamples, 240 mg of Brazikumab is administered subcutaneously on day 85 and every 4 weeks thereafter through week 48.

[0015] Another aspectexample of the disclosure is drawn to a method of selecting a subject amenable to treatment of Crohn's disease comprising (a) obtaining a biological sample from the subject; (b) measuring the level of IL-22 in the sample; (c) comparing the level of IL-22 in the sample to the level of IL-22 in a control; and (d) selecting the subject as amenable to treatment of Crohn's disease if the level of IL-22 is higher in the sample than in the control. In some embodimentexamples, the IL-22 level is at least about 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 pg/ml, such as wherein the IL-22 level is at least about 9 pg/ml, or wherein the IL-22 level is at least about 50 pg/ml, or wherein the IL-22 level is at least 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 pg/ml, or wherein the IL-22 level is at least 9 pg/ml, or wherein the IL-22 level is at least 50 pg/ml. In some embodimentexamples, the control is a biological sample from a healthy subject. As noted above, some embodimentexamples provide for a control that has a threshold level of IL-22 associated with subjects having Crohn's disease, as disclosed in U.S.S.N.

15/759,330, incorporated herein by reference. In one exemplary [embodimentexample](#), the threshold level of IL-22 is about 15.6 picograms/ml. In some [embodimentexamples](#), the Crohn's disease (CD) is ileal CD and/or colonic CD. In some [embodimentexamples](#), the method further comprises a second measure of amenability to treatment of Crohn's disease, such as a blood test for anemia or infection, a stool test for infection, a breath test for hydrogen, a barium enema, an upper endoscopy, an upper gastrointestinal series, a colonoscopy, a sigmoidoscopy, a CT scan or an MRI. In some [embodimentexamples](#), the method further comprises administering to the subject an anti-IL-23 antibody, e.g., brazikumab, in an amount and at an interval of: (a) 720-1440 mg on about days 1, 29, and 57 delivered intravenously, followed by (b) about 240 mg delivered subcutaneously on or about day 85 and about every 4 weeks thereafter through at least week 48.

[0016] Another [aspectexample](#) of the disclosure is a method of identifying a subject as a member of a patient sub-population amenable to treatment for Crohn's disease comprising (a) obtaining a biological sample from the subject; (b) measuring the level of IL-22 in the sample; (c) comparing the level of IL-22 in the sample to the level of IL-22 in a control; and (d) identifying the subject as a member of the patient sub-population amenable to treatment for Crohn's disease if the level of IL-22 in the subject's sample is higher than in the control. In some [embodimentexamples](#), the IL-22 level is at least about 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 pg/ml, such as wherein the IL-22 level is at least about 9 pg/ml, or wherein the IL-22 level is at least about 50 pg/ml, or wherein the IL-22 level is at least 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 pg/ml, or wherein the IL-22 level is at least 9 pg/ml, or wherein the IL-22 level is at least 50 pg/ml. In some [embodimentexamples](#), the control is a biological sample from a healthy subject. In some [embodimentexamples](#), the control is a threshold level of IL-22 associated with subjects having Crohn's disease. In some [embodimentexamples](#), the Crohn's disease (CD) is ileal CD and/or colonic CD. In some [embodimentexamples](#), the method further comprises a second measure of amenability to treatment of Crohn's disease, such as a blood test for anemia or infection, a stool test for infection, a breath test for hydrogen, a barium enema, an upper endoscopy, an upper gastrointestinal series, a colonoscopy, a sigmoidoscopy, a CT scan or an MRI. In some [embodimentexamples](#), the method further comprises administering to the subject an anti-IL-23 antibody, e.g., brazikumab, in an amount and at an interval of: (a) 720-1440 mg on about days 1, 29, and 57 delivered intravenously, followed by (b) about 240 mg delivered subcutaneously on about day 85 and about every 4 weeks thereafter through at least week 48.

[0017] Yet another aspectexample of the disclosure is an anti-IL-23 antibody for use in treating Crohn's disease in a subject in need thereof, wherein the anti-IL-23 antibody is administered in an amount and at an interval of: (a) 720-1440 mg on or about days 1, 29, and 57 delivered intravenously, followed by (b) about 240 mg delivered subcutaneously on or about day 85 and about every 4 weeks thereafter through at least week 48. In some embodimentexamples, the anti-IL-23 antibody has: (a) a heavy chain variable region comprising Complementarity Determining Regions (CDRs) with the following amino acid sequences: (i) CDR1: SYGMH (SEQ ID NO:3), (ii) CDR2: VIWYDGSNEYADSVKGR (SEQ ID NO:4), and (iii) CDR3: DRGYTSSWYPDAFDI (SEQ ID NO:5); and (b) a light chain variable region comprising CDRs with the following amino acid sequences: (i) CDR1: TGSSSNTGAGYDVH (SEQ ID NO:6), (ii) CDR2: GSGNRPS (SEQ ID NO:7), and (iii) CDR3: QSYDSSLGWV (SEQ ID NO:8). In some embodimentexamples, the anti-IL-23 antibody is Brazikumab. In some embodimentexamples, 720-1440 mg of Brazikumab is administered on days 1, 29, and 57. In some embodimentexamples, Brazikumab is administered intravenously on days 1, 29, and 57. In some embodimentexamples, 1440 mg of Brazikumab is administered intravenously on days 1, 29 and 57. In some embodimentexamples, 720 mg of Brazikumab is administered intravenously on days 1, 29 and 57. In some embodimentexamples, 240 mg of Brazikumab is administered subcutaneously on or about day 85 and about every 4 weeks thereafter through at least week 48. In some embodimentexamples, 240 mg of Brazikumab is administered subcutaneously on day 85 and about every 4 weeks thereafter through at least week 48. In some embodimentexamples, 240 mg of Brazikumab is administered subcutaneously on day 85 and every 4 weeks thereafter through at least week 48. In some embodimentexamples, 240 mg of Brazikumab is administered subcutaneously on day 85 and every 4 weeks thereafter through week 48-52. In some embodimentexamples, 240 mg of Brazikumab is administered subcutaneously on day 85 and every 4 weeks thereafter through week 48.

[0018] EmbodimentExample of the method are also contemplated wherein a plurality of intravenous infusions is administered. In some embodimentexamples, the plurality of intravenous infusions each comprise the same quantity of anti-IL-23 antibody. EmbodimentExample of the disclosure also exist wherein the anti-IL-23 antibody is administered subcutaneously. In some of these embodimentexamples, the anti-IL-23 antibody is administered in a plurality of doses.

[0019] Other features and advantages of the disclosure will become apparent from the following detailed description, including the drawing. It should be understood, however, that the detailed description and the specific examples, while indicating embodimentexamples, are provided for illustration only, because various changes and modifications within the spirit and scope of the disclosure will become apparent to those skilled in the art from the detailed description.

WHAT IS CLAIMED IS:

1. Use of an anti-IL-23 antibody in the manufacture of a medicament for~~A method of~~ treating Crohn's disease in a subject in need thereof, wherein the anti-IL-23 antibody is to be administered~~comprising~~ intravenously administration of an anti-IL-23 antibody~~to the subject~~ followed by subcutaneous administration of the anti-IL-23 antibody to the subject.

2. The method-use of claim 1 wherein a biological sample of the subject has an IL-22 level of at least about 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 pg/ml.

~~3. The method of claim 2 wherein the IL-22 level is at least about 9 pg/ml.~~

~~4. The method of claim 2 wherein the IL-22 level is at least about 50 pg/ml.~~

53. The method-use of claim 1 wherein the subject is to~~receives~~ a plurality of intravenous administrations of the anti-IL-23 antibody, a plurality of subcutaneous administrations of the anti-IL-23 antibody, or both.

64. The method-use of claim 5-3 wherein intravenous administrations are to be delivered within 4 weeks of initiating treatment.

~~7. The method of claim 6 wherein intravenous administrations are delivered on days 1, 29 and 57 of treatment.~~

85. The method-use of claim 1 wherein subcutaneous administrations are to be delivered at least 12 weeks after initiating treatment.

96. The method-use of claim 8-5 wherein the subcutaneous administrations are to be delivered on about day 85 and about every 4 weeks thereafter.

~~10. The method of claim 9 wherein the subcutaneous administrations are delivered on day 85 and about every 4 weeks thereafter.~~

~~11. The method of claim 10 wherein the subcutaneous administrations are delivered on day 85 and every 4 weeks thereafter.~~

127. The method-use of claim 1 wherein the anti-IL-23 antibody is to be administered in an amount and at an interval of:

(a) 720-1440 mg on or about days 1, 29, and 57 delivered intravenously, followed by

(b) about 240 mg delivered subcutaneously on or about day 85 and about every 4 weeks thereafter through at least week 48.

~~138.~~ The ~~method-use~~ of claim ~~12-7~~ wherein the anti-IL-23 antibody has:

(a) a heavy chain variable region comprising Complementarity Determining Regions (CDRs) with the following amino acid sequences:

(i) CDR1: SYGMH (SEQ ID NO:3),

(ii) CDR2: VIWYDGSNEYADSVKGR (SEQ ID NO:4), and

(iii) CDR3: DRGYTSSWYPDAFDI (SEQ ID NO:5); and

(b) a light chain variable region comprising CDRs with the following amino acid sequences:

(i) CDR1: TGSSSNTGAGYDVH (SEQ ID NO:6),

(ii) CDR2: GSGNRPS (SEQ ID NO:7), and

(iii) CDR3: QSYDSSLGWW (SEQ ID NO:8).

~~149.~~ The ~~method-use~~ of claim ~~13-8~~ wherein the anti-IL-23 antibody is Brazikumab.

~~1510.~~ The ~~method-use~~ of claim ~~14-9~~ wherein 720-1440 mg of Brazikumab is to be administered on days 1, 29, and 57.

~~16. The method of claim 15 wherein Brazikumab is administered intravenously on days 1, 29, and 57.~~

~~17. The method of claim 15 wherein 1440 mg of Brazikumab is administered intravenously on days 1, 29 and 57.~~

~~18. The method of claim 15 wherein 720 mg of Brazikumab is administered intravenously on days 1, 29 and 57.~~

~~1911.~~ The ~~method-use~~ of claim ~~14-9~~ wherein 240 mg of Brazikumab is to be administered subcutaneously on or about day 85 and about every 4 weeks thereafter through at least week 48.

~~20. The method of claim 19 wherein 240 mg of Brazikumab is administered subcutaneously on day 85 and about every 4 weeks thereafter through at least week 48.~~

~~21. The method of claim 20 wherein 240 mg of Brazikumab is administered subcutaneously on day 85 and every 4 weeks thereafter through at least week 48.~~

~~22. The method of claim 21 wherein 240 mg of Brazikumab is administered subcutaneously on day 85 and every 4 weeks thereafter through week 48-52.~~

~~23. The method of claim 22 wherein 240 mg of Brazikumab is administered subcutaneously on day 85 and every 4 weeks thereafter through week 48.~~

2412. A method of selecting a subject amenable to treatment of Crohn's disease comprising

~~— (a) — obtaining a biological sample from the subject;~~

(ba) measuring the level of IL-22 in ~~the a biological~~ sample obtained from the subject;

(eb) comparing the level of IL-22 in the sample to the level of IL-22 in a control; and

(dc) selecting the subject as amenable to treatment of Crohn's disease if the level of IL-22 is higher in the sample than in the control.

2513. The method of claim 2412 wherein the IL-22 level is at least about 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 pg/ml.

~~26. The method of claim 25 wherein the IL-22 level is at least about 9 pg/ml.~~

~~27. The method of claim 25 wherein the IL-22 level is at least about 50 pg/ml.~~

~~28. The method of claim 24 wherein the control is a biological sample from a healthy subject.~~

~~29. The method of claim 24 wherein the control is a threshold level of IL-22 associated with subjects having Crohn's disease.~~

~~30. The method of claim 24 wherein the Crohn's disease (CD) is ileal CD or colonic CD.~~

~~31. The method of claim 24 further comprising a second measure of amenability to treatment of Crohn's disease.~~

3214. The method of claim 31 ~~wherein the 12 further comprising a~~ second measure of amenability to treatment of Crohn's disease, wherein the second measure is a blood test for anemia or infection, a stool test for blood or infection, a breath test for hydrogen, a barium enema, an upper endoscopy, an upper gastrointestinal series, a colonoscopy, a sigmoidoscopy, a CT scan or an MRI.

~~33. The method of claim 24 further comprising administering to the subject an anti-IL-23 antibody in an amount and at an interval of:~~

~~(a) 720-1440 mg on about days 1, 29, and 57 delivered intravenously, followed by~~

~~(b) about 240 mg delivered subcutaneously on or about day 85 and about every 4 weeks thereafter through at least week 48.~~

~~34. The method of claim 33 wherein the anti-IL-23 antibody is brazikumab.~~

3515. A method of identifying a subject as a member of a patient sub-population amenable to treatment for Crohn's disease comprising

~~(a) obtaining a biological sample from the subject;~~

~~(b)~~ measuring the level of IL-22 in ~~the a biological~~ sample obtained from the subject;

~~(c)~~ comparing the level of IL-22 in the sample to the level of IL-22 in a control; and

~~(d)~~ identifying the subject as a member of the patient sub-population amenable to treatment for Crohn's disease if the level of IL-22 in the subject's sample is higher than in the control.

3616. The method of claim **35-15** wherein the IL-22 level is at least about 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 pg/ml.

~~37. The method of claim 36 wherein the IL-22 level is at least about 9 pg/ml.~~

~~38. The method of claim 36 wherein the IL-22 level is at least about 50 pg/ml.~~

~~39. The method of claim 35 wherein the control is a biological sample from a healthy subject.~~

~~40. The method of claim 35 wherein the control is a threshold level of IL-22 associated with subjects having Crohn's disease.~~

~~41. The method of claim 35 wherein the Crohn's disease (CD) is ileal CD or colonic CD.~~

~~42. The method of claim 35 further comprising a second measure of amenability to treatment of Crohn's disease.~~

~~43~~17. The method of claim ~~42~~ wherein the 15 further comprising a second measure of amenability to treatment of Crohn's disease, wherein the second measure is a blood test for anemia or infection, a stool test for blood or infection, a breath test for hydrogen, a barium enema, an upper endoscopy, an upper gastrointestinal series, a colonoscopy, a sigmoidoscopy, a CT scan or an MRI.

~~44. The method of claim 35 further comprising administering to the subject an anti-IL-23 antibody in an amount and at an interval of:~~

~~(a) 720-1440 mg on about days 1, 29, and 57 delivered intravenously, followed by~~

~~(b) about 240 mg delivered subcutaneously on about day 85 and about every 4 weeks thereafter through at least week 48.~~

~~45. The method of claim 44 wherein the anti-IL-23 antibody is brazikumab.~~