

METHODS OF TREATING ULCERATIVE COLITIS

FIELD OF THE INVENTION

[0001] The present invention relates to methods, uses and pharmaceutical compositions of antibodies that bind to human IL-23p19 (“anti-IL-23p19 antibodies”), such as mirikizumab, for treating ulcerative colitis in pediatric patients. The present invention also relates to doses and dosing regimens for the methods and uses of anti-IL-23p19 antibodies, for treating ulcerative colitis in pediatric patients.

BACKGROUND OF THE INVENTION

[0002] Ulcerative colitis (UC) is a chronic disease of unknown cause, characterized by inflammation in the colon. Patients have intermittent disease flares interspersed with periods of remission; the primary symptoms include blood in the stool, diarrhea, bowel urgency, and abdominal pain. Incidence of pediatric UC has been reported to be rising globally, constituting about 15% to 20% of all UC, and presenting with extensive disease in 60% to 80% of all pediatric cases, twice as often as in adults with more frequent hospitalization for acute severe exacerbation (25%–30% over 3–4 years) and colectomy for medically refractory disease (up to 30%–40% in 10-year follow-up) (Sykora J., et al., *World J Gastroenterol.*, 2018 Jul 7; 24(25): 2741–2763). The presentation and natural history of pediatric UC are distinct from those of adult UC in that the majority of pediatric-onset UC presents with extensive colitis affecting the entire colon, with atypical features, including macroscopic rectal sparing (5–30%), backwash ileitis in association with severe pancolitis, and limited distal disease associated with mild fecal inflammation with an otherwise normal right colon (cecal patch) (Colman RJ., et al., *Frontiers in Pediatrics* 2021 Feb 17; 9: 634739). In addition to more severe colitis, children have unique age-related issues, such as growth and pubertal development delay, nutritional insufficiency, and bone mineral density accretion, as well as differing psychosocial needs. (Sykora J., et al., *World J Gastroenterol.* 2018).

[0003] Interleukin-23 (IL-23), a member of the interleukin-12 (IL-12) family of cytokines, is a heterodimeric protein composed of two subunits: the p40 subunit, which is shared by IL-12, and the p19 subunit, which is specific to IL-23. IL-23 receptor engagement leads to activation of JAKs (mainly TYK2 and JAK2) and signal transducer

and activator of transcription 3 and 4 (STAT3 and STAT4), triggering transcription of downstream target genes. IL-23 promotes the differentiation, maintenance and stabilization of pathogenic T-cell lineages, including populations that simultaneously produce multiple pro-inflammatory cytokines, such as interferon- γ , IL-17A, IL-17F and IL-22, as well as activation and induction of effector function of colitogenic innate lymphoid cells. Therapeutic blockade of p40 has been found to be effective in treatment of UC, and drugs targeting p19 are being studied for the treatment of UC. To date there are no anti-IL23p19 biologics approved for the treatment of pediatric or adult UC.

[0004] The treatment aim in pediatric patients with UC is the induction and maintenance of remission (including steroid-free remission) with endoscopic healing. Conventional treatments such as corticosteroids, immunomodulatory therapies such as thiopurines (e.g., azathioprine (AZA), 6-mercaptopurine (6-MP)), tacrolimus and methotrexate have limitations with respect to efficacy, safety, and tolerability. For example, corticosteroids, although effective in inducing clinical response or remission, are not effective in maintaining remission, and have been reported to have steroid-related complications, including osteopenia, acne, glaucoma, cataracts, growth suppression, with 45% of patients reported to develop corticosteroid dependence and requiring additional medication to successfully discontinue corticosteroids (Turner D, et al., *Journal of Pediatric Gastroenterology and Nutrition* 2018 August 67(2):257-291). Immunomodulatory therapies such as thiopurines (e.g., azathioprine (AZA), 6-mercaptopurine (6-MP)) and tacrolimus, although used to treat UC in pediatric patients, require close monitoring for potential toxicities such as myelosuppression and other toxicities (Turner D, et al., *Journal of Pediatric Gastroenterology and Nutrition* 2018). Anti-TNF biologics indicated for the treatment of moderately to severe UC in patients 5 years of age or older include infliximab and adalimumab, however, shortcomings of their use include for example, the development of anti-drug antibodies and potential side effects.

[0005] Treatment of adult patients with mirikizumab has been reported in WO2019191464. However, due to the distinct and severe presentation of pediatric UC, there remains an unmet medical need for safe and effective therapies and treatment regimens for moderately to severely active UC in pediatric patients.

SUMMARY OF THE INVENTION

[0006] Provided herein are methods, uses and pharmaceutical compositions of anti-IL-23p19 antibodies, such as mirikizumab for treating moderately to severely active ulcerative colitis in pediatric patients. Also, provided herein are doses and dosing regimens for the methods and uses of anti-IL-23p19 antibodies, such as mirikizumab, for treating moderate to severe ulcerative colitis in pediatric patients of 2 years to less than 18 years of age who have an inadequate response to, loss of response to, or are intolerant to non-biologic therapy for UC (biologic-naïve or biologic not failed used interchangeably herein), and/or those who have been exposed to at least 1 biologic and/or advanced therapy for UC (e.g., TNFa and/or JAK inhibitors). Additionally, the doses and dosing regimens as provided herein, demonstrate clinical efficacy by about 4 weeks to about 12 weeks of treatment of such patients, and/ or sustain the clinical efficacy up to about 52 weeks of treatment (e.g., Modified Mayo Score (MMS) clinical remission, MMS clinical response, MMS alternate clinical remission, Pediatric Ulcerative Colitis Activity Index (PUCAI) clinical remission, PUCAI clinical response, endoscopic remission, and/ or symptomatic remission). The doses and dosing regimens as provided herein, further demonstrate Histologic-endoscopic mucosal improvement, Histologic endoscopic mucosal remission, and or corticosteroid free remission by about 52 weeks of treatment. Additionally, the dose and dosing regimen of the invention, have acceptable PK and immunogenicity profiles.

[0007] Accordingly, in a first aspect provided herein are methods of treating moderately to severely active ulcerative colitis (UC) in a patient in need thereof comprising administering an induction dose of mirikizumab to the patient, at about 5 mg/kg to about 10 mg/kg, wherein the patient is 2 years to less than 18 years of age and has a weight of greater than 10 kilogram (kg).

[0008] Accordingly, in a first aspect provided herein are methods of treating moderately to severely active ulcerative colitis (UC) in a patient in need thereof that is nonresponsive, has an inadequate response, loss of response, or is intolerant, to at least one prior therapy, comprising administering an induction dose of mirikizumab to the patient, at about 5 mg/kg to about 10 mg/kg, wherein the patient is 2 years to less than 18 years of age and has a weight of greater than 10 kilogram (kg). In such embodiments the prior therapy can

be a biologic, an advanced therapy, or non-biologic therapies such as immunomodulators or corticosteroids.

[0009] In some embodiments of the methods of the present invention as provided herein, of treating moderately to severely active ulcerative colitis in a patient in need thereof, comprise, administering an induction dose of mirikizumab to the patient, wherein the patient is 2 years to less than 18 years of age and has a weight of greater than 10 kg to less than or equal to 40 kg, the induction dose of mirikizumab is administered to the patient at a dose based on the patient's weight. In such embodiments, an induction dose of mirikizumab is administered to the patient at about 5 mg/kg to about 10 mg/kg (e.g., about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg or about 10 mg/kg). In further embodiments an induction dose of mirikizumab is administered to the patient at about 5 mg/kg. In alternate embodiments, an induction dose of mirikizumab is administered to the patient at about 10 mg/kg.

[0010] In certain embodiments of the methods of the present invention, one, two, or three induction doses of mirikizumab are administered to the patient. In even further embodiments of the methods of the present invention, three induction doses of mirikizumab are administered to the patient. In particular embodiments, the induction doses are administered to the patient at 4-8 week intervals (e.g., 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks). In more particular embodiments, the induction doses are administered to the patient at 4 week intervals. In certain embodiments, the induction dosing period (induction period) is 4, 8, or 12 weeks in duration. In particular embodiment, the induction period is 12 weeks in duration. In even more particular embodiments, the induction doses are administered to the patient at 0, 4, and 8 weeks. The induction dose is delivered over the induction dosing period.

[0011] In embodiments of the present invention, the induction dose of mirikizumab is administered to the patient by intravenous infusion.

[0012] In certain embodiments of the methods of the present invention, if the patient has not achieved a clinical response 4-8 weeks after the last induction dose is administered, one, two or three extended induction doses of mirikizumab are administered to the patient at about 5 mg/kg to about 10 mg/kg, wherein the patient is 2 years to less than 18 years of age and has a weight greater than 10 kilogram (kg). In further embodiments, if the patient has a weight greater than 10 kg to less than or equal to 40 kg, an extended induction dose

of mirikizumab is administered to the patient at about 5 mg/kg to about 10 mg/kg. In further embodiments, an extended induction dose of mirikizumab is administered to the patient at about 5 mg/kg. In alternate embodiments an extended induction dose of mirikizumab is administered to the patient at about 10 mg/kg.

[0013] In a still further embodiment, three extended induction doses of mirikizumab are administered to the patient at 4-8 week intervals. In more particular embodiments of the present invention, three extended induction doses of mirikizumab are administered to the patient at 4 week intervals.

[0014] In embodiments of the present invention, the one, two or three extended induction doses of mirikizumab are administered by intravenous infusion.

[0015] In further embodiments of the present invention, if the patient achieves a clinical response at the end of the induction period or at the end of the extended induction period, maintenance doses of mirikizumab are then administered to the patient. The extended dose is delivered over the extended induction dosing period.

[0016] In certain embodiments of the methods of treating moderately to severely active ulcerative colitis in a patient in need thereof, a maintenance dose of mirikizumab is administered to the patient at about 50 mg to about 100 mg, wherein the maintenance dose is administered to the patient after the last induction dose, or the last extended induction dose is administered. In some embodiments, if the patient has a weight greater than 10 kg to less than or equal to 20 kg, a maintenance dose of mirikizumab is administered to the patient at about 50 mg. In other embodiments, if the patient has a weight of greater than 20 kg to less than or equal to 40 kg, a maintenance dose of mirikizumab is administered to the patient at about 100 mg.

[0017] In such embodiments of the methods of treating moderately to severely active ulcerative colitis in a patient in need thereof, the first maintenance dose of mirikizumab is administered to the patient 2-8 weeks (e.g., 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks) after the last induction dose or the last extended induction dose is administered to the patient. In preferred embodiments, the first maintenance dose of mirikizumab is administered 4-6 weeks after the last induction dose or last extended induction dose is administered. Further preferably, the first maintenance dose is administered 4 weeks after the last induction dose or last extended induction dose is administered. In a still further embodiment, further maintenance doses of mirikizumab are

administered to the patient at 4 or 8 week intervals after administering of the first maintenance dose. Preferably, maintenance doses are administered at 4 week intervals.

[0018] In embodiments of the present invention, the maintenance doses are administered by subcutaneous injection.

[0019] The 4-8 week period of administering the maintenance dose accommodates variation in the period between the administration of last extended induction dose and the end of extended-induction assessment. The variation may arise from variation in the dosing frequency in the extended induction period. In some embodiments, the dosing frequency in the extended induction period is every 4 weeks and the end-of-extended induction assessment occurs 4 weeks after the last extended induction dose is administered. In such embodiments, if the patient achieves clinical response, the first maintenance dose may be administered at the end-of-induction assessment visit (that is, 4 weeks after administration of the last extended induction dose) or may be administered at a subsequent visit scheduled to occur shortly thereafter. Alternatively, the dosing frequency in the extended induction period is every 8 weeks and the end-of-extended induction assessment occurs 8 weeks after the last extended induction dose is administered. If the patient has achieved clinical response, the first maintenance dose may be administered at the end-of-induction assessment visit (that is, 8 weeks after administration of the last extended induction dose) or may be administered at a subsequent visit scheduled to occur shortly thereafter. In such embodiments, the maintenance dose of mirikizumab is administered after the patient achieves a clinical response from the one, two, or three extended induction doses.

[0020] In a still further embodiment of the methods of treating moderately to severely active ulcerative colitis in a patient in need thereof, if the patient develops a loss of response during the maintenance dosing (maintenance period), The maintenance dose is delivered over the maintenance dosing period.

[0021] rescue doses of mirikizumab are administered to the patient at 2-8 weeks after the last maintenance dose. In such embodiments, if the patient has a weight greater than 10 kg to less than or equal to 40 kg, a rescue dose of mirikizumab is administered to the patient at about 5 mg/kg to about 10 mg/kg. In some embodiments, the rescue dose of mirikizumab is administered at about 5mg/kg. In other embodiments, the rescue dose of mirikizumab is administered at about 10 mg/kg.

[0022] In some embodiments of the present invention, one, two or three rescue doses of mirikizumab are administered to the patient at 4-8 week intervals. In a still further embodiment, two or three rescue doses of mirikizumab are administered to the patient at 4-8 week intervals. In preferred embodiments of the present invention, three rescue doses of mirikizumab are administered to the patient at 4 week intervals. The rescue dose is delivered over the rescue dosing period.

[0023] In embodiments of the present invention, the rescue doses are administered by intravenous infusion.

[0024] In further embodiments of the present invention, if the patient achieves a clinical response 4-12 weeks after the one, two, or three rescue doses (rescue dosing period) maintenance doses of mirikizumab are administered to the patient. In such embodiments, maintenance doses are administered to the patient based on the weight and intervals as described herein above.

[0025] In such embodiments of the methods of treating moderately to severely active ulcerative colitis in a patient in need thereof, a maintenance dose of mirikizumab is administered to the patient at about 50 mg to about 100 mg. In some embodiments, if the patient has a weight greater than 10 kg to less than or equal to 20 kg, a maintenance dose of mirikizumab is administered to the patient at about 50 mg. In other embodiments, if the patient has a weight of greater than 20 kg to less than or equal to 40 kg, a maintenance dose of mirikizumab is administered to the patient at about 100 mg.

[0026] In such embodiments of the methods of treating moderately to severely active ulcerative colitis in a patient in need thereof, a maintenance dose of mirikizumab is administered to the patient 2-8 weeks after the last rescue dose is administered to the patient. In preferred embodiments, the maintenance dose of mirikizumab is administered 2-6 weeks after the last rescue dose is administered. Further preferably, the maintenance dose is administered 2 weeks or 4 weeks after the last rescue dose is administered. In a still further embodiment, further maintenance doses of mirikizumab are administered to the patient at 4 or 8 week intervals. Preferably, maintenance doses are administered at 4 week intervals.

[0027] In particular embodiments, of the methods of treating moderately to severely active ulcerative colitis in a patient in need thereof the maintenance doses of mirikizumab are administered to the patient for up to about 4 weeks, 8 weeks, 12 weeks, 16 weeks, 20

weeks, 24 weeks, 28 weeks, 32 weeks, 36 weeks, 40 weeks, 44 weeks, 48 weeks, 52 weeks, 56 weeks, 60 weeks, 64 weeks, 68 weeks, 72 weeks, 76 weeks, 80 weeks, 84 weeks, 88 weeks, 92 weeks, 96 weeks, or 104 weeks to up to about 152 weeks, after the last induction dose, the last extended induction dose, or the last rescue dose is administered. In certain embodiments, the maintenance doses are administered for up to about 1 year, 2 years, 3 years, or about 4 years.

[0028] In embodiments of the methods of the invention, the patient achieves a therapeutic effect of at least one or more of clinical response, clinical remission, endoscopic remission, endoscopic improvement, symptomatic remission, symptomatic response, clinical remission without surgery, corticosteroid free clinical remission, histologic endoscopic mucosal remission, histologic-endoscopic mucosal improvement, bowel urgency remission, improvement in bowel urgency, improvement in stool frequency, improvement in rectal bleeding within about 2 weeks to about 48 weeks of treatment with mirikizumab. In such embodiments of the methods of the invention, at least one or more therapeutic effect is achieved within about 2 weeks, 4 weeks, 8 weeks, 12 weeks, 16, weeks, 20 weeks, 24 weeks, 28 weeks, 32 weeks, 36 weeks, 40 weeks, or 48 weeks of treatment with mirikizumab. Such therapeutic effect may be achieved in the induction period, the extended induction period, and/ or the rescue period. In certain embodiments, a therapeutic effect may be achieved in the maintenance period which may be the maintenance period after the induction period, the maintenance period after the extended induction period, or the maintenance period after the rescue period.

[0029] In embodiments of the methods of the invention, the patient achieves a reduction from baseline in fecal calprotectin and c-reactive protein within about 2 weeks to about 48 weeks of treatment with mirikizumab.

[0030] In further embodiments of the methods of the invention, the patient exhibits sustained therapeutic effect in the maintenance period, of at least one or more of clinical response, clinical remission, endoscopic remission, endoscopic improvement, symptomatic remission, symptomatic response, clinical remission without surgery, corticosteroid free clinical remission, histologic endoscopic mucosal remission, histologic-endoscopic mucosal improvement, bowel urgency remission, improvement in bowel urgency, improvement in stool frequency, improvement in rectal bleeding. In such embodiments, the therapeutic effect is sustained for up to about 4 weeks, 8 weeks, 12

weeks, 24 weeks, 28 weeks, 32 weeks, 36 weeks, 40 weeks, 44 weeks, 48 weeks, 52 weeks, 56 weeks, 60 weeks, 64 weeks, 68 weeks, 72 weeks, 76 weeks, 80 weeks, 84 weeks, 88 weeks, 92 weeks, 96 weeks, 104 weeks to up to about 152 weeks in the maintenance period after the end of the induction period, the extended induction period, or the rescue period.

[0031] In further embodiments, the patient has sustained clinical remission without surgery at Week 52 and no steroid use for at least 12 weeks prior to Week 52 of treatment with mirikizumab.

[0032] In such embodiments, the patient continues maintenance treatment with mirikizumab up until the patient becomes nonresponsive, has an inadequate response, loss of response, or is intolerant to mirikizumab.

[0033] In embodiments of the methods of the present invention an induction dose, extended induction, or rescue dose range of about 5 mg/kg to about 10 mg/kg can be about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg.

[0034] In embodiments of the methods of the invention, the patient is conventional-failed.

[0035] In other embodiments, the patient is biologic-naïve and or advanced therapy naïve.

[0036] In some embodiments, the patient is biologic-experienced and or advanced therapy experienced.

[0037] In some embodiments, the patient is biologic-failed and or advanced therapy failed.

[0038] In some embodiments, the patient is nonresponsive, has an inadequate response, loss of response, or is intolerant, to at least one prior treatment for ulcerative colitis.

[0039] In embodiments of the present invention, the biologic or advanced therapy is an anti-TNF therapeutic, and or an anti- $\alpha 4\beta 7$ therapeutic.

[0040] In some embodiments the advanced therapy is a JAK inhibitor, a S1P receptor modulator, or a TYK2 inhibitor.

[0041] In further embodiments, the patient is one or more of anti-TNF therapeutic failed, anti- $\alpha 4\beta 7$ therapeutic failed, JAK inhibitor failed, S1P receptor modulator failed, or TYK2 inhibitor failed.

- [0042] In a further embodiment, of the methods of the present invention, the method comprises,
- administering three induction doses of mirikizumab to the patient at about 5 mg/kg or at about 10 mg/kg at 4 week intervals by intravenous infusion; and
 - administering maintenance doses of mirikizumab to the patient at about 50 mg, at 4 week intervals by subcutaneous injection, 2-8 weeks after the last induction dose is administered,
- wherein the patient is 2 years to less than 18 years of age and has a weight of greater than 10 kg to less than or equal to 40 kg.
- [0043] In a further embodiment, of the methods of the present invention, the method comprises,
- administering three induction doses of mirikizumab to the patient at about 5 mg/kg or at about 10 mg/kg at 4 week intervals by intravenous infusion; and
 - administering maintenance doses of mirikizumab to the patient at about 100 mg, at 4 week intervals by subcutaneous injection, 2-8 weeks after the last induction dose is administered,
- wherein the patient is 2 years to less than 18 years of age and has a weight of greater than 20 kg to less than or equal to 40 kg.
- [0044] In such embodiment of the methods of the present invention, wherein if the patient has not achieved a clinical response at 4 to 12 weeks after the last induction dose is administered, three extended induction doses of mirikizumab are administered to the patient,
- wherein, if the patient has a weight of greater than 10 kg to less than or equal to 40 kg, an extended induction dose of mirikizumab is administered to the patient at about 5 mg/kg or at about 10 mg/kg; and
 - wherein, the extended induction doses of mirikizumab are administered to the patient at 4 week intervals by intravenous infusion.
- [0045] In further embodiments, wherein if the patient achieves a clinical response at 4 to 12 weeks after the last extended induction dose is administered, maintenance doses of mirikizumab are administered to the patient at 2-8 weeks after the last extended induction dose.

[0046] In such embodiments, wherein if the patient develops a loss of response during the maintenance dosing (maintenance period), one, two or three rescue doses of mirikizumab are administered to the patient,

wherein, if the patient has a weight of 10 kg to less than or equal to 40 kg, the rescue dose of mirikizumab is administered to the patient at about 5 mg/kg or at about 10 mg/kg,;

wherein the rescue doses of mirikizumab are administered to the patient at 4 week intervals by intravenous infusion.

[0047] In such embodiments of the methods present invention, if the patient achieves a clinical response 4-12 weeks after the one, two, or three rescue doses, maintenance doses of mirikizumab are administered to the patient, at 4 week intervals by subcutaneous injection.

[0048] In further embodiments, the patient achieves a therapeutic effect of at least one or more of clinical response, clinical remission, endoscopic remission, endoscopic improvement, symptomatic remission, symptomatic response, clinical remission without surgery, corticosteroid free clinical remission, histologic endoscopic mucosal remission, histologic endoscopic mucosal improvement, bowel urgency remission, improvement in bowel urgency, improvement in stool frequency, improvement in rectal bleeding within about 2 weeks to about 48 weeks of treatment with mirikizumab.

[0049] In even further embodiments of the methods of the present invention, at least one or more therapeutic effect is achieved within about 2 weeks, 4 weeks, 8 weeks, 12 weeks, 16, weeks, 20 weeks, 24 weeks, 28 weeks, 32 weeks, 36 weeks, 40 weeks, or 48 weeks of treatment with mirikizumab. In such embodiments, at least one or more therapeutic effect is achieved in the induction period or the extended induction period.

[0050] In other embodiments, one or more of the therapeutic effects is sustained in the maintenance period.

[0051] In such embodiments, the therapeutic effect is sustained for up to about 4 weeks, 8 weeks, 12 weeks, 24 weeks, 28 weeks, 32 weeks, 36 weeks, 40 weeks, 44 weeks, 48 weeks, 52 weeks, 56 weeks, 60 weeks, 64 weeks, 68 weeks, 72 weeks, 76 weeks, 80 weeks, 84 weeks, 88 weeks, 92 weeks, 96 weeks, 104 weeks to up to about 152 weeks in the maintenance period after the end of the induction period, the extended induction period, or the rescue period.

- [0052] In particular embodiments, the patient has sustained clinical remission without surgery at Week 52 and no steroid use for at least 12 weeks prior to Week 52 of treatment with mirikizumab.
- [0053] In such embodiments, the patient continues maintenance treatment with mirikizumab up until the patient becomes nonresponsive, has an inadequate response, loss of response, or is intolerant to mirikizumab.
- [0054] In embodiments of the methods of the present invention, an induction dose, extended induction, or rescue dose range of about 5 mg/kg to about 10 mg/kg can be about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg.
- [0055] In embodiments of the methods of the invention, the patient is conventional-failed.
- [0056] In other embodiments, the patient is biologic-naïve and or advanced therapy naïve.
- [0057] In some embodiments, the patient is biologic-experienced and or advanced therapy experienced.
- [0058] In some embodiments, the patient is biologic-failed and or advanced therapy failed.
- [0059] In some embodiments, the patient is nonresponsive, has an inadequate response, loss of response, or is intolerant, to at least one prior treatment for ulcerative colitis.
- [0060] In some embodiments, the biologic or advanced therapy is an anti-TNF therapeutic, and or an anti- $\alpha 4\beta 7$ therapeutic.
- [0061] In some embodiments the advanced therapy is a JAK inhibitor, a S1P receptor modulator, or a TYK2 inhibitor.
- [0062] In further embodiments, the patient is one or more of anti-TNF therapeutic failed, anti- $\alpha 4\beta 7$ therapeutic failed, JAK inhibitor failed, S1P receptor modulator failed, or TYK2 inhibitor failed.
- [0063] In an aspect of the present invention, provided herein are mirikizumab, or pharmaceutical composition comprising mirikizumab, for use in treating moderately to severely active ulcerative colitis (UC) in a patient in need thereof comprising administering an induction dose of mirikizumab to the patient, at about 5 mg/kg to about

10 mg/kg, wherein the patient is 2 years to less than 18 years of age and has a weight of greater than 10 kilogram (kg).

[0064] In another aspect, provided herein are mirikizumab, or pharmaceutical composition comprising mirikizumab, for use in treating moderately to severely active ulcerative colitis (UC) in a patient in need thereof that is nonresponsive, has an inadequate response, loss of response, or is intolerant, to at least one prior therapy, comprising administering an induction dose of mirikizumab to the patient, at about 5 mg/kg to about 10 mg/kg, wherein the patient is 2 years to less than 18 years of age and has a weight of greater than 10 kilogram (kg). In such embodiments the prior therapy can be a biologic, an advanced therapy, or non-biologic therapies such as immunomodulators or corticosteroids.

[0065] In some embodiments of the present invention provided herein, if the patient is 2 years to less than 18 years of age and has a weight of greater than 10 kg to less than or equal to 40 kg. In such embodiments, the induction dose of mirikizumab is administered to the patient at a dose based on the patient's weight. In such embodiments, an induction dose of mirikizumab is administered to the patient at about 5 mg/kg to about 10 mg/kg (e.g., about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg or about 10 mg/kg). In some embodiments an induction dose of mirikizumab is administered to the patient at about 5 mg/kg. In alternate embodiments, an induction dose of mirikizumab is administered to the patient at about 10 mg/kg.

[0066] In certain embodiments of the present invention, one, two, or three induction doses of mirikizumab are administered to the patient. In even further embodiments of the present invention, three induction doses of mirikizumab are administered to the patient. In particular embodiments, the induction doses are administered to the patient at 4-8 week intervals (e.g., 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks). In more particular embodiments, the induction doses are administered to the patient at 4 week intervals. In certain embodiments, the induction dosing period (induction period) is 4, 8, or 12 weeks in duration. In particular embodiment, the induction period is 12 weeks in duration. In even more particular embodiments, the induction doses are administered to the patient at 0, 4, and 8 weeks.

[0067] In embodiments of the present invention, the induction dose of mirikizumab is administered to the patient by intravenous infusion.

[0068] In certain embodiments of the present invention, if the patient has not achieved a clinical response 4-8 weeks after the last induction dose is administered, one, two or three extended induction doses of mirikizumab are administered to the patient at about 5 mg/kg to about 10 mg/kg, wherein the patient is 2 years to less than 18 years of age and has a weight greater than 10 kilogram (kg). In further embodiments, if the patient has a weight greater than 10 kg to less than or equal to 40 kg, an extended induction dose of mirikizumab is administered to the patient at about 5 mg/kg to about 10 mg/kg. In further embodiments, an extended induction dose of mirikizumab is administered to the patient at about 5 mg/kg. In alternate embodiments an extended induction dose of mirikizumab is administered to the patient at about 10 mg/kg.

[0069] In a still further embodiment, three extended induction doses of mirikizumab are administered to the patient at 4-8 week intervals. In more particular embodiments of the present invention, three extended induction doses of mirikizumab are administered to the patient at 4 week intervals.

[0070] In embodiments of the present invention, the one, two or three extended induction doses of mirikizumab are administered by intravenous infusion.

[0071] In further embodiments of the present invention, if the patient achieves a clinical response at the end of the induction period or at the end of the extended induction period, maintenance doses of mirikizumab are then administered to the patient.

[0072] In certain embodiments, a maintenance dose of mirikizumab is administered to the patient at about 50 mg to about 100 mg, wherein the maintenance doses are administered to the patient after the last induction dose, or the last extended induction dose is administered. In some embodiments, if the patient has a weight greater than 10 kg to less than or equal to 20 kg, a maintenance dose of mirikizumab is administered to the patient at about 50 mg. In other embodiments, if the patient has a weight of greater than 20 kg to less than or equal to 40 kg, a maintenance dose of mirikizumab is administered to the patient at about 100 mg.

[0073] In such embodiments, the first maintenance dose of mirikizumab is administered to the patient 2-8 weeks (e.g., 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks) after the last induction dose or the last extended induction dose is administered to the patient. In preferred embodiments, the first maintenance dose of mirikizumab is administered 4-6 weeks after the last induction dose or last extended induction dose is

administered. Further preferably, the first maintenance dose is administered 4 weeks after the last induction dose or last extended induction dose is administered. In a still further embodiment, further maintenance doses of mirikizumab are administered to the patient at 4 or 8 week intervals after administering of the first maintenance dose. Preferably, maintenance doses are administered at 4 week intervals.

[0074] In embodiments of the present invention, the maintenance doses are administered by subcutaneous injection.

[0075] The 4-8 week period of administering the maintenance dose accommodates variation in the period between the administration of last extended induction dose and the end of extended-induction assessment. The variation may arise from variation in the dosing frequency in the extended induction period. In some embodiments, the dosing frequency in the extended induction period is every 4 weeks and the end-of-extended induction assessment occurs 4 weeks after the last extended induction dose is administered. In such embodiments, if the patient achieves clinical response, the first maintenance dose may be administered at the end-of-induction assessment visit (that is, 4 weeks after administration of the last extended induction dose) or may be administered at a subsequent visit scheduled to occur shortly thereafter. Alternatively, the dosing frequency in the extended induction period is every 8 weeks and the end-of-extended induction assessment occurs 8 weeks after the last extended induction dose is administered. If the patient has achieved clinical response, the first maintenance dose may be administered at the end-of-induction assessment visit (that is, 8 weeks after administration of the last extended induction dose) or may be administered at a subsequent visit scheduled to occur shortly thereafter. In such embodiments, the maintenance dose of mirikizumab is administered after the patient achieves a clinical response from the one, two, or three extended induction doses.

[0076] In a still further embodiment of the present invention, if the patient develops a loss of response during the maintenance dosing (maintenance period),, rescue doses of mirikizumab are administered to the patient at 2-8 weeks after the last maintenance dose. In such embodiments, if the patient has a weight greater than 10 kg to less than or equal to 40 kg, a rescue dose of mirikizumab is administered to the patient at about 5 mg/kg to about 10 mg/kg. In some embodiments, the rescue dose of mirikizumab is administered at

about 5mg/kg. In other embodiments, the rescue dose of mirikizumab is administered at about 10 mg/kg.

[0077] In some embodiments of the present invention, one, two or three rescue doses of mirikizumab are administered to the patient at 4-8 week intervals. In a still further embodiment, two or three rescue doses of mirikizumab are administered to the patient at 4-8 week intervals. In preferred embodiments of the present invention, three rescue doses of mirikizumab are administered to the patient at 4 week intervals.

[0078] In embodiments of the present invention, the rescue doses are administered by intravenous infusion.

[0079] In further embodiments of the present invention, if the patient achieves a clinical response 4-12 weeks after the one, two, or three rescue doses (rescue dosing period) maintenance doses of mirikizumab are administered to the patient. In such embodiments, maintenance doses are administered to the patient based on the weight and intervals as described herein above.

[0080] In such embodiments, a maintenance dose of mirikizumab is administered to the patient at about 50 mg to about 100 mg. In some embodiments, if the patient has a weight greater than 10 kg to less than or equal to 20 kg, a maintenance dose of mirikizumab is administered to the patient at about 50 mg. In other embodiments, if the patient has a weight of greater than 20 kg to less than or equal to 40 kg, a maintenance dose of mirikizumab is administered to the patient at about 100 mg.

[0081] In such embodiments, a maintenance dose of mirikizumab is administered to the patient 2-8 weeks after the last rescue dose is administered to the patient. In preferred embodiments, the maintenance dose of mirikizumab is administered 2-6 weeks after the last rescue dose is administered. Further preferably, the maintenance dose is administered 2 weeks or 4 weeks after the last rescue dose is administered. In a still further embodiment, further maintenance doses of mirikizumab are administered to the patient at 4 or 8 week intervals. Preferably, maintenance doses are administered at 4 week intervals.

[0082] In particular embodiments, the maintenance doses of mirikizumab are administered to the patient for up to about 4 weeks, 8 weeks, 12 weeks, 16 weeks, 20 weeks, 24 weeks, 28 weeks, 32 weeks, 36 weeks, 40 weeks, 44 weeks, 48 weeks, 52 weeks, 56 weeks, 60 weeks, 64 weeks, 68 weeks, 72 weeks, 76 weeks, 80 weeks, 84 weeks, 88 weeks, 92 weeks, 96 weeks, or 104 weeks to up to about 152 weeks, after the

last induction dose, the last extended induction dose, or the last rescue dose is administered. In certain embodiments, the maintenance doses are administered for up to about 1 year, 2 years, 3 years, or about 4 years.

[0083] In embodiments of the present invention, the patient achieves a therapeutic effect of at least one or more of clinical response, clinical remission, endoscopic remission, endoscopic improvement, symptomatic remission, symptomatic response, clinical remission without surgery, corticosteroid free clinical remission, histologic endoscopic mucosal remission, histologic-endoscopic mucosal improvement, bowel urgency remission, improvement in bowel urgency, improvement in stool frequency, improvement in rectal bleeding within about 2 weeks to about 48 weeks of treatment with mirikizumab. In such embodiments of the invention, at least one or more therapeutic effect is achieved within about 2 weeks, 4 weeks, 8 weeks, 12 weeks, 16 weeks, 20 weeks, 24 weeks, 28 weeks, 32 weeks, 36 weeks, 40 weeks, or 48 weeks of treatment with mirikizumab. Such therapeutic effect may be achieved in the induction period, the extended induction period, and/or the rescue period. In certain embodiments, a therapeutic effect may be achieved in the maintenance period which may be the maintenance period after the induction period, the maintenance period after the extended induction period, or the maintenance period after the rescue period.

[0084] In further embodiments of the invention, one or more of the therapeutic effects is sustained in the maintenance period.

[0085] In such embodiments, the therapeutic effect is sustained for up to about 4 weeks, 8 weeks, 12 weeks, 24 weeks, 28 weeks, 32 weeks, 36 weeks, 40 weeks, 44 weeks, 48 weeks, 52 weeks, 56 weeks, 60 weeks, 64 weeks, 68 weeks, 72 weeks, 76 weeks, 80 weeks, 84 weeks, 88 weeks, 92 weeks, 96 weeks, 104 weeks to up to about 152 weeks in the maintenance period after the end of the induction period, the extended induction period, or the rescue period.

[0086] In further embodiments, the patient has sustained clinical remission without surgery at Week 52 and no steroid use for at least 12 weeks prior to Week 52 of treatment with mirikizumab.

[0087] In such embodiments, the patient continues maintenance treatment with mirikizumab up until the patient becomes nonresponsive, has an inadequate response, loss of response, or is intolerant to mirikizumab.

- [0088] In some embodiments of the present invention, the patient achieves a reduction in fecal calprotectin and c-reactive protein within about 2 weeks to about 48 weeks of treatment with mirikizumab.
- [0089] In embodiments of the present invention an induction dose, extended induction, or rescue dose range of about 5 mg/kg to about 10 mg/kg can be about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg.
- [0090] In embodiments of the invention, the patient is conventional-failed.
- [0091] In other embodiments, the patient is biologic-naïve and or advanced therapy naïve.
- [0092] In some embodiments, the patient is biologic-experienced and or advanced therapy experienced.
- [0093] In some embodiments, the patient is biologic-failed and or advanced therapy failed.
- [0094] In some embodiments, the patient is nonresponsive, has an inadequate response, loss of response, or is intolerant, to at least one prior treatment for ulcerative colitis.
- [0095] In embodiments of the present invention, the biologic or advanced therapy is an anti-TNF therapeutic, and or an anti- $\alpha 4\beta 7$ therapeutic.
- [0096] In some embodiments the advanced therapy is a JAK inhibitor, a S1P receptor modulator, or a TYK2 inhibitor.
- [0097] In further embodiments, the patient is one or more of anti-TNF therapeutic failed, anti- $\alpha 4\beta 7$ therapeutic failed, JAK inhibitor failed, S1P receptor modulator failed, or TYK2 inhibitor failed.
- [0098] In a further aspect of the present invention, provided herein are mirikizumab, or pharmaceutical composition comprising mirikizumab, for use in treating moderately to severely active ulcerative colitis in a patient in need thereof comprising,
administering three induction doses of mirikizumab to the patient at about 5 mg/kg or at about 10 mg/kg at 4 week intervals by intravenous infusion; and
administering maintenance doses of mirikizumab to the patient at about 50 mg, at 4 week intervals by subcutaneous injection, 2-8 weeks after the last induction dose is administered, or
wherein the patient is 2 years to less than 18 years of age and has a weight of greater than 10 kg to less than or equal to 20 kg.

[0099] In a further aspect of the present invention, provided herein are mirikizumab, or pharmaceutical composition comprising mirikizumab, for use in treating moderately to severely active ulcerative colitis in a patient in need thereof comprising,

administering three induction doses of mirikizumab to the patient at about 5 mg/kg or at about 10 mg/kg at 4 week intervals by intravenous infusion; and

administering maintenance doses of mirikizumab to the patient at about 100 mg, at 4 week intervals by subcutaneous injection, 2-8 weeks after the last induction dose is administered,

wherein the patient is 2 years to less than 18 years of age and has a weight of greater than 20 kg to less than or equal to 40 kg.

[0100] In such embodiments of the present invention, wherein if the patient has not achieved a clinical response at 4 to 12 weeks after the last induction dose is administered, three extended induction doses of mirikizumab are administered to the patient,

wherein, if the patient has a weight of greater than 10 kg to less than or equal to 40 kg, an extended induction dose of mirikizumab is administered to the patient at about 5 mg/kg or at about 10 mg/kg;

wherein, the extended induction doses of mirikizumab are administered to the patient at 4 week intervals by intravenous infusion.

[0101] In further embodiments, wherein if the patient achieves a clinical response at 4 to 12 weeks after the last extended induction dose is administered, maintenance doses of mirikizumab are administered to the patient at 2-8 weeks after the last extended induction dose.

[0102] In such embodiments, wherein if the patient develops a loss of response during the maintenance dosing (maintenance period), one, two or three rescue doses of mirikizumab are administered to the patient,

wherein, if the patient has a weight of 10 kg to less than or equal to 40 kg, the rescue dose of mirikizumab is administered to the patient at about 5 mg/kg or at about 10 mg/kg; or

wherein the rescue doses of mirikizumab are administered to the patient at 4 week intervals by intravenous infusion.

[0103] In such embodiments of the present invention, if the patient achieves a clinical response 4-12 weeks after the one, two, or three rescue doses, maintenance doses of

mirikizumab are administered to the patient, at 4 week intervals by subcutaneous injection.

[0104] In further embodiments, the patient achieves a therapeutic effect of at least one or more of clinical response, clinical remission, endoscopic remission, endoscopic improvement, symptomatic remission, symptomatic response, clinical remission without surgery, corticosteroid free clinical remission, histologic endoscopic mucosal remission, histologic endoscopic mucosal improvement, bowel urgency remission, improvement in bowel urgency, improvement in stool frequency, improvement in rectal bleeding within about 2 weeks to about 48 weeks of treatment with mirikizumab.

[0105] In even further embodiments of the present invention, at least one or more therapeutic effect is achieved within about 2 weeks, 4 weeks, 8 weeks, 12 weeks, 16, weeks, 20 weeks, 24 weeks, 28 weeks, 32 weeks, 36 weeks, 40 weeks, or 48 weeks of treatment with mirikizumab. In such embodiments, at least one or more therapeutic effect is achieved in the induction period or the extended induction period.

[0106] In other embodiments, one or more of the therapeutic effects is sustained in the maintenance period. In such embodiments of the present invention, the therapeutic effect is sustained up to about 4 weeks, 8 weeks, 12 weeks, 24 weeks, 28 weeks, 32 weeks, 36 weeks, 40 weeks, 44 weeks, 48 weeks, 52 weeks, 56 weeks, 60 weeks, 64 weeks, 68 weeks, 72 weeks, 76 weeks, 80 weeks, 84 weeks, 88 weeks, 92 weeks, 96 weeks, 104 weeks to up to about 152 weeks in the maintenance period after the end of the induction period, the extended induction period, or the rescue period.

[0107] In particular embodiments, the patient has sustained clinical remission without surgery at Week 52 and no steroid use for at least 12 weeks prior to Week 52 of treatment with mirikizumab. In such embodiments, the patient continues maintenance treatment with mirikizumab up until the patient becomes nonresponsive, has an inadequate response, loss of response, or is intolerant to mirikizumab.

[0108] In embodiments of the present invention, an induction dose, extended induction, or rescue dose range of about 5 mg/kg to about 10 mg/kg can be 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg.

[0109] In embodiments of the invention, the patient is conventional-failed.

[0110] In other embodiments, the patient is biologic-naïve and or advanced therapy naïve.

- [0111] In some embodiments, the patient is biologic-experienced and or advanced therapy experienced.
- [0112] In some embodiments, the patient is biologic-failed and or advanced therapy failed.
- [0113] In some embodiments, the patient is nonresponsive, has an inadequate response, loss of response, or is intolerant, to at least one prior treatment for ulcerative colitis.
- [0114] In some embodiments, the biologic or advanced therapy is an anti-TNF therapeutic, and or an anti- $\alpha 4\beta 7$ therapeutic.
- [0115] In some embodiments the advanced therapy is a JAK inhibitor, a S1P receptor modulator, or a TYK2 inhibitor.
- [0116] In further embodiments, the patient is one or more of anti-TNF therapeutic failed, anti- $\alpha 4\beta 7$ therapeutic failed, JAK inhibitor failed, S1P receptor modulator failed, or TYK2 inhibitor failed.
- [0117] In an aspect of the present invention, provided herein are use of mirikizumab in the manufacture of a medicament for treating moderately to severely active ulcerative colitis in a patient in need thereof comprising administering an induction dose of mirikizumab to the patient, at about 5 mg/kg to about 10 mg/kg, wherein the patient is 2 years to less than 18 years of age and has a weight of greater than 10 kilogram (kg).
- [0118] In another aspect, provided herein are use of mirikizumab in the manufacture of a medicament for treating moderately to severely active ulcerative colitis (UC) in a patient in need thereof that is nonresponsive, has an inadequate response, loss of response, or is intolerant, to at least one prior therapy, comprising administering an induction dose of mirikizumab to the patient, at about 5 mg/kg to about 10 mg/kg, wherein the patient is 2 years to less than 18 years of age and has a weight of greater than 10 kilogram (kg). In such embodiments the prior therapy can be a biologic, an advanced therapy, or non-biologic therapies such as immunomodulators or corticosteroids.
- [0119] In some embodiments of the present invention provided herein, if the patient is 2 years to less than 18 years of age and has a weight of greater than 10 kg to less than or equal to 40 kg. In such embodiments, the induction dose of mirikizumab is administered to the patient at a dose based on the patient's weight. In such embodiments, an induction dose of mirikizumab is administered to the patient at about 5 mg/kg to about 10 mg/kg (e.g., about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, v 9 mg/kg or about 10

mg/kg). In some embodiments an induction dose of mirikizumab is administered to the patient at about 5 mg/kg. In alternate embodiments, an induction dose of mirikizumab is administered to the patient at about 10 mg/kg.

[0120] In certain embodiments of the present invention, one, two, or three induction doses of mirikizumab are administered to the patient. In even further embodiments of the present invention, three induction doses of mirikizumab are administered to the patient. In particular embodiments, the induction doses are administered to the patient at 4-8 week intervals (e.g., 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks). In more particular embodiments, the induction doses are administered to the patient at 4 week intervals. In certain embodiments, the induction dosing period (induction period) is 4, 8, or 12 weeks in duration. In particular embodiment, the induction period is 12 weeks in duration. In even more particular embodiments, the induction doses are administered to the patient at 0, 4, and 8 weeks.

[0121] In embodiments of the present invention, the induction dose of mirikizumab is administered to the patient by intravenous infusion.

[0122] In certain embodiments of the present invention, if the patient has not achieved a clinical response 4-8 weeks after the last induction dose is administered, one, two or three extended induction doses of mirikizumab are administered to the patient at about 5 mg/kg to about 10 mg/kg, wherein the patient is 2 years to less than 18 years of age and has a weight greater than 10 kilogram (kg). In further embodiments, if the patient has a weight greater than 10 kg to less than or equal to 40 kg, an extended induction dose of mirikizumab is administered to the patient at about 5 mg/kg to about 10 mg/kg. In further embodiments, an extended induction dose of mirikizumab is administered to the patient at about 5 mg/kg. In alternate embodiments an extended induction dose of mirikizumab is administered to the patient at about 10 mg/kg.

[0123] In a still further embodiment, three extended induction doses of mirikizumab are administered to the patient at 4-8 week intervals. In more particular embodiments of the present invention, three extended induction doses of mirikizumab are administered to the patient at 4 week intervals.

[0124] In embodiments of the present invention, the one, two or three extended induction doses of mirikizumab are administered by intravenous infusion.

- [0125] In further embodiments of the present invention, if the patient achieves a clinical response at the end of the induction period or at the end of the extended induction period, maintenance doses of mirikizumab are then administered to the patient.
- [0126] In certain embodiments, a maintenance dose of mirikizumab is administered to the patient at about 50 mg to about 100 mg, wherein the maintenance dose is administered to the patient after the last induction dose, or the last extended induction dose is administered. In some embodiments, if the patient has a weight greater than 10 kg to less than or equal to 20 kg, a maintenance dose of mirikizumab is administered to the patient at about 50 mg. In other embodiments, if the patient has a weight of greater than 20 kg to less than or equal to 40 kg, a maintenance dose of mirikizumab is administered to the patient at about 100 mg.
- [0127] In such embodiments, the first maintenance dose of mirikizumab is administered to the patient 2-8 weeks (e.g., 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks) after the last induction dose or the last extended induction dose is administered to the patient. In preferred embodiments, the first maintenance dose of mirikizumab is administered 4-6 weeks after the last induction dose or last extended induction dose is administered. Further preferably, the first maintenance dose is administered 4 weeks after the last induction dose or last extended induction dose is administered. In a still further embodiment, further maintenance doses of mirikizumab are administered to the patient at 4 or 8 week intervals after administering of the first maintenance dose. Preferably, maintenance doses are administered at 4 week intervals.
- [0128] In embodiments of the present invention, the maintenance doses are administered by subcutaneous injection.
- [0129] The 4-8 week period of administering the maintenance dose accommodates variation in the period between the administration of last extended induction dose and the end of extended-induction assessment. The variation may arise from variation in the dosing frequency in the extended induction period. In some embodiments, the dosing frequency in the extended induction period is every 4 weeks and the end-of-extended induction assessment occurs 4 weeks after the last extended induction dose is administered. In such embodiments, if the patient achieves clinical response, the first maintenance dose may be administered at the end-of-induction assessment visit (that is, 4 weeks after administration of the last extended induction dose) or may be administered at

a subsequent visit scheduled to occur shortly thereafter. Alternatively, the dosing frequency in the extended induction period is every 8 weeks and the end-of-extended induction assessment occurs 8 weeks after the last extended induction dose is administered. If the patient has achieved clinical response, the first maintenance dose may be administered at the end-of-induction assessment visit (that is, 8 weeks after administration of the last extended induction dose) or may be administered at a subsequent visit scheduled to occur shortly thereafter. In such embodiments, the maintenance dose of mirikizumab is administered after the patient achieves a clinical response from the one, two, or three extended induction doses.

[0130] In a still further embodiment of the present invention,, if the patient develops a loss of response during the maintenance dosing (maintenance period),, rescue doses of mirikizumab are administered to the patient at 2-8 weeks after the last maintenance dose. In such embodiments, if the patient has a weight greater than 10 kg to less than or equal to 40 kg, a rescue dose of mirikizumab is administered to the patient at about 5 mg/kg to about 10 mg/kg. In some embodiments, the rescue dose of mirikizumab is administered at about 5mg/kg. In other embodiments, the rescue dose of mirikizumab is administered at about 10 mg/kg.

[0131] In some embodiments of the present invention, one, two or three rescue doses of mirikizumab are administered to the patient at 4-8 week intervals. In a still further embodiment, two or three rescue doses of mirikizumab are administered to the patient at 4-8 week intervals. In preferred embodiments of the present invention, three rescue doses of mirikizumab are administered to the patient at 4 week intervals.

[0132] In embodiments of the present invention, the rescue doses are administered by intravenous infusion.

[0133] In further embodiments of the present invention, if the patient achieves a clinical response 4-12 weeks after the one, two, or three rescue doses (rescue dosing period) maintenance doses of mirikizumab are administered to the patient. In such embodiments, maintenance doses are administered to the patient based on the weight and intervals as described herein above.

[0134] In such embodiments, a maintenance dose of mirikizumab is administered to the patient at about 50 mg to about 100 mg. In some embodiments, if the patient has a weight greater than 10 kg to less than or equal to 20 kg, a maintenance dose of mirikizumab is

administered to the patient at about 50 mg. In other embodiments, if the patient has a weight of greater than 20 kg to less than or equal to 40 kg, a maintenance dose of mirikizumab is administered to the patient at about 100 mg.

[0135] In such embodiments, a maintenance dose of mirikizumab is administered to the patient 2-8 weeks after the last rescue dose is administered to the patient. In preferred embodiments, the maintenance dose of mirikizumab is administered 2-6 weeks after the last rescue dose is administered. Further preferably, the maintenance dose is administered 2 weeks or 4 weeks after the last rescue dose is administered. In a still further embodiment, further maintenance doses of mirikizumab are administered to the patient at 4 or 8 week intervals. Preferably, maintenance doses are administered at 4 week intervals.

[0136] In particular embodiments, the maintenance doses of mirikizumab are administered to the patient for up to about 4 weeks, 8 weeks, 12 weeks, 16 weeks, 20 weeks, 24 weeks, 28 weeks, 32 weeks, 36 weeks, 40 weeks, 44 weeks, 48 weeks, 52 weeks, 56 weeks, 60 weeks, 64 weeks, 68 weeks, 72 weeks, 76 weeks, 80 weeks, 84 weeks, 88 weeks, 92 weeks, 96 weeks, or 104 weeks to up to about 152 weeks, after the last induction dose, the last extended induction dose, or the last rescue dose is administered. In certain embodiments, the maintenance doses are administered for up to about 1 year, 2 years, 3 years, or about 4 years.

[0137] In embodiments of the present invention, the patient achieves a therapeutic effect of at least one or more of clinical response, clinical remission, endoscopic remission, endoscopic improvement, symptomatic remission, symptomatic response, clinical remission without surgery, corticosteroid free clinical remission, histologic endoscopic mucosal remission, histologic-endoscopic mucosal improvement, bowel urgency remission, improvement in bowel urgency, improvement in stool frequency, improvement in rectal bleeding within about 2 weeks to about 48 weeks of treatment with mirikizumab. In such embodiments of the invention, at least one or more therapeutic effect is achieved within about 2 weeks, 4 weeks, 8 weeks, 12 weeks, 16, weeks, 20 weeks, 24 weeks, 28 weeks, 32 weeks, 36 weeks, 40 weeks, or 48 weeks of treatment with mirikizumab. Such therapeutic effect may be achieved in the induction period, the extended induction period, and/ or the rescue period. In certain embodiments, a therapeutic effect may be achieved in the maintenance period which may be the maintenance period after the induction period,

the maintenance period after the extended induction period, or the maintenance period after the rescue period.

[0138] In further embodiments of the invention, one or more of the therapeutic effects is sustained in the maintenance period.

[0139] In such embodiments, the therapeutic effect is sustained for up to about 4 weeks, 8 weeks, 12 weeks, 24 weeks, 28 weeks, 32 weeks, 36 weeks, 40 weeks, 44 weeks, 48 weeks, 52 weeks, 56 weeks, 60 weeks, 64 weeks, 68 weeks, 72 weeks, 76 weeks, 80 weeks, 84 weeks, 88 weeks, 92 weeks, 96 weeks, 104 weeks to up to about 152 weeks in the maintenance period after the end of the induction period, the extended induction period, or the rescue period.

[0140] In further embodiments, the patient has sustained clinical remission without surgery at Week 52 and no steroid use for at least 12 weeks prior to Week 52 of treatment with mirikizumab.

[0141] In such embodiments, the patient continues maintenance treatment with mirikizumab up until the patient becomes nonresponsive, has an inadequate response, loss of response, or is intolerant to mirikizumab.

[0142] In embodiments of the present invention an induction dose, extended induction, or rescue dose range of about 5 mg/kg to about 10 mg/kg can be about 5 mg/kg, 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg.

[0143] In embodiments of the invention, the patient is conventional-failed.

[0144] In other embodiments, the patient is biologic-naïve and or advanced therapy naïve.

[0145] In some embodiments, the patient is biologic-experienced and or advanced therapy experienced.

[0146] In some embodiments, the patient is biologic-failed and or advanced therapy failed.

[0147] In some embodiments, the patient is nonresponsive, has an inadequate response, loss of response, or is intolerant, to at least one prior treatment for ulcerative colitis.

[0148] In embodiments of the present invention, the biologic or advanced therapy is an anti-TNF therapeutic, and or an anti- $\alpha 4\beta 7$ therapeutic.

[0149] In some embodiments the advanced therapy is a JAK inhibitor, a S1P receptor modulator, or a TYK2 inhibitor.

[0150] In further embodiments, the patient is one or more of anti-TNF therapeutic failed, anti- $\alpha 4\beta 7$ therapeutic failed, JAK inhibitor failed, SIP receptor modulator failed, or TYK2 inhibitor failed.

[0151] In a further aspect of the present invention, provided herein are use of mirikizumab in the manufacture of a medicament for treating moderately to severely active ulcerative colitis (UC) in a patient in need thereof comprising,

administering three induction doses of mirikizumab to the patient at about 5 mg/kg or at about 10 mg/kg at 4 week intervals by intravenous infusion; and

administering maintenance doses of mirikizumab to the patient at about 50 mg, at 4 week intervals by subcutaneous injection, 2-8 weeks after the last induction dose is administered,

wherein the patient is 2 years to less than 18 years of age and has a weight of greater than 10 kg to less than or equal to 20 kg.

[0152] In a further aspect of the present invention, provided herein are uses of mirikizumab in the manufacture of a medicament for treating moderately to severely active ulcerative colitis (UC) in a patient in need thereof comprising,

administering maintenance doses of mirikizumab to the patient at about 100 mg, at 4 week intervals by subcutaneous injection, 2-8 weeks after the last induction dose is administered,

wherein the patient is 2 years to less than 18 years of age and has a weight of greater than 20 kg to less than or equal to 40 kg.

[0153] In such embodiments of the present invention, wherein if the patient has not achieved a clinical response at 4 to 12 weeks after the last induction dose is administered, three extended induction doses of mirikizumab are administered to the patient,

wherein, if the patient has a weight of greater than 10 kg to less than or equal to 40 kg, an extended induction dose of mirikizumab is administered to the patient at about 5 mg/kg or at about 10 mg/kg;

wherein, the extended induction doses of mirikizumab are administered to the patient at 4 week intervals by intravenous infusion.

[0154] In further embodiments, wherein if the patient achieves a clinical response at 4 to 12 weeks after the last extended induction dose is administered, maintenance doses of

mirikizumab are administered to the patient at 2-8 weeks after the last extended induction dose.

[0155] In such embodiments, wherein if the patient develops a loss of response during the maintenance dosing (maintenance period), one, two or three rescue doses of mirikizumab are administered to the patient,

wherein, if the patient has a weight of 10 kg to less than or equal to 40 kg, the rescue dose of mirikizumab is administered to the patient at about 5 mg/kg or at about 10 mg/kg;

wherein the rescue doses of mirikizumab are administered to the patient at 4 week intervals by intravenous infusion.

[0156] In such embodiments of the present invention, if the patient achieves a clinical response 4-12 weeks after the one, two, or three rescue doses, maintenance doses of mirikizumab are administered to the patient, at 4 week intervals by subcutaneous injection.

[0157] In further embodiments, the patient achieves a therapeutic effect of at least one or more of clinical response, clinical remission, endoscopic remission, endoscopic improvement, symptomatic remission, symptomatic response, clinical remission without surgery, corticosteroid free clinical remission, histologic endoscopic mucosal remission, histologic endoscopic mucosal improvement, bowel urgency remission, improvement in bowel urgency, improvement in stool frequency, improvement in rectal bleeding within about 2 weeks to about 48 weeks of treatment with mirikizumab.

[0158] In even further embodiments of the present invention, at least one or more therapeutic effect is achieved within about 2 weeks, 4 weeks, 8 weeks, 12 weeks, 16, weeks, 20 weeks, 24 weeks, 28 weeks, 32 weeks, 36 weeks, 40 weeks, or 48 weeks of treatment with mirikizumab. In such embodiments, at least one or more therapeutic effect is achieved in the induction period or the extended induction period.

[0159] In other embodiments, one or more of the therapeutic effects is sustained in the maintenance period. In such embodiments of the present invention, the therapeutic effect is sustained up to about 4 weeks, 8 weeks, 12 weeks, 24 weeks, 28 weeks, 32 weeks, 36 weeks, 40 weeks, 44 weeks, 48 weeks, 52 weeks, 56 weeks, 60 weeks, 64 weeks, 68 weeks, 72 weeks, 76 weeks, 80 weeks, 84 weeks, 88 weeks, 92 weeks, 96 weeks, 104

weeks to up to about 152 weeks in the maintenance period after the end of the induction period, the extended induction period, or the rescue period.

[0160] In particular embodiments, the patient has sustained clinical remission without surgery at Week 52 and no steroid use for at least 12 weeks prior to Week 52 of treatment with mirikizumab.

[0161] In some embodiments, the patient continues maintenance treatment with mirikizumab up until the patient becomes nonresponsive, has an inadequate response, loss of response, or is intolerant to mirikizumab.

[0162] In embodiments of the present invention, an induction dose, extended induction, or rescue dose range of about 5 mg/kg to about 10 mg/kg can be about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg.

[0163] In embodiments of the invention, the patient is conventional-failed.

[0164] In other embodiments, the patient is biologic-naïve and or advanced therapy naïve.

[0165] In some embodiments, the patient is biologic-experienced and or advanced therapy experienced.

[0166] In some embodiments, the patient is biologic-failed and or advanced therapy failed.

[0167] In some embodiments, the patient is nonresponsive, has an inadequate response, loss of response, or is intolerant, to at least one prior treatment for ulcerative colitis.

[0168] In some embodiments, the biologic or advanced therapy is an anti-TNF therapeutic, and or an anti- $\alpha 4\beta 7$ therapeutic.

[0169] In some embodiments the advanced therapy is a JAK inhibitor, a S1P receptor modulator, or a TYK2 inhibitor.

[0170] In further embodiments, the patient is one or more of anti-TNF therapeutic failed, anti- $\alpha 4\beta 7$ therapeutic failed, JAK inhibitor failed, S1P receptor modulator failed, or TYK2 inhibitor failed.

DETAILED DESCRIPTION OF THE INVENTION

[0171] Provided herein are methods, uses and pharmaceutical compositions of anti-IL23p19 antibodies, for treating moderately to severely active ulcerative colitis. Also provided herein are doses and dosing regimens for the methods and uses of IL-23p19

antibodies, for treating moderately to severely active ulcerative colitis in pediatric patients. UC is a form of colitis, an inflammatory disease of the intestine, usually the colon, which includes characteristic ulcers. Symptoms of active disease usually include diarrhea mixed with blood, usually accompanied with varying degrees of abdominal pain, from mild discomfort to severely painful cramps. Bowel urgency is also a common and disruptive symptom of ulcerative colitis (UC) and is distinct from stool frequency (SF) and rectal bleeding (RB).

[0172] There are a number of methods for assessing the severity of disease/ clinical metrics, including the Mayo Score, the Modified Mayo Score (MMS), Pediatric Ulcerative Colitis Disease Activity Index (PUCAI), Total Mayo Score, Mayo Endoscopic Subscore, Ulcerative Colitis Endoscopic Index of Severity (UCEIS) Total Score, Geboes Score, Roberts Histopathology Index (RHI) and combinations thereof.

[0173] The Mayo score is a composite instrument comprised of the following 4 subscores:

[0174] Stool Frequency (SF): The SF subscore is a patient-reported measure. This item reports the number of stools in a 24-hour period, relative to the normal number of stools for that patient in the same period, on a 4-point scale. A stool is defined as a trip to the toilet when the patient has either a bowel movement, or passes blood alone, blood and mucus, or mucus only. For a younger child, this includes each diaper change where stool is present. The total number of stools passed in a 24-hour period is recorded by the patient. The reference “normal” SF for that patient is typically recorded at the outset of a study or period of observation. Normal SF for that patient is based on the reported SF when the patient was in remission or, if the patient has never achieved remission, the reported SF before initial onset of signs and symptoms of UC.

<u>Stool Frequency Subscore</u>	<u>Score</u>
Normal number of stools per day for subject	0
1 to 2 stools per day more than normal	1
3 to 4 stools per day more than normal	2
5 or more stools per day more than normal	3

[0175] Rectal Bleeding: The RB subscore is a patient-reported measure. This item reports the most severe amount of blood passed per rectum for a given day, on a 4-point scale.

<u>Rectal Bleeding Subscore</u>	<u>Score</u>
---------------------------------	--------------

No blood seen	0
Streaks of blood with stool less than half of the time	1
Obvious blood (more than just streaks) or streaks of blood with stool most of the time	2
Blood alone passed	3

[0176] Endoscopic Subscore (ES): The ES is a physician-reported measure that reports the worst appearance of the mucosa on flexible sigmoidoscopy or colonoscopy, on a 4-point scale. Consistent with current clinical practice, friability is excluded from the definition of an ES of 1.

Endoscopic Subscore	Score
Normal or inactive disease	0
Mild disease (erythema, decreased vascular pattern)	1
Moderate disease (marked erythema, absent vascular pattern, friability, erosions)	2
Severe disease (spontaneous bleeding, ulceration)	3

[0177] Physician’s Global Assessment (PGA): The PGA is a physician-reported measure that summarizes the assessment of the patient’s UC disease activity on a 4-point scale.

Physician’s Global Assessment	Score
Normal	0
Mild disease	1
Moderate disease	2
Severe disease	3

Each subscore is scored on a 4-point scale, ranging from 0 to 3, to give a maximum Mayo score of 12.

[0178] The Modified Mayo Score or MMS is a modification made to the original Mayo Index reference (Schroeder *et al.*, New Eng J Med, 317(26):1625-1629, 1987) and includes 3 of the 4 subscores of the Mayo Score. It does not include the Physician’s Global Assessment. The MMS evaluates three subscores, each on a scale of 0 to 3 with a maximum total score of 9. Patients who have a Mayo Score of 6-12 or a MMS of 4-9, each with an ES of ≥ 2 , are defined as having moderate to severely active ulcerative colitis.

- [0179] The Mayo score ranges from 0 to 12, with higher scores indicating more severe disease. The partial Mayo score excludes endoscopy and ranges from 0 to 9, while the modified Mayo score excludes the Physician's Global Assessment and also ranges from 0 to 9. The original description of the Mayo score included friability in the definition of an endoscopic subscore of 1.
- [0180] Using the MMS, as used herein, "clinical remission" is defined as a RB subscore of 0, SF subscore of 0 or 1 and ES of 0 or 1 (excluding friability).
- [0181] Using the MMS, as used herein, "clinical response" is defined as achieving a decrease in the MMS subscore of ≥ 2 points and $\geq 30\%$ from baseline, and either a decrease in the RB subscore of ≥ 1 or a RB subscore of 0 or 1.
- [0182] Using the MMS, as used herein, "endoscopic remission" is defined as achieving a Mayo ES of 0. It may also be defined as achieving a Mayo ES of 0 or 1 (excluding friability).
- [0183] Using the MMS, as used herein, "endoscopic improvement" is defined as having achieved a Mayo ES of 0 or 1.
- [0184] "Histologic-endoscopic mucosal improvement (HEMI)" is defined as achieving both endoscopic improvement (centrally read endoscopy subscore of 0 or 1, excluding friability) and histologic improvement (neutrophil infiltration in $<5\%$ of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue based on the Geboes scoring system).
- [0185] "Histologic endoscopic mucosal remission (HEMR)" is defined as achieving both endoscopic remission and histologic remission (defined as Geboes histologic subscores of 0 for the neutrophils in lamina propria, neutrophils in epithelium, and erosion or ulceration parameters or defined as RHI score of ≤ 2).
- [0186] Using the MMS, as used herein "symptomatic remission" is defined as having achieved a SF subscore = 0 or SF subscore = 1 with a ≥ 1 -point decrease from baseline, and a RB subscore = 0.
- [0187] As used herein, "symptomatic response" is defined as $\geq 30\%$ decrease from baseline in composite clinical endpoint of the sum of SF and RB subscores.
- [0188] Using the MMS, as used herein, "loss of response" is defined as: ≥ 2 -point increase from end of induction/extended induction in the Partial Mayo scores on 2

consecutive visits ≥ 5 days apart with confirmation of negative *Clostridium difficile* testing

[0189] An alternate definition for 'loss of response' is defined as: (a) total Partial Mayo Score of ≥ 4 , and (b) PGA subscore of moderate disease or higher (≥ 2) on 2 consecutive visits ≥ 5 days apart with confirmation of negative *Clostridium difficile* testing.

[0190] "Corticosteroid free remission" as used herein is defined as clinical remission at Week 52 without surgery, and no corticosteroid use for ≥ 12 weeks prior to week 52.

[0191] The Pediatric Ulcerative Colitis Activity Index (PUCAI) (Turner et al, 2007) is a 6-item disease activity index intended for use in pediatric UC clinical trials that measures: abdominal pain, rectal bleeding, stool consistency of most stools, number of stools per 24 hours, nocturnal bowel movement (any Diarrhea Episode Causing Wakening), and activity level. All items are answered as an average over the "past 2 days". A total PUCAI disease activity score is calculated from 0 to 85. See Section 10.10 for the definition of disease severity according to the PUCAI:

<u>Abdominal Pain</u>	<u>Score</u>
No pain	0
pain can be ignored	5
pain cannot be ignored	10
<u>Rectal Bleeding</u>	<u>Score</u>
None	0
Small amount only, in less than 50% of stools	10
Small amount with most stools	20
Large amount (>50% of the stool content)	30
<u>Stool Consistency of Most Stools</u>	<u>Score</u>
Formed	0
Partially formed	5
Completely unformed	10
<u>Number of Stools per 24 Hours</u>	<u>Score</u>
0-2	0
3-5	5
6-8	10
>8	15

<u>Nocturnal Bowel Movement (Any Diarrhea Episode Causing Wakening)</u>	
No	0
Yes	10
<u>Activity Level</u>	
No limitation of activity	0
Occasional limitation of activity	5
Severe restricted activity	10
Sum of PUCAI	0-85

- [0192] Using PUCAI, “clinical remission” is defined as a reduction in baseline PUCAI score of ≥ 20 points; “clinical response” is defined as PUCAI score of < 10 points; mild disease activity is defined as PUCAI 10-30; moderate disease activity is defined as PUCAI 35-60; and severe disease activity is defined as PUCAI 65-85.
- [0193] The Ulcerative Colitis Endoscopic Index of Severity (UCEIS) is a central-reader-reported instrument for measuring the endoscopic disease activity of UC on colonoscopy, that includes 3 descriptors (scored on the most severe lesions): vascular pattern, bleeding, and erosions and ulcerations. The central reader will determine the UCEIS for each endoscopy in a blinded manner, as detailed in the Endoscopy Image Review charter.
- [0194] Bowel urgency is measured by a Uniform Numeric Rating Score (UNRS) to assess mean change of bowel urgency severity. Bowel urgency, a sudden or immediate need to have a bowel movement, is a common and burdensome symptom for patients with ulcerative colitis. UNRS is a patient-reported measure of bowel urgency in the past 24 hours using an 11-point scale, from 0 (no urgency) to 10 (worst possible urgency). UNRS score is recorded daily by patients in an eDiary. Change in UNRS from baseline is measured, through week 12, week 28, week 52, or up to about 104 weeks of treatment. Clinically meaningful “improvement in bowel urgency” or clinically meaningful change in bowel urgency severity is defined as the proportion of patients achieving both clinical response, based on the MMS and a UNRS score of ≥ 3 points of improvement from baseline. “Bowel urgency remission” is defined as minimal to no bowel urgency: UNRS [0,1], as assessed at Week 12, week 28, and timepoints thereafter (maintenance) in patients with baseline UNRS ≥ 3 .

- [0195] Other measure of improvement include, abdominal pain NRS, Fatigue NRS, Nocturnal stools, Patient's Global Impression of Change (PGI-C), Patient's Global Rating of Severity (PGR-S). Such measures are evaluated by the participant and or caregiver-reported outcomes.
- [0196] Change in health outcomes and quality of life measures are evaluated by change from baseline at Week 12 and Week 52 in IMPACT-III score, TUMMY-UC, and, or WPAI+CIQ:UC score.
- [0197] IMPACT-III as used herein, is a validated questionnaire that assesses disease-related health quality of life measures and well-being in participants who are ≥ 9 years of age with IBD. The questionnaire is self-administered and comprises 35 questions that cover the following domains: Bowel symptoms (7 items); Systemic symptoms (3 items); Emotional functioning (7 items); Social functioning (12 items); Body image (3 items); Tests and treatments (3 items). The recall period is 2 weeks and the questionnaire takes approximately 10 minutes to complete. The score ranges from 35 to 175, with higher scores suggesting better quality of life (Otley et al. 2002; Otley et al. 2006).
- [0198] The TUMMY-UC as used herein, is a series of questions aimed at capturing disease symptoms of importance to pediatric patients with UC. There are 2 versions of the TUMMY-UC: 1 for children 8 to 18 years of age and 1 for caregivers of children 2 to 7 years of age in which behaviors indicative of subjective concepts are scored rather than the concept directly (for example, caregivers are asked to score behaviors associated with pain rather than themselves scoring the degree of pain). Both the version for children 8 to 18 years and the one for caregivers of children contain 8 items that measure the following symptoms with a 24-hour recall period:
- Abdominal pain, Stool frequency, Most amount of rectal bleeding, Frequency of rectal bleeding, Bristol stool consistency chart, Weakness, Nocturnal stools, and Urgency.
- [0199] The WPAI+CIQ:UC as used herein, is a patient-reported instrument developed to measure the impact on work productivity and activity/classroom impairment attributable to a specific health problem during the past 7 days study in patients ≥ 12 years old. It contains 9 items that measure:
- percent work time missed due to UC (absenteeism), percent impairment while working due to UC (presenteeism), percent overall work impairment due to

UC (work productivity loss), percent class time missed due to UC, percent impairment in the classroom due to UC, percent regular activity (other than work or classes) impairment due to UC (activity impairment). Scores are calculated as impairment percentages (Reilly et al. 1993; 2008), with higher numbers indicating greater impairment and less productivity; that is, worse outcomes.

[0200] The Geboes Score as used herein, is comprised of seven categories (or grades), each of which describes a histologic item, including “structural (architectural change)” (grade 0), “chronic inflammatory infiltrate” (grade 1), “lamina propria eosinophils” (grade 2A), “lamina propria neutrophils” (grade 2B), “neutrophils in epithelium” (grade 3), “crypt destruction” (grade 4) and “surface epithelial injury” (grade 5). Each grade includes subscores that indicate the degree of abnormality seen for that histologic characteristic, with subscores of 0 indicating normal appearance and higher subscores indicating increasingly abnormal appearance. The RHI uses the weighted results from 4 Geboes score categories (“chronic inflammatory infiltrate”, “lamina propria neutrophils”, “neutrophils in epithelium” and “surface epithelial injury”) to derive a continuous score, ranging from 0 (no disease activity) to 33 (severe disease activity). The RHI was developed as a responsive instrument to detect treatment effects in early drug development.

[0201] As such as used herein, a “therapeutic effect” or response to treatment can be any one or more of, clinical response, clinical remission, endoscopic remission, histologic-endoscopic mucosal remission, symptomatic remission, histologic-endoscopic mucosal improvement, corticosteroid free remission, bowel urgency remission, improvement in bowel urgency, improvement in stool frequency, decrease in nocturnal stools, improvement in fatigue, improvement in abdominal pain, improvement in rectal bleeding, , and or improvement in other symptoms associated with ulcerative colitis.

[0202] “Sustained response” as used herein, is the percentage of patients who achieve a therapeutic effect during the maintenance period, among those patients that achieved a therapeutic effect in the induction period. For example, a sustained response as used herein, can be the percentage of patients who achieve clinical remission at week 52, among those patients who achieved clinical remission at week 12.

[0203] The “extended induction dose” as used herein is termed to distinguish from the initial induction dose if the patient does not achieve clinical response at the end of the

initial induction period. The extended induction doses are delivered during the extended induction period. The dose and dosing intervals during the extended induction period may be the same as the dose and dosing intervals of the initial induction period, but may be changed if the attending health care professional has reason to believe that the patient may benefit from changes such as an increased dose of the anti-IL-23p19 antibody or more frequent dosing. For example, the dose dosing intervals may be increased to the next dose level for the particular patient weight group and or may be administered at a more frequent dosing interval.

[0204] The “rescue dose” as used herein is a dose of an anti-IL-23p19 antibody administered to a patient in order to re-induce/re-achieve the clinical response and/ or other therapeutic effect achieved at the end of the induction period. the rescue doses are delivered during the rescued period. The rescue dose and dosing intervals during the rescue dosing period are typically the same as dose and dosing intervals during the initial induction period but may be changed if the attending health care professional has reason to believe that the patient may benefit from changes such as an increased dose of the anti-IL-23p19 antibody or more frequent dosing.

[0205] The term “inadequate response” as used herein refers to inability to achieve good disease control of ulcerative colitis after use of the treatment for the duration recommended by the product prescribing information, which occurs while on the treatment.

[0206] The term “intolerance” as used herein refers to unacceptable toxicity, or, and or improvement in other symptoms associated with ulcerative colitis.

[0207] As used herein, the term “biologic-naïve” used interchangeably or “bio-not failed” used interchangeably herein, and or “advanced therapy-naïve”, refers to patients that have not been administered a biologic or an advanced therapy, for example, an anti-TNF α antibody (e.g., adalimumab, golimumab, infliximab), anti-integrin antibody (e.g., vedolizumab), JAK inhibitor (e.g., tofacitinib, upadacitinib), TYK2 inhibitor, S1P receptor modulator (e.g., ozanimod), for the treatment of UC, in particular, for the treatment of moderate to severe UC. Biologic-naïve or advanced therapy naïve patients, also include patients who have an inadequate response to, loss of response to, or are intolerant to at least one of a corticosteroid or an immunomodulator. Intolerance to an

immunomodulator includes but not limited to nausea/vomiting, abdominal pain, pancreatitis, liver function test abnormalities, and lymphopenia.

[0208] As used herein, the term “biologic experienced” and or “advanced therapy experienced” refers to patients that have been administered at least one prior biologic or advanced therapy for the treatment of UC, which is not an anti-IL23p19 antibody, who have an inadequate response to, loss of response to, or are intolerant to the biologic therapy, such as for example, an anti-TNF α antibody (e.g., adalimumab, golimumab, infliximab), anti-integrin antibody (e.g., vedolizumab), JAK inhibitor (e.g., tofacitinib, upadacitinib), TYK2 inhibitor, S1P receptor modulator (e.g., ozanimod), in particular for the treatment of moderately to severely active UC. Such patients may or may not have been administered a conventional medicine for the treatment of UC. Inadequate response, include signs and symptoms of persistently active disease despite prescribed induction treatment.

[0209] As used herein, the term “biologic-failed” and or advanced therapy failed refers to patients that have been administered at least one prior biologic or advanced therapy for the treatment of UC, for example, an anti-TNF α antibody (e.g., adalimumab, golimumab, infliximab), anti-integrin antibody (e.g., vedolizumab), JAK inhibitor (e.g., tofacitinib, upadacitinib), TYK2 inhibitor, S1P receptor modulator (e.g., ozanimod), in particular for the treatment of moderately to severely active UC. Such patients may or may not have been administered a conventional therapy for the treatment of UC. Such patients have an inadequate response to, loss of response to, or are intolerant to biologic or advanced therapy for UC, which is not an anti-IL23p19 antibody. In the context of the terms biologic-failed or advanced therapy failed, inadequate response means signs and symptoms of persistently active disease despite induction treatment at the approved induction dosing that was indicated in the product label at the time of use. In the context of the term biologic-failed or advanced therapy failed, loss of response is defined as recurrence of signs and symptoms of active disease during maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify as having failed or being intolerant to UC biologic therapy). In the context of the term biologic-failed or advanced therapy failed, intolerance means a history of intolerance to for example, an anti-TNF- α antibody, anti-integrin antibody, JAK inhibitor, TYK2 inhibitor, S1P receptor modulator, examples of which include, infliximab, adalimumab,

golimumab, ustekinumab, vedolizumab, tofacitinib, upadacitinib, deucravacitinib, ozanimod, or other such approved therapies.

[0210] “Loss of response”, as used herein, includes recurrence of signs and symptoms of active disease during prescribed maintenance dosing following prior clinical benefit. Intolerance includes a history of intolerance to the biologic or advanced therapy, which includes, but not limited to infusion-related event, demyelination, congestive heart failure, or any other drug-related AE that led to a reduction in dose or discontinuation of the medication) or stopped taking a biologic for any other reason.

[0211] As used herein, the term “conventional-failed” refers to patients who have not been treated with a biologic previously and have an inadequate response to, loss of response to, or are intolerant to at least one of the following medications:

Corticosteroids

- Corticosteroid-refractory colitis is defined as signs or symptoms of active UC despite taking oral prednisone, or equivalent oral corticosteroid, at doses of ≥ 30 mg/day for ≥ 2 weeks.
- Corticosteroid-dependent colitis, defined as (a) an inability to taper or reduce corticosteroid dose below the equivalent of prednisone 10 mg/kg/day within 3 months of starting corticosteroids without a return of signs or symptoms of active UC, or (b) a relapse within ≤ 3 months of completing a course of corticosteroids.
- A history of intolerance of corticosteroids includes, but is not limited to, cataracts, Cushing’s syndrome, hyperglycemia, hypertension, osteopenia/osteoporosis, or neuropsychiatric side-effects, including insomnia.

Immunomodulators:

- signs and/or symptoms of persistently active disease despite ≥ 3 months treatment with one of the following:
 - oral AZA (≥ 1.5 mg/kg/day) or 6-MP (≥ 0.75 mg/kg/day)
 - oral AZA or 6-MP within a therapeutic range as judged by thioguanine metabolite testing, or
 - a combination of a thiopurine and allopurinol within a therapeutic range as judged by thioguanine metabolite testing

- A history of intolerance to at least one immunomodulator includes but is not limited to nausea/vomiting, abdominal pain, pancreatitis, liver function test abnormalities, and lymphopenia

Conventional-failed patients have neither failed nor demonstrated an intolerance to a biologic, (anti-TNF antibody or anti-integrin antibody) or JAK, S1P, or TYK2 inhibitor, that is indicated for the treatment of UC

[0212] The term “about” as used herein, means in reasonable vicinity of the stated numerical value, such as plus or minus 10% of the stated numerical value.

[0213] The term “antibody,” as used herein, refers to an immunoglobulin molecule that binds an antigen. Embodiments of an antibody include a monoclonal antibody, polyclonal antibody, human antibody, humanized antibody, chimeric antibody, or conjugated antibody. The antibodies can be of any class (e.g., IgG, IgE, IgM, IgD, IgA) and any subclass (e.g., IgG1, IgG2, IgG3, IgG4).

[0214] An exemplary antibody is an immunoglobulin G (IgG) type antibody comprised of four polypeptide chains: two heavy chains (HC) and two light chains (LC) that are cross-linked via inter-chain disulfide bonds. The amino-terminal portion of each of the four polypeptide chains includes a variable region of about 100-125 or more amino acids primarily responsible for antigen recognition. The carboxyl-terminal portion of each of the four polypeptide chains contains a constant region primarily responsible for effector function. Each heavy chain is comprised of a heavy chain variable region (VH) and a heavy chain constant region. Each light chain is comprised of a light chain variable region (VL) and a light chain constant region. The IgG isotype may be further divided into subclasses (e.g., IgG1, IgG2, IgG3, and IgG4).

[0215] The VH and VL regions can be further subdivided into regions of hyper-variability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). The CDRs are exposed on the surface of the protein and are important regions of the antibody for antigen binding specificity. Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxyl-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. Herein, the three CDRs of the heavy chain are referred to as “HCDR1, HCDR2, and HCDR3” and the three CDRs of the light chain are referred to as “LCDR1, LCDR2 and LCDR3”. The CDRs contain most of the residues that form specific

interactions with the antigen. Assignment of amino acid residues to the CDRs may be done according to the well-known schemes, including those described in Kabat (Kabat et al., "Sequences of Proteins of Immunological Interest," National Institutes of Health, Bethesda, Md. (1991)), Chothia (Chothia et al., "Canonical structures for the hypervariable regions of immunoglobulins", Journal of Molecular Biology, 196, 901-917 (1987); Al-Lazikani et al., "Standard conformations for the canonical structures of immunoglobulins", Journal of Molecular Biology, 273, 927-948 (1997)), North (North et al., "A New Clustering of Antibody CDR Loop Conformations", Journal of Molecular Biology, 406, 228-256 (2011)), or IMGT (the international ImMunoGeneTics database available on at www.imgt.org; see Lefranc et al., Nucleic Acids Res. 1999; 27:209-212). Assignment of amino acid residues to the CDRs may be done according to a combination of the schemes described above.

[0216] Embodiments of the present disclosure also include antibody fragments or antigen-binding fragments that, as used herein, comprise at least a portion of an antibody retaining the ability to specifically interact with an antigen or an epitope of the antigen, such as Fab, Fab', F(ab')₂, Fv fragments, scFv antibody fragments, scFab, disulfide-linked Fvs (sdFv), a Fd fragment.

[0217] As used herein "anti-IL-23p19 antibody" refers to an antibody that binds to the p19 subunit of human IL-23 but does not bind to the p40 subunit of human IL-23. An anti-IL-23p19 antibody thus binds to human IL-23 but does not bind to human IL-12. Examples of anti-IL23p19 antibodies include mirikizumab, guselkumab, tildrakizumab, risankizumab, and brazikumab.

[0218] Mirikizumab, CAS Registry No. 1884201-71-1, is a humanized, IgG4-kappa monoclonal antibody targeting the p19 subunit of human IL-23. The antibody and methods of making same are described in US Patent No. 9,023,358. Mirikizumab comprises the following heavy chain variable region (HCVR), light chain variable region (LCVR), heavy chain (HC), and light chain (LC) amino acid sequences:

- HCVR – SEQ ID NO: 1
- LCVR – SEQ ID NO: 2
- HC – SEQ ID NO: 3
- LC – SEQ ID NO: 4

Mirikizumab is particularly suitable for use in many aspects of the present invention.

[0219] The terms “bind” and “binds” as used herein are intended to mean, unless indicated otherwise, the ability of a protein or molecule to form a chemical bond or attractive interaction with another protein or molecule, which results in proximity of the two proteins or molecules as determined by common methods known in the art.

[0220] As used herein, “treatment” or “treating” refers to all processes wherein there may be a slowing, controlling, delaying, or stopping of the progression of the disorders or disease disclosed herein, or ameliorating disorder or disease symptoms, but does not necessarily indicate a total elimination of all disorder or disease symptoms. Treatment includes administration of a protein or nucleic acid or vector or composition for treatment of a disease or condition in a patient, particularly in a human.

EXAMPLES

[0221] **Example 1: A Multicenter, Open-Label PK Study of Mirikizumab in Pediatric Patients with Moderately to Severely Active Ulcerative Colitis**

[0222] Study AMBU is an open-label study to evaluate the safety, PK, pharmacodynamics, and clinical response to mirikizumab to establish induction and maintenance doses to evaluate in Phase 3, in children and adolescents with ulcerative colitis, aged 2 to less than 18 years. The study population includes pediatric patients with moderately to severely active UC, who have an inadequate response to, loss of response to, or are intolerant to non-biologic therapy for UC (biologic-naïve), and/or those who have been exposed to at least 1 biologic and/or JAK inhibitor therapy for UC (biologic/JAK inhibitor-experienced). Mirikizumab is also abbreviated as “Miri” herein.

[0223] ***Objectives and Endpoints:***

[0224] The following primary, secondary, and exploratory objectives and endpoints are evaluated for this study. Statistical analyses of the primary and key secondary endpoints are performed.

Table 1: Shows the Objectives and Endpoints of AMBU

Objectives	Endpoints
Primary	
To evaluate the pharmacokinetics (PK)	Clearance and volume of distribution of mirikizumab

Objectives	Endpoints
of mirikizumab treatment in pediatric patients	
Secondary	
To evaluate the effect of treatment with mirikizumab on achieving clinical remission at Week 12 and/or Week 52.	- The proportion of patients in modified Mayo score (MMS) clinical remission at Week 12 - The proportion of patients in MMS clinical remission at Week 52 - The proportion of patients in MMS clinical remission at Week 52 among the MMS clinical remitters at Week 12 (durable clinical remission) - The proportion of patients in MMS clinical remission at Week 52 among the MMS clinical responders from Week 12 MMS clinical remission is defined as: - Stool frequency (SF) subscore = 0, or SF = 1, and - Rectal bleeding (RB) subscore = 0, and - Endoscopic subscore (ES) = 0 or 1 (excluding friability) MMS clinical response is defined below
To evaluate the effect of treatment with mirikizumab on achieving clinical response at Week 12 and/or Week 52	- The proportion of patients in clinical response at Week 12 - The proportion of patients in clinical response at Week 52 - The proportion of patients in clinical response at Week 12 who achieve clinical response at Week 52 Clinical response is based on the MMS and is defined as: - A decrease in the MMS of ≥ 2 points and $\geq 30\%$ decrease from baseline, and - A decrease of ≥ 1 point in the RB subscore from baseline or a RB score of 0 or 1
To evaluate the effect of treatment with mirikizumab on achieving corticosteroid-free remission without	- The proportion of patients who are in MMS clinical remission at Week 52 without the use of corticosteroids Corticosteroid-free remission without surgery at Week 52 defined as: - Clinical remission at Week 52, and

Objectives	Endpoints
surgery among patients in clinical remission at Week 52 and receiving corticosteroids at baseline	No corticosteroid use or UC-related surgery for ≥ 12 weeks prior to Week 52
To evaluate the effect of treatment with mirikizumab on PUCAI clinical remission at Week 12 and/or Week 52	- The proportion of patients in PUCAI clinical remission at Week 12 - The proportion of patients in PUCAI clinical remission at Week 52 - The proportion of patients in PUCAI clinical remission at Week 12 who achieve clinical remission at Week 52 - The proportion of patients in PUCAI clinical response at Week 12 who achieve clinical remission at Week 52 PUCAI clinical remission is defined as a PUCAI score of < 10 points PUCAI clinical response is defined below
To evaluate the effect of treatment with mirikizumab on PUCAI clinical response at Week 12 and/or Week 52	- The proportion of patients in PUCAI clinical response at Week 12 - The proportion of patients in PUCAI clinical response at Week 52 - The proportion of patients in PUCAI clinical response at Week 12 who achieve PUCAI clinical response at Week 52 PUCAI clinical response is defined as a reduction in baseline PUCAI score of ≥ 20 points
To evaluate the effect of treatment with mirikizumab on achieving endoscopic remission at Week 12 and/or Week 52	- The proportion of patients in endoscopic remission at Week 12 - The proportion of patients in endoscopic remission at Week 52 - The proportion of patients in endoscopic remission at Week 12 who maintain endoscopic remission at Week 52 (durable endoscopic remission) Endoscopic remission is defined as: - ES = 0 or 1 (excluding friability)
To evaluate the effect of treatment with	- The proportion of patients with ES = 0 at Week 12 - The proportion of patients with ES = 0 at Week 52

Objectives	Endpoints
mirikizumab on achieving ES = 0 at Week 12 or Week 52	
To evaluate the effect of treatment with mirikizumab on symptomatic remission over time	- Proportion of patients in symptomatic remission at applicable study visits Symptomatic remission is defined as: - SF = 0, or SF = 1 with a ≥ 1-point decrease from baseline and - RB = 0
To evaluate the effect of treatment with mirikizumab on height velocity at Weeks 12, 24, and 52	Observed height velocity by gender and age group will be calculated at baseline, Week 12, Week 24, and Week 52
To evaluate the effect of treatment with mirikizumab on weight throughout the trial	Change from baseline in weight (kg) at all study visits by gender and age group
To evaluate the effect of treatment with mirikizumab on pubertal development throughout the trial in appropriate patient groups	Hormone levels and/or other related clinical measures will be evaluated
To evaluate the effect of treatment with mirikizumab on improving patient-reported outcome endpoints at Week 12 and Week 52	- Change from baseline in 7-day average of Abdominal Pain (in past 24 hours) NRS score at Week 12 and Week 52 - The proportion of patients with a NRS pain score ≥ 3 at baseline who achieve an improvement of $\geq 30\%$ from baseline in 7-day average abdominal pain NRS score at Week 12 and Week 52 - Change from baseline in Urgency NRS score at Week 12 and Week 52
To evaluate histologic-endoscopic mucosal remission following mirikizumab treatment at Week 12 or Week 52	- Proportion of patients with histologic-endoscopic mucosal remission at Week 12 - Proportion of patients with histologic-endoscopic mucosal remission at Week 52

Objectives	Endpoints
	Histologic-endoscopic mucosal remission is defined as achieving both histologic remission and endoscopic remission. Histologic remission will be defined in the SAP.
To evaluate the development of anti-mirikizumab antibodies and their effect on efficacy, safety, and mirikizumab exposure	Proportion of patients who have treatment-emergent anti-drug antibodies (TEADA)
Exploratory	
To evaluate the effect of treatment with mirikizumab on changes in biomarkers	- Change from baseline in fecal calprotectin - Change from baseline in C-reactive protein
To evaluate the loss of clinical response among responders to induction treatment during the maintenance period using MMS criteria	- During the maintenance period, loss of clinical response is defined as - An increase from the Week 12 Partial Mayo score of ≥ 2 points at 2 consecutive visits at least 5 days apart (with confirmation of negative C. difficile testing)
To evaluate the time to symptomatic response	Time to symptomatic response (defined as at least a 30% decrease from baseline in the composite clinical endpoint of the sum of SF and RB subscores)
To evaluate the time to symptomatic remission	Time to symptomatic remission (defined as SF = 0, or SF = 1 with a ≥ 1-point decrease from baseline, and RB = 0)
To evaluate the numerical value and change from baseline of individual MMS subscores and the composite symptom subscore over time in patients receiving mirikizumab	- The numerical value and change from baseline in each of the following items: - SF (Weeks 2, 4, 8, 12, 24, 36, and 52) - RB (Weeks 2, 4, 8, 12, 24, 36, and 52) - ES (Weeks 12 and 52) - The composite clinical endpoint of the sum of the SF and RB subscores (Weeks 2, 4, 8, 12, 24, 36, and 52)

Objectives	Endpoints
To evaluate the effect of treatment with mirikizumab on changes in urgency and abdominal pain NRS at Week 12	- Change from baseline in - Urgency NRS at Week 12 - Abdominal pain NRS at Week 12
To evaluate the effect of treatment with mirikizumab on reducing the proportion of emergency room visits for UC, hospitalizations for UC, and to undergo surgery for UC over the course of the study	- Proportion of patients who had UC related emergency room visits - Proportion of patients who had UC related hospitalizations - Proportion of patients who had UC related surgeries
To evaluate the effect of treatment with mirikizumab on improving patient-reported outcome endpoints at Week 52	- Proportion of patients with the following at Week 52 - Improvement of symptoms on PGI-C score - Change from baseline at Week 52 in the following: - PGRS score - Bristol Stool Scale score - Nocturnal stool - Fatigue NRS score
To evaluate the relationship between mirikizumab exposure and efficacy	Relationship between mirikizumab exposure and clinical response, clinical remission, histologic-endoscopic mucosal remission, and change in the MMS at Weeks 12 and 52
To evaluate the effect of treatment with mirikizumab on UCEIS at Week 12 or Week 52.	The proportion of patients with an Ulcerative Colitis Endoscopic Index of Severity (UCEIS) score of ≤ 1 at Week 12 or at Week 52

Abbreviations: NRS – numeric rating scale; PGI-C – Patient’s Global Impression of Change; PGRS = Patient’s Global Rating of Severity; PUCAI = Pediatric Ulcerative Colitis Activity Index; SAP = statistical analysis plan; UC = ulcerative colitis.

[0225] **Study Design:**

[0226] Patients weighing >40 kg will receive a mirikizumab induction dose of 300 mg via IV infusion and patients weighing ≤ 40 kg will receive induction doses of 5 mg/kg or 10 mg/kg via IV infusion at Weeks 0, 4, and 8. Enrollment will begin with the 300 mg and 5 mg/kg

dose cohorts. Patients in the 10 mg/kg cohort will be enrolled after 5 patients in the 5 mg/kg dose cohort have received 4 weeks of mirikizumab, an evaluation of the available PK in the 5 mg/kg cohort has been conducted, and enrollment of the 5 mg/kg dose cohort has been filled.

[0227] Patients who achieve a Modified Mayo Score (MMS) clinical response at Week 12 will proceed to the maintenance period and receive SC doses of 200 mg (weight >40 kg), or 100 mg (weight >20 kg to ≤40 kg), or 50 mg (weight ≤20 kg) mirikizumab Q4W through Week 48

[0228] Patients who do not meet the MMS clinical response definition at Week 12 may receive extended IV induction dosing (either at the same dose or for the 5 mg/kg dose cohort, escalate to the 10 mg/kg dose) for 12 more weeks or discontinue. Following the completion of IV dosing at Week 24, if the investigator determines that the patient has improved, the patient will proceed to the maintenance period and receive Q4W SC doses based on weight class through Week 48. If the investigator determines that sufficient improvement was not made, the patient will discontinue study drug and undergo procedures for early termination of the study drug, including post-treatment follow-up as described in the Schedule of Activities.

[0229] Upon completion of the maintenance period (Week 52), all patients will have the option to enter the 3-year long-term extension Study I6T-MC-AMAZ (AMAZ) or enter the post-treatment follow-up period (12 weeks if last dose was administered SC or 16 weeks if last dose was administered IV).

Table 2: Mirikizumab doses based on the participant’s weight.

Patient Weight	Induction dose, frequency and route of administration	Extended Induction or Rescue dose, frequency and route of administration	Maintenance dose, frequency and route of administration
>10 kg ≤20 kg	mirikizumab 5 mg/kg IV Q4W X3, or mirikizumab 10 mg/kg IV Q4W X3,	mirikizumab 5 mg/kg IV Q4W X3, or mirikizumab 10 mg/kg IV Q4W X3,	mirikizumab 50 mg SC Q4W
>20 to ≤40 kg	mirikizumab 5 mg/kg IV Q4W X3, or mirikizumab 10 mg/kg IV Q4W X3,	mirikizumab 5 mg/kg IV Q4W X3, or mirikizumab 10 mg/kg IV Q4W X3,	mirikizumab 100 mg SC Q4W
>40 kg	mirikizumab 300 mg IV Q4W X3,	300 mg IV Q4W X3,	mirikizumab 200 mg SC Q4W

[0230] ***Inclusion Criteria:***

[0231] patients eligible for inclusion in this trial must fulfil all of the following criteria:

1. Male or female patients weighing >10 kg AND ≥ 2 and <18 years of age at the time of informed consent.
2. Have an established diagnosis of UC of ≥ 3 months in duration before baseline, which includes endoscopic evidence of UC corroborated by a histopathology report.
3. Have moderately to severely active UC as defined by a MMS of 4 to 9 with an ES ≥ 2 within 14 days before first dose of study treatment (baseline).
4. Have evidence of UC extending proximal to the rectum involving the distal sigmoid colon.
5. Prior Medication Failure Criteria: Patients must have an inadequate response to, loss of response to, or intolerance to at least 1 of the medications described. Documentation of dose, frequency, route of administration, and duration of the prior failed treatment is required.
 - a. Biologic-naïve patients: Patients who have an inadequate response to, loss of response to, or are intolerant to at least 1 of the following medications:
 - Corticosteroids
 - Corticosteroid-refractory colitis, defined as signs and/or symptoms of active UC despite a 2-week course of oral prednisone at a dose or equivalent of ≥ 0.75 mg/kg/day or a 2-week course of oral prednisone at a dose of ≥ 40 mg/day; or
 - Corticosteroid-dependent colitis, defined as:
 - a. an inability to taper corticosteroids without a return of signs and/or symptoms of active UC; or
 - b. a relapse within 3 months of completing a course of corticosteroids; or
 - History of intolerance of corticosteroids (which includes evidence of a side effect sufficiently serious as to precluding continued treatment with corticosteroids including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, growth delay, or neuropsychiatric side-effects, including insomnia, associated with corticosteroid treatment).
 - Immunomodulators:
 - Signs and/or symptoms of persistently active disease despite at least 3 months' treatment with 1 of the following:

- Oral AZA (≥ 1 mg/kg/day) or 6-MP (≥ 0.5 mg/kg/day), or
- Oral AZA or 6-MP within a therapeutic range as judged by thioguanine metabolite testing, or
- A combination of a thiopurine and allopurinol within a therapeutic range as judged by thioguanine metabolite testing, or
- MTX, either alone or in combination with another therapy.
- History of intolerance to at least 1 immunomodulator (including but not limited to nausea/vomiting, abdominal pain, pancreatitis, liver function test abnormalities, and lymphopenia).

Discontinuation despite clinical benefit does not qualify as having failed or being intolerant to UC non-biologic therapy.

- b. Biologic/JAK inhibitor-experienced patients: Patients who have an inadequate response to, loss of response to, or are intolerant to biologic therapy for UC (such as anti-TNF antibodies or anti-integrin antibodies) and/or to JAK inhibitors (such as tofacitinib), as described below. Investigators must document an adequate trial of the medication. Patients should fulfill at least 1 of the following criteria:
- Inadequate response: Signs and symptoms of persistently active disease despite prescribed induction treatment, or
 - Loss of response: Recurrence of signs and symptoms of active disease during prescribed maintenance dosing following prior clinical benefit, or
 - Intolerance: History of intolerance to infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, or other biologics or JAK inhibitors (including but not limited to infusion-related event, demyelination, congestive heart failure, or any other drug-related AE that led to a reduction in dose or discontinuation of the medication), or
 - Stopped taking a biologic for any other reason.

Discontinuation despite clinical benefit does not qualify as having an inadequate response to or being intolerant to UC biologic or JAK inhibitor therapy.

6. Dose Stabilization Inclusion Criteria: Are on stable doses of the following permitted drugs:
- Oral 5-ASA compounds: if the prescribed dose has been stable for at least 2 weeks before screening endoscopy.

- Oral corticosteroid therapy (prednisone 0.5 mg/kg/day up to 30 mg/day or equivalent): if the prescribed dose has been stable for at least 1 week before the screening endoscopy.
- AZA, 6-MP, and MTX: if these immunomodulators have been prescribed at a stable dose for at least 8 weeks before the screening endoscopy.

[0232] **Results: Interim Analysis for AMBU following 12 Week Induction Period and 40 Week Maintenance Period**

[0233] PK, efficacy, and safety analysis in 26 pediatric participants (≤40 kg (n=15), and >40 kg (n=11), with moderately to severely active UC from the Phase 2 Study AMBU, following a 12-week induction period was conducted. Participants were assessed at Week 12 and, or at Week 52 for clinical response, clinical remission, and endoscopic remission and were monitored for safety throughout the trial. For pediatric patients >40 kg, the observed and PK model-estimated exposures were similar to adults treated with 300 mg mirikizumab IV Q4W. No new safety findings were identified compared to the prior induction study (AMAN) conducted in adult patients with moderate to severe ulcerative colitis.

- [0234] At the interim data cut-off:
- 20 participants were ongoing or had completed treatment, of whom:
 - 11 had completed 52 weeks of treatment, and
 - 9 were receiving ongoing treatment, and
 - 6 participants had discontinued treatment during the Maintenance Period, including
 - 1 participant in the >40 kg 300 mg mirikizumab group due to an adverse event of worsening of UC
 - 1 participant in the ≤ 40 kg 5 mg/kg mirikizumab group due to lack of efficacy, and
 - 4 participants in the > 40 kg 300 mg mirikizumab group due to lack of efficacy.

Table 3. summarizes the baseline characteristics of the patients.

[0235] **Table 3: Summary of Baseline Demographics at Interim Analysis (Week 12)**

	≤40 kg 5 mg/kg IV N=10	≤40 kg 10 mg/kg IV N=5	>40 kg 300 mg IV N=11	Total N=26
Sex, n (%)				
Female	6 (60.0)	3 (60.0)	6 (54.5)	15 (57.7)
Male	4 (40.0)	2 (40.0)	5 (45.5)	11 (42.3)
Mean Age, years (SD)	9.6 (4.22)	11.6 (1.14)	14.0 (1.26)	11.8 (3.37)
Age Category, n (%)				
2 to < 8 years	3 (30.0)	0	0	3 (11.5)
8 to < 12 years	2 (20.0)	2 (40.0)	0	4 (15.4)
12 to <18 years	5 (50.0)	3 (60.0)	11 (100.0)	19 (73.1)
Weight category, n (%)				
≤20 kg	2 (20.0)	0	0	2 (7.7)
>20 to ≤40 kg	8 (80.0)	5 (100.0)	0	13 (50.0)
>40 kg	0	0	11 (100.0)	11 (42.3)
Race, n (%)				
Asian	4 (40.0)	2 (40.0)	1 (10.0)	7 (28.0)
White	5 (50.0)	3 (60.0)	9 (90.0)	17 (68.0)
Multiple	1 (10.0)	0	0	1 (4.0)
Ethnicity, n (%)				
Hispanic/Latino	3 (60.0)	0	0	3 (18.8)
Non-hispanic/non-latino	2 (40.0)	3 (100.0)	8 (100.0)	13 (81.3)

Abbreviations: BMI = body mass index; IV = intravenous; miri = mirikizumab; N = number of participants in the analysis population; n = number of participants within each specific category; SD = standard deviation.

[0236] ***Efficacy Endpoints Analysis***

[0237] As demonstrated in Table 4, the interim analysis induction efficacy endpoints at Week 12 showed that the pediatric patients across the weight and dose ranges achieved clinically meaningful improvement in Clinical Response, Clinical Remission and Endoscopic Remission as measured by MMS and PUCAI. While maintenance efficacy data is available for less than half the patients at Week 52 due to the interim data cut, the 9 patients summarized in Table 5 also demonstrated clinically meaningful improvement in Clinical Response, Clinical Remission and Endoscopic Remission as measured by MMS and PUCAI. Furthermore, no significant new safety findings were observed. The benefit-risk balance was considered favorable.

[0238] **Table 4: Study AMBU Induction Period Efficacy Endpoints at Week 12**

	≤40 kg 5 mg/kg miri IV N=10	≤40 kg 10 mg/kg miri IV N=5	>40 kg 300 mg miri IV N=11	Total N=26
MMS Clinical Remission				
Response, n (%), NRI	5 (50.0)	1 (20.0)	4 (36.4)	10 (38.5)
95% CI ^a	(23.7, 76.3)	(3.6, 62.4)	(15.2, 64.6)	(22.4, 57.5)
MMS Clinical Response				
Response, n (%), NRI	8 (80.0)	5 (100.0)	5 (45.5)	18 (69.2)
95% CI ^a	(49.0, 94.3)	(56.6, 100)	(21.3, 72.0)	(50.0, 83.5)
Endoscopic Remission^b				
Response, n (%), NRI	6 (60.0)	3 (60.0)	5 (45.5)	14 (53.8)
95% CI ^a	(31.3, 83.2)	(23.1, 88.2)	(21.3, 72.0)	(35.5, 71.2)
PUCAI Clinical Remission				
Response, n (%), NRI	6 (60.0)	0 (0.0)	4 (36.4)	10 (38.5)
95% CI ^a	(31.3, 83.2)	(0.0, 43.4)	(15.2, 64.6)	(22.4, 57.5)
PUCAI Clinical Response				
Response, n (%), NRI	9 (90.0)	4 (80.0)	7 (63.6)	20 (76.9)
95% CI ^a	(59.6, 98.2)	(37.6, 96.4)	(35.4, 84.8)	(57.9, 89.0)
Symptomatic Remission				
Response, n (%), NRI	6 (60.0)	2 (40.0)	4 (36.4)	12 (46.2)
95% CI ^a	(31.3, 83.2)	(11.8, 76.9)	(15.2, 64.6)	(28.8, 64.5)
Histologic-Endoscopic Mucosal Improvement				
Response, n (%), NRI	1 (10.0)	1 (20.0)	2 (18.2)	4 (15.4)
95% CI ^a	(1.8, 40.4)	(3.6, 62.4)	(5.1, 47.7)	(6.2, 33.5)
Histologic-Endoscopic Mucosal Remission				
Response, n (%), NRI	0 (0.0)	0 (0.0)	1 (9.1)	1 (3.8)
95% CI ^a	(0.0, 27.8)	(0.0, 43.4)	(1.6, 37.7)	(0.7, 18.9)
Alternate MMS Clinical Remission^c				
Response, n (%), NRI	5 (50.0)	1 (20.0)	3 (27.3)	9 (34.6)
95% CI ^a	(23.7, 76.3)	(3.6, 62.4)	(9.7, 56.6)	(19.4, 53.8)

Abbreviations: IV = intravenous; miri = mirikizumab; MMS = modified Mayo score; N = number of participants in the analysis population; n = number of participants within each specific category; PUCAI = pediatric ulcerative colitis activity index.

a. Response confidence intervals are constructed using Wilson method, without continuity correction.

b. Endoscopic remission defined as MMS endoscopic subscore = 0 or 1 (excluding friability)

c. Alternate MMS clinical remission is defined as SF subscore = 0, or SF = 1 with a ≥1-point decrease from baseline, and RB subscore = 0, and ES subscore = 0 or 1 (excluding friability).

[0239] **Table 5: Study AMBU Maintenance Period Efficacy Endpoints at Week 52**
(Limited dataset available at the Interim Analysis)

	≤20 kg 50 mg miri SC N=1	>20 kg and ≤40 kg 100 mg miri SC N=1	>40 kg 200 mg miri SC N=7	Total N=9
MMS Clinical Remission				
Response, n (%), NRI	0 (0.0)	1 (100.0)	5 (71.4)	6 (66.7)
95% CI ^a	(0.0, 79.3)	(20.7, 100)	(35.9, 91.8)	
MMS Clinical Response				
Response, n (%), NRI	0 (0.0)	1 (100.0)	6 (85.7)	7 (77.8)
95% CI ^a	(0.0, 79.3)	(20.7, 100)	(48.7, 97.4)	
Endoscopic Remission^b				
Response, n (%), NRI	0 (0.0)	0 (0.0)	5 (71.4)	5 (55.6)
95% CI ^a	(0.0, 79.3)	(0.0, 79.3)	(35.9, 91.8)	
PUCAI Clinical Remission				
Response, n (%), NRI	0 (0.0)	1 (100.0)	6 (85.7)	7 (77.8)
95% CI ^a	(0.0, 79.3)	(20.7, 100)	(48.7, 97.4)	
PUCAI Clinical Response				
Response, n (%), NRI	0 (0.0)	1 (100.0)	6 (85.7)	7 (77.8)
95% CI ^a	(0.0, 79.3)	(20.7, 100)	(48.7, 97.4)	

Abbreviations: IV = intravenous; miri = mirikizumab; MMS = modified Mayo score; N = number of participants in the analysis population; n = number of participants within each specific category; PUCAI = pediatric ulcerative colitis activity index.

- a. Response confidence intervals are constructed using Wilson method, without continuity correction.
- b. Endoscopic remission defined as MMS endoscopic subscore = 0 or 1 (excluding friability)

[0240] **Results: Final Analysis for AMBU at Week 52**

[0241] Table 6 summarizes key demographic and baseline disease characteristics collected at AMBU baseline) for the mITT population. Overall, demographic and disease characteristics were well balanced across the treatment groups and consistent with a population with moderately to severely active UC (Walsh et al. 2014; Peyrin-Biroulet et al. 2016). Note, the safety population in Study AMBU is the same as the mITT population.

[0242] **Table 6: Study AMBU Summary of Demographics and Other Baseline Characteristics (mITT population)**

Parameter	Induction Treatment			
	5 mg/kg Miri IV	10 mg/kg	300 mg Miri IV	Total (N = 26)

		(N = 10)	Miri IV (N = 5)	(N = 11)	
Demographics characteristics					
Age (years), mean (SD)		9.6 (4.2)	11.6 (1.1)	14.0 (1.3)	11.8 (3.4)
Age category (years), n (%)	2 to <8	3 (30.0)	0	0	3 (11.5)
	8 to <12	2 (20.0)	2 (40.0)	0	4 (15.4)
	≥12	5 (50.0)	3 (60.0)	11 (110.0)	19 (73.1)
Sex, n (%)	Female	6 (60.0)	3 (60.0)	6 (54.5)	15 (57.7)
	Male	4 (40.0)	2 (40.0)	5 (45.5)	11 (42.3)
Race, n (%)	Asian	4 (40.0)	2 (40.0)	1 (10.0)	7 (28.0)
	White	5 (50.0)	3 (60.0)	9 (90.0)	17 (68.0)
	Multiple	1 (10.0)	0	0	1 (4.0)
Weight (kg), mean (SD)		28.6 (9.0)	33.0 (2.4)	54.7 (13.3)	40.5 (16.0)
Weight category (kg), n (%)	≤20	2 (20.0)	0	0	2 (7.7)
	>20 and ≤40	8 (80.0)	5 (100.0)	0	13 (50.0)
	>40	0	0	11 (100.0)	11 (42.3)
BMI (kg/m ²), mean (SD)		15.8 (2.3)	17.0 (0.6)	21.1 (5.0)	18.3 (4.3)
Baseline disease characteristics					
Baseline MMS, mean (SD)		6.4 (1.3)	6.6 (0.6)	6.2 (1.3)	6.3 (1.2)
Baseline MMS category, n (%)	Moderate (4-6) ^a	7 (70.0)	2 (40.0)	6 (54.5)	15 (57.7)
	Severe (7-9)	3 (30.0)	3 (60.0)	5 (45.5)	11 (42.3)
Duration of UC (years), mean (SD)		1.3 (1.1)	3.1 (3.5)	2.4 (2.1)	2.1 (2.2)
Baseline PUCAI, n (%)	Mild (10-30)	1 (10.0)	0	0	1 (3.8)
	Moderate (35-60)	4 (40.0)	4 (80.0)	8 (72.7)	16 (61.5)
	Severe (65-85)	5 (50.0)	1 (20.0)	3 (27.3)	9 (34.6)
Baseline Rectal Bleeding Mayo Subscore, n (%)	0	0	1 (20.0)	1 (9.1)	2 (7.7)
	1	3 (30.0)	0	3 (27.3)	6 (23.1)

	2	5 (50.0)	3 (60.0)	6 (54.5)	14 (53.8)
	3	2 (20.0)	1 (20.0)	1 (9.1)	4 (15.4)
Baseline Stool Frequency Mayo Subscore, n (%)	0	0	1 (20.0)	0	1 (3.8)
	1	3 (30.0)	0	2 (18.2)	5 (19.2)
	2	4 (40.0)	1 (20.0)	6 (54.5)	11 (42.3)
	3	3 (30.0)	3 (30.0)	3 (27.3)	9 (34.6)
Baseline C-reactive protein (µg/g), mean (SD)		2.6 (4.8)	6.1 (8.1)	3.6 (3.8)	3.7 (5.1)
Baseline Fecal Calprotectin (µg/g), mean (SD)		4952.0 (5128.4)	2829.0 (1466.3)	3962.9 (5698.4)	4097.6 (4782.4)

Abbreviations: IV = intravenous; kg = kilogram; mg = milligram; miri = mirikizumab; MMS = modified Mayo score; N = number of patients in the analysis population; n = number of patients in the specified category; PUCAI = Pediatric Ulcerative Colitis Activity Index; SD = standard deviation; UC = ulcerative colitis.

a. Study inclusion criteria classified moderate disease severity as an MMS of 4-6; whereas currently the criterion has been revised to an MMS of 5 to 6. In this study, 1 of the 26 participants had a baseline MMS of 4, all others (96%) had a baseline MMS of 5 or greater.

[0243] Table 7 provides the Week 52 efficacy data from Study AMBU. Consistent with induction data noting clinically meaningful changes in efficacy endpoints at Week 12, further improvement in the efficacy endpoints of Clinical Remission, Clinical Response, Endoscopic Remission and Symptomatic Remission was observed at Week 52. At Week 52 among Week 12 responders 10/18 (55.6%) patients were in clinical remission by MMS, endoscopic remission and also in corticosteroid-free remission. Further, PUCAI response and remission rates were 77.8 and 72.2% at Week 52, respectively. Lastly, among the Week 12 clinical responders, 50% of pediatric participants met criteria for Histologic- Endoscopic Mucosal Remission at Week 52.

[0244] **Table 7: Study AMBU Week 52 Efficacy Data Among Week 12 Clinical Responders**

Measure n (%)^a	≤40 kg 50 mg Miri SC (N = 1)	≤40 kg 100 mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	Total (N = 18)
MMS Clinical Remission ^b	0	5 (62.5)	5 (55.6)	10 (55.6)
MMS Clinical Response ^c	0	6 (75.0)	8 (88.9)	14 (77.8)
PUCAI Clinical Remission ^d	0	6 (75.0)	7 (77.8)	13 (72.2)
PUCAI Clinical Response ^e	0	6 (75.0)	8 (88.9)	14 (77.8)

Corticosteroid-Free Clinical Remission ^f	0	5 (62.5)	5 (55.6)	10 (55.6)
Endoscopic Remission ^g	0	5 (62.5)	5 (55.6)	10 (55.6)
Endoscopic Subscore of 0	0	4 (50.0)	2 (22.2)	6 (33.3)
Symptomatic Remission ^h	0	6 (75.0)	6 (66.7)	12 (66.7)
Histologic-Endoscopic Mucosal Improvement ⁱ	0	5 (62.5)	4 (44.4)	9 (50.0)
Histologic-Endoscopic Mucosal Remission ^j	0	5 (62.5)	4 (44.4)	9 (50.0)
Alternate MMS Clinical Remission ^k	0	5 (62.5)	4 (44.4)	9 (50.0)

Abbreviations: CI = confidence interval; mITT = modified intent-to-treat; IV = intravenous; Miri = mirikizumab; N = number of patients in the mITT Population; n = number of patients within each specific category; NRI = nonresponder imputation; PUCAI = Pediatric Ulcerative Colitis Disease Activity Index.

Note: Patients who experience loss of response and receive rescue dosing during the maintenance period are defined and imputed as non-responders at Week 52.

a. Percentage of response is calculated by $n/N \times 100\%$

b. Clinical remission is defined as: SF subscore = 0, or SF = 1, and RB subscore = 0; and ES = 0 or 1 (excluding friability)

c. Clinical response is defined as: a decrease in the MMS of ≥ 2 points and $\geq 30\%$ decrease from baseline, and a decrease of ≥ 1 point in the RB subscore from baseline or a RB score of 0 or 1

d. PUCAI clinical remission is defined as: a PUCAI score of < 10 points

e. PUCAI clinical response is defined as: a reduction in baseline PUCAI score of ≥ 20 points

f. Corticosteroid-Free Clinical Remission is defined as: MMS clinical remission at Week 52 and no corticosteroid use or UC-related surgery for ≥ 12 weeks prior to Week 52

g. Endoscopic remission is defined as: ES = 0 or 1 (excluding friability)

h. Symptomatic remission is defined as: SF = 0, or SF = 1 with ≥ 1 point decrease from baseline, and RB = 0

i. Histologic-endoscopic mucosal improvement is defined as: achieving both histologic improvement and endoscopic improvement.

j. Histologic-endoscopic mucosal remission is defined as: achieving both histologic remission and endoscopic remission.

k. Alternate MMS Clinical remission is defined as: SF subscore = 0, or SF = 1 with a ≥ 1 -point decrease from baseline, and RB subscore = 0, and ES subscore = 0 or 1 (excluding friability).

[0245] Tables 8 through 25 provide subgroup analyses in prior biologic-failed and biologic not failed pediatric participants at Week 52 for key efficacy endpoints.

Modified Mayo Score Clinical Remission at Week 52: Clinical Remission by Subgroup
(Prior Biologic failure category)

A total of 29.4% of participants among the biologic failed subgroup and 55.6% of participants among the biologic not failed subgroup achieved clinical remission at Week 52 (Table 8).

Table 8. Clinical Remission at Week 52 by Subgroup (NRI; mITT Population)

	≤20 kg 50mg Miri SC (N = 1)	>20 kg and ≤40kg 100mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10mg/kg Miri IV/50 mg Miri SC non- responder (N = 1)	>20kg and ≤40kg 10mg/kg Miri IV/100 mg Miri SC non- responder (N = 0)	>40 kg 300 mg Miri IV/200 mg Miri SC non-responder (N = 0)	Total (N = 26)
Failed (Ns)	1	5	5	1	0	5	17
Response, n (%) ^a	0 (0.0)	3 (60.0)	2 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (29.4)
95% CI ^b	(0.0, 79.3)	(23.1, 88.2)	(11.8, 76.9)	(0.0, 79.3)	(0.0, 0.0)	(0.0, 43.4)	(13.3, 53.1)
Not Failed (Ns)	0	3	4	0	1	1	9
Response, n (%) ^a	0 (0.0)	2 (66.7)	3 (75.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (55.6)
95% CI ^b	(0.0, 0.0)	(20.8, 93.9)	(30.1, 95.4)	(0.0, 0.0)	(0.0, 79.3)	(0.0, 79.3)	(26.7, 81.1)

Abbreviations: CI = confidence interval; mITT = modified intent-to-treat; SC = subcutaneous; IV = intravenous; Miri = mirikizumab; N = number of patients in the mITT Population; n = number of patients within each specific category; NRI = nonresponder imputation; kg = kilogram; mg = milligram; Ns = number of patients in each subgroup.
a. Percentage of response is calculated by n/Ns*100%.
b. Response confidence intervals are constructed using Wilson method, without continuity correction.

[0246] **Clinical Remission at Week 52 among the Induction Clinical Responders by Subgroup (Prior Biologic failure category)**

Among the induction clinical responders (n=18), a total of 45.5% of participants among the biologic failed subgroup and 71.4% of participants among the biologic not failed subgroup achieved clinical remission at Week 52 (Table 9).

Table 9. Clinical Remission at Week 52 by Subgroup (NRI; mITT Population Induction Clinical Responders)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	Total (N = 18)
Failed (Ns)	1	5	5	11
Response, n (%) ^a	0 (0.0)	3 (60.0)	2 (40.0)	5 (45.5)
95% CI ^b	(0.0, 79.3)	(23.1, 88.2)	(11.8, 76.9)	(21.3, 72.0)
Not Failed (Ns)	0	3	4	7
Response, n (%) ^a	0 (0.0)	2 (66.7)	3 (75.0)	5 (71.4)
95% CI ^b	(0.0, 0.0)	(20.8, 93.9)	(30.1, 95.4)	(35.9, 91.8)

Abbreviations: kg = kilogram; miri = mirikizumab; mg = milligram; SC = subcutaneous; CI = confidence interval; N = number of patients in the analysis population; n = number of patients in the specified category; NRI = nonresponder imputation; Ns = number of patients in each subgroup.

a. Percentage of response is calculated by $n/Ns \times 100\%$.

b. Response confidence intervals are constructed using Wilson method, without continuity correction.

[0247] **MMS Clinical Response at Week 52 Clinical Response by Subgroup (Prior Biologic failure category)**

A total of 41.2% of participants among the biologic failed subgroup and 77.8% of participants among the biologic not failed subgroup achieved clinical response at Week 52 (see Table 10).

Table 10. Clinical Response at Week 52 by Subgroup (NRI; mITT Population)

	≤20 kg 50mg Miri SC (N = 1)	>20 kg and ≤40kg 100mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10mg/kg Miri IV/50 mg Miri SC non- responder (N = 1)	>20kg and ≤40kg 10mg/kg Miri IV/100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/200 mg Miri SC non- responder (N = 6)	Total (N = 26)
Failed (Ns)	1	5	5	1	0	5	17
Response, n (%) ^a	0 (0.0)	3 (60.0)	4 (80.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (41.2)
95% CI ^b	(0.0, 79.3)	(23.1, 88.2)	(37.6, 96.4)	(0.0, 79.3)	(0.0, 0.0)	(0.0, 43.4)	(21.6, 64.0)

	≤20 kg 50mg Miri SC (N = 1)	>20 kg and ≤40kg 100mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10mg/kg Miri IV/50 mg Miri SC non- responder (N = 1)	>20kg and ≤40kg 10mg/kg Miri IV/100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/200 mg Miri SC non- responder (N = 6)	Total (N = 26)
Not Failed (Ns)	0	3	4	0	1	1	9
Response, n (%) ^a	0 (0.0)	3 (100.0)	4 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (77.8)
95% CI ^b	(0.0, 0.0)	(43.9, 100)	(51.0, 100)	(0.0, 0.0)	(0.0, 79.3)	(0.0, 79.3)	(45.3, 93.7)

Abbreviations: CI = confidence interval; mITT = modified intent-to-treat; SC = subcutaneous; IV = intravenous; Miri = mirikizumab; N = number of patients in the mITT Population; n = number of patients within each specific category; NRI = nonresponder imputation; kg = kilogram; mg = milligram; Ns = number of patients in each subgroup

a. Percentage of response is calculated by $n/Ns \times 100\%$

b. Response confidence intervals are constructed using Wilson method, without continuity correction

**[0248] Clinical Response at Week 52 among Induction Clinical Responders by Subgroup
(Prior Biologic failure category)**

Among the induction clinical responders (n=18), a total of 63.6% of participants among the biologic failed subgroup and 100.0% of participants among the biologic not failed subgroup achieved clinical response at Week 52 (see Table 11).

Table 11. Clinical Response at Week 52 by Subgroup (NRI; mITT Population Induction Clinical Responders)

	≤20 kg 50mg Miri SC (N = 1)	>20 kg and ≤40kg 100mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	Total (N = 18)
Failed (Ns)	1	5	5	11
Response, n (%) ^a	0 (0.0)	3 (60.0)	4 (80.0)	7 (63.6)
95% CI ^b	(0.0, 79.3)	(23.1, 88.2)	(37.6, 96.4)	(35.4, 84.8)
Not Failed (Ns)	0	3	4	7
Response, n (%) ^a	0 (0.0)	3 (100.0)	4 (100.0)	7 (100.0)

	≤20 kg 50mg Miri SC (N = 1)	>20 kg and ≤40kg 100mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	Total (N = 18)
95% CI ^b	(0.0, 0.0)	(43.9, 100)	(51.0, 100)	(64.6, 100)

Abbreviations: kg = kilogram; miri = mirikizumab; mg = milligram; SC = subcutaneous; CI = confidence interval; N = number of patients in the analysis population; n = number of patients in the specified category; NRI = nonresponder imputation; Ns = number of patients in each subgroup

a. Percentage of response is calculated by $n/Ns \times 100\%$

b. Response confidence intervals are constructed using Wilson method, without continuity correction

[0249] **PUCAI Clinical Remission at Week 52 by Subgroup (Prior Biologic Failure Category)**

A total of 35.3% of participants among the biologic failed subgroup and 77.8% of participants among the biologic not failed subgroup achieved clinical remission at Week 52 (see Table 12).

Table 12. AMBU PUCAL Clinical Remission at Week 52 by Subgroup (NRI; mITT Population)

	≤20 kg 50mg Miri SC (N = 1)	>20 kg and ≤40kg 100mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10mg/kg Miri IV/50 mg Miri SC non-responder (N = 1)	>20kg and ≤40kg 10mg/kg Miri IV/100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/200 mg Miri SC non-responder (N = 6)	Total (N = 26)
Failed (Ns)	1	5	5	1	0	5	17
Response, n (%) ^a	0 (0.0)	3 (60.0)	3 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (35.3)
95% CI ^b	(0.0, 79.3)	(23.1, 88.2)	(23.1, 88.2)	(0.0, 79.3)	(0.0, 0.0)	(0.0, 43.4)	(17.3, 58.7)
Not Failed (Ns)	0	3	4	0	1	1	9
Response, n (%) ^a	0 (0.0)	3 (100.0)	4(100)	0 (0.0)	0 (0.0)	0 (0.0)	7(77.8)
95% CI ^b	(0.0, 0.0)	(43.9, 100)	(51.0, 100)	(0.0, 0.0)	(0.0, 79.3)	(0.0, 79.3)	(45.3, 93.7)

Abbreviations: CI = confidence interval; mITT = modified intent-to-treat; SC = subcutaneous; IV = intravenous; Miri = mirikizumab; N = number of patients in the mITT Population; n = number of patients within each specific category; NRI = nonresponder imputation; kg = kilogram; mg = milligram; Ns = number of patients in each subgroup

a. Percentage of response is calculated by $n/Ns \times 100\%$

b. Response confidence intervals are constructed using Wilson method, without continuity correction

[0250] PUCAI Clinical Response by Subgroup (Prior Biologic Failure Category)

A total of 41.2% of participants among the biologic failed subgroup and 77.8% of participants among the biologic not failed subgroup achieved PUCAI clinical response at Week 52 (see Table 13).

Table 13: AMBU PUCAI Clinical Response at Week 52 by Subgroup (NRI; mITT Population)

	≤20 kg 50mg Miri SC (N = 1)	>20 kg and ≤40kg 100mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10mg/kg Miri IV/50 mg Miri SC non- responder (N = 1)	>20kg and ≤40kg 10mg/kg Miri IV/100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/200 mg Miri SC non- responder (N = 6)	Total (N = 26)
Failed (Ns)	1	5	5	1	0	5	17
Response, n (%) ^a	0 (0.0)	3 (60.0)	4 (80.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (41.2)
95% CI ^b	(0.0, 79.3)	(23.1, 88.2)	(37.6, 96.4)	(0.0, 79.3)	(0.0, 0.0)	(0.0, 43.4)	(21.6, 64.0)
Not Failed (Ns)	0	3	4	0	1	1	9
Response, n (%) ^a	0 (0.0)	3 (100.0)	4 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (77.8)
95% CI ^b	(0.0, 0.0)	(43.9, 100)	(51.0, 100)	(0.0, 0.0)	(0.0, 79.3)	(0.0, 79.3)	(45.3, 93.7)

Abbreviations: CI = confidence interval; mITT = modified intent-to-treat; SC = subcutaneous; IV = intravenous; Miri = mirikizumab; N = number of patients in the mITT Population; n = number of patients within each specific category; NRI = nonresponder imputation; kg = kilogram; mg = milligram; Ns = number of patients in each subgroup

a. Percentage of response is calculated by $n/Ns \times 100\%$

b. Response confidence intervals are constructed using Wilson method, without continuity correction

[0251] Corticosteroid-Free Remission by Subgroup (Prior Biologic Failure Category)

A total of 29.4% of participants among the biologic failed subgroup and 55.6% of participants among the biologic not failed subgroup achieved corticosteroid-free clinical remission at Week 52 (see Table 14).

Table 14. Corticosteroid-Free Remission at Week 52 by Subgroup (NRI; mITT Population)

	≤20 kg 50mg Miri SC (N = 1)	>20 kg and ≤40kg 100mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10mg/kg Miri IV/50 mg Miri SC non-responder (N = 1)	>20kg and ≤40kg 10mg/kg Miri IV/100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/200 mg Miri SC non-responder (N = 6)	Total (N = 26)
Failed (Ns)	1	5	5	1	0	5	17
Response, n (%) ^a	0 (0.0)	3 (60.0)	2 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (29.4)
95% CI ^b	(0.0, 79.3)	(23.1, 88.2)	(11.8, 76.9)	(0.0, 79.3)	(0.0, 0.0)	(0.0, 43.4)	(13.3, 53.1)
Not Failed (Ns)	0	3	4	0	1	1	9
Response, n (%) ^a	0 (0.0)	2 (66.7)	3 (75.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (55.6)
95% CI ^b	(0.0, 0.0)	(20.8, 93.9)	(30.1, 95.4)	(0.0, 0.0)	(0.0, 79.3)	(0.0, 79.3)	(26.7, 81.1)

Abbreviations: CI = confidence interval; mITT = modified intent-to-treat; SC = subcutaneous; IV = intravenous; Miri = mirikizumab; N = number of patients in the mITT Population; n = number of patients within each specific category; NRI = nonresponder imputation; kg = kilogram; mg = milligram; Ns = number of patients in each subgroup

a. Percentage of response is calculated by $n/Ns \times 100\%$

b. Response confidence intervals are constructed using Wilson method, without continuity correction

[0252] Endoscopic Remission at Week 52 by Subgroup (Prior Biologic Failure Category)

A total of 29.4% of participants among the biologic failed subgroup and 55.6% of participants among the biologic not failed subgroup achieved endoscopic remission at Week 52 (see Table 15).

Table 15. Endoscopic Remission at Week 52 by Subgroup (NRI; mITT Population)

	≤20 kg 50mg Miri SC (N = 1)	>20 kg and ≤40kg 100mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10mg/kg Miri IV/50 mg Miri SC non- responder (N = 1)	>20kg and ≤40kg 10mg/kg Miri IV/100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/200 mg Miri SC non- responder (N = 6)	Total (N = 26)
Failed (Ns)	1	5	5	1	0	5	17
Response, n (%) ^a	0 (0.0)	3 (60.0)	2 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (29.4)
95% CI ^b	(0.0, 79.3)	(23.1, 88.2)	(11.8, 76.9)	(0.0, 79.3)	(0.0, 0.0)	(0.0, 43.4)	(13.3, 53.1)
Not Failed (Ns)	0	3	4	0	1	1	9
Response, n (%) ^a	0 (0.0)	2 (66.7)	3 (75.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (55.6)
95% CI ^b	(0.0, 0.0)	(20.8, 93.9)	(30.1, 95.4)	(0.0, 0.0)	(0.0, 79.3)	(0.0, 79.3)	(26.7, 81.1)

Abbreviations: CI = confidence interval; mITT = modified intent-to-treat; SC = subcutaneous; IV = intravenous; Miri = mirikizumab; N = number of patients in the mITT Population; n = number of patients within each specific category; NRI = nonresponder imputation; kg = kilogram; mg = milligram; Ns = number of patients in each subgroup

a. Percentage of response is calculated by $n/Ns \times 100\%$

b. Response confidence intervals are constructed using Wilson method, without continuity correction

[0253] **Endoscopic Remission at Week 52 among the Induction Endoscopic****Remitters by Subgroup (Prior Biologic Failure Category)**

Among the induction endoscopic remitters (n=14), a total of 55.6% of participants among the biologic failed subgroup and 80.0% of participants among the biologic not failed subgroup achieved endoscopic remission at Week 52 (see Table 16).

Table 16. Endoscopic Remission at Week 52 by Subgroup (NRI; mITT Population - Induction Endoscopic Remitters)

	≤20 kg 50mg Miri SC (N = 1)	>20 kg and ≤40kg 100mg Miri SC (N = 6)	>40 kg 200 mg Miri SC (N = 6)	≤20 kg 10mg/kg Miri IV/50 mg Miri SC non- responder (N = 0)	>20kg and ≤40kg 10mg/kg Miri IV/100 mg Miri SC non-responder (N = 0)	>40 kg 300 mg Miri IV/200 mg Miri SC non- responder (N = 1)	Total (N = 14)
Failed (Ns)	1	4	3	0	0	1	9
Response, n (%) ^a	0 (0.0)	3 (75.0)	2 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	5 (55.6)
95% CI ^b	(0.0, 79.3)	(30.1, 95.4)	(20.8, 93.9)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 79.3)	(26.7, 81.1)
Not Failed (Ns)	0	2	3	0	0	0	5
Response, n (%) ^a	0 (0.0)	1 (50.0)	3 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (80.0)
95% CI ^b	(0.0, 0.0)	(9.5, 90.5)	(43.9, 100)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(37.6, 96.4)

Abbreviations: kg = kilogram; miri = mirikizumab; mg = milligram; SC = subcutaneous; CI = confidence interval; N = number of patients in the analysis population; n = number of patients in the specified category; NRI = nonresponder imputation; Ns = number of patients in each subgroup

a. Percentage of response is calculated by $n/Ns \times 100\%$

b. Response confidence intervals are constructed using Wilson method, without continuity correction

[0254] **Endoscopic Subscore (ES) = 0 at Week 52 by Subgroup (Prior Biologic Failure Category)**

A total of 17.6% of participants among the biologic failed subgroup and 33.3% of participants among the biologic not failed subgroup achieved endoscopic subscore of 0 at Week 52 (Table 17).

Table 17. Endoscopic Subscore 0 at Week 52 by Subgroup (NRI; mITT Population)

	≤20 kg 50mg Miri SC (N = 1)	>20 kg and ≤40kg 100mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10mg/kg Miri IV/50 mg Miri SC non- responder (N = 1)	>20kg and ≤40kg 10mg/kg Miri IV/100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/200 mg Miri SC non- responder (N = 6)	Total (N = 26)
<i>Failed (Ns)</i>	1	5	5	1	0	5	17
Response, n (%) ^a	0 (0.0)	2 (40.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (17.6)
95% CI ^b	(0.0, 79.3)	(11.8, 76.9)	(3.6, 62.4)	(0.0, 79.3)	(0.0, 0.0)	(0.0, 43.4)	(6.2, 41.0)
<i>Not Failed (Ns)</i>	0	3	4	0	1	1	9
Response, n (%) ^a	0 (0.0)	2 (66.7)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (33.3)
95% CI ^b	(0.0, 0.0)	(20.8, 93.9)	(4.6, 69.9)	(0.0, 0.0)	(0.0, 79.3)	(0.0, 79.3)	(12.1, 64.6)

Abbreviations: CI = confidence interval; mITT = modified intent-to-treat; SC = subcutaneous; IV = intravenous; Miri = mirikizumab; N = number of patients in the mITT Population; n = number of patients within each specific category; NRI = nonresponder imputation; kg = kilogram; mg = milligram; Ns = number of patients in each subgroup

a. Percentage of response is calculated by $n/Ns \times 100\%$

b. Response confidence intervals are constructed using Wilson method, without continuity correction

[0255] **Symptomatic Remission During the Maintenance Period at Week 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52**

The proportion of patients in symptomatic remission at applicable study visits increased from baseline at all applicable visits during the maintenance period. The NRI analysis

showed that a total of 14 (53.8%) participants were in symptomatic remission at Week 20 and the proportion of patients achieving symptomatic remission remained relatively stable at all the following applicable visits. A total of 12 (46.2%) participants were in symptomatic remission at Week 52 (Table 18).

Table 18. Symptomatic Remission by Visit in Maintenance (NRI; mITT Population)

		≤20 kg 50mg Miri SC (N = 1)	>20 kg and ≤40kg 100mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10mg/kg Miri IV/50 mg Miri SC non- responder (N = 1)	>20kg and ≤40kg 10mg/kg Miri IV/100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/200 mg Miri SC non- responder (N = 6)	Total (N = 26)
Week 16	Response, n (%)	0 (0.0)	5 (62.5)	6 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	11 (42.3)
	95% CI ^a	(0.0, 79.3)	(30.6, 86.3)	(35.4, 87.9)	(0.0, 79.3)	(0.0, 79.3)	(0.0, 39.0)	(25.5, 61.1)
Week 20	Response, n (%)	0 (0.0)	7 (87.5)	7 (77.8)	0 (0.0)	0 (0.0)	0 (0.0)	14 (53.8)
	95% CI ^a	(0.0, 79.3)	(52.9, 97.8)	(45.3, 93.7)	(0.0, 79.3)	(0.0, 79.3)	(0.0, 39.0)	(35.5, 71.2)
Week 24	Response, n (%)	0 (0.0)	5 (62.5)	6 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	11 (42.3)
	95% CI ^a	(0.0, 79.3)	(30.6, 86.3)	(35.4, 87.9)	(0.0, 79.3)	(0.0, 79.3)	(0.0, 39.0)	(25.5, 61.1)
Week 28	Response, n (%)	0 (0.0)	5 (62.5)	6 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	11 (42.3)
	95% CI ^a	(0.0, 79.3)	(30.6, 86.3)	(35.4, 87.9)	(0.0, 79.3)	(0.0, 79.3)	(0.0, 39.0)	(25.5, 61.1)
Week 32	Response, n (%)	0 (0.0)	6 (75.0)	6 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	12 (46.2)
	95% CI ^a	(0.0, 79.3)	(40.9, 92.9)	(35.4, 87.9)	(0.0, 79.3)	(0.0, 79.3)	(0.0, 39.0)	(28.8, 64.5)
Week 36	Response, n (%)	0 (0.0)	5 (62.5)	7 (77.8)	0 (0.0)	0 (0.0)	0 (0.0)	12 (46.2)
	95% CI ^a	(0.0, 79.3)	(30.6, 86.3)	(45.3, 93.7)	(0.0, 79.3)	(0.0, 79.3)	(0.0, 39.0)	(28.8, 64.5)
Week 52	Response, n (%)	0 (0.0)	6 (75.0)	7 (77.8)	0 (0.0)	0 (0.0)	0 (0.0)	13 (50.0)

		≤20 kg 50mg Miri SC (N = 1)	>20 kg and ≤40kg 100mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10mg/kg Miri IV/50 mg Miri SC non- responder (N = 1)	>20kg and ≤40kg 10mg/kg Miri IV/100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/200 mg Miri SC non- responder (N = 6)	Total (N = 26)
	95% CI ^a	(0.0, 79.3)	(40.9, 92.9)	(45.3, 93.7)	(0.0, 79.3)	(0.0, 79.3)	(0.0, 39.0)	(32.1, 67.9)
Week 44	Response, n (%)	0 (0.0)	6 (75.0)	6 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	12 (46.2)
	95% CI ^a	(0.0, 79.3)	(40.9, 92.9)	(35.4, 87.9)	(0.0, 79.3)	(0.0, 79.3)	(0.0, 39.0)	(28.8, 64.5)
Week 48	Response, n (%)	0 (0.0)	6 (75.0)	7 (77.8)	0 (0.0)	0 (0.0)	0 (0.0)	13 (50.0)
	95% CI ^a	(0.0, 79.3)	(40.9, 92.9)	(45.3, 93.7)	(0.0, 79.3)	(0.0, 79.3)	(0.0, 39.0)	(32.1, 67.9)
Week 52	Response, n (%)	0 (0.0)	6 (75.0)	6 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	12 (46.2)
	95% CI ^a	(0.0, 79.3)	(40.9, 92.9)	(35.4, 87.9)	(0.0, 79.3)	(0.0, 79.3)	(0.0, 39.0)	(28.8, 64.5)

Abbreviations: CI = confidence interval; mITT = modified intent-to-treat; IV = intravenous; Miri = mirikizumab; N = number of patients in the mITT Population; n = number of patients within each specific category; NRI = nonresponder imputation; SC = subcutaneous.

a. Response confidence intervals are constructed using Wilson method, without continuity correction

[0256] Symptomatic Remission at Week 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 by Subgroup (Prior Biologic Failure Category)

The proportion of participants among the biologic failed subgroup in symptomatic remission increased from baseline at all applicable visits and remained relatively stable from Week 16 until Week 52 (n=6 [35.3%]). The proportion of participants among the biologic not failed subgroup in symptomatic remission increased from baseline at all applicable visits and remained relatively stable from Week 16 until Week 52 (n=6 [66.7%]) (Table 19).

Table 19: Symptomatic Remission at each Visit by Subgroup, Biologic Failure Subgroup (NRI; mITT Population)

		≤20 kg 50mg Miri SC (N = 1)	>20 kg and ≤40kg 100mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10mg/kg Miri IV/50 mg Miri SC non- responder (N = 1)	>20kg and ≤40kg 10mg/kg Miri IV/100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/200 mg Miri SC non- responder (N = 6)	Total (N = 26)
Week 16	Failed (Ns)	1	5	5	1	0	5	17
	Response, n (%) ^a	0 (0.0)	2 (40.0)	3 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (29.4)
	95% CI ^b	(0.0, 79.3)	(11.8, 76.9)	(23.1, 88.2)	(0.0, 79.3)	(0.0, 0.0)	(0.0, 43.4)	(13.3, 53.1)
	Not Failed (Ns)	0	3	4	0	1	1	9
	Response, n (%) ^a	0 (0.0)	3 (100.0)	3 (75.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (66.7)
	95% CI ^b	(0.0, 0.0)	(43.9, 100)	(30.1, 95.4)	(0.0, 0.0)	(0.0, 79.3)	(0.0, 79.3)	(35.4, 87.9)
Week 20	Failed (Ns)	1	5	5	1	0	5	17
	Response, n (%) ^a	0 (0.0)	4 (80.0)	3 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (41.2)
	95% CI ^b	(0.0, 79.3)	(37.6, 96.4)	(23.1, 88.2)	(0.0, 79.3)	(0.0, 0.0)	(0.0, 43.4)	(21.6, 64.0)
	Not Failed (Ns)	0	3	4	0	1	1	9
	Response, n (%) ^a	0 (0.0)	3 (100.0)	4 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (77.8)
	95% CI ^b	(0.0, 0.0)	(43.9, 100)	(51.0, 100)	(0.0, 0.0)	(0.0, 79.3)	(0.0, 79.3)	(45.3, 93.7)
Week 24	Failed (Ns)	1	5	5	1	0	5	17
	Response, n (%) ^a	0 (0.0)	2 (40.0)	3 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (29.4)
	95% CI ^b	(0.0, 79.3)	(11.8, 76.9)	(23.1, 88.2)	(0.0, 79.3)	(0.0, 0.0)	(0.0, 43.4)	(13.3, 53.1)
	Not Failed (Ns)	0	3	4	0	1	1	9
	Response, n (%) ^a	0 (0.0)	3 (100.0)	3 (75.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (66.7)
	95% CI ^b	(0.0, 0.0)	(43.9, 100)	(30.1, 95.4)	(0.0, 0.0)	(0.0, 79.3)	(0.0, 79.3)	(35.4, 87.9)
Week 24	Failed (Ns)	1	5	5	1	0	5	17

	Response, n (%) ^a	0 (0.0)	2 (40.0)	3 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (29.4)
	95% CI ^b	(0.0, 79.3)	(11.8, 76.9)	(23.1, 88.2)	(0.0, 79.3)	(0.0, 0.0)	(0.0, 43.4)	(13.3, 53.1)
	Not Failed (Ns)	0	3	4	0	1	1	9
	Response, n (%) ^a	0 (0.0)	3 (100.0)	3 (75.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (66.7)
	95% CI ^b	(0.0, 0.0)	(43.9, 100)	(30.1, 95.4)	(0.0, 0.0)	(0.0, 79.3)	(0.0, 79.3)	(35.4, 87.9)
Week 32	Failed (Ns)	1	5	5	1	0	5	17
	Response, n (%) ^a	0 (0.0)	3 (60.0)	3 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (35.3)
	95% CI ^b	(0.0, 79.3)	(23.1, 88.2)	(23.1, 88.2)	(0.0, 79.3)	(0.0, 0.0)	(0.0, 43.4)	(17.3, 58.7)
	Not Failed (Ns)	0	3	4	0	1	1	9
	Response, n (%) ^a	0 (0.0)	3 (100.0)	3 (75.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (66.7)
	95% CI ^b	(0.0, 0.0)	(43.9, 100)	(30.1, 95.4)	(0.0, 0.0)	(0.0, 79.3)	(0.0, 79.3)	(35.4, 87.9)
Week 36	Failed (Ns)	1	5	5	1	0	5	17
	Response, n (%) ^a	0 (0.0)	2 (40.0)	3 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (29.4)
	95% CI ^b	(0.0, 79.3)	(11.8, 76.9)	(23.1, 88.2)	(0.0, 79.3)	(0.0, 0.0)	(0.0, 43.4)	(13.3, 53.1)
	Not Failed (Ns)	0	3	4	0	1	1	9
	Response, n (%) ^a	0 (0.0)	3 (100.0)	4 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (77.8)
	95% CI ^b	(0.0, 0.0)	(43.9, 100)	(51.0, 100)	(0.0, 0.0)	(0.0, 79.3)	(0.0, 79.3)	(45.3, 93.7)
Week 40	Failed (Ns)	1	5	5	1	0	5	17
	Response, n (%) ^a	0 (0.0)	3 (60.0)	3 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (35.3)
	95% CI ^b	(0.0, 79.3)	(23.1, 88.2)	(23.1, 88.2)	(0.0, 79.3)	(0.0, 0.0)	(0.0, 43.4)	(17.3, 58.7)
	Not Failed (Ns)	0	3	4	0	1	1	9
	Response, n (%) ^a	0 (0.0)	3 (100.0)	4 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (77.8)
	95% CI ^b	(0.0, 0.0)	(43.9, 100)	(51.0, 100)	(0.0, 0.0)	(0.0, 79.3)	(0.0, 79.3)	(45.3, 93.7)
Week 44	Failed (Ns)	1	5	5	1	0	5	17

	Response, n (%) ^a	0 (0.0)	3 (60.0)	3 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (35.3)
	95% CI ^b	(0.0, 79.3)	(23.1, 88.2)	(23.1, 88.2)	(0.0, 79.3)	(0.0, 0.0)	(0.0, 43.4)	(17.3, 58.7)
	Not Failed (Ns)	0	3	4	0	1	1	9
	Response, n (%) ^a	0 (0.0)	3 (100.0)	3 (75.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (66.7)
	95% CI ^b	(0.0, 0.0)	(43.9, 100)	(30.1, 95.4)	(0.0, 0.0)	(0.0, 79.3)	(0.0, 79.3)	(35.4, 87.9)
Week 48	Failed (Ns)	1	5	5	1	0	5	17
	Response, n (%) ^a	0 (0.0)	3 (60.0)	3 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (35.3)
	95% CI ^b	(0.0, 79.3)	(23.1, 88.2)	(23.1, 88.2)	(0.0, 79.3)	(0.0, 0.0)	(0.0, 43.4)	(17.3, 58.7)
	Not Failed (Ns)	0	3	4	0	1	1	9
	Response, n (%) ^a	0 (0.0)	3 (100.0)	4 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (77.8)
	95% CI ^b	(0.0, 0.0)	(43.9, 100)	(51.0, 100)	(0.0, 0.0)	(0.0, 79.3)	(0.0, 79.3)	(45.3, 93.7)
Week 52	Failed (Ns)	1	5	5	1	0	5	17
	Response, n (%) ^a	0 (0.0)	3 (60.0)	3 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (35.3)
	95% CI ^b	(0.0, 79.3)	(23.1, 88.2)	(23.1, 88.2)	(0.0, 79.3)	(0.0, 0.0)	(0.0, 43.4)	(17.3, 58.7)
	Not Failed (Ns)	0	3	4	0	1	1	9
	Response, n (%) ^a	0 (0.0)	3 (100.0)	3 (75.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (66.7)
	95% CI ^b	(0.0, 0.0)	(43.9, 100)	(30.1, 95.4)	(0.0, 0.0)	(0.0, 79.3)	(0.0, 79.3)	(35.4, 87.9)

Abbreviations: CI = confidence interval; mITT = modified intent-to-treat; IV = intravenous; Miri = mirikizumab; N = number of patients in the mITT Population; n = number of patients within each specific category; NRI = nonresponder imputation; kg = kilogram; mg = milligram; Ns = number of patients in each subgroup; SC = subcutaneous.

a. Percentage of response is calculated by $n/Ns \times 100\%$

b. Response confidence intervals are constructed using Wilson method, without continuity correction

[0257] **Histologic-Endoscopic Mucosal Improvement at Week 52 by Subgroup (Prior Biologic Failure Category)**

Five (29.4%) participants among the biologic failed subgroup and 4 (44.4%) participants in the not failed subgroup achieved histologic-endoscopic mucosal improvement at Week 52 (Table 20).

Table 20: Histologic-Endoscopic Mucosal Improvement at Week 52 by Subgroup (NRI; mITT Population)

	≤20 kg 50mg Miri SC (N = 1)	>20 kg and ≤40kg 100mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10mg/kg Miri IV/50 mg Miri SC non- responder (N = 1)	>20kg and ≤40kg 10mg/kg Miri IV/100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/200 mg Miri SC non- responder (N = 6)	Total (N = 26)
Failed (Ns)	1	5	5	1	0	5	17
Response, n (%) ^a	0 (0.0)	3 (60.0)	2 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (29.4)
95% CI ^b	(0.0, 79.3)	(23.1, 88.2)	(11.8, 76.9)	(0.0, 79.3)	(0.0, 0.0)	(0.0, 43.4)	(13.3, 53.1)
Not Failed (Ns)	0	3	4	0	1	1	9
Response, n (%) ^a	0 (0.0)	2 (66.7)	2 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (44.4)
95% CI ^b	(0.0, 0.0)	(20.8, 93.9)	(15.0, 85.0)	(0.0, 0.0)	(0.0, 79.3)	(0.0, 79.3)	(18.9, 73.3)

Abbreviations: CI = confidence interval; mITT = modified intent-to-treat; IV = intravenous; Miri = mirikizumab; N = number of patients in the mITT Population; n = number of patients within each specific category; NRI = nonresponder imputation; kg = kilogram; mg = milligram; Ns = number of patients in each subgroup; SC = subcutaneous.

a. Percentage of response is calculated by $n/Ns \times 100\%$.

b. Response confidence intervals are constructed using Wilson method, without continuity correction.

[0258] Histologic-Endoscopic Mucosal Remission at Week 52 by Subgroup (Prior Biologic Failure Category)

A total of 29.4% of participants among the biologic failed subgroup and 44.4% of participants among the biologic not failed subgroup achieved histologic-endoscopic mucosal remission at Week 52 (Table 1).

Table 2121: Histologic-Endoscopic Mucosal Remission at Week 52 by Subgroup (NRI; mITT Population)

	≤20 kg 50mg Miri SC (N = 1)	>20 kg and ≤40kg 100mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10mg/kg Miri IV/50 mg Miri SC non-responder (N = 1)	>20kg and ≤40kg 10mg/kg Miri IV/100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/200 mg Miri SC non-responder (N = 6)	Total (N = 26)
Failed (Ns)	1	5	5	1	0	5	17
Response, n (%) ^a	0 (0.0)	3 (60.0)	2 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (29.4)
95% CI ^b	(0.0, 79.3)	(23.1, 88.2)	(11.8, 76.9)	(0.0, 79.3)	(0.0, 0.0)	(0.0, 43.4)	(13.3, 53.1)
Not Failed (Ns)	0	3	4	0	1	1	9
Response, n (%) ^a	0 (0.0)	2 (66.7)	2 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (44.4)
95% CI ^b	(0.0, 0.0)	(20.8, 93.9)	(15.0, 85.0)	(0.0, 0.0)	(0.0, 79.3)	(0.0, 79.3)	(18.9, 73.3)

Abbreviations: CI = confidence interval; mITT = modified intent-to-treat; SC = subcutaneous; IV = intravenous; Miri = mirikizumab; N = number of patients in the mITT Population; n = number of patients within each specific category; NRI = nonresponder imputation; kg = kilogram; mg = milligram; Ns = number of patients in each subgroup

a. Percentage of response is calculated by $n/Ns \times 100\%$

b. Response confidence intervals are constructed using Wilson method, without continuity correction

[0259] Alternate Modified Mayo Clinical Remission at Week 52: Clinical Remission by Subgroup (Prior Biologic Failure Category)

A total of 29.4% of participants among the biologic failed subgroup and 44.4% of participants among the biologic not failed subgroup achieved alternate MMS clinical remission at Week 52 (Table 22).

Table 22: Alternate Modified Mayo Clinical Remission at Week 52 by Subgroup (NRI; mITT Population)

	≤20 kg 50mg Miri SC (N = 1)	>20 kg and ≤40kg 100mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10mg/kg Miri IV/50 mg Miri SC non- responder (N = 1)	>20kg and ≤40kg 10mg/kg Miri IV/100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/200 mg Miri SC non- responder (N = 6)	Total (N = 26)
Failed (Ns)	1	5	5	1	0	5	17
Response, n (%) ^a	0 (0.0)	3 (60.0)	2 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (29.4)
95% CI ^b	(0.0, 79.3)	(23.1, 88.2)	(11.8, 76.9)	(0.0, 79.3)	(0.0, 0.0)	(0.0, 43.4)	(13.3, 53.1)
Not Failed (Ns)	0	3	4	0	1	1	9
Response, n (%) ^a	0 (0.0)	2 (66.7)	2 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (44.4)
95% CI ^b	(0.0, 0.0)	(20.8, 93.9)	(15.0, 85.0)	(0.0, 0.0)	(0.0, 79.3)	(0.0, 79.3)	(18.9, 73.3)

Abbreviations: CI = confidence interval; mITT = modified intent-to-treat; SC = subcutaneous; IV = intravenous; Miri = mirikizumab; N = number of patients in the mITT Population; n = number of patients within each specific category; NRI = nonresponder imputation; kg = kilogram; mg = milligram; Ns = number of patients in each subgroup

a. Percentage of response is calculated by $n/Ns \times 100\%$

b. Response confidence intervals are constructed using Wilson method, without continuity correction

[0260] Alternate MMS Clinical Remission at Week 52 among the Induction Clinical Responders by Subgroup (Prior Biologic Failure Category)

Among the induction clinical responders (n=18), a total of 45.5% of participants among the biologic failed subgroup and 57.1% of participants among the biologic not failed subgroup achieved clinical remission at Week 52 (Table 23).

Table 23. Clinical Remission at Week 52 by Subgroup (NRI; mITT Population Induction Clinical Responders)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	Total (N = 18)
Failed (Ns)	1	5	5	11
Response, n (%) ^a	0 (0.0)	3 (60.0)	2 (40.0)	5 (45.5)
95% CI ^b	(0.0, 79.3)	(23.1, 88.2)	(11.8, 76.9)	(21.3, 72.0)
Not Failed (Ns)	0	3	4	7
Response, n (%) ^a	0 (0.0)	2 (66.7)	2 (50.0)	4 (57.1)
95% CI ^b	(0.0, 0.0)	(20.8, 93.9)	(15.0, 85.0)	(25.0, 84.2)

Abbreviations: kg = kilogram; miri = mirikizumab; mg = milligram; SC = subcutaneous; CI = confidence interval; N = number of patients in the analysis population; n = number of patients in the specified category; NRI = nonresponder imputation; Ns = number of patients in each subgroup.

a. Percentage of response is calculated by $n/Ns \times 100\%$.

b. Response confidence intervals are constructed using Wilson method, without continuity correction.

[0261] **Fecal Calprotectin at Week 52**

Table 24 provides a summary of fecal calprotectin (change from baseline) at Week 52. Following maintenance with mirikizumab, participants had a mean reduction in fecal calprotectin from baseline of -3447.54.

Table 24. Fecal calprotectin at Week 52 (Change from baseline; mBOCF) (mITT Population)

≤20 kg 50mg Miri SC (N = 1)	>20 kg and ≤40kg 100mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10mg/kg Miri IV/50 mg Miri SC non-responder (N = 1)	>20kg and ≤40kg 10mg/kg Miri IV/100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/200 mg Miri SC non-responder (N = 6)	Total (N = 26)
--------------------------------	---	----------------------------------	--	--	--	-------------------

Number of patients	0	8	9	1	1	5	24
Mean (SD)	N/A	-3939.50 (5437.16)	-4177.22 (5706.83)	1367.00 (-)	-8281.00 (-)	-1343.20 (2320.13)	-3447.54 (4953.81)

Abbreviations: IV = intravenous; kg = kilogram; miri = mirikizumab; mBOCF = modified baseline carried forward; mg = milligram; N = number of patients in the analysis population; Q4W = every 4 weeks; SC = subcutaneous; SD = standard deviation; mITT = modified intent-to-treat

[0261] **CRP at Week 52**

Table 25 provides a summary of serum C-reactive protein (change from baseline) at Week 52. Following maintenance with mirikizumab, participants had a mean reduction in CRP from baseline of -2.65.

Table 25. CRP at Week 52 (Change from baseline; mBOCF) (mITT Population)

	≤20 kg 50mg Miri SC (N = 1)	>20 kg and ≤40kg 100mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10mg/kg Miri IV/50 mg Miri SC non- responder (N = 1)	>20kg and ≤40kg 10mg/kg Miri IV/100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/200 mg Miri SC non- responder (N = 6)	Total (N = 26)
Number of patients	1	8	9	1	1	6	26
Mean (SD)	0.00 (-))	-1.32 (2.30)	-4.98 (7.63)	0.01 (-)	0.42 (-)	-2.35 (2.93)	-2.65 (5.03)

Abbreviations: IV = intravenous; kg = kilogram; miri = mirikizumab; mBOCF = modified baseline carried forward; mg = milligram; N = number of patients in the analysis population; Q4W = every 4 weeks; SC = subcutaneous; SD = standard deviation; mITT = modified intent-to-treat

[0260] **EXAMPLE 2. A Multicenter, Phase 3, Open-Label study to Investigate the Efficacy, Pharmacokinetics and Safety of Mirikizumab in Participants 2 Years to Less Than 18 Years of Age with Moderately to Severely Active Ulcerative Colitis**

[0261] Study AMBA is a multicenter, open-label, Phase 3 study to investigate the efficacy, pharmacokinetics and safety of mirikizumab in male and female children and adolescents 2 years to less than 18 years of age with moderately to severely active UC, defined as MMS of 5 to 9 with an endoscopic subscore ≥ 2 within 28 days before the first dose.

[0262] **Primary estimand**: What is the proportion of children and adolescents with moderately to severely active UC that achieved clinical response at Week 12 after mirikizumab induction therapy, that achieve MMS clinical remission at Week 52, compared to the proportion of adults in Study AMBG who were re-randomized to placebo treatment after having achieved clinical response at Week 12 of Study AMAN while receiving mirikizumab induction therapy, without discontinuing study intervention or receiving rescue medication prior to Week 52.

[0263] ***Objectives and Endpoints:***

[0264] The following primary, secondary, and exploratory objectives and endpoints are evaluated for this study. Statistical analyses of the primary and key secondary endpoints are performed.

Table 26: Shows the Objectives and Endpoints of AMBA

Objectives	Endpoints
Primary	
To demonstrate superiority of mirikizumab treatment compared to adult placebo in achieving MMS clinical remission among those who were clinical responders at Week 12	Proportion of participants with MMS clinical remission at Week 52 among the Week 12 clinical responders
Secondary	

To evaluate the efficacy of mirikizumab in pediatric participants compared to adult placebo on the following at Week 12 • clinical remission	Proportion of participants achieving: • MMS clinical remission at Week 12
• clinical response	• MMS clinical response at Week 12
• endoscopic remission	• Endoscopic remission at Week 12
• endoscopic improvement	• Endoscopic improvement at Week 12
To evaluate the proportion of pediatric participants achieving PUCAI remission and response at Week 12	Proportion of participants achieving: • PUCAI clinical response at Week 12 • PUCAI clinical remission at Week 12
To evaluate the efficacy of mirikizumab in pediatric participants compared to adult placebo on the following at Week 52, among those who were clinical responders at Week 12 • clinical response	Proportion of participants achieving: • MMS clinical response at Week 52
• endoscopic remission	• Endoscopic remission at Week 52
• endoscopic improvement	• Endoscopic improvement at Week 52
To evaluate the proportion of pediatric participants achieving the following at Week 52, regardless of their Week 12 clinical response status • clinical remission	Proportion of participants achieving: • MMS clinical remission at Week 52 • PUCAI clinical remission at Week 52
• clinical response	• MMS clinical response at Week 52 • PUCAI clinical response at Week 52
• endoscopic remission	• Endoscopic remission at Week 52
• endoscopic improvement	• Endoscopic improvement at Week 52

To evaluate the proportion of participants achieving symptomatic remission over time	Proportion of participants in symptomatic remission at applicable study visits
To evaluate the efficacy of mirikizumab in pediatric participants compared to adult placebo on corticosteroid-free remission without surgery at Week 52 among clinical responders at Week 12	The proportion of participants achieving MMS clinical remission without surgery at Week 52 and without the use of corticosteroids
To evaluate the PK of mirikizumab	AUC and C _{max}
To evaluate the development of anti-mirikizumab antibodies and their effect on efficacy, safety, and mirikizumab exposure	• Proportion of participants who have TEADA • Relationship between TEADA and efficacy • Relationship between TEADA and safety • Relationship between TEADA and mirikizumab PK
To evaluate tolerability and acceptability of subcutaneous injections	Compare reports of injection site pain to total number of injections per participant
To evaluate histologic-endoscopic mucosal remission in pediatric participants treated with mirikizumab	• Proportion of participants with histologic-endoscopic mucosal remission at Week 12 • Proportion of participants with histologic-endoscopic mucosal remission at Week 52
Exploratory	
To evaluate the efficacy of mirikizumab in pediatric participants compared to adult placebo on changes in inflammatory biomarkers	Change from baseline at Weeks 12, 24, and 52 in • CRP • Fecal calprotectin
To evaluate the change in growth and pubertal development for pediatric participants treated with mirikizumab	Change from baseline at Weeks 12, 24, and 52 in: • Weight • Weight percentiles • Height • Height percentiles • Height velocity

	Change in Tanner Stage from baseline at Weeks 24 and 52 in participants with maturation potential (Tanner Stage <5) at baseline
To evaluate the improvement of participant /caregiver-reported outcomes for pediatric participants treated with mirikizumab	Change from baseline at Weeks 12 and 52 in • Urgency NRS • Abdominal Pain NRS • Fatigue NRS • Nocturnal Stools • PGI-C • PGR-S
To evaluate the change in health outcome and quality of life measures for pediatric participants treated with mirikizumab	Change from baseline at Weeks 12 and 52 in • IMPACT-III score • TUMMY-UC • WPAI+CIQ:UC score
To evaluate the efficacy of mirikizumab in reducing the proportion of ER visits for UC, hospitalizations for UC, and to undergo surgery for UC compared to adult placebo during the study	Proportion of participants who had • UC-related emergency room visits • UC-related hospitalizations • UC-related surgeries
To evaluate selected objectives in the conventional-failed and biologic-failed subgroups of participants compared to adult placebo	• Endoscopic improvement at Week 52 • Endoscopic remission at Week 52 • MMS Clinical remission at Week 12 • MMS Clinical remission at Week 52
To compare the efficacy of mirikizumab in pediatric participants to adult placebo using the UCEIS	Proportion of participants with an • UCEIS score of ≤ 1 at Week 12 • UCEIS score of ≤ 1 at Week 52

Abbreviations: AUC = Area under the curve; C_{max} = highest concentration of a drug in the blood after a dose is given ; CRP = C-reactive protein; MMS = modified Mayo Score; NRS =Numeric Rating Scale; PGI-C = Patient's Global Impression of Change; PGR-S = Patient's Global Rating of Severity; PK = Pharmacokinetics; PUCAI = Pediatric Ulcerative Colitis Activity Index; TEADA = Treatment-emergent anti-drug antibodies; UC = Ulcerative colitis; UCEIS = Ulcerative Colitis Endoscopic Index of Severity; WPAI+CIQ:UC = Work Productivity and Activity Impairment Questionnaire + Classroom Impairment Questions Ulcerative Colitis.

[0265] **Study Design:**

[0266] The study will have 4 study periods

Period I Screening

Period II - mirikizumab open-label induction

Visits 2 through 6, Weeks 0 through 12 Induction period - Participants will receive 3 induction doses according to their weight at each dosing visit.

Period III - mirikizumab open-label maintenance

Visits 7 through 17, Weeks 12 through 52 Maintenance period = Participants will receive mirikizumab extended induction doses or maintenance doses through Week 52 according to their weight at each dosing visit.

Period II - mirikizumab open-label induction

Visits 2 through 6, Weeks 0 through 12 Induction period - Participants will receive 3 induction doses according to their weight at each dosing visit.

Period III - mirikizumab open-label maintenance

Visits 7 through 17, Weeks 12 through 52 Maintenance period - Participants will receive mirikizumab extended induction doses or maintenance doses through Week 52 according to their weight at each dosing visit.

Visit 17, Week 52 - After Week 52, all participants will have the option to enter the Study AMAZ or enter the post-treatment follow-up period.

With sponsor approval, additional dosing at Week 52 and UV beyond Week 52 may occur as needed for participants eligible to enroll in Study AMAZ where the clinical trial site is not yet open.

Participants must have completed all procedures at Visit 16 and additional dosing should occur at 4-week intervals (± 7 days) from the prior dose.

Period IV: safety follow-up for approximately 16 weeks after the last treatment visit

The study will also evaluate the safety and efficacy of extended induction for participants who did not have a clinical response at Week 12, and rescue treatment for participants who lose clinical response in the maintenance phase.

[0267] Participants who in the opinion of the investigator are receiving clinical benefit may proceed to the 3-year long-term extension study (I6T-MC-AMAZ) instead of safety follow-up.

[0268] **Table 27. Mirikizumab doses based on the participant’s weight.**

Weight	Induction dose, frequency and route of administration	Extended Induction or Rescue dose, frequency and route of administration	Maintenance dose, frequency and route of administration
>40 kg	300 mg mirikizumab IV Q4W X 3 doses	300 mg mirikizumab IV Q4W X 3 doses	200 mg mirikizumab SC Q4W
>20 kg to ≤40 kg	5 mg/kg mirikizumab IV Q4W X 3 doses	5 mg/kg mirikizumab IV Q4W X 3 doses	100 mg mirikizumab SC Q4W
>10kg to ≤20 kg	5 mg/kg mirikizumab IV Q4W X 3 doses	5 mg/kg mirikizumab IV Q4W X 3 doses	50 mg mirikizumab SC Q4W

[0269] ***Inclusion Criteria:***

[0270] patients eligible for inclusion in this trial must fulfil all of the following criteria:

1. Male or female patients weighing >10 kg AND ≥2 and <18 years of age at the time of informed consent.
2. Have an established diagnosis of UC of ≥3 months in duration before baseline, which includes endoscopic evidence of UC corroborated by a histopathology report.
3. Have moderately to severely active UC as defined by a MMS of 5 to 9 with an ES ≥2 within 28 days before first dose of study treatment (baseline).
4. Have evidence of UC extending proximal to the rectum involving the distal sigmoid colon.
5. Prior Medication Failure Criteria: Patients must have an inadequate response to, loss of response to, or intolerance to at least 1 of the medications described. Documentation of dose, frequency, route of administration, and duration of the prior failed treatment is required.

- a. Biologic-naïve patients: Patients who have an inadequate response to, loss of response to, or are intolerant to at least 1 of the following medications:
 - Corticosteroids
 - Corticosteroid-refractory colitis, defined as signs and/or symptoms of active UC despite a 2-week course of oral prednisone at a dose or equivalent of ≥ 0.75 mg/kg/day or a 2-week course of oral prednisone at a dose of ≥ 40 mg/day or an 8-week course of budesonide MMX of 9 mg/day;
 - Corticosteroid-dependent colitis, defined as:
 - a. an inability to taper corticosteroids without a return of signs and/or symptoms of active UC; or
 - b. a relapse within 3 months of completing a course of corticosteroids; or
 - Intolerance to corticosteroids (which includes evidence of an adverse event sufficiently serious as to precluding continued treatment with corticosteroids including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, growth delay, or neuropsychiatric side-effects, including insomnia, associated with corticosteroid treatment).
 - Immunomodulators:
 - Signs and/or symptoms of persistently active disease despite at least 3 months' treatment with 1 of the following:
 - Oral AZA (≥ 1 mg/kg/day) or 6-MP (≥ 0.5 mg/kg/day), or
 - Oral AZA or 6-MP within a therapeutic range as judged by thioguanine metabolite testing, or
 - A combination of a thiopurine and allopurinol within a therapeutic range as judged by thioguanine metabolite testing, or
 - MTX, either alone or in combination with another therapy.
 - History of intolerance to at least 1 immunomodulator (including but not limited to nausea/vomiting, abdominal pain, pancreatitis, liver function test abnormalities, and lymphopenia).

Elective discontinuation despite clinical benefit does not qualify as having failed or being intolerant to UC non-biologic therapy.

- b. Biologic/JAK inhibitor-experienced patients: Patients who have an inadequate response to, loss of response to, or are intolerant to biologic therapy for UC (such as

anti-TNF antibodies or anti-integrin antibodies) and/or to JAK inhibitors (such as tofacitinib), as described below. Investigators must document an adequate trial of the medication. Patients should fulfill at least 1 of the following criteria:

- Inadequate response: Signs and symptoms of persistently active disease despite prescribed induction treatment, or
- Loss of response: Recurrence of signs and symptoms of active disease during prescribed maintenance dosing following prior clinical benefit, or
- Intolerance: History of intolerance to infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, upadacitinib, or other biologics or JAK inhibitors (including but not limited to infusion-related event, demyelination, congestive heart failure, or any other drug-related AE that led to a reduction in dose or discontinuation of the medication), or
- Stopped taking a biologic for any other reason.

Discontinuation despite clinical benefit does not qualify as having an inadequate response to or being intolerant to UC biologic or JAK inhibitor therapy.

6. Dose Stabilization Inclusion Criteria: Are on stable doses of the following permitted drugs:
- Oral 5-ASA compounds: if the prescribed dose has been stable for at least 2 weeks before screening endoscopy.
 - Oral corticosteroid therapy (prednisone ≤ 1.5 mg/kg/day up to 40 mg/day or equivalent): if the prescribed dose has been stable for at least 1 week before the screening endoscopy.
 - AZA, 6-MP, and MTX: for at least 8 weeks before the screening endoscopy.

[0271] **SEQUENCES**

[0272] **SEQ ID NO: 1 mirikizumab heavy chain variable region (HCVR)**

QVQLVQSGAEVKKPGSSVKVSCKASGYKFTRYVMHWVRQAPGGLEWMGYINPY
NDGTNYNEKFKGRVTITADKSTSTAYMELSSLRSED TAVYYCARNWDTGLWGQGT
TVTVSS

[0273] **SEQ ID NO: 2 mirikizumab light chain variable region (LCVR)**

DIQMTQSPSSLSASVGDRVITITCKASDHILKFLTWYQQKPGKAPKLLIYGATSLETGV
PSRFGSGSGTDFTLTISLQPEDFATYYCQMYWSTPFTFGGGTKVEIK

[0274] **SEQ ID NO: 3 mirikizumab heavy chain (HC)**

QVQLVQSGAEVKKPGSSVKVSCKASGYKFTRYVMHWVRQAPGGLEWMGYINPY
NDGTNYNEKFKGRVTITADKSTSTAYMELSSLRSED TAVYYCARNWDTGLWGQGT
TVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHT
FPAVLQSSGLYSLSSVVTVPSSSLGTKYTCNV DHKPSNTKVDKRVESKYGPPCPPCP
APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVVSQEDPEVQFNWYVDGVEVHN
AKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP
REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDS
DGSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLSLG

[0275] **SEQ ID NO: 4 mirikizumab light chain (LC)**

DIQMTQSPSSLSASVGDRVITITCKASDHILKFLTWYQQKPGKAPKLLIYGATSLETGV
PSRFGSGSGTDFTLTISLQPEDFATYYCQMYWSTPFTFGGGTKVEIKRTVAAPSVFI
FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY
SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

CLAIMS

We claim:

1. A method of treating moderately to severely active ulcerative colitis (UC) in a patient in need thereof, comprising administering at least one induction dose of mirikizumab to the patient, at about 5 mg/kg to about 10 mg/kg, and wherein the patient is 2 years to less than 18 years of age and has a weight of greater than 10 kilogram (kg).
2. The method of claim 1, wherein the patient has a weight of greater than 10 kg to less than or equal to 40 kg, an induction dose of mirikizumab is administered to the patient at about 5 mg/kg to about 10 mg/kg.
3. The method of any one of claims 1-2, wherein the induction dose of mirikizumab is administered to the patient at about 5 mg/kg.
4. The method of any one of claims 1-2, wherein the induction dose of mirikizumab is administered to the patient at about 10 mg/kg.
5. The method of any one of claims 1-4, wherein three induction doses of mirikizumab are administered to the patient.
6. The method of any one of claims 1-5, wherein the induction doses of mirikizumab are administered to the patient at 4-8 week intervals.
7. The method of any one of claims 1-6, wherein the induction doses of mirikizumab are administered to the patient at 4 week intervals.
8. The method of any one of claims 1-7, wherein the induction doses of mirikizumab are administered to the patient at 0, 4, and 8 weeks.
9. The method of any one of claims 1-8, wherein the induction dose is delivered over an induction dosing period of 12 weeks.

10. The method of any one of claims 1-9, wherein if the patient has not achieved a clinical response at 4 to 12 weeks after the last induction dose is administered, one, two, or three extended induction doses of mirikizumab are administered to the patient at about 5 mg/kg to about 10 mg/kg.
11. The method of claim 10, wherein if the patient has a weight of greater than 10 kg to less than or equal to 40 kg, an extended induction dose of mirikizumab is administered to the patient at about 5 mg/kg or about 10 mg/kg.
12. The method of claims 10-11, wherein if the patient has a weight of greater than 10 kg to less than or equal to 40 kg an extended induction dose of mirikizumab is administered to the patient at about 10 mg/kg.
13. The method of claims 10-11, wherein if the patient has a weight of greater than 10 kg to less than or equal to 40 kg an extended induction dose of mirikizumab is administered to the patient at about 5 mg/kg.
14. The method of any one of claims 10-13, wherein at least one extended induction dose is administered to the patient 4-8 week after the last maintenance dose.
15. The method of any one of claims 10-14, wherein three extended induction doses of mirikizumab are administered to the patient.
16. The method of any one of claims 10-15, wherein the extended induction doses of mirikizumab are administered to the patient at 4-8 week intervals.
17. The method of any one of claims 10-16, wherein the extended induction doses of mirikizumab are administered to the patient at 4 week intervals.
18. The method of any one of claims 1 to 17, further comprising administering at least one maintenance dose of mirikizumab to the patient at about 50 mg to about 100 mg, wherein the maintenance dose is administered after the last induction dose or the last extended induction dose.

19. The method of claim 18, wherein if the patient has a weight of greater than 10 kg to less than or equal to 20 kg a maintenance dose of mirikizumab is administered to the patient at about 50 mg.
20. The method of claim 18, wherein if the patient has a weight of greater than 20 kg to less than or equal to 40 kg a maintenance dose of mirikizumab is administered to the patient at about 100 mg.
21. The method of any one of claims 18-20, wherein the maintenance dose of mirikizumab is administered to the patient, if the patient achieves a clinical response from the last induction or extended induction dose administered to the patient.
22. The method of any one of claims 18-21, wherein, if the patient develops a loss of response during the maintenance dosing, one, two or three rescue doses of mirikizumab are administered to the patient at about 5 mg/kg to about 10 mg/kg.
23. The method of claim 22, wherein if the patient has a weight of 10 kg to less than or equal to 20 kg, a rescue dose of mirikizumab is administered to the patient at about 5 mg/kg.
24. The method of claim 22, wherein if the patient has a weight of greater than 20 kg to less than or equal to 40 kg, a rescue dose of mirikizumab is administered to the patient at about 10 mg/kg.
25. The method of any one of claims 22-24, wherein the rescue doses are administered to the patient 4-8 weeks after the last maintenance dose.
26. The method of any one of claims 22-25, wherein the rescue doses are administered to the patient at 4-8 week intervals.
27. The method of any one of claims 22-26, wherein the rescue doses are administered to the patient at 4 week intervals.

28. The method of any one of claims 22-27, wherein if the patient achieves clinical response 4-12 weeks after one, two, or three rescue doses, then maintenance doses of mirikizumab are administered to the patient at about 50 mg or at about 100 mg.
29. The method of any one of claims 18-21, or 28, wherein the maintenance doses of mirikizumab are administered to the patient 2-8 weeks after the last induction dose, rescue dose, or extended induction dose.
30. The method of any one of claims 18-21, or 28-29, wherein the maintenance doses of mirikizumab are administered to the patient 4 weeks after the last induction dose, rescue dose, or extended induction dose.
31. The method of any one of claims 18-21 or 28-30, wherein the maintenance doses of mirikizumab are administered to the patient at 4 to 8, week intervals.
32. The method of any one of claims 18-21 or 28-31, wherein the maintenance doses of mirikizumab are administered to the patient at 4 week intervals.
33. The method of any one of claims 18-21 or 28-32, wherein the maintenance dose of mirikizumab is administered to the patient by subcutaneous injection.
34. The method of claim 1, comprising,
administering three induction doses of mirikizumab to the patient at about 5 mg/kg or at about 10 mg/kg at 4 week intervals by intravenous infusion; and then
administering maintenance doses of mirikizumab to the patient at about 50 mg, at 4 week intervals by subcutaneous injection, 2-8 weeks after the last induction dose is administered,
wherein the patient is 2 years to less than 18 years of age and has a weight of greater than 10 kg to less than or equal to 20 kg.
35. The method of claim 1, comprising,

administering three induction doses of mirikizumab to the patient at about 5 mg/kg or at about 10 mg/kg at 4 week intervals by intravenous infusion; and then administering maintenance doses of mirikizumab to the patient at about 100 mg, at 4 week intervals by subcutaneous injection, 2-8 weeks after the last induction dose is administered,

wherein the patient is 2 years to less than 18 years of age and has a weight of greater than 20 kg to less than or equal to 40 kg.

36. The method of any one of claims 34-35, wherein if the patient has not achieved a clinical response at 4 to 12 weeks after the last induction dose is administered, then three extended induction doses of mirikizumab are administered to the patient,
wherein, if the patient has a weight of greater than 10 kg to less than or equal to 40 kg, an extended induction dose of mirikizumab is administered to the patient at about 5 mg/kg or at about 10 mg/kg, and
wherein, the extended induction doses of mirikizumab are administered to the patient at 4 week intervals by intravenous infusion.
37. The method of claim 36, wherein if the patient achieves a clinical response at 4 to 12 weeks after the last extended induction dose is administered, maintenance doses of mirikizumab are administered to the patient at 2-8 weeks after the last extended induction dose.
38. The method of any one of claims 34-37, wherein, if the patient develops a loss of response during the maintenance dosing, one, two or three rescue doses of mirikizumab are administered to the patient,
wherein, if the patient has a weight of 10 kg to less than or equal to 40 kg, the rescue dose of mirikizumab is administered to the patient at about 5 mg/kg or at about 10 mg/kg; and
wherein the rescue doses of mirikizumab are administered to the patient at 4 week intervals by intravenous infusion.

39. The method of claim 38, wherein if the patient achieves a clinical response 4-12 weeks after the one, two, or three rescue doses, further maintenance doses of mirikizumab are administered to the patient, at 4 week intervals by subcutaneous injection.
40. The method of any one of claims 1-39, wherein the patient achieves a therapeutic effect of at least one or more of clinical response, clinical remission, endoscopic remission, endoscopic improvement, symptomatic remission, symptomatic response, clinical remission without surgery, corticosteroid free clinical remission, histologic endoscopic mucosal remission, histologic endoscopic mucosal improvement, bowel urgency remission, improvement in bowel urgency, improvement in stool frequency, improvement in rectal bleeding within about 2 weeks to about 48 weeks of administration of mirikizumab.
41. The method of claim 46, wherein at least one or more therapeutic effect is achieved within about 2 weeks, 4 weeks, 8 weeks, 12 weeks, 16, weeks, 20 weeks, 24 weeks, 28 weeks, 32 weeks, 36 weeks, 40 weeks, or 48 weeks of treatment with mirikizumab.
42. The method of claim 40-41, wherein at least one or more therapeutic effect is achieved during the induction dosing or the extended induction dosing.
43. The method of any one of claims 40-42, wherein one or more of the therapeutic effects is sustained in maintenance period.
44. The method of claim 43, wherein the patient has sustained clinical remission without surgery at 52 weeks and no steroid use for at least 12 weeks prior to Week 52 of administration of mirikizumab.
45. The method of any one of claims 1-44, wherein the patient is biologic-naïve and/ or advanced therapy naïve.
46. The method of any one of claims 1-45, wherein the patient is conventional-failed.

47. The method of any one of claims 1-44 or 46, wherein the patient is biologic-experienced and/or advanced therapy experienced.
48. The method of any one of claims 1-44 or 46-47, wherein the patient is biologic-failed and/or advanced therapy failed.
49. The method of any one of claims 1-44 or 46-48, wherein the patient is nonresponsive, has an inadequate response, loss of response, or is intolerant, to at least one prior treatment for ulcerative colitis.
50. The method of any one of claims 47-49, wherein the biologic is an anti-TNF therapeutic and or an anti- $\alpha 4\beta 7$ therapeutic.
51. The method of any one of claims 47-49, wherein the advanced therapy is a JAK inhibitor, a S1P receptor modulator, or a TYK2 inhibitor.
52. Mirikizumab for use in treating moderately to severely active ulcerative colitis (UC) in a patient in need thereof, wherein an induction dose of mirikizumab is administered to the patient, at about 5 mg/kg to about 10 mg/kg, and wherein the patient is 2 years to less than 18 years of age and has a weight of greater than 10 kilogram (kg).
53. Mirikizumab for use of according to one of claims 52, wherein if the patient has a weight of greater than 10 kg to less than or equal to 40 kg, the induction dose of mirikizumab is administered to the patient at about 5 mg/kg to about 10 mg/kg.
54. Mirikizumab for use according to any one of claims 52-53, wherein the induction dose of mirikizumab is administered to the patient at about 5 mg/kg.
55. Mirikizumab for use according to any one of claims 52-53, wherein the induction dose of mirikizumab is administered to the patient at about 10 mg/kg.
56. Mirikizumab for use according to any one of claims 52-55, wherein three induction doses of mirikizumab are administered to the patient.

57. Mirikizumab for use according to any one of claims 52-56, wherein the induction doses of mirikizumab are administered to the patient at 4-8 week intervals.
58. Mirikizumab for use according to any one of claims 52-57, wherein the induction doses of mirikizumab are administered to the patient at 4 week intervals.
59. Mirikizumab for use according to any one of claims 52-58, wherein the induction doses of mirikizumab are administered to the patient at 0, 4, and 8 weeks.
60. Mirikizumab for use according to any one of claims 52-59, wherein the induction dose is delivered over an induction dosing period of 12 weeks.
61. Mirikizumab for use according to any one of claims 52-60, wherein if the patient has not achieved a clinical response at 4 to 12 weeks after the last induction dose is administered, one, two, or three extended induction doses of mirikizumab are administered to the patient at about 5 mg/kg to about 10 mg/kg.
62. Mirikizumab for use according to claim 61, wherein if the patient has a weight of greater than 10 kg to less than or equal to 40 kg, an extended induction dose of mirikizumab is administered to the patient at about 5 mg/kg or about 10 mg/kg.
63. Mirikizumab for use according to any one of claims 61-62, wherein if the patient has a weight of greater than 10 kg to less than or equal to 40 kg an extended induction dose of mirikizumab is administered to the patient at about 10 mg/kg.
64. Mirikizumab for use according to any one of claims 61-62, wherein if the patient has a weight of greater than 10 kg to less than or equal to 40 kg an extended induction dose of mirikizumab is administered to the patient at about 5 mg/kg.
65. Mirikizumab for use according to any one of claims 61-64, wherein the extended induction doses are administered to the patient 4-8 week after the last maintenance dose.

66. Mirikizumab for use according to any one of claims 61-65, wherein three extended induction doses of mirikizumab are administered to the patient.
67. Mirikizumab for use according to any one of claims 61-66, wherein the extended induction doses of mirikizumab are administered to the patient at 4-8 week intervals.
68. Mirikizumab for use according to any one of claims 61-67, wherein the extended induction doses of mirikizumab are administered to the patient at 4 week intervals.
69. Mirikizumab for use according to any one of claims 61-68, comprising administering maintenance dose of mirikizumab to the patient at about 50 mg to about 100 mg, wherein the maintenance doses are administered after the last induction dose, or the last extended induction dose is administered.
70. Mirikizumab for use according to claim 69, wherein if the patient has a weight of greater than 10 kg to less than or equal to 20 kg a maintenance dose of mirikizumab is administered to the patient at about 50 mg.
71. Mirikizumab for use according to claim 69, wherein if the patient has a weight of greater than 20 kg to less than or equal to 40 kg a maintenance dose of mirikizumab is administered to the patient at about 100 mg.
72. Mirikizumab for use according to any one of claims 69-71, wherein the maintenance dose of mirikizumab is administered to the patient, if the patient achieves a clinical response from the last induction or extended induction dose administered to the patient.
73. Mirikizumab for use according to any one of claims 69-72, wherein, if the patient develops a loss of response during the maintenance dosing, one, two or three rescue doses of mirikizumab are administered to the patient at about 5 mg/kg to about 10 mg/kg.

74. Mirikizumab for use according to claim 73, wherein if the patient has a weight of 10 kg to less than or equal to 20 kg, the rescue dose of mirikizumab is administered to the patient at about 5 mg/kg.
75. Mirikizumab for use according to claim 73, wherein if the patient has a weight of greater than 20 kg to less than or equal to 40 kg, a rescue dose of mirikizumab is administered to the patient at 10 mg/kg.
76. Mirikizumab for use according to any one of claims 73-75, wherein the rescue doses are administered to the patient 4-8 week after the last maintenance dose.
77. Mirikizumab for use according to any one of claims 73-76, wherein the rescue doses are administered to the patient at 4-8 week intervals.
78. Mirikizumab for use according to any one of claims 73-77, wherein the rescue doses are administered to the patient at 4 week intervals.
79. Mirikizumab for use according to any one of claims 73-78, wherein if the patient achieves clinical response 4-12 weeks after one, two, or three rescue doses, a maintenance dose is administered to the patient at about 50 mg or at about 100 mg,
80. Mirikizumab for use according to any one of claims 69-72 or 79, wherein the maintenance doses of mirikizumab are administered to the patient 2-8 weeks after the last induction dose, rescue dose, or extended induction dose.
81. Mirikizumab for use according to any one of claims 69-72 or 79-80, wherein the maintenance doses of mirikizumab are administered to the patient 4 weeks after the last induction dose, rescue dose, or extended induction dose.
82. Mirikizumab for use according to any one of claims 69-72 or 79-81, wherein the maintenance doses of mirikizumab are administered to the patient at 4 to 8, week intervals.

83. Mirikizumab for use according to any one of claims 69-72 or 79-82, wherein the maintenance doses of mirikizumab are administered to the patient at 4 week intervals.
84. Mirikizumab for use according to any one of claims 69-72 or 79-83, wherein the maintenance doses of mirikizumab are administered to the patient by subcutaneous injection.
85. Mirikizumab for use according to claim 52, comprising,
administering three induction doses of mirikizumab to the patient at about 5 mg/kg or at about 10 mg/kg at 4 week intervals by intravenous infusion; and
administering maintenance doses of mirikizumab to the patient at about 50 mg, at 4 week intervals by subcutaneous injection, 2-8 weeks after the last induction dose is administered,
wherein the patient is 2 years to less than 18 years of age and has a weight of greater than 10 kg to less than or equal to 20 kg.
86. Mirikizumab for use according to any one of claims 52, comprising,
administering three induction doses of mirikizumab to the patient at about 5 mg/kg or at about 10 mg/kg at 4 week intervals by intravenous infusion; and
administering maintenance doses of mirikizumab to the patient at about 100 mg, at 4 week intervals by subcutaneous injection, 2-8 weeks after the last induction dose is administered,
wherein the patient is 2 years to less than 18 years of age and has a weight of greater than 20 kg to less than or equal to 40 kg.
87. Mirikizumab for use according to any one of claims 85-86, wherein if the patient has not achieved a clinical response at 4 to 12 weeks after the last induction dose is administered, three extended induction doses of mirikizumab are administered to the patient,
wherein, if the patient has a weight of greater than 10 kg to less than or equal to 40 kg, the extended induction dose of mirikizumab is administered to the patient at about 5 mg/kg or at about 10 mg/kg.

wherein, the extended induction doses of mirikizumab are administered to the patient at 4 week intervals by intravenous infusion.

88. Mirikizumab for use according to any one of claims 87, wherein if the patient achieves a clinical response at 4 to 12 weeks after the last extended induction dose is administered, maintenance doses of mirikizumab are administered to the patient at 2-8 weeks after the last extended induction dose.
89. Mirikizumab for use according to any one of claims 85-102, wherein, if the patient develops a loss of response during the maintenance dosing, one, two or three rescue doses of mirikizumab are administered to the patient,

wherein, if the patient has a weight of 10 kg to less than or equal to 40 kg, the rescue dose of mirikizumab is administered to the patient at about 5 mg/kg or at about 10 mg/kg;

wherein the rescue doses of mirikizumab are administered to the patient at 4 week intervals by intravenous infusion.
90. Mirikizumab for use according to claim 89, wherein if the patient achieves a clinical response 4-12 weeks after the one, two, or three rescue doses, maintenance doses of mirikizumab are administered to the patient, at 4 week intervals by subcutaneous injection.
91. Mirikizumab for use according to any one of claims 52-90, wherein the patient achieves a therapeutic effect of at least one or more of clinical response, clinical remission, endoscopic remission, endoscopic improvement, symptomatic remission, symptomatic response, clinical remission without surgery, corticosteroid free clinical remission, histologic endoscopic mucosal remission, improvement in endoscopic histologic inflammation, bowel urgency remission, improvement in bowel urgency, stool frequency remission, improvement in stool frequency, improvement in rectal bleeding within about 2 weeks to about 48 weeks of treatment with mirikizumab.

92. Mirikizumab for use according to claim 91, wherein at least one or more therapeutic effect is achieved within about 2 weeks, 4 weeks, 8 weeks, 12 weeks, 16, weeks, 20 weeks, 24 weeks, 28 weeks, 32 weeks, 36 weeks, 40 weeks, or 48 weeks of treatment with mirikizumab.
93. Mirikizumab for use according to any one of 91-92, wherein at least one or more therapeutic effect is achieved in the induction period or the extended induction period.
94. Mirikizumab for use according to 91-93, wherein one or more of the therapeutic effects is sustained in the maintenance period.
95. Mirikizumab for use according to claim 94, wherein the patient has sustained clinical remission without surgery at 52 Weeks and no steroid use for at least 12 weeks prior to Week 52 of treatment with mirikizumab.
96. Mirikizumab for use according to any one of claims 52-95, wherein the patient is biologic-naïve and or advanced therapy naïve.
97. Mirikizumab for use according to any one of claims 52-96, wherein the patient is conventional-failed.
98. Mirikizumab for use according to any one of claims 52-95 or 97, wherein the patient is biologic-experienced and or advanced therapy experienced.
99. Mirikizumab for use according to any one of claims 52-95 or 97-98, wherein the patient is biologic-failed and or advanced therapy failed.
100. Mirikizumab for use according to any one of claims 52-95 or 97-99, wherein the patient is nonresponsive, has an inadequate response, loss of response, or is intolerant, to at least one prior treatment for ulcerative colitis.
101. Mirikizumab for use according to any one of claims 98-100, wherein the biologic is an anti-TNF therapeutic and or an anti- $\alpha 4\beta 7$ therapeutic.

102. Mirikizumab for use according to any one of claims 98-100, wherein the advanced therapy is a JAK inhibitor, a S1P receptor modulator, or a TYK2 inhibitor.
103. Use of mirikizumab in the manufacture of a medicament for treating moderately to severely active ulcerative colitis (UC) in a patient in need thereof, wherein an induction dose of mirikizumab is administered to the patient, at about 5 mg/kg to about 10 mg/kg, and wherein the patient is 2 years to less than 18 years of age and has a weight of greater than 10 kilogram (kg).
104. Use according to any one of claims 103, wherein if the patient has a weight of greater than 10 kg to less than or equal to 40 kg, the induction dose of mirikizumab is administered to the patient at about 5 mg/kg to about 10 mg/kg.
105. Use according to any one of claims 103-104, wherein the induction dose of mirikizumab is administered to the patient at about 5 mg/kg.
106. Use according to any one of claims 103-104, wherein the induction dose of mirikizumab is administered to the patient at about 10 mg/kg.
107. Use according to any one of claims 103-106, wherein three induction doses of mirikizumab are administered to the patient.
108. Use according to any one of claims 103-107, wherein the induction doses of mirikizumab are administered to the patient at 4-8 week intervals.
109. Use according to any one of claims 103-108, wherein the induction doses of mirikizumab are administered to the patient at 4 week intervals.
110. Use according to any one of claims 103-109, wherein the induction doses of mirikizumab are administered to the patient at 0, 4, and 8 weeks.

111. Use according to any one of claims 103-110, wherein the induction doses are delivered over an induction dosing period of 12 weeks.
112. Use according to any one of claims 103-111, wherein if the patient has not achieved a clinical response at 4 to 12 weeks after the last induction dose is administered, one, two, or three extended induction doses of mirikizumab are administered to the patient at 5 mg/kg to about 10 mg/kg.
113. Use according to claim 112, wherein if the patient has a weight of greater than 10 kg to less than or equal to 40 kg, the extended induction dose of mirikizumab is administered to the patient at about 5 mg/kg or about 10 mg/kg.
114. Use according to any one of claims 112-113, wherein if the patient has a weight of greater than 10 kg to less than or equal to 40 kg the extended induction dose of mirikizumab is administered to the patient at about 10 mg/kg.
115. Use according to any one of claims 112-113, wherein if the patient has a weight of greater than 10 kg to less than or equal to 40 kg the extended induction dose of mirikizumab is administered to the patient at about 5 mg/kg.
116. Use according to any one of claims 112-115, wherein the extended induction dose of mirikizumab is administered to the patient 4-8 week after the last maintenance dose.
117. Use according to any one of claims 112-116, wherein three extended induction doses of mirikizumab are administered to the patient.
118. Use according to any one of claims 112-117, wherein the extended induction doses of mirikizumab are administered to the patient at 4-8 week intervals.
119. Use according to any one of claims 112-118, wherein the extended induction doses of mirikizumab are administered to the patient at 4 week intervals.

120. Use according to any one of claims 112-119, further comprising administering maintenance doses of mirikizumab to the patient at about 50 mg to about 100 mg, wherein the maintenance doses are administered after the last induction dose, or the last extended induction dose is administered.
121. Use according to claim 120, wherein if the patient has a weight of greater than 10 kg to less than or equal to 20 kg the maintenance dose of mirikizumab is administered to the patient at about 50 mg.
122. Use according to claim 120, wherein if the patient has a weight of greater than 20 kg to less than or equal to 40 kg the maintenance dose of mirikizumab is administered to the patient at about 100 mg.
123. Use according to any one of claims 120-122, wherein the maintenance doses of mirikizumab are administered to the patient, if the patient achieves a clinical response from the last induction or extended induction dose administered to the patient.
124. Use according to any one of claims 120-123, wherein, if the patient develops a loss of response during maintenance dosing, one, two or three rescue doses of mirikizumab are administered to the patient at about 5 mg/kg to about 10 mg/kg.
125. Use according to claim 124, wherein if the patient has a weight of 10 kg to less than or equal to 20 kg, the rescue dose of mirikizumab is administered to the patient at about 5 mg/kg.
126. Use according to claim 124, wherein if the patient has a weight of greater than 20 kg to less than or equal to 40 kg, the rescue dose of is administered to the patient at 10 mg/kg.
127. Use according to any one of claims 124-126, wherein the rescue doses are administered to the patient 4-8 week after the last maintenance dose.

128. Use according to any one of claims 124-127, wherein the rescue doses are administered to the patient at 4-8 week intervals.
129. Use according to any one of claims 124-128, wherein the rescue doses are administered to the patient at 4 week intervals.
130. Use according to any one of claims 124-129, wherein if the patient achieves clinical response 4-12 weeks after one, two, or three rescue doses, a maintenance dose is administered to the patient at about 50 mg or at about 100, mg.
131. Use according to any one of claims 120-123, or 130, wherein maintenance doses of mirikizumab is administered to the patient 2-8 weeks after the last induction dose, rescue dose, or extended induction dose.
132. Use according to any one of claims 120-123, or 130-131, wherein the maintenance doses of mirikizumab are administered to the patient 4 weeks after the last induction dose, rescue dose, or extended induction dose.
133. Use according to any one of claims 120-123 or 130-132, wherein the maintenance doses of mirikizumab are administered to the patient at 4 to 8, week intervals.
134. Use according to any one of claims 120-123 or 130-133, wherein the maintenance doses of mirikizumab are administered to the patient at 4 week intervals.
135. Use according to any one of claims 120-123 or 130-134, wherein the maintenance doses of mirikizumab are administered to the patient by subcutaneous injection.
136. Use according to claim 103, comprising,
administering three induction doses of mirikizumab to the patient at about 5 mg/kg or at about 10 mg/kg at 4 week intervals by intravenous infusion; and then

administering maintenance doses of mirikizumab to the patient at about 50 mg, at 4 week intervals by subcutaneous injection, 2-8 weeks after the last induction dose is administered,

wherein the patient is 2 years to less than 18 years of age and has a weight of greater than 10 kg to less than or equal to 20 kg.

137. Use according to claim 103, comprising,

administering three induction doses of mirikizumab to the patient at about 5 mg/kg or at about 10 mg/kg at 4 week intervals by intravenous infusion; and then administering maintenance doses of mirikizumab to the patient at about 100 mg, at 4 week intervals by subcutaneous injection, 2-8 weeks after the last induction dose is administered.

wherein the patient is 2 years to less than 18 years of age and has a weight of greater than 20 kg to less than or equal to 40 kg.

138. Use according to any one of claims 136-137, wherein if the patient has not achieved a clinical response at 4 to 12 weeks after the last induction dose is administered, three extended induction doses of mirikizumab are administered to the patient,

wherein, if the patient has a weight of greater than 10 kg to less than or equal to 40 kg, extended induction doses of mirikizumab are administered to the patient at about 5 mg/kg or about 10 mg/kg; and

wherein, the extended induction doses of mirikizumab are administered to the patient at 4 week intervals by intravenous infusion.

139. Use according to claim 138, wherein if the patient achieves a clinical response at 4 to 12 weeks after the last extended induction dose is administered, maintenance doses of mirikizumab are administered to the patient at 2-8 weeks after the last extended induction dose.

140. Use according to any one of claims 136-139, wherein, if the patient develops a loss of response during the maintenance dosing, one, two or three rescue doses of mirikizumab are administered to the patient,

wherein, if the patient has a weight of 10 kg to less than or equal to 40 kg, the rescue dose of mirikizumab is administered to the patient at about 5 mg/kg or at about 10 mg/kg,

wherein the rescue doses of mirikizumab are administered to the patient at 4 week intervals by intravenous infusion.

141. Use according to claim 140, wherein if the patient achieves a clinical response 4-12 weeks after the one, two, or three rescue doses, maintenance doses of mirikizumab are administered to the patient, at 4 week intervals by subcutaneous injection.
142. Use according to any one of claims 103-141, wherein the patient achieves a therapeutic effect of at least one or more of clinical response, clinical remission, endoscopic remission, endoscopic improvement, symptomatic remission, symptomatic response, clinical remission without surgery, corticosteroid free clinical remission, histologic endoscopic mucosal remission, improvement in endoscopic histologic inflammation, bowel urgency remission, improvement in bowel urgency, stool frequency remission, improvement in stool frequency, improvement in rectal bleeding within about 2 weeks to about 48 weeks of treatment with mirikizumab.
143. Use according to claim 142, wherein at least one or more therapeutic effect is achieved within about 2 weeks, 4 weeks, 8 weeks, 12 weeks, 16, weeks, 20 weeks, 24 weeks, 28 weeks, 32 weeks, 36 weeks, 40 weeks, or 48 weeks of treatment with mirikizumab.
144. Use according to any one of 142-143, wherein at least one or more therapeutic effect is achieved in the induction period or the extended induction period.
145. Use according to any one of claims 142-143, wherein one or more of the therapeutic effects is sustained in the maintenance period.

146. Use according to claim 145, wherein the patient has sustained clinical remission without surgery at 52 Weeks and no steroid use for at least 12 weeks prior to 52 weeks of treatment with mirikizumab.
147. Use according to any one of claims 103-146, wherein the patient is biologic-naïve and or advanced therapy naïve.
148. Use according to any one of claims 103-147, wherein the patient is conventional-failed.
149. Use according to any one of claims 103-146 or 148, wherein the patient is biologic-experienced and or advanced therapy experienced.
150. Use according to any one of claims 103-146 or 148-149, wherein the patient is biologic-failed and or advanced therapy failed.
151. Use according to any one of claims 103-146 or 148-150, wherein the patient is nonresponsive, has an inadequate response, loss of response, or is intolerant, to at least one prior treatment for ulcerative colitis.
152. Use according to any one of claims 149-151, wherein the biologic is an anti-TNF therapeutic and or an anti- $\alpha 4\beta 7$ therapeutic.
153. Use according to any one of claims 149-151, wherein the advanced therapy is a JAK inhibitor, a S1P receptor modulator, or a TYK2 inhibitor.