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Methods of treating Crohn's disease and ulcerative colitis

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(54) Title: METHODS OF TREATING CROHN'S DISEASE AND ULCERATIVE COLITIS

(57) Abstract: The present disclosure is directed to methods for treating Crohn's disease, and in particular, to methods for inducing clinical remission and/or endoscopic improvement of Crohn's disease, using a JAK1 inhibitor. In certain embodiments, the patient is administered an induction dose of the JAK1 inhibitor to induce clinical remission and/or endoscopic improvement of the Crohn's disease, followed by administration of at least one maintenance dose of the JAK1 inhibitor thereafter. In other embodiments, the present disclosure is directed to methods for treating ulcerative colitis using a JAK1 inhibitor.

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METHODS OF TREATING CROHN'S DISEASE AND ULCERATIVE COLITIS

RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 62/469,337, filed March 9, 2017, U.S. Provisional Application No. 62/470,565, filed March 13, 2017, U.S. Provisional Application 62/483,289, filed April 7, 2017 and U.S. Provisional Application No. 62/593,629, filed December 1, 2017, each of which is incorporated by reference in its entirety.

FIELD OF THE DISCLOSURE

[0002] The present disclosure is directed to methods for treating inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, and in particular, to methods for inducing clinical remission and endoscopic improvement of Crohn's disease or a clinical remission and endoscopic improvement of ulcerative colitis, using a JAK1 inhibitor. In certain embodiments, the patient is administered an induction dose of the JAK1 inhibitor to induce clinical remission and/or endoscopic improvement of the Crohn's disease or a clinical remission of ulcerative colitis, followed by administration of at least one maintenance dose of the JAK1 inhibitor thereafter.

BACKGROUND OF THE DISCLOSURE

[0003] Inflammatory bowel disease (IBD) involves chronic inflammation of a patient's digestive tract. IBD includes both Crohn's disease and ulcerative colitis. The exact cause of IBD is not known. The IBD can be idiopathic IBD.

[0004] Crohn's Disease (CD) encompasses a spectrum of clinical and pathological processes manifested by focal asymmetric, transmural, and occasionally granulomatous inflammation that can affect any segment of the gastrointestinal tract (Lichtenstein GR, Hanauer SB, Sandborn WJ; Practice Parameters Committee of American College of Gastroenterology, Management of Crohn's disease in adults, *Am J Gastroenterol*. 2009;104(2):465-83). The disease can affect persons of any age, and its onset is most common in the second and third decades. Females are affected slightly more than males, and the risk for disease is higher in some ethnic groups (Loftus EV Jr., "Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences," *Gastroenterology*, 2004; 126(6):1504-17; Probert CS, Jayanthi V, Rampton DS, et al., "Epidemiology of inflammatory bowel disease in different ethnic and religious groups: limitations and aetiological clues," *Int. J Colorectal Dis*., 1996;11(1):25-28). In North America, the incidence of CD is estimated to be 3.1 to 14.6 cases per 100,000 persons. Prevalence rates range from 26 to 99 cases per 100,000 persons. In Europe, CD has an incidence of 0.7 to 9.8 cases per 100,000 persons and a prevalence of 8.3 to 214 cases per 100,000 persons

(Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. *Gastroenterology*. 2004; 126(6):1504-17).

[0005] CD has been characterized by significant morbidity including abdominal pain, diarrhea, weight loss/malnutrition, fatigue and a progressive nature that leads to complications such as fistulas, strictures and abscesses. In a population based study from southeastern Norway, a substantial number of patients demonstrated a stricturing or penetrating phenotype at 10 years after diagnosis (Solberg IC, Vatn MH, Hoie O, et al; IBSEN Study Group. Clinical course in Crohn's disease: results of a Norwegian population-based ten-year follow-up study. *Clin Gastroenterol Heptaol*. 2007;5(12):1430-8). Moreover, approximately 80% of patients diagnosed with CD will require at least 1 surgery related to the disease at some point in time (Munkholm P, Langholz E, Davidsen M, et al. Intestinal cancer risk and mortality in patients with Crohn's disease. *Gastroenterology*. 1993:105(6):1716-23).

[0006] Ulcerative colitis (UC) is one of the two primary forms of idiopathic inflammatory bowel disease (IBD). It is postulated that UC is caused by unregulated and exaggerated local immune response to environmental triggers in genetically susceptible individuals (Hanauer SB. Update on the etiology, pathogenesis and diagnosis of ulcerative colitis. *Nat Clin Pract Gastroenterol Hepatol*. 2004;1(1):26-31). UC is a chronic, relapsing inflammatory disease of the large intestine characterized by inflammation and ulceration of mainly the mucosal and occasionally submucosal intestinal layers. The highest annual incidence of UC was 24.3 per 100,000 person-years in Europe, 6.3 per 100,000 person-years in Asia and the Middle East, and 19.2 per 100,000 person-years in North America, with a prevalence of 505 cases per 100,000 persons in Europe and 249 cases per 100,000 persons in North America. (Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology*. 2012:142(1):46-54). There is increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. (*Gastroenterology*. 2012;142(1):46-54.e42; quiz e30.) The burden of UC on the healthcare system is profound, accounting for nearly 500,000 physician visits and more than 46,000 hospitalizations per year in the United States (US) alone. (Sandler RS, Everhart JE, Donowitz M, et al., *Gastroenterology*, 2002;122(5):1500-11).

[0007] The hallmark clinical symptoms of UC include bloody diarrhea associated with rectal urgency and tenesmus. The clinical course is marked by exacerbation and remission. The diagnosis of UC is suspected on clinical grounds and supported by diagnostic testing, and elimination of infectious causes. (Dignass A, Eliakim R, Magro F, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. *J Crohn's Colitis*. 2012;6(10):965-90)

[0008] The most severe intestinal manifestations of UC are toxic megacolon and perforation. Extraintestinal complications include arthritis (peripheral or axial involvement), dermatological conditions (erythema nodosum, aphthous stomatitis, and pyoderma gangrenosum), inflammation of the eye (uveitis), and liver dysfunction (primary sclerosing cholangitis). Patients with UC are at an increased risk for colon cancer, and the risk increases with the duration of disease as well as extent of colon affected by the

disease. (Rutter M, Saunders B, Wilkinson K, et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. (*Gastroenterology*, 2004;126(2):451-9).

[0009] The aim of medical treatment in UC is to control inflammation and reduce symptoms. Available pharmaceutical therapies are limited, do not always completely abate the inflammatory process, and may have significant adverse effects. Therapies for mild to moderate active UC include 5-aminosalicylic acid derivatives and immunosuppressants.

[0010] Corticosteroids are used in patients with more severe UC symptoms but are not useful for longer term therapy. (Truelove SC, Witts LJ. Cortisone and corticotrophin in ulcerative colitis. *Br Med J.* 1959;1(5119):387-94). The frequency and severity of corticosteroid toxicities are significant, including infections, emotional and psychiatric disturbances, skin injury, and metabolic bone disease. Corticosteroids are not effective for the maintenance of remission and the UC practice guidelines from the American College of Gastroenterology recommend against chronic steroid treatment. (Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol.* 2010;105(3):501-23; quiz 524). Patients with moderate to severe symptoms may derive some benefits from immunosuppressant agents (azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]); however, the use of these agents is limited as induction treatment due to a slow onset of action (3 to 6 months) and as maintenance therapy due to adverse events (AEs), including bone marrow suppression, infections, hepatotoxicity, pancreatitis, and malignancies. (Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol.*, 2010;105(3):501-23; quiz 524; Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet.* 2009;374(9701):1617-25). Despite these therapies, approximately 15% of ulcerative colitis patients experience a severe clinical course, and 30% of these patients require removal of the colon/rectum, to eliminate the source of the inflammatory process, although accompanied by significant morbidity (Aratari A, Papi C, Clemente V, et al. Colectomy rate in acute severe ulcerative colitis in the infliximab era. *Dig Liver Dis.* 2008;40(10):821-6; Turner D, Walsh CM, Steinhart AH, et al. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. *Clin Gastroenterol Hepatol.* 2007;5(1):103-10).

[0011] Biological agents targeting specific immunological pathways have been evaluated for their therapeutic effect in treating patients with UC. Anti-tumor necrosis factor (TNF) agents were the first biologics to be used for IBD. Infliximab, adalimumab, and golimumab are successfully being used for the treatment of UC. Recently, vedolizumab, an anti-adhesion therapy, has been approved for the treatment of UC by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), and clinical development is ongoing in Japan.

[0012] Anti-TNF therapies are an effective treatment for patients who are steroid refractory or steroid dependent, who had inadequate response to a thiopurine, or who are intolerant to these medications. Potential risks with anti-TNF therapies include infusion or injection site reactions, serious infections, lymphoma, heart failure, lupus-like syndromes, and demyelinating conditions (Sandborn WJ. State-of-the-art: immunosuppression and biologic therapy. *Dig Dis*. 2010; 28(3):536-42). Despite the beneficial results achieved with the available biologic agents, only 17% to 45% of patients who receive them are able to achieve clinical remission. (Rutgeerts P, Sandborn W, Feagan B, et al., Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2005, 353(23):2462-76; Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*, 2012, 142(2):257-65; Feagan B, Greenberg G, Wild G, et al., Treatment of ulcerative colitis with a humanized antibody to the alpha4beta7 integrin, *N. Engl. J. Med*. 2005, 352(24):2499-507; Sandborn W, Feagan B, Marano C, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis, *Gastroenterology*, 2014, 146(1):85-95; quiz e14-5), Thus, there remains a clear medical need for additional therapeutic options in UC for patients with inadequate response to or intolerance to conventional therapies and biologic therapies

[0013] Given that no known medical or surgical cure currently exists for CD, the therapeutic strategy is to reduce symptoms, improve quality of life, reduce endoscopic evidence of inflammation, and minimize short- and long term toxicity and complications (Lichtenstein GR, Hanauer SB, Sandborn WJ; Practice Parameters Committee of American College of Gastroenterology, Management of Crohn's disease in adults, *Am J Gastroenterol*., 2009, 104(2):465-83). Currently, patients with moderate to severe disease are usually treated with conventional pharmacologic interventions, which include corticosteroids and immunosuppressant agents such as azathioprine, 6-mercaptopurine, or methotrexate (MTX) (Lichtenstein GR, Hanauer SB, Sandborn WJ, Practice Parameters Committee of American College of Gastroenterology, Management of Crohn's disease in adults, *Am J Gastroenterol*, 2009, 104(2):465-83; Dignass A, Van Assche G, Lindsay JO, et al., European Crohn's and Colitis Oganisation (ECCO), The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: current management, *J Crohn's Colitis*, 2010, 4(1):28-62, Erratum in: *J Crohn's Colitis,* 2010, 4(3):353).

[0014] The potential risks from long term use of corticosteroids are well-known. Adverse events (AEs) associated with short-term use of corticosteroids include acne, moon face, edema, skin striae, glucose intolerance, and sleep/mood disturbances, while potential AEs observed with longer term use (usually 12 weeks or longer but sometimes shorter durations) include posterior subcapsular cataracts, osteoporosis, osteonecrosis of the femoral head, myopathy, and susceptibility to infection (Irving PM, Gearry RB, Sparrow MP, et al., Review article: appropriate use of corticosteroids in Crohn's disease, *Aliment Pharmacol Ther*., 2007, 26(3):313-29; Rutgeerts PJ, Review article: the limitations of corticosteroid therapy in Crohn's disease, *Aliment Pharmacol Ther*., 2001, 15(10):1515-25). The safety

risks for azathioprine and 6-mercaptopurine include pancreatitis, bone marrow depression, infectious complications, and malignant neoplasms (Sandborn, WJ, State-of-the-art: immunosuppression and biologic therapy, *Dig Dis*., 2010, 28(3):536-42). MTX may be associated with nausea, bone marrow depression and liver and pulmonary toxicity (Siegel, et al., Review article: Practical Management of Inflammatory Bowel Disease Patients Taking Immunosuppressants, *Aliment Pharmacol Ther*., 2005, 22:1-16). Patients who do not respond to conventional therapies are treated with anti-TNF-α therapies (i.e., biologics) (Lichtenstein GR, Hanauer SB, Sandborn WJ, Practice Parameters Committee of American College of Gastroenterology, Management of Crohn's disease in adults, *Am J Gastroenterol*., 2009, 104(2):465-83; Dignass A, Van Assche G, Lindsay JO, et al., European Crohn's and Colitis Oganisation (ECCO), The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: current management, *J Crohn's Colitis,* 2010, 4(1):28-62, Erratum in: *J. Crohn's Colitis*, 2010, 4(3):353). Potential risks with biologics include infusion or injection site reactions, serious infections, lymphoma and other malignancies, heart failure, cytopenias, lupus-like syndromes, and demyelinating conditions (Sandborn WJ, State-of-the-art: immunosuppression and biologic therapy, *Dig. Dis.*, 2010, 28(3):536-42).

[0015] Despite the beneficial results achieved with the available anti-TNF-α agents, approximately 40% of patients who receive them for the first time do not have a clinically meaningful response (primary nonresponders) (Targan SR, Hanauer SB, van Deventer SJ, et al., A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease, *N. Engl. J. Med*., 1997, 337(15):1029-35; Hanauer SB, Feagan BG, Lichtenstein GR, et al., ACCENT I Study Group, Maintenance infliximab for Crohn's disease: the ACCENT I randomized trial, *Lancet*, 2002, 359(9317):1541-9; Hanauer SB, Sandborn WJ, Rutgeerts P, et al., Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial, *Gastroenterology*, 2007, 132(1):52-65; Colombel JF, Sandborn WJ, Rutgeerts P, et al., Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial, *Gastroenterology*, 2007, 132(1):52-65; Sandborn WJ, Feagan BG, Stoinov S, et al., PRECISE I Study Investigators, Certolizumab pegol for the treatment of Crohn's disease, *N. Engl. J. Med*., 2007, 357(3):228-38). Among patients who initially respond and continue to receive maintenance treatment for longer durations, approximately 38% become nonresponders after 6 months (Schribeinger S, Khaliq-Kareemi M, Lawrance IC, et al; PRECISE 2 Study Investigators, Maintenance therapy with certolizumab pegol for Crohn's disease, *N. Engl. J. Med*., 2007, 357(3):239-50, Erratum in: *N. Engl. J. Med*., 2007, 357(13):1357) and approximately 50% become nonresponders at 1 year lose response (secondary nonresponders) (Hanauer SB, Feagan BG, Lichtenstein GR, et al., ACCENT I Study Gorup, Maintenance infliximab for Crohn's disease: the ACCENT I randomized trial, *Lancet,* 2002, 359(9317):1541-9; Colombel JF, Sandborn WJ, Rutgeerts P, et al., Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial, *Gastroenterology*, 2007, 132(1):52-65). Patients who initially respond to a first anti-TNF agent but then lose response tend to have lower response and remission rates to the second anti-TNF

agent (Colombel JF, Sandborn WJ, Rutgeerts P, et al., Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial, Gastroenterology, 2007, 132(1):52-65; Sandborn, et al., "Natalizumab induction and maintenance therapy for Crohn's disease," N Engl. J Med., 2005, 353(18):1912-25).

[0016] New classes of biologics has been studied in patients with prior anti-TNF use. Natalizumab, a humanized monoclonal antibody to a4Pl and a4p7 integrins, showed promise for patients with prior exposure to anti-TNF-a therapy; more than half of the patients had a response to the induction regimen (Sandbom, et al., "Natalizumab induction and maintenance therapy for Crohn's disease," N Engl. J Med., 2005, 353(18):1912-25). However, natalizumab's use after approval in 2008 has been severely limited due to the serious risk for progressive multifocal leukoencephalopathy (PML) attributed to activation of the latent JC virus (Van Assche G, Van Ranst M, Sciot R, et al., "Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease," N Engl. J Med., 2005, 353(4):362 8). Vedolizumab is specific to the $\alpha 4\beta 7$ integrin, which does not affect lymphocyte trafficking to the brain. Therefore, it is presumed to not have the PML risk associated with natalizumab. However, it does not fulfill many of the unmet needs of patients who have failed treatment with anti-TNFs, such as the improvement of extra-intestinal manifestations (Rubin, et al., Inflammatory Bowel Diseases, 2016, 22 Suppl. 1:S42-S43). In the induction study with vedolizumab, the primary endpoint of clinical remission in patients who had previously failed treatment with an anti TNF was not statistically significant nor was it clinically meaningful since there was only a 3% difference from placebo (Sands, et al., "Effects of Vedolizumab Induction Therapy for Patients With Crohn's Disease in Whom Tumor Necrosis Factor Antagonist Treatment Failed," Gastroenterology, 2014, 147:618-627). Ustekinumab, a human monoclonal antibody that selectively targets IL-12 and IL-23, has efficacy in both patients who have responded to and patients who have not responded to prior anti-TNFa therapy. The efficacy of ustekinumab, however, is broadly similar to that of anti-TNF agents, and therefore subject to similar drawbacks (Ther. Adv. Gastroenterology, 2016, Vol. 9(1), pp. 26-36). Clearly, the need for additional therapeutic options in CD for patients who fail or are intolerant to conventional therapies, and anti-TNF-α agents or other biologic therapies remains.

[0016a] Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

[0016b] Unless the context clearly requires otherwise, throughout the description and the claims, the words “comprise”, “comprising”, and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of “including, but not limited to”.

SUMMARY OF THE DISCLOSURE

[0017] The present disclosure addresses the above needs and provides methods for treating Crohn's disease and ulcerative colitis. In some aspects, the present disclosure provides methods for treating Crohn's disease in patients that have moderately to severely active Crohn's disease. In some aspects, the present disclosure provides methods for treating ulcerative colitis in patients that have moderately to severely active ulcerative colitis. The patient may have had an inadequate response to or experienced intolerance to conventional treatment, such as aminosalicylates, corticosteroids or immunosuppressants, or to a previous treatment with an anti-TNF therapy or another biologic agent.

[0017a] In one aspect, the present invention provides a method of inducing clinical remission of ulcerative colitis in an adult patient having moderately to severely active ulcerative colitis, the method comprising orally administering to the patient a 45 mg induction dose of upadacitinib once a day for 8 weeks, wherein the patient achieves clinical remission per Adapted Mayo score at 8 weeks after the administration of the initial said 45 mg induction dose of upadacitinib; and administering a first maintenance dose of 15 mg or 30 mg upadacitinib to the patient after the last induction dose is administered, and administering at least one additional maintenance dose of 15 mg or 30 mg upadacitinib to the patient once daily thereafter, whereby the clinical remission is maintained.

[0017b] In another aspect, the present invention provides a method of inducing endoscopic improvement of ulcerative colitis in an adult patient having moderately to severely active ulcerative colitis, the method comprising orally administering to the patient a 45 mg induction dose of upadacitinib once a day for 8 weeks, wherein the patient achieves endoscopic improvement at 8 weeks after the administration of the initial said 45 mg induction dose of upadacitinib; and administering a first maintenance dose of 15 mg or 30 mg upadacitinib to the patient after the last induction dose is administered, and administering at least one additional maintenance dose of 15 mg or 30 mg upadacitinib to the patient once daily thereafter, whereby the endoscopic improvement is maintained.

[0017c] In a further aspect, the present invention provides a method of inducing histologic-endoscopic mucosal remission of ulcerative colitis in an adult patient having moderately to severely active ulcerative colitis, the method comprising orally administering to the patient a 45 mg induction dose of upadacitinib once a day for 8 weeks, wherein the patient achieves histologic-endoscopic mucosal remission at 8 weeks after the administration of the initial said 45 mg induction dose of upadacitinib; and administering a first maintenance dose of

15 mg or 30 mg upadacitinib to the patient after the last induction dose is administered, and administering at least one additional maintenance dose of 15 mg or 30 mg upadacitinib to the patient once daily thereafter, whereby the histologic-endoscopic mucosal remission is maintained.

[0017d] In yet a further aspect, the present invention provides a method of inducing clinical response of ulcerative colitis in an adult patient having moderately to severely active ulcerative colitis, the method comprising orally administering to the patient a 45 mg induction dose of upadacitinib once a day for 16 weeks, wherein the patient achieves clinical response at 16 weeks after the administration of the initial said 45 mg induction dose of upadacitinib; and administering a first maintenance dose of 15 mg or 30 mg upadacitinib to the patient after the last induction dose is administered, and administering at least one additional maintenance dose of 15 mg or 30 mg upadacitinib to the patient once daily thereafter, whereby the clinical response is maintained.

[0017e] In again another aspect, the present invention provides a method of inducing clinical response of ulcerative colitis in an adult patient having moderately to severely active ulcerative colitis, the method comprising:

a) orally administering to the patient a 45 mg induction dose of upadacitinib once a day for 8 weeks;

b) evaluating the patient for clinical response at 8 weeks after the administration of the initial said 45 mg induction dose of upadacitinib, and if the patient has not achieved clinical response per Adapted Mayo score at 8 weeks after the administration of the initial said 45 mg induction dose of upadacitinib;

c) continuing to orally administer to the patient a 45 mg dose of upadacitinib once a day for an additional 8 weeks, wherein the patient achieves clinical response per Adapted Mayo score at 16 weeks after the administration of the initial said 45 mg induction dose of upadacitinib; and

d) administering a first maintenance dose of 15 mg or 30 mg upadacitinib to the patient after the last induction dose is administered, and administering at least one additional maintenance dose of 15 mg or 30 mg upadacitinib to the patient once daily thereafter, whereby the clinical response is maintained.

[0017f] In

one embodiment, the patient is an adult with moderately to severely active Crohn's disease and has had an inadequate response to, or were intolerant to, corticosteroid, immunomodulator, or biologic therapy.

[0018] In one embodiment, the present disclosure is directed to a method of inducing clinical remission of Crohn's disease in a patient, said method comprising: a) administering to the patient at least one induction dose of (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide (upadacitinib), or a pharmaceutically acceptable salt or solid state form thereof, wherein said induction dose comprises 30 to 45 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the method further comprises maintaining the clinical remission of Crohn's disease, wherein the method further comprises b) administering a first maintenance dose of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof to the patient after the last induction dose is administered; and c) administering at least one additional maintenance dose once daily thereafter.

[0019] In another embodiment, the present disclosure is directed to a method of inducing endoscopic improvement of Crohn's disease in a patient, said method comprising: a) administering to the patient at least one induction dose of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, wherein said induction dose comprises 30 to 45 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the method further comprises maintaining the endoscopic improvement of Crohn's disease, wherein the method further comprises b) administering a first maintenance dose of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof to the patient after the last induction dose is administered; and c) administering at least one additional maintenance dose once daily thereafter.

[0020] In another embodiment, the present disclosure is directed to a method of inducing clinical remission of Crohn's disease in a patient, said method comprising: a) administering to the patient at least one induction dose of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, wherein said induction dose comprises 45 mg of upadacitinib, or a pharmaceutically acceptable or solid state form salt thereof. In one embodiment, the method further comprises maintaining the clinical remission of Crohn's disease, wherein the method further comprises b) administering a first maintenance dose of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof to the patient after the last induction dose is administered; and c) administering at least one additional maintenance dose once daily thereafter.

[0021] In another embodiment, the present disclosure is directed to a method of inducing endoscopic remission of Crohn's disease in a patient, said method comprising: a) administering to the patient at least one induction dose of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, wherein said induction dose comprises 45 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the method further comprises maintaining the endoscopic remission of Crohn's disease, wherein the method further comprises b) administering a first maintenance dose of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof to

the patient after the last induction dose is administered; and c) administering at least one additional maintenance dose once daily thereafter.

[0022] In one embodiment, the induction dose comprises 45 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof.

[0023] In one embodiment, the patient had an inadequate response to or experienced intolerance to a previous treatment with a corticosteroid, an immunosuppressant, or a biologic agent. In one embodiment, the patient had an inadequate response to or experienced intolerance to a previous treatment with an anti-TNF agent. In one embodiment, the patient had moderately to severely active Crohn's disease prior to administration of the induction dose.

[0024] In one embodiment, the induction dose is administered orally to the patient. In one embodiment, the induction dose is administered once daily to the patient.

[0025] In one embodiment, clinical remission is achieved within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, clinical remission is achieved within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof.

[0026] In one embodiment, endoscopic improvement is achieved within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, endoscopic improvement is achieved within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof.

[0027] In one embodiment, clinical remission is achieved within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, clinical remission is achieved within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof.

[0028] In one embodiment, endoscopic remission is achieved within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, endoscopic remission is achieved within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof.

[0029] In one embodiment, after administration of at least one induction dose, the patient's Simplified Endoscopic Score for Crohn's Disease (SES-CD) is greater than a 50% decrease or endoscopic remission versus the patient's baseline SES-CD. In one embodiment, after administration of at least one induction dose, the patient's Simplified Endoscopic Score for Crohn's Disease (SES-CD) is at least a 2 point reduction versus the patient's baseline SES-CD. In one embodiment, after administration of at least one induction dose, the patient achieves an endoscopic remission. In one embodiment, after administration of at least one induction dose, the patient achieves a clinical response. In one embodiment, the patient achieves a clinical response as early as two weeks from the first induction dose. In one embodiment, after administration of at least one induction dose, the patient achieves a CDAI score of less than 150.

[0030] In one embodiment, the first maintenance dose comprises 15 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the first maintenance dose comprises 30 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof.

[0031] In one embodiment, the at least one additional maintenance dose comprises 15 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the at least one additional maintenance dose comprises 30 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof.

[0032] In one embodiment, the first maintenance dose and said at least one additional maintenance dose are administered orally. In one embodiment, the first maintenance dose and said at least one additional maintenance dose are administered once daily.

[0033] In one embodiment, the patient maintains clinical remission. In one embodiment, the patient maintains endoscopic improvement. In one embodiment, the patient maintains endoscopic remission.

[0034] In one embodiment, the patient maintains a Simplified Endoscopic Score for Crohn's Disease (SES-CD) that is greater than a 50% decrease or endoscopic remission versus the patient's baseline SES-CD. In one embodiment, the said patient maintains a Simplified Endoscopic Score for Crohn's Disease (SES-CD) that is at least a 2 point reduction versus the patient's baseline SES-CD. In one embodiment, the patient maintains an endoscopic remission. In one embodiment, the patient maintains a CDAI score of less than 150. In one embodiment, the patient maintains a clinical response.

[0035] In one embodiment, the patient achieves a CDAI score of less than 150 before administration of the first maintenance dose. In one embodiment, the patient achieves a clinical response before administration of the first maintenance dose.

[0036] In one embodiment, the induction dose comprises 45 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, administered orally once daily, the first maintenance dose comprises 30 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, administered orally once daily, and the at least one additional maintenance dose comprises 30 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, administered orally once daily.

[0037] In one embodiment, the induction dose comprises 45 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, administered orally once daily, the first maintenance dose comprises 15 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, administered orally once daily, and the at least one additional maintenance dose comprises 15 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, administered orally once daily.

[0038] In one embodiment, the induction dose is in a once-daily, modified release formulation. In one embodiment, the first maintenance dose and the at least one additional maintenance dose are each in a once-daily, modified release formulation.

[0039] In one embodiment, the present disclosure is directed to a method for treating Crohn's disease comprising administering to a patient 15 mg to 45 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the method comprising administering 15 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the method comprising administering 30 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the method comprising administering 45 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof is administered orally to the patient. In one embodiment, upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof is administered once daily to the patient.

[0040] In one embodiment, the present disclosure is directed to a method for treating Crohn's disease comprising: a) administering to a patient at least one induction dose of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, wherein said induction dose comprises 45 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the method further comprises b) administering a first maintenance dose of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof to the patient after the last induction dose is administered; and c) administering at least one additional maintenance dose to the patient once daily thereafter.

[0041] In one such embodiment, the first maintenance dose comprises 15 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the first maintenance dose comprises 30 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the first maintenance dose is administered orally.

[0042] In one embodiment, the at least one additional maintenance dose comprises 15 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the at least one additional maintenance dose comprises 30 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the at least one additional maintenance dose is administered orally.

[0043] In one embodiment, the patient maintains a CDAI score of less than 150.

[0044] In one embodiment, the patient had an inadequate response to or experienced intolerance to a previous treatment with a corticosteroid, an immunosuppressant, or a biologic agent. In one embodiment, the patient had an inadequate response to or experienced intolerance to a previous treatment with an anti-TNF agent.

[0045] In one embodiment, the patient achieves a clinical remission after administration of at least one induction dose. In one embodiment, the patient achieves an endoscopic improvement after administration of at least one induction dose. In one embodiment, the patient achieves an endoscopic remission after administration of at least one induction dose. In one embodiment, the patient achieves a clinical response after administration of at least one induction dose.

[0046] In one embodiment, the induction dose comprises 45 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, administered orally once daily, said first maintenance dose comprises 30 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, administered orally once daily, and said at least one additional maintenance dose comprises 30 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, administered orally once daily.

[0047] In one embodiment, the induction dose comprises 45 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, administered orally once daily, said first maintenance dose comprises 15 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, administered orally once daily, and said at least one additional maintenance dose comprises 15 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, administered orally once daily.

[0048] In one embodiment, the induction dose is in a once-daily, modified release formulation. In one embodiment, the first maintenance dose and the at least one additional maintenance dose are each in a once-daily, modified release formulation. In one embodiment, the patient had moderately to severely active Crohn's disease prior to administration of the induction dose.

[0049] In one embodiment, the present disclosure is directed to a method of inducing remission in a patient having moderately to severely active Crohn's disease, the method comprising administering 45 mg of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof, to the patient. In one such embodiment, the patient had an inadequate response to or was intolerant to aminosalicylates, corticosteroids, immunosuppressants, biologic agents, anti-TNF agents, or combinations thereof.

[0050] In one embodiment, the present disclosure is directed to a method of inducing clinical remission in a patient having moderately to severely active Crohn's disease the method comprising administering 45 mg of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof, to the patient. In one such embodiment, the patient had an inadequate response to or was intolerant to aminosalicylates, corticosteroids, immunosuppressants, biologic agents, anti-TNF agents, or combinations thereof.

[0051] In one embodiment, the present disclosure is directed to a method of inducing endoscopic improvement in a patient having moderately to severely active Crohn's disease the method comprising administering 45 mg of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof to the patient. In one such embodiment, the patient had an inadequate response to or was intolerant to aminosalicylates, corticosteroids, immunosuppressants, biologic agents, anti-TNF agents, or combinations thereof.

[0052] In one embodiment, the present disclosure is directed to a method of treating a refractory patient having moderately to severely active Crohn's disease the method comprising administering 45 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, to the patient. In one such embodiment, clinical remission is induced within 16 weeks of administering the initial dose of

upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one such embodiment, endoscopic improvement is induced within 12 weeks or within 16 weeks of administering the initial dose of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof.

[0053] In one embodiment, the induction dose comprises 45 mg of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In another embodiment, the first maintenance dose and/or the at least one additional maintenance doses comprise 15 mg to 30 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof.

[0054] In one embodiment, the present disclosure is directed to a method of inducing a clinical response in a patient with moderately to severely active ulcerative colitis, said method comprising: a) administering to the patient at least one induction dose of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, wherein said induction dose comprises 45 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one such embodiment, the clinical response is a clinical response is wherein the patient has a decrease from a baseline Adapted Mayo score greater than or equal to 2 points and greater than or equal to 30% accompanied by a decrease in rectal bleeding subscore of greater than or equal to 1 or an absolute rectal bleeding subscore of 0 or 1. In another such embodiment, the clinical response is a clinical response is wherein the patient has a decrease from a baseline Full Mayo score greater than or equal to 3 points and greater than or equal to 30% accompanied by a decrease in rectal bleeding subscore from baseline of greater than or equal to 1 or an absolute rectal bleeding subscore of 0 or 1.

[0055] In yet another embodiment, the method further comprising maintaining the clinical response, said method further comprising: b) administering a first maintenance dose of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof to the patient after the last induction dose is administered; and c) administering at least one additional maintenance dose once daily thereafter.

[0056] In another embodiment, the induction dose comprises 45 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In another embodiment, the first maintenance dose and/or the at least one additional maintenance dose comprises 15 mg to 30 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof.

[0057] In one embodiment, the method of the present disclosure is a method of inducing clinical remission of Crohn's disease in a patient, the method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 4 weeks and comprises 45 mg of upadacitinib, or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; and b) wherein said patient achieves clinical remission within 12 weeks of administration of the first induction dose.

[0058] In one embodiment, clinical remission of Crohn's disease is induced within 4 weeks of the first induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof.

[0059] In one embodiment, the method is a method of inducing clinical response of Crohn's disease in a patient, said method comprising: a) administering to the patient an induction dose of

upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 2 weeks and comprises 45 mg of upadacitinib or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; and b) wherein said patient achieves clinical response.

[0060] In one embodiment, the clinical response of Crohn's disease is induced within 4 weeks of the first induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof. In one embodiment, the clinical response of Crohn's disease is induced within 12 weeks of the first induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof.

[0061] In one embodiment, the method is a method of inducing endoscopic remission of Crohn's disease in a patient, said method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 12 weeks and comprises 45 mg of upadacitinib, or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; and b) wherein said patient achieves endoscopic remission within 12 weeks of administration of the first induction dose.

[0062] In one embodiment, the endoscopic remission of Crohn's disease is induced within 4 weeks of the first induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof.

[0063] In one embodiment, the endoscopic remission of Crohn's disease is induced within 12 weeks of the first induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof.

[0064] In one embodiment, the method is a method of inducing endoscopic response of Crohn's disease in a patient, said method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 12 weeks and comprises 45 mg of upadacitinib, or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; and b) wherein said patient achieves endoscopic response within 12 weeks of administration of the first induction dose.

[0065] In one embodiment, the endoscopic response of Crohn's disease is induced within 12 weeks of the first induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof.

[0066] In one embodiment, the method is a method of inducing corticosteroid-free remission of Crohn's disease in a patient, said method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 12 weeks and comprises 45 mg of upadacitinib, or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; and b) wherein said patient achieves steroid-free remission within 4 weeks of administration of the first induction dose.

[0067] In one embodiment, the patient is an adult with moderately to severely active Crohn's disease.

[0068] In one embodiment, the patient experiences a CDAI reduction of greater than 150 within 12 weeks of administration of the first induction dose.

[0069] In one embodiment, the patient had an inadequate response to or experienced intolerance to a previous treatment with a corticosteroid, an immunosuppressant, or a biologic agent.

[0070] In one embodiment, the patient had an inadequate response to or experienced intolerance to a previous treatment with an anti-TNF agent.

[0071] In one embodiment, the patient had an inadequate response to or experienced intolerance to an infliximab, adalimumab or certolizumab pegol.

[0072] In one embodiment, the patient has had a diagnosis of Crohn's disease for more than ten years and has had an inadequate response to or experienced intolerance to one or more previous treatments. In one embodiment, the previous treatments are selected from the group consisting of corticosteroids, immunosuppressants, antibiotics and biologic therapies.

[0073] In one embodiment, the method comprises a method of inducing and maintaining clinical remission of Crohn's disease in a patient, said method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 4 weeks and comprises 45 mg of upadacitinib, or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; b) wherein said patient achieves clinical remission within 12weeks of administration of the first induction dose; c) administering to the patient a first maintenance dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said first maintenance dose is administered orally once a day and comprises 30 mg of upadacitinib, or a 30 mg free base equivalent amount of a pharmaceutically acceptable salt thereof after the last induction dose is administered; d) administering at least one additional maintenance dose to the patient of upadacitinib, or a pharmaceutically acceptable salt thereof; and e) wherein said patient maintains clinical remission for 52 weeks after administration of the first induction dose.

[0074] In one embodiment, the method comprises a method of inducing and maintaining clinical response of Crohn's disease in a patient, said method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 2 weeks and comprises 45 mg of upadacitinib, or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; and b) wherein said patient achieves clinical response within 2 weeks of administration of the first induction dose; c) administering to the patient a first maintenance dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said first maintenance dose is administered orally once a day and comprises 30 mg of upadacitinib, or a 30 mg free base equivalent amount of a pharmaceutically acceptable salt thereof after the last induction dose is administered; d) administering at least one additional maintenance dose to the patient of upadacitinib, or a pharmaceutically acceptable salt thereof, and e) wherein said patient maintains clinical response for 52 weeks after administration of the first induction dose.

[0075] In one embodiment, the clinical response of Crohn's disease is induced within 4 weeks of the first induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof.

[0076] In one embodiment, the clinical response of Crohn's disease is induced within 12 weeks of the first induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof.

[0077] In one embodiment, the method comprises a method of inducing and maintaining endoscopic remission of Crohn's disease in a patient, said method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 4 weeks and comprises 45 mg of upadacitinib, or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; and b) wherein said patient achieves endoscopic remission within 12 weeks of administration of the first induction dose; c) administering to the patient a first maintenance dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said first maintenance dose is administered orally once a day and comprises 30 mg of upadacitinib, or a 30 mg free base equivalent amount of a pharmaceutically acceptable salt thereof after the last induction dose is administered; d) administering at least one additional maintenance dose to the patient of upadacitinib, or a pharmaceutically acceptable salt thereof; and e) wherein said patient maintains endoscopic remission for 52 weeks after administration of the first induction dose.

[0078] In one embodiment, the endoscopic remission of Crohn's disease is induced within 12 weeks of the first induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof.

[0079] In one embodiment, the method is a method of inducing and maintaining endoscopic response of Crohn's disease in a patient, said method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 4 weeks and comprises 45 mg of upadacitinib, or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; and b) wherein said patient achieves endoscopic response within 4 weeks of administration of the first induction dose; c) administering to the patient a first maintenance dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said first maintenance dose is administered orally once a day and comprises 30 mg of upadacitinib, or a 30 mg free base equivalent amount of a pharmaceutically acceptable salt thereof after the last induction dose is administered; d) administering at least one additional maintenance dose to the patient of upadacitinib, or a pharmaceutically acceptable salt thereof; and e) wherein said patient maintains endoscopic response for 52 weeks after administration of the first induction dose.

[0080] In one embodiment, the endoscopic response of Crohn's disease is induced within 12 weeks of the first induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof.

[0081] In one embodiment, the method is a method of inducing and maintaining corticosteroid-free remission of Crohn's disease in a patient, said method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 12 weeks and comprises 45 mg of upadacitinib, or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; b) wherein said patient achieves steroid-free remission within 4 weeks of administration of the first induction dose; c) administering to the patient a first maintenance dose of upadacitinib, or a pharmaceutically acceptable salt

thereof, wherein said first maintenance dose is administered orally once a day and comprises 30 mg of upadacitinib, or a 30 mg free base equivalent amount of a pharmaceutically acceptable salt thereof after the last induction dose is administered and; d) administering at least one additional maintenance dose to the patient of upadacitinib, or a pharmaceutically acceptable salt thereof; and e) wherein said patient maintains corticosteroid-free remission for 52 weeks after administration of the first induction dose.

[0082] In one embodiment, the patient is an adult with moderately to severely active Crohn's disease.

[0083] In one embodiment, the patient experiences improvement in stool frequency one week after the first induction dose. In one embodiment the patient experiences improvement in abdominal pain at 8 weeks after the first induction dose.

[0084] In one embodiment, the patient experiences a CDAI reduction of greater than 150 within 12 weeks of administration of the first induction dose.

[0085] In one embodiment, the patient had an inadequate response to or experienced intolerance to a previous treatment with a corticosteroid, an immunosuppressant, or a biologic agent.

[0086] In one embodiment, the patient had an inadequate response to or experienced intolerance to a previous treatment with an anti-TNF agent.

[0087] In one embodiment, the anti-TNF agent is infliximab, adalimumab or certolizumab pegol.

[0088] In one embodiment, the patient has had a diagnosis of Crohn's disease for more than ten years and has had an inadequate response to or experienced intolerance to a previous treatment.

[0089] In one embodiment, the previous treatments are selected from corticosteroids, immunosuppressants, antibiotics and biologic therapies.

[0090] In one embodiment, the method is a method of inducing and maintaining clinical remission of Crohn's disease in a patient, said method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 4 weeks and comprises 45 mg of upadacitinib, or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; b) wherein said patient achieves clinical remission within 4 weeks of administration of the first induction dose; c) administering to the patient a first maintenance dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said first maintenance dose is administered orally once a day and comprises 15 mg of upadacitinib, or a 15 mg free base equivalent amount of a pharmaceutically acceptable salt thereof after the last induction dose is administered; d) administering at least one additional maintenance dose to the patient of upadacitinib, or a pharmaceutically acceptable salt thereof; and e) wherein said patient maintains clinical remission for 52 weeks after administration of the first induction dose.

[0091] In one embodiment, the method is a method of inducing and maintaining clinical response of Crohn's disease in a patient, said method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 2 weeks and comprises 45 mg of upadacitinib, or a 45 mg

free base equivalent amount of a pharmaceutically acceptable salt thereof; and b) wherein said patient achieves clinical response within 2 weeks of administration of the first induction dose; c) administering to the patient a first maintenance dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said maintenance dose is administered orally once a day and comprises 15 mg of upadacitinib, or a 15 mg free base equivalent amount of a pharmaceutically acceptable salt thereof after the last induction dose is administered; d) administering at least one additional maintenance dose to the patient of upadacitinib, or a pharmaceutically acceptable salt thereof, and e) wherein said patient maintains clinical response for 52 weeks after administration of the first induction dose.

[0092] In one embodiment, the clinical response of Crohn's disease is induced within 4 weeks of the first induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof.

[0093] In one embodiment, the clinical response of Crohn's disease is induced within 12 weeks of the first induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof.

[0094] In one embodiment, the method is a method of inducing and maintaining endoscopic remission of Crohn's disease in a patient, said method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 4 weeks and comprises 45 mg of upadacitinib, or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; and b) wherein said patient achieves endoscopic remission within 4 weeks of administration of the first induction dose; c) administering to the patient a first maintenance dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said first maintenance dose is administered orally once a day and comprises 15 mg of upadacitinib, or a 15 mg free base equivalent amount of a pharmaceutically acceptable salt thereof after the last induction dose is administered; d) administering at least one additional maintenance dose to the patient of upadacitinib, or a pharmaceutically acceptable salt thereof; and e) wherein said patient maintains endoscopic remission for 52 weeks after administration of the first induction dose.

[0095] In one embodiment, the method is a method of inducing and maintaining endoscopic remission of Crohn's disease in a patient, said method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 12 weeks and comprises 45 mg of upadacitinib, or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; and b) wherein said patient achieves endoscopic remission within 4 weeks of administration of the first induction dose; c) administering to the patient a first maintenance dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said first maintenance dose is administered orally once a day and comprises 15 mg of upadacitinib, or a 15 mg free base equivalent amount of a pharmaceutically acceptable salt thereof after the last induction dose is administered; d) administering at least one additional maintenance dose to the patient of upadacitinib, or a pharmaceutically acceptable salt thereof; and e) wherein said patient maintains endoscopic remission for 52 weeks after administration of the first induction dose.

[0096] In one embodiment, the endoscopic remission of Crohn's disease is induced within 12 weeks of the first induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof.

[0097] In one embodiment, the method is a method of inducing and maintaining endoscopic response of Crohn's disease in a patient, said method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 4 weeks and comprises 45 mg of upadacitinib, or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; and b) wherein said patient achieves endoscopic response within 4 weeks of administration of the first induction dose; c) administering to the patient a first maintenance dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said maintenance dose is administered orally once a day and comprises 15 mg of upadacitinib, or a 15 mg free base equivalent amount of a pharmaceutically acceptable salt thereof after the last induction dose is administered; d) administering at least one additional maintenance dose to the patient of upadacitinib, or a pharmaceutically acceptable salt thereof; and e) wherein said patient maintains endoscopic response for 52 weeks after administration of the first induction dose.

[0098] In one embodiment, the endoscopic response of Crohn's disease is induced within 12 weeks of the first induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof.

[0099] In one embodiment, the method is a method of inducing and maintaining corticosteroid-free remission of Crohn's disease in a patient, said method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 12 weeks and comprises 45 mg of upadacitinib, or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; b) wherein said patient achieves steroid-free remission within 12weeks of administration of the first induction dose; c) administering to the patient a first maintenance dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said first maintenance dose is administered orally once a day and comprises 15 mg of upadacitinib, or a 15 mg free base equivalent amount of a pharmaceutically acceptable salt thereof after the last induction dose is administered and; d) administering at least one additional maintenance dose to the patient of upadacitinib, or a pharmaceutically acceptable salt thereof; and e) wherein said patient maintains corticosteroid-free remission for 52 weeks after administration of the first induction dose.

[0100] In one embodiment, the patient is an adult with moderately to severely active Crohn's disease.

[0101] In one embodiment, the patient experiences a CDAI reduction of > 150 within 12 weeks of administration of the first induction dose.

[0102] In one embodiment, the patient had an inadequate response to or experienced intolerance to a previous treatment with a corticosteroid, an immunosuppressant, or a biologic agent.

[0103] In one embodiment, the patient had an inadequate response to or experienced intolerance to a previous treatment with an anti-TNF agent.

[0104] In one embodiment, the patient had an inadequate response to or experienced intolerance to a previous treatment anti-TNF agent is infliximab, adalimumab or certolizumab pegol.

[0105] In one embodiment, the patient has had a diagnosis of Crohn's disease for more than ten years and has had an inadequate response to or experienced intolerance to one or more previous treatment.

[0106] In one embodiment, the method comprises a method wherein the previous treatments are selected from corticosteroids, immunodulators, antibiotics and biologic therapies.

[0107] In one embodiment, the method comprises inducing clinical remission of ulcerative colitis in a patient, said method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 4 weeks and comprises 45 mg of upadacitinib, or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; and b) wherein said patient achieves clinical remission within 4 weeks of administration of the first induction dose.

[0108] In one embodiment, the method comprises inducing clinical remission of ulcerative colitis in a patient, said method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 6 weeks and comprises 45 mg of upadacitinib, or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; and b) wherein said patient achieves clinical remission within 6 weeks of administration of the first 45 mg induction dose.

[0109] In one embodiment, the method comprises inducing clinical remission of ulcerative colitis in a patient, said method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 8 weeks and comprises 45 mg of upadacitinib, or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; and b) wherein said patient achieves clinical remission within 8 weeks of administration of the first 45 mg induction dose.

[0110] In one embodiment, the method comprises a method of inducing endoscopic improvement of ulcerative colitis in a patient, said method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 8 weeks and comprises 45 mg of upadacitinib, or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; and b) wherein said patient achieves endoscopic improvement within 8 weeks of administration of the first induction dose.

[0111] In one embodiment, the method comprises a method of inducing endoscopic remission of ulcerative colitis in a patient, said method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 8 weeks and comprises 45 mg of upadacitinib, or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; and b) wherein said patient achieves endoscopic remission within 8 weeks of administration of the first 45 mg induction dose.

[0112] In one embodiment, the patient has moderately to severely active ulcerative colitis.

[0113] In one embodiment, the patient is taking corticosteroids at the time of the first induction dose.

[0114] In one embodiment, the clinical remission, endoscopic improvement or endoscopic remission is corticosteroid free.

[0115] In one embodiment, the patient demonstrated an inadequate response to, loss of response to or intolerance to one or more corticosteroids, immunosuppressants or biologic therapies.

[0116] In one embodiment, the immunosuppressants are selected form oral azathioprine, 6-mercaptopurine, injectable methotrexate and tacrolimus.

[0117] In one embodiment, the biologic therapy is selected from infliximab, adalimumab, golimumab and vedolizumab.

[0118] In one embodiment, the inadequate response in said patient taking corticosteroids is defined as said patient experiencing signs and symptoms of persistently active disease despite a history of at least one induction regimen that included a dose equivalent to prednisone ≥40 mg/day orally for 3 to 4 weeks or intravenously for one week.

[0119] In one embodiment, the patient is unable to taper corticosteroid below a dose equivalent to prednisone 10 mg daily orally without recurrent active disease.

[0120] In one embodiment, the intolerance of said patient to corticocosteroids leads to Cushing's syndrome, osteopenia, osteoporosis, hyperglycemia, insominia or infection.

[0121] In one embodiment, the patient experiencing the inadequate response to immunosuppressants experienced signs and symptoms of persistently active disease despite a history of at least one 90-day regimen of oral azathioprine, 6-mercaptopurine, injectable methotrexate or tacrolimus.

[0122] In one embodiment, the patient experiencing the inadequate response to immunosuppressants experienced nausea, vomiting, abdominal pain, pancreatitis, liver enzyme abnormalities, lymphopenia or infection.

[0123] In one embodiment, the patient experiencing the inadequate response to biologic therapies experienced signs and symptoms of persistently active disease despite a history of a) at least one 6-week induction regimen of infliximab comprising a ≥5 mg/kg intravenous dose at 0, 2 and 6 weeks; b) at least one 4-week induction regimen of adalimumab comprising one 160 mg subcutaneous dose followed by one 80 mg subcutaneous dose or one 80 mg subcutaneous dose, followed by one 40 mg subcutaneous dose at least two weeks apart; c) at least one 2-week induction regimen of golimumab comprising one 200 mg subcutaneous dose followed by one 100 mg subcutaneous dose at least 2 weeks apart); d) at least one 6-week induction regimen of vedolizumab comprising a 300 mg intravenous dose at 0, 2 and 6 weeks.

[0124] In one embodiment, the patient experiencing inadequate response to biologic therapies experienced recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit.

[0125] In one embodiment, the patient experiencing intolerance to biologic therapies experienced infusion-related reaction, demyelination, congestive heart failure or infection.

[0126] In one embodiment, the method is a method of inducing and maintaining clinical remission of ulcerative colitis in a patient, said method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 4 weeks and comprises 45 mg of upadacitinib, or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; b) wherein said patient achieves clinical remission within 4 weeks of administration of the first induction dose) administering to the patient a first maintenance dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said first maintenance dose is administered orally once a day and comprises 30 mg of upadacitinib, or a 30 mg free base equivalent amount of a pharmaceutically acceptable salt thereof after the last induction dose is administered; d) administering at least one additional maintenance dose to the patient of upadacitinib, or a pharmaceutically acceptable salt thereof; and e) wherein said patient maintains clinical remission for 52 weeks after administration of the first induction dose.

[0127] In one embodiment, the method is a method of inducing and maintaining clinical remission of ulcerative colitis in a patient, said method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 6 weeks and comprises 45 mg of upadacitinib, or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; b) wherein said patient achieves clinical remission within 6 weeks of administration of the first 45 mg induction dose; and c) administering to the patient a first maintenance dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said first maintenance dose is administered orally once a day and comprises 30 mg of upadacitinib, or a 30 mg free base equivalent amount of a pharmaceutically acceptable salt thereof after the last induction dose is administered; d) administering at least one additional maintenance dose to the patient of upadacitinib, or a pharmaceutically acceptable salt thereof; and e) wherein said patient maintains clinical remission for 52 weeks after administration of the first induction dose.

[0128] In one embodiment, the method is a method of inducing and maintaining clinical remission of ulcerative colitis in a patient, said method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 8 weeks and comprises 45 mg of upadacitinib, or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; and b) wherein said patient achieves clinical remission within 8 weeks of administration of the first 45 mg induction dose; c) administering to the patient a first maintenance dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said first maintenance dose is administered orally once a day and comprises 30 mg of upadacitinib, or a 30 mg free base equivalent amount of a pharmaceutically acceptable salt thereof after the last induction dose is administered; d) administering at least one additional maintenance dose to the patient of upadacitinib, or a pharmaceutically acceptable salt thereof; and e) wherein said patient maintains clinical remission for 52 weeks after administration of the first induction dose.

[0129] In one embodiment, the method is inducing and maintaining endoscopic improvement of ulcerative colitis in a patient, said method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 8 weeks and comprises 45 mg of upadacitinib, or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; and b) wherein said patient achieves endoscopic improvement within 8 weeks of administration of the first induction dose; c) administering to the patient a first maintenance dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said first maintenance dose is administered orally once a day and comprises 30 mg of upadacitinib, or a 30 mg free base equivalent amount of a pharmaceutically acceptable salt thereof after the last induction dose is administered; d) administering at least one additional maintenance dose to the patient of upadacitinib, or a pharmaceutically acceptable salt thereof; and e) wherein said patient maintains clinical remission for 52 weeks after administration of the first induction dose.

[0130] In one embodiment, the method comprises inducing and maintaining endoscopic remission of ulcerative colitis in a patient, said method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 8 weeks and comprises 45 mg of upadacitinib, or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; and b) wherein said patient achieves endoscopic remission within 8 weeks of administration of the first 45 mg induction dose; c) administering to the patient a first maintenance dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said first maintenance dose is administered orally once a day and comprises 30 mg of upadacitinib, or a 30 mg free base equivalent amount of a pharmaceutically acceptable salt thereof after the last induction dose is administered; d) administering at least one additional maintenance dose to the patient of upadacitinib, or a pharmaceutically acceptable salt thereof; and e) wherein said patient maintains clinical remission for 52 weeks after administration of the first induction dose.

[0131] In one embodiment, the method comprises inducing and maintaining endoscopic remission of ulcerative colitis in a patient, said method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 8 weeks and comprises 45 mg of upadacitinib, or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; and b) wherein said patient achieves endoscopic remission within 8 weeks of administration of the first 45 mg induction dose; c) administering to the patient a first maintenance dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said first maintenance dose is administered orally once a day and comprises 15 mg of upadacitinib, or a 15 mg free base equivalent amount of a pharmaceutically acceptable salt thereof after the last induction dose is administered; d) administering at least one additional maintenance dose to the patient of upadacitinib, or a pharmaceutically acceptable salt thereof; and e) wherein said patient maintains clinical remission for 52 weeks after administration of the first induction dose.

[0132] In one embodiment, the patient has moderately to severely active ulcerative colitis. In one embodiment the patient is an adult. In one embodiment, the patient has had an inadequate response corticosteroid, immunomodulatory or biologic therapy. In one embodiment, the patient has had loss of response to aminosalicylate, corticosteroid, immunomodulatory or biologic therapy. In one embodiment, the patient was intolerant to corticosteroid, immunomodulatory or biologic therapy. In one embodiment, the patient is an adult and has moderately to severely active ulcerative colitis and has had an inadequate response to, loss of response to, or was intolerant to aminosalicylate, corticosteroid, immunomodulatory (IMM), or biologic therapy.

[0133] In one embodiment, the patient is taking corticosteroids at the time of the first induction dose.

[0134] In one embodiment, the clinical remission, endoscopic improvement or endoscopic remission is corticosteroid free.

[0135] In one embodiment, the patient demonstrated an inadequate response to, loss of response to or intolerance to one or more corticosteroids, immunosuppressants or biologic therapies.

[0136] In one embodiment, the immunosuppressants are selected form oral azathioprine, 6-mercaptopurine, injectable methotrexate and tacrolimus.

[0137] In one embodiment, the biologic therapy is selected from infliximab, adalimumab, golimumab and vedolizumab.

[0138] In one embodiment, the inadequate response in said patient taking corticosteroids is defined as said patient experiencing signs and symptoms of persistently active disease despite a history of at least one induction regimen that included a dose equivalent to prednisone ≥40 mg/day orally for 3 to 4 weeks or intravenously for one week.

[0139] In one embodiment, the patient is unable to taper corticosteroid below a dose equivalent to prednisone 10 mg daily orally without recurrent active disease.

[0140] In one embodiment, the intolerance of said patient to corticocosteroids leads to Cushing's syndrome, osteopenia, osteoporosis, hyperglycemia, insominia or infection.

[0141] In one embodiment, the patient experiencing the inadequate response to immunosuppressants experienced signs and symptoms of persistently active disease despite a history of at least one 90-day regimen of oral azathioprine, 6-mercaptopurine, injectable methotrexate or tacrolimus.

[0142] In one embodiment, the patient experiencing the inadequate response to immunosuppressants experienced nausea, vomiting, abdominal pain, pancreatitis, liver enzyme abnormalities, lymphopenia or infection.

[0143] In one embodiment, the ulcerative colitis or Crohn's disease patient experiencing the inadequate response to biologic therapies experienced signs and symptoms of persistently active disease despite a history of a) at least one 6-week induction regimen of infliximab comprising a ≥5 mg/kg intravenous dose at 0, 2 and 6 weeks; b) at least one 4-week induction regimen of adalimumab comprising one 160 mg subcutaneous dose followed by one 80 mg subcutaneous dose or one 80 mg subcutaneous

dose, followed by one 40 mg subcutaneous dose at least two weeks apart; c) at least one 2-week induction regimen of golimumab comprising one 200 mg subcutaneous dose followed by one 100 mg subcutaneous dose at least 2 weeks apart; d) at least one 6-week induction regimen of vedolizumab comprising a 300 mg intravenous dose at 0, 2 and 6 weeks.

[0144] In one embodiment, the patient experiencing inadequate response to biologic therapies experienced recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit.

[0145] In one embodiment, the patient experiencing intolerance to biologic therapies experienced infusion-related reaction, demyelination, congestive heart failure or infection.

[0146] In one embodiment, the method is a method of inducing and maintaining clinical remission of ulcerative colitis in a patient, said method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 4 weeks and comprises 45 mg of upadacitinib, or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; b) wherein said patient achieves clinical remission within 4 weeks of administration of the first induction dose; c) administering to the patient a first maintenance dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said first maintenance dose is administered orally once a day and comprises 15 mg of upadacitinib, or a 15 mg free base equivalent amount of a pharmaceutically acceptable salt thereof after the last induction dose is administered; d) administering at least one additional maintenance dose to the patient of upadacitinib, or a pharmaceutically acceptable salt thereof; and e) wherein said patient maintains clinical remission for 52 weeks after administration of the first induction dose.

[0147] In one embodiment, the method is a method of inducing and maintaining clinical remission of ulcerative colitis in a patient, said method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 6 weeks and comprises 45 mg of upadacitinib, or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; b) wherein said patient achieves clinical remission within 6 weeks of administration of the first 45 mg induction dose; and c) administering to the patient a first maintenance dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said maintenance dose is administered orally once a day and comprises 15 mg of upadacitinib, or a 15 mg free base equivalent amount of a pharmaceutically acceptable salt thereof after the last induction dose is administered; d) administering at least one additional maintenance dose to the patient of upadacitinib, or a pharmaceutically acceptable salt thereof; and e) wherein said patient maintains clinical remission for 52 weeks after administration of the first induction dose.

[0148] In one embodiment, the method is a method of inducing and maintaining clinical remission of ulcerative colitis in a patient, said method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 8 weeks and comprises 45 mg of upadacitinib, or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; and b) wherein said patient

achieves clinical remission within 8 weeks of administration of the first 45 mg induction dose; c) administering to the patient a first maintenance dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said first maintenance dose is administered orally once a day and comprises 15 mg of upadacitinib, or a 15 mg free base equivalent amount of a pharmaceutically acceptable salt thereof after the last induction dose is administered; d) administering at least one additional maintenance dose to the patient of upadacitinib, or a pharmaceutically acceptable salt thereof; and e) wherein said patient maintains clinical remission for 52 weeks after administration of the first induction dose.

[0149] In one embodiment, the method is a method of inducing and maintaining endoscopic improvement of ulcerative colitis in a patient, said method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 8 weeks and comprises 45 mg of upadacitinib, or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; and b) wherein said patient achieves endoscopic improvement within 8 weeks of administration of the first induction dose; c) administering to the patient a first maintenance dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said first maintenance dose is administered orally once a day and comprises 15 mg of upadacitinib, or a 15 mg free base equivalent amount of a pharmaceutically acceptable salt thereof after the last induction dose is administered; d) administering at least one additional maintenance dose to the patient of upadacitinib, or a pharmaceutically acceptable salt thereof; and e) wherein said patient maintains clinical remission for 52 weeks after administration of the first induction dose.

[0150] In one embodiment, the method is a method of inducing and maintaining endoscopic remission of ulcerative colitis in a patient, said method comprising: a) administering to the patient an induction dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said induction dose is administered orally once a day for at least 8 weeks and comprises 45 mg of upadacitinib, or a 45 mg free base equivalent amount of a pharmaceutically acceptable salt thereof; and b) wherein said patient achieves endoscopic remission within 8 weeks of administration of the first 45 mg induction dose; c) administering to the patient a first maintenance dose of upadacitinib, or a pharmaceutically acceptable salt thereof, wherein said first maintenance dose is administered orally once a day and comprises 15 mg of upadacitinib, or a 15 mg free base equivalent amount of a pharmaceutically acceptable salt thereof after the last induction dose is administered; d) administering at least one additional maintenance dose to the patient of upadacitinib, or a pharmaceutically acceptable salt thereof; and e) wherein said patient maintains clinical remission for 52 weeks after administration of the first induction dose.

[0151] In one embodiment, the patient has moderately to severely active ulcerative colitis.

[0152] In one embodiment, the patient is taking corticosteroids at the time of the first induction dose.

[0153] In one embodiment, the clinical remission, endoscopic improvement or endoscopic remission is corticosteroid free.

[0154] In one embodiment, the patient demonstrated an inadequate response to, loss of response to or intolerance to one or more corticosteroids, immunosuppressants or biologic therapies.

[0155] In one embodiment, the immunosuppressants are selected form oral azathioprine, 6-mercaptopurine, injectable methotrexate and tacrolimus.

[0156] In one embodiment, the biologic therapy is selected from infliximab, adalimumab, golimumab and vedolizumab.

[0157] In one embodiment, the inadequate response in said patient taking corticosteroids is defined as said patient experiencing signs and symptoms of persistently active disease despite a history of at least one induction regimen that included a dose equivalent to prednisone ≥40 mg/day orally for 3 to 4 weeks or intravenously for one week.

[0158] In one embodiment, the patient is unable to taper corticosteroid below a dose equivalent to prednisone 10 mg daily orally without recurrent active disease.

[0159] In one embodiment, the intolerance of said patient to corticocosteroids leads to Cushing's syndrome, osteopenia, osteoporosis, hyperglycemia, insominia or infection.

[0160] In one embodiment, the patient experiencing the inadequate response to immunosuppressants experienced signs and symptoms of persistently active disease despite a history of at least one 90-day regimen of oral azathioprine, 6-mercaptopurine, injectable methotrexate or tacrolimus.

[0161] In one embodiment, the patient experiencing the intolerance to immunosuppressants experienced nausea, vomiting, abdominal pain, pancreatitis, liver enzyme abnormalities, lymphopenia or infection.

[0162] In one embodiment, the patient experiencing the inadequate response to biologic therapies experienced signs and symptoms of persistently active disease despite a history of a) at least one 6-week induction regimen of infliximab comprising a ≥5 mg/kg intravenous dose at 0, 2 and 6 weeks; b) at least one 4-week induction regimen of adalimumab comprising one 160 mg subcutaneous dose followed by one 80 mg subcutaneous dose or one 80 mg subcutaneous dose, followed by one 40 mg subcutaneous dose at least two weeks apart; c) at least one 2-week induction regimen of golimumab comprising one 200 mg subcutaneous dose followed by one 100 mg subcutaneous dose at least 2 weeks apart; d) at least one 6-week induction regimen of vedolizumab comprising a 300 mg intravenous dose at 0, 2 and 6 weeks.

[0163] In one embodiment, the patient experiencing inadequate response to biologic therapies experienced recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit.

[0164] In one embodiment, the patient experiencing intolerance to biologic therapies experienced infusion-related reaction, demyelination, congestive heart failure or infection.

BRIEF DESCRIPTION OF THE DRAWINGS

[0165] Figure 1 is a schematic representation of the study design for the clinical study described in Example 8.

[0166] Figure 2 is a schematic representation of the 36 week extension phase for the clinical study described in Example 8. Patients who did not adequately respond during the double-blind portion of the extension phase were eligible to receive open-label therapy.

[0167] Figures 3A-3I are graphs depicting the relationship between upadacitinib plasma concentration and clinical response (Week 16; Figure 3A), (NRI) clinical remission (Week 16; Figure 3B), modified clinical remission (Week 16; Figure 3C); decrease in CDAI $\geq$ 70 (Week 16; Figure 3D); decrease in CDAI $\geq$ 100 (Week 16; Figure 3E); CDAI <150 (Week 16; Figure 3F); endoscopic response (Week 12 or Week 16; Figure 3G); endoscopic improvement (Week 16; Figure 3H); and endoscopic remission (Week 12 or Week 16; Figure 3I) as determined in the Example 8 clinical study. Arrows indicate the median exposure (in mg) for each immediate release dose. The maximum and minimum plasma concentrations for each exposure bin are indicated in brackets.

[0168] Figures 4A-4F are graphs depicting the model-predicted efficacy (NRI) for different upadacitinib doses for immediate-release (IR) BID formulations or modified-release (MR) QD formulations (simulating for 200 patients/arm) at Weeks 12 or 16.. The predicted results are based on the exposure-response relationships as determined in the Example 8 study.

[0169] Figures 5A-5H are graphs depicting the relationship between upadacitinib plasma concentration and the change from baseline for select measured laboratory parameters at week 16 (LOCF) of the Example 8 clinical study. The maximum and minimum plasma concentrations for each data point are indicated in brackets.

[0170] Figures 6A and 6B are graphs depicting the percent of subjects who achieved clinical response or clinical remission at week 12 of the Example 8 study. Figure 6A shows results for subjects who were not on steroids at baseline, and Figure 6B shows results for subjects who were on steroids at baseline, and who underwent mandatory taper of steroid dose, starting at week 2 of the Example 8 clinical study.

[0171] Figure 7 shows the upadacitinib mean plasma concentration versus time following administration of 6 mg twice daily immediate release capsules (Regimen K) or a 15 mg once-daily modified release tablet (Regimen L) for seven days under fasting conditions.

[0172] Figure 8 shows the upadacitinib mean plasma concentration versus time following administration of 12 mg twice daily immediate release capsules (Regimen M) or a 30 mg once-daily modified release tablet (Regimen N) for seven days under fasting conditions.

[0173] Figure 9 shows the clinical remission and endoscopic response in a refractory patient population administered upadacitinib or placebo in the Example 8 Crohn's disease clinical study.

[0174] Figures 10A-10E are graphs depicting the percentage of subjects who achieved modified clinical remission at week 2 (Figure 10A), week 4 (Figure 10B), week 8 (Figure 10C), week 12 (Figure 10D) and week 16 (Figure 10E) of the Example 8 study.

[0175] Figures 11A-11E are graphs depicting the percentage of subjects who achieved enhanced clinical response at week 2 (Figure 11A), week 4 (Figure 11B), week 8 (Figure 11C), week 12 (Figure 11D) and week 16 (Figure 11E) of the Example 8 study.

[0176] Figure 12 shows the mean change in hs-CRP (percentage over baseline) versus time (weeks) following administration of placebo (PBO), upadacitinib at 3, 6, 12, 24 mg twice daily (BID) and 24 mg once daily (QD) for 16 weeks. Modified clinical remission was analyzed in patients with SF$\geqslant$4, AP$\geqslant$2.0 at baseline.

[0177] Figure 13 is a schematic representation of the study design for the ulcerative colitis clinical study described in Example 12.

[0178] Figure 14 schematically illustrates one method of preparing the Amorphous Freebase.

[0179] Figure 15 schematically illustrates one method of preparing the Freebase Hydrate Form C.

[0180] Figure 16 schematically illustrates one method of preparing the Tartrate Hydrate.

[0181] Figures 17A and 17B are powder X-ray diffraction patterns corresponding to the Amorphous Freebase (via precipitation) and the Amorphous Freebase (via dehydration), respectively.

[0182] Figure 18 is a powder X-ray diffraction pattern corresponding to the Freebase Solvate Form A (Isopropyl Acetate/Water Solvate).

[0183] Figure 19 is a powder X-ray diffraction pattern corresponding to the Freebase Hydrate Form B.

[0184] Figure 20 is a powder X-ray diffraction pattern corresponding to the Freebase Hydrate Form C.

[0185] Figure 21 is a powder X-ray diffraction pattern corresponding to the Tartrate Hydrate. The experimental PXRD pattern is shown at the bottom of Figure 21 and the calculated PXRD pattern is shown at the top of Figure 21.

[0186] Figure 22 is a powder X-ray diffraction pattern corresponding to the Freebase Anhydrate Form D.

[0187] Figures 23A-23F are graphs depicting the exposure-response model-predicted efficacy for clinical and endoscopic endpoints for extended-release formulation QD regimens. Figure 23A is the percentage of subjects predicted to achieve clinical response at week 12; Figure 23B is the percentage of subjects predicted to achieve modified clinical remission at week 12; Figure 23C is the percentage of subjects expected to achieve CDAI remission at week 12; Figure 23D is the percentage of subjects predicted to achieve endoscopic response at week 12/16; Figure 23E is the percentage of patients

predicted to achieve endoscopic improvement at week 12/16; Figure 23F is the percentage of patients predicted to achieve endoscopic remission at week 12/16.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0188] This written description uses examples to disclose the invention and also to enable any person skilled in the art to practice the invention, including making and using any of the disclosed compositions, and performing any of the disclosed methods or processes. The patentable scope of the invention is defined by the claims, and may include other examples that occur to those skilled in the art. Such other examples are intended to be within the scope of the claims if they have elements that do not differ from the literal language of the claims, or if they include equivalent elements.

I. Definitions

[0189] Section headings as used in this section and the entire disclosure are not intended to be limiting.

[0190] Where a numeric range is recited, each intervening number within the range is explicitly contemplated with the same degree of precision. For example, for the range 6 to 9, the numbers 7 and 8 are contemplated in addition to 6 and 9, and for the range 6.0 to 7.0, the numbers 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9 and 7.0 are explicitly contemplated. In the same manner, all recited ratios also include all sub-ratios falling within the broader ratio.

[0191] The singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise.

[0192] The term “about” generally refers to a range of numbers that one of skill in the art would consider equivalent to the recited value (i.e., having the same function or result). In many instances, the term "about" may include numbers that are rounded to the nearest significant figure.

[0193] The term “Adapted Mayo” or “Adapted Mayo score” when used in connection with ulcerative colitis refers to the Mayo Scoring System for Assessment of Ulcerative Colitis Activity, excluding the Physician’s Global Assessment subscore.

[0194] The term “adult” refers to a person 16 years of age or older.

[0195] The abbreviation “AE” refers to adverse event.

[0196] The term “alkyl” refers to straight chained or branched hydrocarbons which are completely saturated. For purposes of exemplification, which should not be construed as limiting the scope of this invention, examples of alkyls include methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, and isomers thereof.

[0197] The term “alkenyl” refers to a hydrocarbon moiety containing two to eight carbons, including straight chained or branched hydrocarbons which contain one or more double bonds. Non-limiting examples of alkenyls are ethenyl, propenyl, and butenyl.

[0198] The term "amorphous" as applied to a compound refers to a state in which the material lacks long range order at the molecular level and, depending upon temperature, may exhibit the physical properties of a solid or a liquid. Typically such materials do not give distinctive X-ray diffraction patterns and, while exhibiting the properties of a solid, are more formally described as a liquid. Upon heating, a change from solid to liquid properties occurs which is characterized by a change of state, typically second order ("glass transition").

[0199] The term "anhydrate" as applied to a compound refers to a solid state wherein the compound contains no structural water within the crystal lattice.

[0200] The abbreviation "AP" refers to abdominal pain score. Unless otherwise indicated, the AP measurement discussed herein is an unweighted average of daily AP scores for seven days. The AP measurements are calculated by averaging the daily AP score used in calculating the CDAI (discussed below), without the weighting factor applied.

[0201] The term "aryl" refers to a mono-, bi-, or tricyclic aromatic hydrocarbon radical. Examples include phenyl, naphthyl, biphenyl, and 1,2,3,4-tetrahydronaphthyl.

[0202] As used herein, the term "AUC_{24}" refers to the area under the plasma concentration time curve from time zero to twenty-four hours after administration of the referent drug following a single dose.

[0203] The term "baseline" refers to the day of first dosing with the JAK1 inhibitor, and is also referred to herein as "Day 1" or "Week 0".

[0204] The abbreviation "BID" means twice a day.

[0205] The abbreviation "BL" means baseline.

[0206] As used herein, the term "C_{12}" is the plasma concentration of the referent drug observed 12 hours after administration of a single dose, or the indicated number of doses, of the referent drug.

[0207] As used herein, the term "C_{24}" is the plasma concentration of the referent drug observed 24 hours after administration of a single dose, or the indicated number of doses, of the referent drug.

[0208] The term "C_{ave}" refers to the average plasma concentration of a drug during a dosage interval at steady-state (multiple-dosing).

[0209] The abbreviation "Cbz" refers to carboxybenzyl.

[0210] The abbreviation "CDI" refers to carbonyldiimidazole.

[0211] The abbreviation "CI" means confidence interval.

[0212] The abbreviation "CDAI" means Crohn's Disease Activity Index.

[0213] The term "clinical remission" when used in connection with Crohn's disease means average daily liquid/very soft stool frequency $\leq$ 2.8 and not greater than baseline and average daily abdominal pain $\leq$ 1.0 and not greater than baseline. As used in connection with clinical remission of Crohn's disease, the phrase "not greater than baseline" means the average daily SF or average daily AP score is not higher than the average daily SF score or average daily AP score, respectively, at baseline (i.e., prior to treatment).

[0214] The term "clinical remission" when used in connection with ulcerative colitis means a stool frequency (SF) subscore ≤1, a rectal bleeding subscore (RBS) of 0, and an endoscopic subscore of ≤0. The SF subscore, rectal bleeding subscore, and endoscopic subscore refer to the subscores used in the Mayo Scoring System for Assessment of Ulcerative Colitis Activity. This is also referred to as "clinical remission per Adapted Mayo Score".

[0215] The term "clinical response" when used in connection with Crohn's disease is defined as an average daily liquid/very soft SF score reduction of at least 30% from BL (i.e., ≥30% decrease from BL) and an average daily AP not greater than BL and/or "clinical response" is defined as an average daily AP score reduction of at least 30% from BL (i.e., ≥30% decrease from BL), and an average daily liquid/very soft SF score not greater than at BL (i.e., prior to treatment).

[0216] The term "clinical response" when used in connection with ulcerative colitis is defined as a decrease from baseline in the Adapted Mayo score ≥2 points and ≥30% from baseline accompanied by a decrease in RBS ≥1 or an absolute RBS ≤1.

[0217] The term "enhanced clinical response" when used in connection with Crohn's disease is defined as ≥ 60% decrease in average daily SF and/or ≥35% decrease in average daily AP and both not greater than baseline, and/or clinical remission.

[0218] Unless the context requires otherwise, the terms "comprise," "comprises," and "comprising" are used on the basis and clear understanding that they are to be interpreted inclusively, rather than exclusively, and that Applicant intends each of those words to be so interpreted in construing this patent, including the claims below.

[0219] The term "C_{max}" refers to the plasma concentration of the referent drug at T_{max}, expressed herein as ng/mL, produced by the oral ingestion of a single dose, or indicated number of doses, of the dosage form or pharmaceutical composition, such as the dosage forms and compositions of the present disclosure. Unless specifically indicated, C_{max} refers to the overall maximum observed concentration.

[0220] The term "C_{min}" refers to the minimum concentration of drug in blood plasma.

[0221] The term "corticosteroid-free" means a patient who was taking corticosteroids at the time of the first induction dose of upadacitinib and has completely discontinued use of corticosteroids.

[0222] The term "C_p" refers to plasma drug concentration at any time t.

[0223] The term "crystalline" as applied to a compound refers to a solid phase in which the material has a regular ordered internal structure at the molecular level and gives a distinctive X-ray diffraction pattern with defined peaks. Such materials when heated sufficiently will also exhibit the properties of a liquid, but the change from solid to liquid is characterized by a phase change, typically first order ("melting point").

[0224] The term "crystallization" as used throughout this application can refer to crystallization and/or recrystallization depending upon the applicable circumstances relating to the preparation of the compound.

[0225] The abbreviation "%CV" refers to the coefficient of variation, expressed as a percent. % CV is calculated according to the following equation: %CV = (SD/x) * 100, wherein x is the mean value and SD is the standard deviation.

[0226] A "disorder", as used herein, is any condition that would benefit from treatment with a JAK1 inhibitor described herein. This includes chronic and acute disorders or diseases including those pathological conditions that predispose a mammal to the disorder in questions.

[0227] The term "endoscopic healing" means an SES-CD ulcerated surface subscore of 0 in subjects with SES-CD ulcerated surface subscore $\geqslant$ 1 at baseline.

[0228] The term "endoscopic improvement" (also known as "endoscopic response by 50%") when used in connection with Crohn's disease means decrease in SES-CD > 50% from baseline (or for subjects with an SES-CD of 4 at baseline of the induction study, at least a 2 point reduction from baseline).

[0229] The term "endoscopic improvement" when used in connection with ulcerative colitis means an endoscopic subscore $\leq$ 1 at week 8 during the induction phase and an endoscopic subscore of 0 at week 8 during the maintenance phase. The endoscopic subscore refers to the subscore used in the Mayo Scoring System for Assessment of Ulcerative Colitis Activity.

[0230] The term "endoscopic remission", when used in connection with Crohn's disease, unless otherwise indicated, means an SES-CD of $\leq$4 ($\leq$2 for patients with isolated ileal CD) and at least a two point reduction in SES-CD versus BL and no subscore >1 in any individual variable used to calculate the SES-CD.

[0231] The term "endoscopic remission (by IOIBD (International Organization for the Study of Inflmmatory Bowel Diseases) definition), when used in connection with Crohn's disease, means SDS $\leqslant$ 2.

[0232] The term "endoscopic remission" when used in connection with ulcerative colitis means an endoscopic subscore of 0. The endoscopic subscore refer to the endoscopic subscore used in the Mayo Scoring System for Assessment of Ulcerative Colitis Activity.

[0233] The term "endoscopic response" when used in connection with Crohn's disease means at least a 50% reduction in SES-CD score from BL.

[0234] The abbreviation "EtOAc" refers to ethyl acetate.

[0235] The abbreviation "EtOH" refers to ethanol.

[0236] The term "Geboes score" means a histological score based on measurement of fecal calprotein and high-sensitivity C-reactive protein.

[0237] The term "histologic improvement" when used in connection with ulcerative colitis means a decrease from baseline in Geboes score.

[0238] The abbreviation "HDL" refers to high density lipoprotein.

[0239] The abbreviation "Hgb" refers to hemoglobin.

[0240] The abbreviation "HOAc" refers to acetic acid.

[0241] The abbreviation "HPMC" refers to hydroxypropyl methylcellulose.

[0242] As used herein, the term "inducing" or "induced", when used in connection with a particular therapeutic effect, means the therapeutic effect has been achieved. Typically, the therapeutic effect is induced in a patient previously suffering from a disease condition, such as in a patient having moderately to severely active Crohn's disease or moderately to severely active ulcerative colitis. For instance, in one embodiment, inducing a particular therapeutic effect, when used in connection with Crohn's disease, means the patient is brought from a state where the patient has 1) an average daily liquid/very soft stool frequency score ≥ 2.5 or average daily abdominal pain score ≥ 2, 2) CDAI ≥ 220 and ≤ 450 or 3) Simplified Endoscopic Score for Crohn's disease (SES-CD) ≥ 6 (or ≥ 4 for subjects with disease limited to the ileum) and bringing the patient to a state where the patient achieve the parameters for the specified therapeutic effect (e.g., endoscopic remission, clinical remission, endoscopic response, clinical response).

[0243] The abbreviation "IPAc" refers to isopropyl acetate.

[0244] The abbreviation "IR" means immediate release, unless otherwise indicated.

[0245] As used herein, the term "JAK1 inhibitor" or "upadacitinib" refers to the compound (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide.

[0246] The abbreviation "LDL" refers to low density lipoprotein.

[0247] The abbreviation "LOCF" means last observation carried forward method.

[0248] The abbreviation "Mayo" means the Mayo Scoring System for Assessment of Ulcerative Colitis Activity.

[0249] The term "moderately to severely active Crohn's disease", unless otherwise indicated, is defined as average daily very soft or lliquid/soft stool frequency ≥ 4 and/or average daily abdominal pain score ≥ 2.0 and evidence of mucosal inflammation, defined as Simplified Endoscopic Score ofor CD (SES-CD)≥ 6 (≥ 4 for subjects with isolated ileal disease), excluding the presence of narrowing component.

[0250] The term "moderately to severely active ulcerative colitis", unless otherwise indicated, is defined as having an Adapted Mayo score of 5 to 9, with an endoscopy subscore of 2 or 3.

[0251] The term "modified clinical remission" when used in connection with Crohn's disease is defined as an average daily liquid/very soft SF score of ≤ 2.8 and not greater than BL and an average daily AP score of ≤ 1.0 and not greater than BL. As used in connection with clinical remission, the phrase "not greater than baseline" means that average daily liquid/very soft SF score or average daily AP score is not higher than the average daily liquid/very soft SF score or average daily AP score, respectively, at baseline (i.e., prior to treatment).

[0252] The abbreviation "MR" means modified release.

[0253] The abbreviation "MTX" refers to methotrexate.

[0254] The term "patient" or "subject", used interchangeably herein, refers to a human patient or subject.

[0255] The term "NK cells" refers to natural killer cells.

[0256] The abbreviation "NRI" means non-responder imputation method.

[0257] The abbreviation "PBO" means placebo.

[0258] The abbreviation "Pd/C" refers to palladium on carbon.

[0259] The abbreviation "$Pd(OH_2)/C$" refers to palladium hydroxide on carbon.

[0260] The term "pharmaceutically acceptable" (such as in the recitation of a "pharmaceutically acceptable salt" or a "pharmaceutically acceptable diluent") refers to a material that is compatible with administration to a human subject, *e.g.*, the material does not cause an undesirable biological effect. Examples of pharmaceutically acceptable salts are described in "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002). Examples of pharmaceutically acceptable excipients are described in the "Handbook of Pharmaceutical Excipients," Rowe et al., Ed. (Pharmaceutical Press, 7th Ed., 2012).

[0261] The abbreviation "pTsOH" refers to p-toluene sulfonic acid.

[0262] The abbreviation "PVA" refers to polyvinyl acetate.

[0263] The abbreviation "PXRD" means powder X-ray diffraction.

[0264] The abbreviation "QD" means once daily.

[0265] The abbreviation "RBC" means red blood cells.

[0266] The abbreviation "RBS" means rectal bleeding subscore. The rectal bleeding subscore refers to the subscore used in the Mayo Scoring System for Assessment of Ulcerative Colitis Activity.

[0267] The term "refractory patient" means a patient with moderately to severely active Crohn's disease, who has had Crohn's disease for more than ten years and who has failed several treatments, including biologic treatments.

[0268] The term "remission" when used in connection with Crohn's disease is defined as both endoscopic remission and clinical remission.

[0269] The term "response" when used in connection with Crohn's disease is defined as both endoscopic response and clinical response.

[0270] The abbreviation "SC" means subcutaneous.

[0271] The abbreviation "(S)-Segphos $Ru(OAc)_2$" refers to diacetato[(S)-(-)5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole]ruthenium(II).

[0272] The term "SES-CD" refers to the Simplified Endoscopic Score for Crohn's disease, which is calculated using the parameters listed in Table 2 below.

[0273] The abbreviation "SF" refers to stool frequency. Unless otherwise indicated, the SF measurement discussed herein when used in connection with Crohn's disease is an unweighted average of daily liquid/very soft SF scores for seven days. The SF measurements are calculated by averaging the daily liquid/very soft SF scores used in calculating the CDAI (discussed below), without the weighting

factor applied. Unless otherwise indicated, the SF measurement discussed herein when used in connection with ulcerative colitis refers to the stool frequency subscore used in the Mayo Scoring System for Assessment of Ulcerative Colitis Activity.

[0274] The term "therapeutically effective amount" is used to refer to an amount of an active agent that relieves or ameliorates one or more of the symptoms of the disorder being treated. In another aspect, the therapeutically effective amount refers to a target serum concentration that has been shown to be effective in, for example, slowing disease progression. Efficacy can be measured in conventional ways, depending on the condition to be treated.

[0275] The abbreviation "6-TGN" refers to 6-tioguanine (thioguanine) nucleotides.

[0276] The abbreviation "THF" refers to tetrahydrofuran.

[0277] As used herein, the term "T_{max}" refers to the time to peak plasma concentration of the referent drug after oral ingestion of a single dose, or indicated number of doses, of the referent drug.

[0278] The terms "treating", "treatment", and "therapy" and the like, as used herein, are meant to include therapeutic as well as prophylactic, or suppressive measures for a disease or disorder leading to any clinical desirable or beneficial effect, including but not limited to alleviation or relief of one or more symptoms, regression, slowing or cessation of progression of the disease or disorder. Thus, for example, the term treatment includes the administration of an agent prior to or following the onset of a symptom of a disease or disorder thereby preventing or removing one or more signs of the disease or disorder. As another example, the term includes the administration of an agent after clinical manifestation of the disease to combat the symptoms of the disease. Further, administration of an agent after onset and after clinical symptoms have developed where administration affects clinical parameters of the disease or disorder, such as the degree of tissue injury or the amount or extent of metastasis, whether or not the treatment leads to amelioration of the disease, comprises "treatment" or "therapy" as used herein. Moreover, as long as the compositions of the disclosure either alone or in combination with another therapeutic agent alleviate or ameliorate at least one symptom of a disorder being treated as compared to that symptom in the absence of use of the JAK1 inhibitor composition, the result should be considered an effective treatment of the underlying disorder regardless of whether all the symptoms of the disorder are alleviated or not.

[0279] The abbreviation "TNF" means tumor necrosis factor.

[0280] As used herein, the term "$t_{1/2}$" refers to the terminal half-life of the referent drug after oral ingestion of a single dose, or indicated number of doses, of the referent drug.

[0281] The abbreviation "UC" refers to ulcerative colitis.

[0282] The abbreviation "w/w" refers to weight/weight.

II. JAK1-Associated Disorders and JAK1 Inhibitors

[0283] In one aspect, the present disclosure provides methods for treating and/or inducing clinical remission, endoscopic improvement, and/or endoscopic remission of Crohn's disease. In another aspect, the present disclosure provides methods for treating ulcerative colitis and/or for inducing a clinical remission of ulcerative colitis. In one aspect, the methods comprise administering a JAK1 inhibitor to the patient.

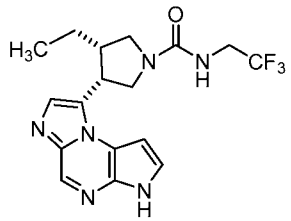
[0284] Targeting the JAK (Janus activated kinase) signaling pathway for autoimmune diseases, such as rheumatoid arthritis (RA) and CD, is well-supported by the involvement of various pro-inflammatory cytokines that signal via JAK pathways in the pathogenesis of these immune-related disorders. The activation of the JAK signaling initiates expression of survival factors, cytokines, chemokines, and other molecules that facilitate leukocyte cellular trafficking and cell proliferation, which contribute to inflammatory and autoimmune disorders.

[0285] Although the pathogenesis of CD is not completely understood, the imbalance between anti-inflammatory and pro-inflammatory cytokines in the mucosal immune system is thought to play an important role in CD. Cells from the innate mucosal immune system, i.e. TH1 or TH17, are over-activated and secrete various pro-inflammatory cytokines such as interferon (INF)-g, TNFα, interleukin IL-6, IL1b, IL-12, IL23. These cytokines signal via JAK pathways.

[0286] The JAK comprises four family members: JAK1, 2, 3, and Tyrosine kinase 2 (Tyk2). These cytoplasmic tyrosine kinases transduce cytokine-mediated signals, and are associated with membrane cytokine receptors such as common gamma-chain (CGC) receptors and the glycoprotein 130 (gp130) trans-membrane proteins.

[0287] JAK3 and JAK1 are components of the CGC cytokine receptor complexes and blockade of either inhibits signaling by the inflammatory cytokines IL-2, -4, -7, -9, -15 and -21. Cytokines such as IL-6 bind to gp130 and transduce its signal predominantly via JAK1. Targeting the IL-6 receptor (IL-6R) is a promising approach given the fact that expression of IL-6 and soluble IL-6 receptors is elevated in patients with active CD. Further, a proof of concept study in patients with active CD with tocilizumab, a humanized monoclonal antibody against IL-6R, showed an encouraging clinical response. Thus, inhibition of JAK1 is expected to attenuate the signaling of IL-6 and other pro-inflammatory cytokines (i.e. IFN-g), that are involved in development of CD.

[0288] Thus, in one aspect, the present disclosure provides a compound useful in the treatment of Crohn's Disease and ulcerative colitis. In one aspect, the JAK1 inhibitor used in the methods of the present disclosure is the compound (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide ($C_{17}H_{19}F_3N_6O$), or a pharmaceutically acceptable salt or solid state form thereof. The compound (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide is also referred to herein as "upadacitinib", and has the structure shown below:



[0289] "Pharmaceutically acceptable salts" refers to those salts which retain the biological effectiveness and properties of the free bases and which are obtained by reaction with inorganic acids, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, and phosphoric acid or organic acids such as sulfonic acid, carboxylic acid, organic phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, citric acid, fumaric acid, maleic acid, succinic acid, benzoic acid, salicylic acid, lactic acid, mono-malic acid, mono oxalic acid, tartaric acid such as mono tartaric acid (*e.g.*, (+) or (-)-tartaric acid or mixtures thereof), amino acids (*e.g.*, (+) or (-)-amino acids or mixtures thereof), and the like. These salts can be prepared by methods known to those skilled in the art

III. Methods of Treatment of Crohn's Disease

[0290] In one aspect, the present disclosure is directed to methods for the treatment of Crohn's disease. In one aspect, the present disclosure provides methods for treating Crohn's disease, in particular methods comprising administering a JAK1 inhibitor to a patient in certain amounts and/or at certain intervals. In one aspect, the JAK1 inhibitor is upadacitinib or a pharmaceutically acceptable salt or solid state form thereof.

[0291] In one aspect, the present disclosure provides a JAK1 inhibitor for use in the treatment of Crohn's disease, by administration in certain amounts and/or at certain intervals as described herein. In one aspect, the JAK1 inhibitor is upadacitinib or a pharmaceutically acceptable salt or solid state form thereof.

[0292] In one aspect, the present disclosure provides for the use of a JAK1 inhibitor for the preparation of a medicament for the treatment of Crohn's disease, by administration in certain amounts and/or at certain intervals as described herein. In one aspect, the JAK1 inhibitor is upadacitinib or a pharmaceutically acceptable salt or solid state form thereof.

[0293] In one aspect, the present disclosure is directed to methods for inducing clinical remission and/or endoscopic remission of Crohn's disease. In one aspect, the present disclosure provides methods for inducing clinical remission and/or endoscopic remission of Crohn's disease, in particular methods comprising administering a JAK1 inhibitor to a patient in certain amounts and/or at certain intervals. In one aspect, the JAK1 inhibitor is upadacitinib or a pharmaceutically acceptable salt or solid state form thereof.

[0294] In one aspect, the present disclosure provides a JAK1 inhibitor for use in inducing clinical remission and/or endoscopic remission of Crohn's disease by administration in certain amounts

and/or at certain intervals as described herein. In one aspect, the JAK1 inhibitor is upadacitinib or a pharmaceutically acceptable salt or solid state form thereof.

[0295] In one aspect, the present disclosure provides for the use of a JAK1 inhibitor for the preparation of a medicament for inducing clinical remission and/or endoscopic remission of Crohn's Disease by administration in certain amounts and/or at certain intervals as described herein. In one aspect, the JAK1 inhibitor is upadacitinib or a pharmaceutically acceptable salt or solid state form thereof.

[0296] In one aspect, the present disclosure is directed to methods for inducing clinical remission and/or endoscopic improvement of Crohn's disease, in particular, methods comprising administering a JAK1 inhibitor to a patient in certain amounts and/or at certain intervals. In one aspect, the JAK1 inhibitor is upadacitinib or a pharmaceutically acceptable salt or solid state form thereof.

[0297] In one aspect, the present disclosure provides a JAK1 inhibitor for use in inducing clinical remission and/or endoscopic improvement of Crohn's disease by administration in certain amounts and/or at certain intervals as described herein. In one aspect, the JAK1 inhibitor is upadacitinib or a pharmaceutically acceptable salt or solid state form thereof.

[0298] In one aspect, the present disclosure provides for the use of a JAK1 inhibitor for the preparation of a medicament for inducing clinical remission and/or endoscopic improvement of Crohn's disease, by administration in certain amounts and/or at certain intervals as described herein. In one aspect, the JAK1 inhibitor is upadacitinib or a pharmaceutically acceptable salt or solid state form thereof.

[0299] In one particular aspect, the disease is moderately to severely active Crohn's disease. In one aspect, in the context of the present disclosure, a patient is naïve to, or was previously treated with immunosuppressants (e.g., methotrexate), aminosalicylates, corticosteroids, and/or a biologic agent (e.g., vedolizumab, ustekinumab, natalizumab, etc.). In one aspect, the patient is naïve to, or was previously treated with an anti-TNF therapy (e.g., infliximab, adalimumab, certolizumab pegol, golimumab, etc.). In one aspect, in the context of a method of the present disclosure a patient was previously treated with one, two, three or more TNF antagonist(s) (also referred to herein as anti-TNF agents). In one embodiment, the patient is a patient who had an inadequate response with, lost response, or was intolerant to a TNF antagonist. In one aspect, in the context of a method of the present disclosure a patient was previously treated with one, two, three or more biologic(s). In one embodiment, the patient is a patient who had an inadequate response with, lost response, or was intolerant to a biologic agent. In one embodiment, the patient is a patient who had an inadequate response with, lost response, or was intolerant to a TNF antagonist, aminosalicylates, corticosteroids, immunosuppressants, and/or a biologic agent. In one embodiment, the patient is a refractory patient who has moderately to severely active Crohn's disease. In one embodiment, the patient is either naïve to or has stopped using corticosteroids prior to treatment with the JAK1 inhibitor.

Biologic agents for Crohn's Disease:

1) Demonstrated an inadequate response to, loss of response to, recurrence of signs and symptoms or intolerance to any biologoic therapy as defined below:
   a. at least one 6-week induction regimen of infliximab (≥ 5 mg/kg intravenous [IV] at 0, 2 and 6 weeks),
   b. at least one 4-week induction regimen of adalimumab (one 160 mg subcutaneous (SC) dose at Week 0, followed by one 80 mg SC dose at Week 2 [or one 80 mg SC doseat Week 0, followed by one 40 mg SC dose at at Week 2, in countries where this dosing regimen is approved]),
   c. at least one 4-week induction regimen of certolizumab pegol (400 mg SC at Weeks 0, 2 and 4),
   d. at least one 6-week induction regimen of vedolizumab (300 mg IV at 0, 2 and 6 weeks),
   e. at least one 12-week induction regimen of natalizumab (300 mg IV every 4 weeks),
   f. at least on 8-week induction regimen of ustekinumab [260 mg(<55 kg) or 390 mg (56-85 kg) or 520 mg (>86 kg), followed by 90 mg SC at week 8]or
2) Recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify), or
3) History of intolerance to at least one biologic agent (including, but not limited to infusion-related reaction, demyelination, congestive heart failure (CHF), infection).

[0300] Disease severity for Crohn's disease may be measured using a variety of indexes, including the Crohn's Disease Activity Index (CDAI), the Simplified Endoscopic Score for CD (SES-CD), average daily liquid/very soft stool frequency (SF) (patient reported); and/or average daily abdominal pain (AP) score (patient reported). Unless otherwise indicated, the SF and AP scores discussed herein refer to their respective unweighted average of the daily scores that are used in calculation of the CDAI (discussed below). Measures for assessing health-related quality of life include the Inflammatory Bowel Disease Questionnaire (IBDQ). The IBDQ is a well-known 32 item validated questionnaire that assesses a patient's inflammatory bowel disease symptoms, general well-being, and mood, and may be used as a tool to evaluate a patient's quality of life (Guyatt, et al., Gastroenterology, 1989, 96:804-810). The IBDQ questionnaire is described in further detail below.

[0301] CDAI is a composite score used to quantify symptoms of patients with Crohn's disease. In one aspect, the index consists of eight factors added together after adjusting for a predefined weighting factor (see Table 1 below). CDAI scores range from 0 to 600. Index values of 150 and below are associated with quiescent disease; values above 150 are associated with active disease, and values above 450 are seen with extremely severe disease. In one aspect, a patient to be treated by a method according to the present disclosure has a CDAI score of 220 to 450 prior to treatment, which may be indicative of moderately to severely active CD.

Table 1: Format for Calculation of the CDAI

Clinical or laboratory variable	Weighting factor
Number of liquid or very soft stools in the previous 7 days (sum of daily scores)	x2
AP (graded from 0 (mild) to 3 (severe) on severity) each day for 7 days (sum of daily score)	x5
General wellbeing, subjectively assessed from 0 (generally well) to 4 (terrible) each day for 7 days (sum of daily score)	x7
Number of complications patient now has: (record 0 if none) • Arthritis/arthralgia • Iritis/uveitis • Erythema nodosum/pyoderma gangrenosum/aphthous stomatitis • Fissure, abscess and/or anal fistula (draining/non-draining) • Other cutaneous fistula (draining/non-draining) • Fever over 100°F (37.8°C) during past week	x20
Taking lomotil/imodium/loperamide or opiates for diarrhea (0 = no, 1= yes)	x30
Presence of an abdominal mass (0 as none, 2 as questionable, 5 as defined)	x10
Hematocrit (Male: 47-hematocrit; Female: 42-hematocrit; if hematocrit >normal, enter 0	x6
Percentage under standard weight	x1

[0302] SES-CD is calculated using the following parameters listed in Table 2:

Table 2: Parameters for Calculating SES-CD

	Rectum	Sigmoid and left colon	Transverse Colon	Right colon	Ileum	Total
Size of Ulcers Enter: 0 if none 1 if aphthous ulcer (Ø 0.01 to 0.5 cm) 2 if large ulcers (Ø 0.05 to 2 cm) 3 if very large ulcer (Ø > 2 cm)						
Ulcerated Surface Enter: 0 if none 1 if < 10% 2 if 10% - 30% 3 if > 30%						
Affected Surface Enter: 0 if unaffected segments 1 if < 50% 2 if 50% - 75% 3 if > 75%						
Presence of Narrowing Enter: 0 if none 1 if single, can be passed 2 if multiple, can be passed 3 if cannot be passed						

					Total =	

[0303] In one aspect, the patient to be treated has moderately to severely active Crohn's disease. Moderately to severely active Crohn's disease is characterized by a SES-CD of greater than or equal to 6 (or a SES-CD of greater than or equal to 4 for patients with disease limited to the ileum).

[0304] In one embodiment, the patient is a patient who had an inadequate response with, lost response, or was intolerant to a conventional therapy (e.g., aminosalicylates, corticosteroids, immunosuppressants), or to a biologic agent. In one embodiment, the patient is a patient who had an inadequate response with, lost response, or was intolerant to a TNF antagonist. Examples of such anti-TNF agents include infliximab, adalimumab, and certolizumab pegol. Criteria for determining if a patient has had an inadequate response to or experienced intolerance to previous treatment with an anti-TNF agent is defined as:

1) Signs and symptoms of persistently active disease despite a history of at least one 4-week induction regimen of one of the following agents:
   - Infliximab: 5 mg/kg IV, 2 doses at least 2 weeks apart,
   - Adalimumab: one 160 mg subcutaneous dose followed by one 80 mg subcutaneous dose (or one 80 mg subcutaneous dose) followed by one 40 mg dose at least 2 weeks apart,
   - Certolizumab pegol: 400 mg subcutaneous, two doses at least two doses apart; or 2) Recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify); or
2) Recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify); or
3) History of intolerance of at least one TNF antagonist (including, but not limited to infusion related reaction, demyelination, congestive heart failure and infection).

[0305] In one aspect, the patient is one who has previously been treated with, or is currently being treated with aminosalicylates, immunosuppressants, corticosteroids, and/or a biologic agent.

[0306] In one aspect, CDAI or any of the evaluations described in the Examples herein below is/are used to assess the efficacy of upadacitinib in the treatment of Crohn's disease, for example moderately to severely active Crohn's disease.

[0307] In one embodiment, in the context of the present disclosure, the treatment of a patient, or the induction of clinical remission and/or endoscopic remission in a patient, or the induction of clinical remission and/or endoscopic improvement in a patient comprises an induction phase and a maintenance phase. In the induction phase, one or more doses of the JAK1 inhibitor, for example referred to herein as induction doses, are administered to the patient, for example, orally. In the maintenance phase, a first dose of the JAK1 inhibitor, for example referred to herein as the maintenance dose, is administered to the patient followed by at least one additional dose of the JAK1 inhibitor, for example, also referred to herein as a maintenance dose. The maintenance doses are, for example, administered orally. The JAK1 inhibitor

may be, for example, upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. Examples of induction phases and maintenance phases are described herein.

[0308] In one aspect, a certain therapeutic result is achieved by the patient during or at the end of the induction phase, for example clinical remission, endoscopic remission, or both clinical remission and endoscopic remission (referred to herein as "remission"). In one aspect, the patient achieves clinical remission during or by the end of the induction phase. In one aspect, the patient achieves endoscopic remission during or by the end of the induction phase.

[0309] In another aspect, a certain therapeutic result is achieved by the patient during or at the end of the induction phase, for example clinical remission, endoscopic improvement, or both clinical remission and endoscopic improvement. In one aspect, the patient achieves clinical remission during or by the end of the induction phase. In one aspect, the patient achieves endoscopic improvement during or by the end of the induction phase

[0310] In one embodiment, the induction phase lasts for up to 16 weeks (e.g., for up to 16 weeks following initiation of administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof). Thus, in one embodiment, the induction phase is 16 weeks. In another embodiment, the induction phase optionally lasts for less than 16 weeks, for instance, for 2 weeks, for 4 weeks, for 5 weeks, for 6 weeks, for 7 weeks, for 8 weeks, for 9 weeks, for 10 weeks, for 11 weeks, for 12 weeks, for 13 weeks, for 14 weeks, or for 15 weeks. In one aspect, the patient achieves an endoscopic remission within 12 weeks, or within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one aspect, the patient achieves a clinical remission within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one aspect, the patient achieves an endoscopic improvement within 12 weeks, or within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one aspect, the patient achieves a clinical remission within 12 weeks, or within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof.

[0311] In one embodiment, the patient achieves clinical remission within 2 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the patient achieves clinical remission within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof.

[0312] In one embodiment, the patient achieves both 1) average daily liquid/very soft SF score of ≤ 1.5 and not worse than BL, and 2) average daily AP score of ≤ 1.0 and not worse than baseline within 2 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. As used in connection with clinical remission, the phrase "not worse than baseline" means that the average daily liquid/very soft SF score or average daily AP score is not higher than the average daily liquid/very soft SF score or average daily AP score, respectively, at baseline (i.e., prior to treatment).

[0313] In one embodiment, the patient achieves both 1) average daily liquid/very soft SF score of ≤ 1.5 and not worse than BL, and 2) average daily AP score of ≤1.0 and not worse than baseline within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. As used in connection with clinical remission, the phrase "not worse than baseline" means that the average daily liquid/very soft SF score or average daily AP score is not higher than the average daily liquid/very soft SF score or average daily AP score, respectively, at baseline (i.e., prior to treatment).

[0314] In one embodiment, the patient achieves endoscopic remission and/or endoscopic improvement within 2 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the patient achieves endoscopic remission and/or endoscopic improvement within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof.

[0315] In one embodiment, the patient achieves corticosteroid-free remission within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof.

[0316] In some embodiments, during or by the end of the induction phase (e.g., lasting for up to 16 weeks, including for 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks or for 16 weeks), the patient achieves at least one therapeutic result selected from the group consisting of:

1) a CDAI of less than 150 within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,
2) a CDAI of less than 150 within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,
3) a CDAI of less than 150 within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,
4) a decrease in CDAI of greater than or equal to 70 points from baseline within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,
5) a decrease in CDAI of greater than or equal to 70 points from baseline within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,
6) a decrease in CDAI of greater than or equal to 70 points from baseline within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,
7) a clinical remission within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,
8) a clinical remission within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,
9) remission within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof (i.e., both endoscopic remission within 12 weeks or

within 16 weeks and clinical remission within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof),

10) remission within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof (i.e., both endoscopic remission within 12 weeks and clinical remission within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof),

11) remission within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof (i.e., both endoscopic remission within 4 weeks and clinical remission within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof),

12) response within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof (i.e., both endoscopic response within 12 weeks or within 16 weeks and clinical response within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof),

13) response within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof (i.e., both endoscopic response within 12 weeks and clinical response within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof),

14) response within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof (i.e., both endoscopic response within 4 weeks and clinical response within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof),

15) endoscopic response within 12 weeks or within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,

16) endoscopic response within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,

17) clinical response within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,

18) clinical response within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,

19) clinical response within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,

20) clinical response within 2 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof

21) a change from baseline in fecal calprotectin level within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,

22) a change from baseline in fecal calprotectin level within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,

23) a change from baseline in fecal calprotectin level within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,

24) a change from baseline in hs-CRP (high sensitivity C-reactive protein) within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,

25) a change from baseline in hs-CRP (high sensitivity C-reactive protein) within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,

26) a change from baseline in hs-CRP (high sensitivity C-reactive protein) within 8 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,

27) a change from baseline in hs-CRP (high sensitivity C-reactive protein) within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,

28) a change from baseline in hs-CRP (high sensitivity C-reactive protein) within 2 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,

29) a change in Inflammatory Bowel Disease Questionnaire (IBDQ) score from baseline within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,

30) a change in Inflammatory Bowel Disease Questionnaire (IBDQ) score from baseline within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,

31) a change in Inflammatory Bowel Disease Questionnaire (IBDQ) score from baseline within 8 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,

32) modified clinical remission within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,

33) enhanced clinical response within 8 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof

and combinations thereof,

34) 4 steroid-free endoscopic improvement within 4 weeks of administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,

35) steroid-free endoscopic improvement within 8 weeks of administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,

36) steroid-free endoscopic improvement within 16 weeks of administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,

37) steroid-free endoscopic response within 4 weeks of administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,

38) steroid-free endoscopic response within 8 weeks of administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,

39) steroid-free endoscopic response within 16 weeks of administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,

40) steroid-free endoscopic remission within 4 weeks of administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,

41) steroid-free endoscopic remission within 8 weeks of administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof,

42) steroid-free endoscopic remission within 16 weeks of administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof.

[0317] In some embodiments, the patient achieves either a clinical remission within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, or an endoscopic remission within 12 weeks or within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, and further achieves any combination of additional therapeutic results selected from the group consisting of therapeutic results 1), 2), 3), 4), 5), 6), 7), 8), 9), 10), 11), 12), 13), 14), 15), 16), 17), 18), 19), 20), 21), 22), 23), 24), 25), 26), 27), 28), 29), and combinations thereof. In one such embodiment, the induction phase is 16 weeks.

[0318] In one embodiment, the induction phase is 12 weeks, and the patient achieves either a clinical remission within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, or an endoscopic remission within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, and further achieves any combination of additional therapeutic results selected from the group consisting of therapeutic results 2), 3), 5), 6), 7), 8), 10), 11), 13), 14), 15), 16), 18), 19), 20), 22), 23), 25), 26), 28), 29), and combinations thereof, wherein the therapeutic result is achieved within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof.

[0319] In one embodiment, the induction phase is 4 weeks, and the patient achieves either a clinical remission within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, or an endoscopic remission within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, and further achieves any combination of additional therapeutic results selected from the group consisting of therapeutic results 3), 6), 8), 11), 14), 16), 19), 20), 23), 26), 29), and combinations thereof, wherein the therapeutic result is achieved within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof.

[0320] In one embodiment, the patient achieves a clinical remission within 12 weeks, or within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, and/or achieves an endoscopic improvement within 12 weeks or within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, and further achieves any combination of additional therapeutic results selected from the group consisting of therapeutic results 1), 2), 3), 4), 5), 6), 7), 8), 9), 10), 11), 12), 13), 14), 15), 16), 17), 18), 19), 20), 21), 22), 23), 24), 25), 26), 27), 28), 29), and combinations thereof. In one such embodiment, the induction phase is 16 weeks.

[0321] In one embodiment, the induction phase is 12 weeks, and the patient achieves a clinical remission within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, and/or achieves an endoscopic improvement within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, and further achieves any combination of additional therapeutic results selected from the group consisting of therapeutic results 2), 3), 5), 6), 7), 8), 10), 11), 13), 14), 15), 16), 18), 19), 20), 22), 23), 25), 26), 28), 29), and combinations thereof, wherein the therapeutic result is achieved within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof.

[0322] In one embodiment, the induction phase is 16 weeks, and the patient achieves a clinical remission within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, and/or achieves an endoscopic improvement within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, and further achieves any combination of additional therapeutic results selected from the group consisting of therapeutic results 1), 2), 3), 4), 5), 6), 7), 8), 9), 10), 11), 12), 13), 14), 15), 16), 17), 18), 19), 20), 21), 22), 23), 24), 25), 26), 27), 28), 29), and combinations thereof, wherein the therapeutic result is achieved within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof.

[0323] In one embodiment, the induction phase is 4 weeks, and the patient achieves a clinical remission within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, and/or achieves an endoscopic improvement within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, and further achieves any combination of additional therapeutic results selected from the group consisting of therapeutic results 3), 6), 8), 11), 14), 16), 19), 20), 23), 26), 29), and combinations thereof, wherein the therapeutic result is achieved within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof.

[0324] In one embodiment, the patient achieves a clinical remission within 4 weeks, 12 weeks, or within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, and/or achieves an endoscopic improvement within 4 weeks, 12 weeks or within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state

form thereof, and further achieves an additional therapeutic result selected from the group consisting of a CDAI of less than 150 within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a CDAI of less than 150 within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a CDAI of less than 150 within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; an endoscopic remission within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; an endoscopic remission within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; an endoscopic remission within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a clinical response within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a clinical response within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a clinical response within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a clinical response within 2 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; and combinations thereof. In one such embodiment, the induction phase is 16 weeks, and the additional therapeutic result is selected from the group consisting of a CDAI of less than 150 within 16 weeks, or within 12 weeks, or within 4 weeks, or within 2 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, an endoscopic remission within 16 weeks or within 12 weeks or within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a clinical response within 16 weeks or within 12 weeks or within 4 weeks, or within 2 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; and combinations thereof. In one such embodiment, the induction phase is 12 weeks, and the additional therapeutic result is selected from the group consisting of a CDAI of less than 150 within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; an endoscopic remission within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a clinical response within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; and combinations thereof.

[0325] In one embodiment, the additional therapeutic result may further be a clinical remission within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, wherein the patient has an average daily liquid/very soft SF score of greater than or equal to 2.5 and an average daily AP score of greater than or equal to 2.0 at baseline. In one embodiment, when the patient is one who was taking corticosteroids at baseline but who discontinued corticosteroid use during treatment with the JAK1 inhibitor, the additional therapeutic result may be selected from the group consisting of a CDAI score of less than 150 within 16 weeks of initiating administration of upadacitinib,

or a pharmaceutically acceptable salt or solid state form thereof; an endoscopic remission within 12 weeks or within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof and a clinical remission within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a clinical remission within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; and an endoscopic remission within 12 weeks or within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; and combinations thereof. In one embodiment, when the patient has isolated ileal Crohn's disease, the additional therapeutic result may further be remission within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one aspect, a patient achieves a CDAI score of less than 150 during or by the end of the induction phase.

[0326] In one aspect, the patient may achieve an additional therapeutic result selected from the group consisting of a clinical remission (i.e., average daily SF score ≤ 2.8 and not greater than baseline and average daily AP score ≤ 1.0 and not greater than baseline) within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; an endoscopic improvement (i.e., SES-CD score that is greater than a 50% decrease from baseline or at least a 2 point reduction in SES-CD score from baseline or endoscopic remission) within 4 weeks, within 6 weeks, within 12 weeks, or within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; and combinations thereof.

[0327] In one aspect, the patient may achieve an additional therapeutic result selected from the group consisting of a decrease in CDAI score from baseline of greater than or equal to 70, and a decrease in CDAI score from baseline of greater than or equal to 100. In one embodiment, the induction phase is 16 weeks and the decrease in CDAI occurs within 16 weeks or within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the induction phase is 12 weeks and the decrease in CDAI occurs within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof.

[0328] In one particular embodiment, the induction phase is 16 weeks, and the patient achieves a clinical remission within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; an endoscopic improvement (i.e., SES-CD score that is greater than a 50% decrease from baseline or at least a 2 point reduction in SES-CD score from baseline, or endoscopic remission) within 4 weeks, within 6 weeks, within 12 weeks or within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; and combinations thereof. In another embodiment, the induction phase is 12 weeks, and the patient achieves a clinical remission within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; an endoscopic improvement within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; or combinations thereof.

[0329] In one embodiment, the patient is administered upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, for at least 52 weeks. The administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, may include an induction phase (e.g., an induction phase of up to 16 weeks), and additional weeks (e.g., 36 weeks or longer) of a maintenance phase (discussed hereinafter). In other embodiments, the administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, may include a shorter induction phase (e.g., up to 2 weeks, up to 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, etc.), and a longer maintenance phase (e.g., a 12 week induction phase and a 40 week or longer maintenance phase). In some such embodiments, the patient may achieve at least one therapeutic result selected from the group consisting of: remission within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; endoscopic remission within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; clinical remission within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; endoscopic improvement within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; response within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; endoscopic response within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof pharm; clinical response within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; CDAI of less than 150 within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a decrease in CDAI of greater than or equal to 70 points from baseline within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a change from baseline in fecal calprotectin level within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a change from baseline in hs-CRP within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a change in IBDQ score from baseline within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a change in extra-intestinal manifestations (EIMS) from baseline within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; and combinations thereof.

[0330] In some embodiment when the patient is administered upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, for at least 52 weeks, when the patient is one who was taking corticosteroids at baseline but who discontinued corticosteroid use during treatment with the JAK1 inhibitor, the additional therapeutic result may be selected from the group consisting of a CDAI of less than 150 within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a remission within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a clinical remission within

52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; and an endoscopic remission within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; and combinations thereof. In one embodiment, when the patient has isolated ileal Crohn's disease, the additional therapeutic result may further be remission within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof.

[0331] In one embodiment, in a method of the present disclosure, a patient is evaluated during or at the end of the induction phase for a therapeutic result selected from the group consisting of clinical remission, endoscopic improvement, endoscopic remission, endoscopic response, clinical response, CDAI, average daily liquid/very soft SF score, average daily AP score, fecal calprotectin level, hs-CRP, IBDQ score, and combinations thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for clinical remission during or at the end of the induction phase. In one embodiment, in a method of the present disclosure, a patient is evaluated for endoscopic improvement during or at the end of the induction phase. In one embodiment, in a method of the present disclosure, a patient is evaluated for endoscopic remission during or at the end of the induction phase.

[0332] In one embodiment, the patient is administered at least 14 doses, at least 28 doses, at least 42 doses, at least 70 doses, or at least 84 doses, or at least 112 doses, or at least 140 doses, or at least 168 doses, or at least 224 doses, or 70 doses, or 84 doses, or 112 doses, or 140 doses, or 168 doses, or 224 doses of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, during the induction phase.

[0333] In one aspect, a certain therapeutic result is maintained by the patient during the maintenance phase. The maintenance phase may last for an indefinite period of time. In one embodiment, the maintenance phase is at least 36 weeks, including at least 37 weeks, at least 38 weeks, at least 39 weeks, at least 40 weeks, at least 41 weeks, at least 42 weeks, at least 43 weeks, at least 44 weeks, at least 45 weeks, at least 46 weeks, at least 47 weeks, or at least 48 weeks. In one embodiment, the maintenance phase is at least 40 additional weeks. In one embodiment, the therapeutic result maintained by the patient during the maintenance phase is selected from the group consisting of clinical remission, endoscopic remission, and combinations thereof. In one embodiment, the therapeutic result maintained by the patient during the maintenance phase is selected from the group consisting of clinical response, endoscopic improvement, and combinations thereof. In one aspect, a patient maintains a CDAI score of less than 150 during the maintenance phase. In one aspect, a patient maintains a SES-CD that is greater than a 50% decrease versus the patient's baseline SES-CD. In one embodiment, the patient maintains a SES-CD that is at least a 2 point reduction versus the patient's baseline SES-CD. In one embodiment, the therapeutic result maintained by the patient during the maintenance phase is clinical response. In one embodiment, the therapeutic result maintained by the patient during the maintenance phase is endoscopic remission.

[0334] In one embodiment, in a method of the present disclosure, a patient is evaluated for clinical remission during the maintenance phase. In one embodiment, a patient is evaluated for endoscopic

improvement during the maintenance phase. In one embodiment, in a method of the present disclosure, a patient is evaluated for endoscopic remission during the maintenance phase.

[0335] In one embodiment, the present disclosure provides a method for treating an inflammatory disease, in one aspect for treating Crohn's Disease, comprising (a) administering to a patient a dose of a JAK1 inhibitor (e.g., upadacitinib or a pharmaceutically acceptable salt or solid state form thereof) at week 0 and once daily (QD) thereafter for 16 weeks, wherein the dose is 45 mg QD. In one embodiment, the method further comprises (b) administering to the patient additional doses once daily thereafter for at least 36 additional weeks, wherein the dose is 15 mg or 30 mg QD. In one embodiment the dose is administered orally.

[0336] In one embodiment, at week 12 (i.e., 12 weeks after initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof), a patient is evaluated for clinical remission (average daily liquid/very soft SF score $\leq$ 2.8 and not worse than baseline and average daily AP score $\leq$ 1.0 and not worse than baseline) and/or for endoscopic remission (SES-CD $\leq$4 (or SES-CD $\leq$2 for patients with isolated ileal CD) and at least a two point reduction in SES-CD versus BL and no subscore >1 in any individual variable used to calculate SES-CD). In one embodiment, at week 16 (i.e., 16 weeks after initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof), a patient is evaluated for clinical remission and/or for endoscopic remission.

[0337] In one embodiment, at week 4 (i.e., 4 weeks after initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof), a patient is evaluated for clinical remission (average daily liquid/very soft SF score $\leq$ 2.8 and not worse than baseline and average daily AP score $\leq$ 1.0 and not worse than baseline) and/or for endoscopic remission (SES-CD $\leq$4 (or SES-CD $\leq$2 for patients with isolated ileal CD) and at least a two point reduction in SES-CD versus BL and no subscore >1 in any individual variable used to calculate SES-CD).

[0338] In one embodiment, at week 16 (i.e., 16 weeks after initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof), a patient is evaluated for remission, for example defined as reaching clinical remission (average daily liquid/very soft SF score $\leq$ 2.8 and not worse than baseline and average daily AP score $\leq$ 1.0 and not worse than baseline) and endoscopic remission (SES-CD $\leq$4 (or SES-CD $\leq$2 for patients with isolated ileal CD) and at least a two point reduction in SES-CD versus BL and no subscore >1 in any individual variable used to calculate SES-CD).

[0339] In one embodiment, at week 12 (i.e., 12 weeks after initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof), a patient is evaluated for clinical remission and/or for endoscopic improvement. In one embodiment, at week 16 (i.e., 16 weeks after initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof), a patient is evaluated for clinical remission and/or for endoscopic improvement.

[0340] In one embodiment, at week 4 (i.e., 4 weeks after initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof), a patient is evaluated for

clinical remission and/or for endoscopic improvement. In one embodiment, at week 2 (i.e., 2 weeks after initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof), a patient is evaluated for clinical remission and/or for endoscopic improvement.

[0341] In one embodiment, the present disclosure provides a method for treating Crohn's disease, comprising (a) administering to a patient a dose of a JAK1 inhibitor (e.g., upadacitinib or a pharmaceutically acceptable salt or solid state form thereof) at week 0 and once daily thereafter via an oral route, wherein the doses of the JAK1 inhibitor comprise 15 mg, 30 mg, or 45 mg QD, or any combination thereof.

[0342] In one embodiment, the present disclosure provides a method for treating Crohn's disease, comprising administering to a patient 15 mg to 45 mg of a JAK1 inhibitor. In one embodiment, the present disclosure provides a method for treating Crohn's disease, comprising administering to a patient orally 15 mg of a JAK1 inhibitor QD. In one embodiment, the present disclosure provides a method for treating Crohn's disease, comprising administering to a patient orally 30 mg of a JAK1 inhibitor QD. In one embodiment, the present disclosure provides a method for treating Crohn's disease, comprising administering to a patient orally 45 mg of a JAK1 inhibitor QD. In any such embodiments, the JAK1 inhibitor may be upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In any such embodiment, the JAK1 inhibitor may be in a once daily modified release formulation. In any such embodiment, the patient may have moderately to severely active Crohn's disease prior to treatment.

[0343] In one embodiment, the administration of a JAK1 inhibitor according to the present disclosure is further described in the Examples herein below or in Figure 1.

[0344] In one embodiment, the present disclosure provides a method for treating Crohn's disease, said method comprising a) administering at least one induction dose of a JAK1 inhibitor (e.g., upadacitinib or a pharmaceutically acceptable salt or solid state form thereof) to a patient, wherein said induction dose comprises 45 mg of the JAK 1 inhibitor. In one aspect, the induction dose is administered orally. In one aspect, the induction dose is administered QD. In one aspect, the induction dose is administered for 12 weeks. In one aspect the induction dose is administered for 16 weeks. In one embodiment, the induction dose is administered for up to 16 weeks, including for 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, or 15 weeks.

[0345] In one embodiment, the induction dose comprises 45 mg of the JAK1 inhibitor administered QD.

[0346] In one embodiment, the JAK1 inhibitor is upadacitinib or a pharmaceutically acceptable salt or solid state form thereof.

[0347] In one embodiment, the induction dose is in a once daily modified release formulation.

[0348] In one embodiment, the method further comprises b) administering a first maintenance dose of a JAK1 inhibitor (e.g., upadacitinib, or pharmaceutically acceptable salt or solid state form

thereof), to the patient after the last induction dose is administered; and c) administering at least one additional maintenance dose to the patient once daily thereafter.

[0349] In one embodiment, the first maintenance dose comprises 15 mg to 30 mg of the JAK1 inhibitor. In one aspect, the first maintenance dose comprises 15 mg or 30 mg of the JAK1 inhibitor. In one aspect, the first maintenance dose is smaller than the induction dose. In one aspect, the first maintenance dose is administered QD. In one aspect the first maintenance dose is 15 mg. In one aspect the first maintenance dose is 30 mg. In one aspect, the first maintenance dose is administered orally. In one aspect, the first maintenance dose is in a once daily modified release formulation.

[0350] In one aspect, the at least one additional maintenance dose comprises 15 mg to 30 mg of the JAK 1 inhibitor. In one aspect, the at least one additional maintenance dose comprises 15 mg or 30 mg. In one aspect, the at least one additional maintenance dose is administered orally. In one aspect, the at least one additional maintenance dose is administered QD. In one embodiment, the at least one additional maintenance dose comprises 15 mg of the JAK1 inhibitor administered QD. In one embodiment, the at least one additional maintenance dose comprises 30 mg of the JAK1 inhibitor administered QD. In one aspect, the at least one additional maintenance dose is in a once daily modified release formulation.

[0351] In any of the foregoing embodiments, the JAK1 inhibitor may be upadacitinib or a pharmaceutically acceptable salt or solid state form thereof.

[0352] In one aspect, in any of the foregoing embodiments, the patient maintains a CDAI score of less than 150.

[0353] In one aspect, in any of the foregoing embodiments, the patient is one who had an inadequate response to or experienced intolerance to conventional treatment (e.g., aminosalicylates, corticosteroids, immunosuppressants) or to a previous treatment with a biologic agent. In one aspect, in any of the foregoing embodiments, the patient is one who had an inadequate response to or experienced intolerance to a previous treatment with an anti-TNF agent. In one aspect, in any of the foregoing embodiments, the patient is a refractory patient.

[0354] In one aspect, in any of the foregoing embodiments, the patient is one who is naïve to previous treatment with aminosalicylates, a corticosteroid, an immunosuppressant, a biologic agent or an anti-TNF agent.

[0355] In one aspect, in any of the foregoing embodiments, the patient is one who had moderately to severely active Crohn's disease prior to treatment or administration of the induction dose.

[0356] In one embodiment, the present disclosure further provides a method for inducing clinical remission of Crohn's Disease in a patient, said method comprising a) administering to the patient at least one induction dose of a JAK1 inhibitor as described above or herein (e.g., upadacitinib or a pharmaceutically acceptable salt or solid state form thereof). In one embodiment, the induction dose comprises 45 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, an induction dose is administered at week 0 and once daily (QD) thereafter for up to 16

weeks (e.g., for 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, or 16 weeks), wherein the dose is 45 mg QD. In one embodiment, the method further comprises maintaining clinical remission of Crohn's disease, said method further comprising b) administering a first maintenance dose of said JAK1 inhibitor to the patient after the last induction dose is administered and c) administering at least one additional maintenance dose to the patient as described above or herein. In one embodiment, the at least one additional maintenance dose is administered once daily. In one embodiment, the additional maintenance doses are administered once daily for at least 36 additional weeks, including for at least 37 weeks, at least 38 weeks, at least 39 weeks, at least 40 weeks, at least 41 weeks, at least 42 weeks, at least 43 weeks, at least 44 weeks, at least 45 weeks, at least 46 weeks, at least 47 weeks, or at least 48 weeks. In one embodiment, the additional maintenance doses are administered once daily for at least 40 additional weeks. In one embodiment, the maintenance dose is 15 mg or 30 mg QD. In one embodiment the induction and maintenance doses are administered orally. In one embodiment, the patient has a CDAI score of 220 to 450 before administration of the first induction dose. In one embodiment, the patient has moderately to severely active Crohn's disease prior to administration of the first induction dose. In one embodiment, the patient has had an inadequate response to or experienced intolerance to conventional treatment (e.g., aminosalicylates, corticosteroids, immunosuppressants) or to a previous treatment with a biologic agent and/or an anti-TNF agent. In one embodiment, the patient is naïve to previous treatment with a corticosteroid, an immunosuppressant, a biologic agent, and/or an anti-TNF agent. In one embodiment, the clinical remission is achieved within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the clinical remission is achieved within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the clinical remission is achieved within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the patient achieves a CDAI score of less than 150 before administration of the first maintenance dose. In one embodiment, the induction and maintenance doses are in once-daily, modified release formulations.

[0357] In one embodiment, the present disclosure provides a method for inducing endoscopic remission of Crohn's disease, the method comprising (a) administering to a patient at least one induction dose of a JAK1 inhibitor (e.g., upadacitinib or a pharmaceutically acceptable salt or solid state form thereof), wherein the induction dose comprises 45 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, an induction dose is administered at week 0 and once daily (QD) thereafter for up to 16 weeks (e.g., for 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, or 16 weeks), wherein the dose is 45 mg QD. In one embodiment, the method further comprises maintaining endoscopic remission of Crohn's disease, said method further comprising (b) administering to the patient a first maintenance dose of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, after the last induction dose

is administered, and (c) administering at least one additional maintenance dose once daily thereafter. In one embodiment, the additional maintenance doses are administered once daily for at least 36 additional weeks, including for at least 37 weeks, at least 38 weeks, at least 39 weeks, at least 40 weeks, at least 41 weeks, at least 42 weeks, at least 43 weeks, at least 44 weeks, at least 45 weeks, at least 46 weeks, at least 47 weeks, or at least 48 weeks. In one embodiment, the additional maintenance doses are administered once daily for at least 40 additional weeks. In one embodiment, the maintenance dose is 15 mg or 30 mg QD. In one embodiment the induction and maintenance doses are administered orally. In one embodiment, the patient has a CDAI score of 220 to 450 before administration of the first induction dose. In one embodiment, the patient has moderately to severely active Crohn's disease prior to administration of the first induction dose. In one embodiment, the patient has had an inadequate response to or experienced intolerance to conventional treatment (e.g., aminosalicylates, corticosteroids, immunosuppressants) or to a previous treatment with a biologic and/or an anti-TNF agent. In one embodiment, the patient is naïve to previous treatment with a corticosteroid, an immunosuppressant, an anti-TNF agent and/or a biologic agent. In one embodiment, the endoscopic remission is achieved within 12 weeks or within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the endoscopic remission is achieved within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the patient achieves a CDAI score of less than 150 before administration of the first maintenance dose. In one embodiment, the induction and maintenance doses are in once-daily, modified release formulations.

[0358] In one embodiment, the present disclosure further provides a method for inducing endoscopic improvement of Crohn's Disease in a patient, said method comprising a) administering to the patient at least one induction dose of a JAK1 inhibitor as described above or herein (e.g., upadacitinib or a pharmaceutically acceptable salt or solid state form thereof). In one embodiment, the induction dose comprises 45 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, an induction dose is administered at week 0 and once daily (QD) thereafter for up to 16 weeks (e.g., for 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, or 16 weeks), wherein the dose is 45 mg QD. In one embodiment, the method further comprises maintaining endoscopic improvement of Crohn's disease, said method further comprising b) administering a first maintenance dose of said JAK1 inhibitor to the patient after the last induction dose is administered and c) administering at least one additional maintenance dose to the patient as described above or herein. In one embodiment, the at least one additional maintenance dose is administered once daily. In one embodiment, the additional maintenance doses are administered once daily for at least 36 additional weeks, including for at least 37 weeks, at least 38 weeks, at least 39 weeks, at least 40 weeks, at least 41 weeks, at least 42 weeks, at least 43 weeks, at least 44 weeks, at least 45 weeks, at least 46 weeks, at least 47 weeks, or at least 48 weeks. In one embodiment, the additional maintenance doses are administered once daily for at least 40 additional weeks. In one embodiment, the

maintenance dose is 15 mg or 30 mg QD. In one embodiment the induction and maintenance doses are administered orally. In one embodiment, the patient has a CDAI score of 220 to 450 before administration of the first induction dose. In one embodiment, the patient has moderately to severely active Crohn's disease prior to administration of the first induction dose. In one embodiment, the patient has had an inadequate response to or experienced intolerance to a conventional treatment (e.g., aminosalicylates, corticosteroids, immunosuppressants) or to a previous treatment with a biologic agent and/or an anti-TNF agent. In one embodiment, the patient is naïve to previous treatment with a corticosteroid, an immunosuppressant, a biologic agent and/or an anti-TNF agent. In one embodiment, the endoscopic improvement is achieved within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the endoscopic improvement is achieved within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the endoscopic improvement is achieved within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the patient achieves a CDAI score of less than 150 before administration of the first maintenance dose. In one embodiment, the induction and maintenance doses are in once-daily, modified release formulations.

[0359] In one embodiment, the present disclosure further provides a method of maintaining clinical remission of Crohn's Disease in a patient, said method comprising administering 15 mg or 30 mg of upadacitinib or a pharmaceutically acceptable salt form thereof to the patient. In one embodiment, the upadacitinib or a pharmaceutically acceptable salt form thereof is administered once daily for at least 36 weeks, including for at least 37 weeks, at least 38 weeks, at least 39 weeks, at least 40 weeks, at least 41 weeks, at least 42 weeks, at least 43 weeks, at least 44 weeks, at least 45 weeks, at least 46 weeks, at least 47 weeks, or at least 48 weeks. In one embodiment the upadacitinib or a pharmaceutically acceptable salt form thereof is administered orally. In one embodiment, the patient has had an inadequate response to or experienced intolerance to a conventional treatment (e.g., aminosalicylates, corticosteroids, immunosuppressants) or to a previous treatment with a biologic agent and/or an anti-TNF agent. In one embodiment, the patient is naïve to previous treatment with a corticosteroid, an immunosuppressant, a biologic agent and/or an anti-TNF agent. In one embodiment, the patient is a refractory patient. In one embodiment, the upadacitinib or a pharmaceutically acceptable salt form thereof is a once-daily, modified release formulation.

[0360] In one embodiment, the present disclosure further provides a method of maintaining endoscopic improvement of Crohn's Disease in a patient, said method comprising administering 15 mg or 30 mg of upadacitinib or a pharmaceutically acceptable salt form thereof to the patient. In one embodiment, the upadacitinib or a pharmaceutically acceptable salt form thereof is administered once daily for at least 36 weeks, including for at least 37 weeks, at least 38 weeks, at least 39 weeks, at least 40 weeks, at least 41 weeks, at least 42 weeks, at least 43 weeks, at least 44 weeks, at least 45 weeks, at least 46 weeks, at least 47 weeks, or at least 48 weeks. In one embodiment the upadacitinib or a

pharmaceutically acceptable salt form thereof is administered orally. In one embodiment, the patient has had an inadequate response to or experienced intolerance to a conventional treatment (e.g., aminosalicylates, corticosteroids, immunosuppressants) or to a previous treatment with a biologic agent and/or an anti-TNF agent. In one embodiment, the patient is naïve to previous treatment with a corticosteroid, an immunosuppressant, a biologic agent and/or an anti-TNF agent. In one embodiment, the patient is a refractory patient. In one embodiment, the upadacitinib or a pharmaceutically acceptable salt form thereof is a once-daily, modified release formulation.

[0361] In one embodiment, the present disclosure further provides a method of maintaining endoscopic remission of Crohn's Disease in a patient, said method comprising administering 15 mg or 30 mg of upadacitinib or a pharmaceutically acceptable salt form thereof to the patient. In one embodiment, the upadacitinib or a pharmaceutically acceptable salt form thereof is administered once daily for at least 36 weeks, including for at least 37 weeks, at least 38 weeks, at least 39 weeks, at least 40 weeks, at least 41 weeks, at least 42 weeks, at least 43 weeks, at least 44 weeks, at least 45 weeks, at least 46 weeks, at least 47 weeks, or at least 48 weeks. In one embodiment the upadacitinib or a pharmaceutically acceptable salt form thereof is administered orally. In one embodiment, the patient has had an inadequate response to or experienced intolerance to a conventional treatment (e.g., aminosalicylates, corticosteroids, immunosuppressants) or to a previous treatment with a biologic agent and/or an anti-TNF agent. In one embodiment, the patient is naïve to previous treatment with a corticosteroid, an immunosuppressant, a biologic agent and/or an anti-TNF agent. In one embodiment, the patient is a refractory patient. In one embodiment, the upadacitinib or a pharmaceutically acceptable salt form thereof is a once-daily, modified release formulation.

[0362] In one embodiment, the present disclosure further provides a method of maintaining remission of Crohn's Disease in a patient, said method comprising administering 15 mg or 30 mg of upadacitinib or a pharmaceutically acceptable salt form thereof to the patient. In one embodiment, the upadacitinib or a pharmaceutically acceptable salt form thereof is administered once daily for at least 36 weeks, including for at least 37 weeks, at least 38 weeks, at least 39 weeks, at least 40 weeks, at least 41 weeks, at least 42 weeks, at least 43 weeks, at least 44 weeks, at least 45 weeks, at least 46 weeks, at least 47 weeks, or at least 48 weeks. In one embodiment the upadacitinib or a pharmaceutically acceptable salt form thereof is administered orally. In one embodiment, the patient has had an inadequate response to or experienced intolerance to a conventional treatment (e.g., aminosalicylates, corticosteroids, immunosuppressants) or to a previous treatment with a biologic agent and/or an anti-TNF agent. In one embodiment, the patient is naïve to previous treatment with a corticosteroid, an immunosuppressant, a biologic agent and/or an anti-TNF agent. In one embodiment, the patient is a refractory patient. In one embodiment, the upadacitinib or a pharmaceutically acceptable salt form thereof is in a once-daily, modified release formulation.

[0363] In one aspect, induction doses for the methods disclosed herein are administered for 12 weeks in a dose regimen described in Table 3. In one aspect, induction doses are administered for 16

weeks in a dose regimen described in Table 3. In one aspect, maintenance doses are administered for 36 weeks or more in a dose regimen described in Table 3. In one aspect, induction doses for the methods disclosed herein are administered for 16 weeks and the maintenance doses are administered for 36 weeks in a dosing regimen as described in Table 3.

Table 3: Doses and Dosing Regimens (BID)

Induction Dose (mg)	Frequency of induction doses	Maintenance dose (mg)	Frequency of maintenance dose
3	BID	3	BID
6	BID	3	BID
6	BID	6	BID
12	BID	3	BID
12	BID	6	BID
12	BID	12	BID
24	BID	3	BID
24	BID	6	BID
24	BID	12	BID
24	QD[1]	3	BID
24	QD[1]	6	BID
24	QD[1]	12	BID

[1]The 24 mg QD dose is two 12 mg tablets administered simultaneously.

[0364] In one aspect, the induction doses for the methods disclosed herein are administered for 2 weeks in a dose regimen described in Table 4. In one aspect, the induction doses for the methods disclosed herein are administered for 4 weeks in a dose regimen described in Table 4. In one aspect, induction doses for the methods disclosed herein are administered for 12 weeks in a dose regimen described in Table 4. In one aspect, induction doses are administered for 16 weeks in a dose regimen described in Table 4. In one aspect, maintenance doses are administered for 36 weeks or more in a dose regimen described in Table 4. In one aspect, induction doses for the methods disclosed herein are administered for 2 weeks and the maintenance doses are administered for 36 or 40 weeks in a dosing regimen as described in Table 4. In one aspect, induction doses for the methods disclosed herein are administered for 4 weeks and the maintenance doses are administered for 36 or 40 weeks in a dosing regimen as described in Table 4. In one aspect, induction doses for the methods disclosed herein are administered for 12 weeks and the maintenance doses are administered for 36 or 40 weeks in a dosing regimen as described in Table 4. In one aspect, induction doses for the methods disclosed herein are administered for 16 weeks and the maintenance doses are administered for 36 or 40 weeks in a dosing regimen as described in Table 4.

Table 4: Doses and Dose Regimens (QD)

Induction Dose (mg)	Frequency of induction doses	Maintenance dose (mg)	Frequency of maintenance dose
45	QD	15	QD

45	QD	30	QD

[0365] In one particular embodiment, the induction dose is 45 mg of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof administered QD, and the maintenance dose, and any additional maintenance dose administered thereafter, is 30 mg of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof administered QD. In another embodiment, the induction dose is 45 mg of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof administered QD, and the maintenance dose, and any additional maintenance dose administered thereafter, is 15 mg of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof administered QD. In one embodiment, the maintenance and induction doses are in once-daily, modified release formulations.

IV. Methods of Treatment of Ulcerative Colitis

[0366] In one aspect, the present disclosure is directed to methods for the treatment of ulcerative colitis. In one aspect, the present disclosure provides methods for treating ulcerative colitis, in particular methods comprising administering a JAK1 inhibitor to a patient in certain amounts and/or at certain intervals. In one aspect, the JAK1 inhibitor is upadacitinib or a pharmaceutically acceptable salt or solid state form thereof.

[0367] In one aspect, the present disclosure provides a JAK1 inhibitor for use in the treatment of ulcerative colitis, by administration in certain amounts and/or at certain intervals as described herein. In one aspect, the JAK1 inhibitor is upadacitinib or a pharmaceutically acceptable salt or solid state form thereof.

[0368] In one aspect, the present disclosure provides for the use of a JAK1 inhibitor for the preparation of a medicament for the treatment of ulcerative colitis, by administration in certain amounts and/or at certain intervals as described herein. In one aspect, the JAK1 inhibitor is upadacitinib or a pharmaceutically acceptable salt or solid state form thereof.

[0369] In one aspect, the present disclosure is directed to methods for inducing clinical remission and/or endoscopic remission of ulcerative colitis. In one aspect, the present disclosure provides methods for inducing clinical remission and/or endoscopic remission of ulcerative colitis, in particular methods comprising administering a JAK1 inhibitor to a patient in certain amounts and/or at certain intervals as described herein. In one aspect, the present disclosure is further directed to methods for inducing clinical remission wherein the patient has a SF score $\leq$1, RBS of 0 and endoscopy score $\leq$1 at week 48 following administration of the JAK1 inhibitor. In one aspect the patient achieves clinical remission per Full Mayo score $\leq$ 2 with no subscore > 1) plus fecal calprotectin below 150 mg/kg at Week 8 following administration of the JAK1 inhibitor. In one aspect the patient has an increase of IBDQ$\geq$16 from baseline at week 8 following administration of the JAK1 inhibitor. In one aspect, the patient has a RBS$\geq$1 or an absolute RBS$\leq$1 at week 8 following administration of the JAK1 inhibitor. In one aspect,

the patient has a SF subscore ≤1 at week 8 following administration of the JAK1 inhibitor. In one aspect, the patient achieves a RBS of 0 at week 8. In one aspect the patient achieves a fecal calprotectin below 150 mg/kg at week 8 following administration of the JAK1 inhibitor. In one aspect the patient achieves histologic improvement at week 8 following administration of the JAK1 inhibitor. In one aspect, the JAK1 inhibitor is upadacitinib or a pharmaceutically acceptable salt or solid state form thereof.

[0370] In one aspect, the present disclosure provides a JAK1 inhibitor for use in inducing clinical remission of ulcerative colitis by administration in certain amounts and/or at certain intervals as described herein. In one aspect, the present disclosure provides a JAK1 inhibitor for use in inducing clinical remission and/or clinical response and/or endoscopic improvement and/or endoscopic remission of ulcerative colitis by administration in certain amounts and/or at certain intervals as described herein. In one aspect, the JAK1 inhibitor is upadacitinib or a pharmaceutically acceptable salt or solid state form thereof.

[0371] In one aspect, the present disclosure provides for the use of a JAK1 inhibitor for the preparation of a medicament for inducing clinical remission of ulcerative colitis by administration in certain amounts and/or at certain intervals as described herein. In one aspect, the present disclosure provides for the use of a JAK1 inhibitor for the preparation of a medicament for inducing clinical remission and/or clinical response and/or endoscopic improvement and/or endoscopic remission of ulcerative colitis by administration in certain amounts and/or at certain intervals as described herein. In one aspect, the JAK1 inhibitor is upadacitinib or a pharmaceutically acceptable salt or solid state form thereof.

[0372] In one particular aspect, the disease is moderately to severely active ulcerative colitis. In one aspect, in the context of the present disclosure, a patient is naïve to, or was previously treated with immunosuppressants (e.g., methotrexate), aminosalicylate, corticosteroid, and/or a biologic agent (e.g., vedolizumab, ustekinumab, natalizumab, etc.). In one aspect, the patient is naïve to, or was previously treated with an anti-TNF therapy (e.g., infliximab, adalimumab, certolizumab pegol, golimumab, etc.). In one aspect, in the context of a method of the present disclosure a patient was previously treated with one, two, three or more TNF antagonist(s) (also referred to herein as anti-TNF agents). In one embodiment, the patient is a patient who had an inadequate response with, lost response, or was intolerant to a TNF antagonist. In one aspect, in the context of a method of the present disclosure a patient was previously treated with one, two, three or more biologic agent(s). In one embodiment, the patient is a patient who had an inadequate response with, lost response, or was intolerant to a biologic agent. In one embodiment, the patient is a patient who had an inadequate response with, lost response, or was intolerant to a TNF antagonist, aminosalicylates, corticosteroids, immunosuppressants, and/or a biologic agent. In one embodiment, the patient is a refractory patient who has moderately to severely active ulcerative colitis. In one embodiment, the patient is either naïve to or has stopped using corticosteroids prior to treatment with the JAK1 inhibitor.

[0373] Disease severity for ulcerative colitis may be measured using a variety of indexes, including the Mayo Scoring System for Assessment of Ulcerative Colitis Activity ("Full Mayo"), the Adapted Mayo Score (consisting of the stool frequency subscore, rectal bleeding subscore and endoscopy subscore of the Full Mayo), the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) score system, the Inflammatory Bowel Disease Questionnaire (IBDQ), the Work Productivity and Activity Impairment Questionnaire for Ulcerative Colitis (version 2.0) (WPAI:UC), the European Quality of Life 5 Dimensions 5 Levels (EQ-5D-5L), the Short Form 36 Item (SF-36) Health Survey (version 2), the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Ulcerative Colitis Symptoms Questionnaire (UC-SQ), and the Patient Global Impression of Change (PGIC).

[0374] The Mayo Scoring System for Assessment of Ulcerative Colitis Activity, shown below, is a composite of the following subscores: Stool Frequency Subscore, Rectal Bleeding Subscore (RBS), Endoscopy Subscore, and Physician's Global Assessment Subscore.

Table 5: Mayo Scoring System for Assessment of Ulcerative Colitis Activity (Full Mayo)

Stool frequency Subscore* 0 = Normal number of stools for this subject 1 = 1 – 2 stools more than normal 2 = 3 – 4 stools more than normal 3 = 5 or more stools more than normal * Each patient serves as his or her own control to establish normal stool frequency and the degree of abnormal stool frequency.
Rectal bleeding Subscore** 0 = No blood seen 1 = Streaks of blood with stool less than half the time 2 = Obvious blood with stool most of the time 3 = Blood alone passed ** The daily bleeding score represents the most severe bleeding of the day.
Endoscopy Subscore: Findings of flexible sigmoidoscopy 0 = Normal or inactive disease 1 = Mild disease (erythema, decreased vascular pattern, mild friability) 2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions) 3 = Severe disease (spontaneous bleeding, ulceration)
Physician's Global Assessment Subscore*** 0 = Normal (Subscores are 0) 1 = Mild disease (Subscores are mostly 1's) 2 = Moderate disease (Subscores are 1 to 2)

3 = Severe disease (Subscores are 2 to 3) *** The physician's global assessment acknowledges the three other subscores, the subject's daily record of abdominal discomfort and functional assessment, and other observations such as physical findings, and the subject's performance status.

[0375] The IBDQ is a well-known 32 item validated questionnaire that assesses a patient's inflammatory bowel disease symptoms, general well-being, and mood, and may be used as a tool to evaluate a patient's quality of life (Guyatt, et al., Gastroenterology, 1989, 96:804-810). The IBDQ questions and answer options are set forth below in Table 6.

Table 6: IBDQ

Question	Answer Options
1. How frequent have your bowel movements been during the last two weeks?	1 Bowel movements as or more frequent than they have ever been 2 Extremely Frequent 3 Very frequent 4 Moderate increase in frequency of bowel movements 5 Some increase in frequency of bowel movements 6 Slight increase in frequency of bowel movements 7 Normal, no increase in frequency of bowel movements
2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks?	1 All of the time 2 Most of the time 3 A good bit of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
3. How often during the last 2 weeks have you felt frustrated, impatient, or restless?	1 All of the time 2 Most of the time 3 A good bit of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
4. How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem?	1 All of the time 2 Most of the time 3 A good bit of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
5. How much of the time during the last 2 weeks have your bowel movements been loose?	1 All of the time 2 Most of the time 3 A good bit of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
6. How much energy have you had during the last 2 weeks?	1 No energy at all 2 Very little energy 3 A little energy 4 Some energy

Question	Answer Options
	5 A moderate amount of energy 6 A lot of energy 7 Full of energy
7. How often during the last 2 weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem?	1 All of the time 2 Most of the time 3 A good bit of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
8. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem?	1 All of the time 2 Most of the time 3 A good bit of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
9. How often during the last 2 weeks have you been troubled by cramps in your abdomen?	1 All of the time 2 Most of the time 3 A good bit of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
10. How often during the last 2 weeks have you felt generally unwell?	1 All of the time 2 Most of the time 3 A good bit of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
11. How often during the last 2 weeks have you been troubled because of fear of not finding a washroom?	1 All of the time 2 Most of the time 3 A good bit of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks?	1A great deal of difficulty; activities made impossible 2 A lot of difficulty 3 A fair bit of difficulty 4 Some difficulty 5 A little difficulty 6 Hardly any difficulty 7 No difficulty; the bowel problems did not limit sports or leisure activities
13. How often during the last 2 weeks have you been troubled by pain in the abdomen?	1 All of the time 2 Most of the time 3 A good bit of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
14. How often during the last 2 weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night?	1 All of the time 2 Most of the time 3 A good bit of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time

Question	Answer Options
	7 None of the time
15. How often during the last 2 week shave you felt depressed or discouraged?	1 All of the time 2 Most of the time 3 A good bit of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
16. How often during the last 2 weeks have you had to avoid attending events where there was no washroom close at hand?	1 All of the time 2 Most of the time 3 A good bit of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
17. Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of gas?	1 A major problem 2 A big problem 3 A significant problem 4 Some trouble 5 A little trouble 6 Hardly any trouble 7 No trouble
18. Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to, the weight you would like to be at?	1 A major problem 2 A big problem 3 A significant problem 4 Some trouble 5 A little trouble 6 Hardly any trouble 7 No trouble
19. Many patients with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better, and worries about having a relapse. In general, how often during the last 2 weeks have you felt worried or anxious?	1 All of the time 2 Most of the time 3 A good bit of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
20. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating?	1 All of the time 2 Most of the time 3 A good bit of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
21. How often during the last 2 weeks have you felt relaxed and free of tension?	1 None of the time 2 A little of the time 3 Some of the time 4 A good bit of the time 5 Most of the time 6 Almost all of the time 7 All of the time
22. How much of the time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements?	1 All of the time 2 Most of the time 3 A good bit of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
23. How much of the time during the last	1 All of the time

Question	Answer Options
2 weeks have you felt embarrassed as a result of your bowel problem?	2 Most of the time 3 A good bit of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
24. How much of the time during the last 2 week shave you been troubled by a feeling of having to go to the bathroom even though your bowels were empty?	1 All of the time 2 Most of the time 3 A good bit of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
25. How much of the time during the last 2 weeks have you felt tearful or upset?	1 All of the time 2 Most of the time 3 A good bit of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
26. How much of the time during the last 2 weeks have you been troubled by accidental soiling of your underpants?	1 All of the time 2 Most of the time 3 A good bit of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
27. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem?	1 All of the time 2 Most of the time 3 A good bit of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
28. To what extent has your bowel problem limited sexual activity during the last 2 weeks?	1 No sex as a result of bowel disease 2 Major limitation as a result of bowel disease 3 Moderate limitation as a result of bowel disease 4 Some limitation as a result of bowel disease 5 A little limitation as a result of bowel disease 6 Hardly any limitation as a result of bowel disease 7 No limitation as a result of bowel disease
29. How much of the time during the last 2 weeks have you been troubled by nausea or feeling sick to your stomach?	1 All of the time 2 Most of the time 3 A good bit of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
30. How much of the time during the last 2 weeks have you felt irritable?	1 All of the time 2 Most of the time 3 A good bit of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
31. How often during the past 2 weeks have you felt a lack of understanding from others?	1 All of the time 2 Most of the time 3 A good bit of the time 4 Some of the time

Question	Answer Options
	5 A little of the time 6 Hardly any of the time 7 None of the time
32. How satisfied, happy, or leased have you been with your personal life during the past 2 weeks?	1 Very dissatisfied, unhappy most of the time 2 Generally dissatisfied, unhappy 3 Somewhat dissatisfied, unhappy 4 Generally satisfied, pleased 5 Satisfied most of the time, happy 6 Very satisfied most of the time, happy 7 Extremely satisfied, could not have been more happy or pleased

[0376] The Work Productivity and Activity Impairment Questionnaire for Ulcerative Colitis (WPAI:UC) and Crohn's Disease (WPAI:CD) assesses the impact of the condition on work productivity losses and impairment in daily activity. WPAI:UC has six items covering four domains: Absenteeism (work time missed), measured as the number of hours missed from work in the past 7 days due to a condition related problem. Scores are expressed as impairment percentages, adjusting for hours actually worked according to the WPAI:UC or WPAI:CD scoring algorithm; Presenteeism (impairment at work/reduced on-the-job effectiveness), measured as the impact of the condition on productivity while at work (i.e., reduced amount or kind of work, or not as focused as usual). Responses are recorded on a 0 – 10 Likert scale (where, 0 = no effect of UC or CD on work and 10 = severe impact of UC or CD while at work); productivity loss (overall work impairment), measured as the sum of hours missed due to condition i.e., absenteeism and number of hours worked with impairment i.e., product of number of hours worked and presenteeism; and activity impairment (i.e., activities other than paid work like work around house, cleaning, shopping, traveling, studying), recorded and scored in the same way as presenteeism. Higher numbers indicate greater impairment and less productivity. The WPAI:UC/WPAI:CD questions and answer options are set forth in Table 7.

Table 7: WPAI:UC* and WPAI:CD

Questions	Answer Options
1. Are you currently employed (working for pay)? *If no, skip to question 6.*	No or yes
2. During the past seven days, how many hours did you miss from work because of problems associated with your ulcerative colitis? *Include hours you missed on sick days, times you went in late, left early, etc., because of your ulcerative colitis. Do not include time you missed to participate in this study.*	Number of hours
3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?	Number of hours
4. During the past seven days, how many hours did you actually work?	Number of hours (*if 0, skip to question 6*)
5. During the past seven days, how much did your ulcerative	Select number on a scale of 0 (UC

colitis affect your productivity while you were working? *Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If ulcerative colitis affected your work only a little, choose a low number. Choose a high number if ulcerative colitis affected your work a great deal.*	had no effect on work) to 10 (UC completely prevented me from working), representing how much ulcerative colitis affected productivity while at work
6. During the past 7 days, how much did your ulcerative colitis affect your ability to do your regular daily activities, other than work at a job? *Regular activities means usual activities, such as work around the house, shopping, childcare, exercising, studying, etc. Consider times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If ulcerative colitis affected your activities only a little, choose a low number. Choose a high number if ulcerative colitis affected your activities a great deal.*	Select number on a scale of 0 (UC had no effect on daily activities) to 10 (UC completely prevented me from doing daily activities), representing how much ulcerative colitis affected ability to do regular daily activities, other than work at a job

* Questions 2-7 are about the previous seven days, not including the day the questionnaire is completed.

[0377] The European Quality of Life 5 Dimensions 5 Levels (EQ-5D-5L) is a standardized non-disease specific instrument for describing and valuing health-related quality of life. The EQ-5D-5L consists of 5 dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problem, slight problem, moderate problem, severe problem or unable to do the activity. It also contains a Visual Analogue Scale (VAS). Subjects are asked to indicate the level that describes their current level of function or experience for each dimension. As a measure of health status, it provides a descriptive profile and can be used to generate a single index value for health status, where full health is equal to 1 and death is equal to 0. The VAS records the subject's assessment of his/her own health along a vertical 20 cm line, which has health state scores between 0 and 100. The EQ-5D-5L questions and answer options are set forth in Table 8.

Table 8: EQ-5D-5L Questionnaire

Dimension	Answer Options	Score
Mobility	I have no problems walking	MB1
	I have slight problems walking	MB2
	I have moderate problems walking	MB3
	I have severe problems walking	MB4
	I am unable to walk	MB5
Self-Care	I have no problems washing or dressing myself	SC1
	I have slight problems washing or dressing myself	SC2
	I have moderate problems washing or dressing myself	SC3
	I have severe problems washing or dressing myself	SC4
	I am unable to wash or dress myself	SC5
Usual Activities*	I have no problems doing my usual activities	UA1
	I have slight problems doing my usual activities	UA2
	I have moderate problems doing my usual activities	UA3
	I have severe problems doing my usual activities	UA4
	I am unable to do my usual activities	UA5
Pain/Discomfort	I have no pain or discomfort	PD1
	I have slight pain or discomfort	PD2
	I have moderate pain or discomfort	PD3

	I have severe pain or discomfort I have extreme pain or discomfort	PD4 PD5
Anxiety/Depression	I am not anxious or depressed I am slightly anxious or depressed I am moderately anxious or depressed I am severely anxious or depressed I am extremely anxious or depressed	AD1 AD2 AD3 AD4 AD5
How good or bad is your health today?	We would like to know how good or bad your health is TODAY. This scale is numbered from 0 to 100. 100 means the best health you can imagine. 0 means the worst health you can imagine. Mark an X on the scale to indicate how your health is TODAY. Now, please write the number you marked on the scale in the box below.	

*E.g., work, study, housework, family or leisure activities

[0378] The SF-36 questionnaire is a self-administered multi-domain scale with 36 items. Eight subscales cover a range of functioning: physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH). The scoring yields a physical component score, a mental component summary score, and subscale scores. Higher scores represent better outcomes. The concepts measured by the SF-36 are not specific to any age, disease, or treatment group, allowing comparison of relative burden of different diseases and the benefit of different treatments. The SF-36 questions and answer options are set forth below in Table 9.

Table 9: SF-36 Health Survey

Function – Question number	**Question**	**Answer Options**
GH - 1	In general, would you say your health is:	Excellent Very good Good Fair Poor
	Compared to one year ago, how would you rate your health in general now?	Much better now than one year ago Somewhat better now than one year ago About the same as one year ago Somewhat worse now than one year ago Much worse now than one year ago
PF – 1[1]	Does your health now limit you in vigorous activities, such as running, lifting heavy objects, participating in strenuous sports? If so, how much?	Yes, limited a lot Yes, limited a little No, not limited at all
PF - 2[1]	Does your health now limit you in moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf? If so, how much?	Yes, limited a lot Yes, limited a little No, not limited at all
PF - 3[1]	Does your health now limit you in lifting or carrying groceries? If so, how much?	Yes, limited a lot Yes, limited a little No, not limited at all
PF - 4[1]	Does your health now limit you in climbing several flights of stairs? If so, how much?	Yes, limited a lot Yes, limited a little No, not limited at all
PF - 5[1]	Does your health now limit you in climbing one flight of stairs? If so, how much?	Yes, limited a lot Yes, limited a little No, not limited at all

Function – Question number	Question	Answer Options
PF – 6[1]	Does your health now limit you in bending, kneeling, or stooping? If so, how much?	Yes, limited a lot Yes, limited a little No, not limited at all
PF - 7[1]	Does your health now limit you in walking more than a mile? If so, how much?	Yes, limited a lot Yes, limited a little No, not limited at all
PF – 8[1]	Does your health now limit you in walking several hundred yards? If so, how much?	Yes, limited a lot Yes, limited a little No, not limited at all
PF – 9[1]	Does your health now limit you in walking one hundred yards? If so, how much?	Yes, limited a lot Yes, limited a little No, not limited at all
PF - 10[1]	Does your health now limit you in bathing or dressing yourself? If so, how much?	Yes, limited a lot Yes, limited a little No, not limited at all
RP – 1[2]	Cut down on the amount of time you spent on work or other activities as a result of your physical health	All of the time Most of the time Some of the time A little of the time None of the time
RP – 2[2]	Accomplished less than you would like as a result of your physical health	All of the time Most of the time Some of the time A little of the time None of the time
RP – 3[2]	Were limited in the kind of work or other activities as a result of your physical health	All of the time Most of the time Some of the time A little of the time None of the time
RP - 4[2]	Had difficulty performing the work or other activities as a result of your physical health (for example, it took extra effort)	All of the time Most of the time Some of the time A little of the time None of the time
RE – 1[2]	Cut down on the amount of time you spent on work or other activities as a result of any emotional problems (such as feeling depressed or anxious)	All of the time Most of the time Some of the time A little of the time None of the time
RE – 2[2]	Accomplished less than you would like as a result of any emotional problems (such as feeling depressed or anxious)	All of the time Most of the time Some of the time A little of the time None of the time
RE - 3[2]	Did work or other activities less carefully than usual as a result of any emotional problems (such as feeling depressed or anxious)	All of the time Most of the time Some of the time A little of the time None of the time
SF – 1	During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?	Not at all Slightly Moderately Quite a bit Extremely

Function – Question number	Question	Answer Options
BP – 1	How much bodily pain have you had during the past 4 weeks?	None Very mild Mild Moderate Severe Very severe
BP - 2	During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	Not at all A little bit Moderately Quite a bit Extremely
VT – 1[3]	How much of the time during the past 4 weeks did you feel full of life?	All of the time Most of the time Some of the time A little of the time None of the time
MH – 1[3]	How much of the time during the past 4 weeks have you been very nervous?	All of the time Most of the time Some of the time A little of the time None of the time
MH – 2[3]	How much of the time during the past 4 weeks have you felt so down in the dumps that nothing could cheer you up?	All of the time Most of the time Some of the time A little of the time None of the time
MH – 3[3]	How much of the time during the past 4 weeks have you felt calm and peaceful?	All of the time Most of the time Some of the time A little of the time None of the time
VT – 2[3]	How much of the time during the past 4 weeks did you have a lot of energy?	All of the time Most of the time Some of the time A little of the time None of the time
MH – 4[3]	How much of the time during the past 4 weeks have you felt downhearted and depressed?	All of the time Most of the time Some of the time A little of the time None of the time
VT – 3[3]	How much of the time during the past 4 weeks did you feel worn out?	All of the time Most of the time Some of the time A little of the time None of the time
MH – 5[3]	How much of the time during the past 4 weeks have you been happy?	All of the time Most of the time Some of the time A little of the time None of the time
VT – 4[3]	How much of the time during the past 4 weeks did you feel tired?	All of the time Most of the time Some of the time A little of the time None of the time

Function – Question number	Question	Answer Options
SF – 2	During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?	All of the time Most of the time Some of the time A little of the time None of the time
GH – 2[4]	I seem to get sick a little easier than other people.	Definitely true Mostly true Don't know Mostly false Definitely false
GH – 3[4]	I am as healthy as anybody I know.	Definitely true Mostly true Don't know Mostly false Definitely false
GH – 4[4]	I expect my health to get worse.	Definitely true Mostly true Don't know Mostly false Definitely false
GH - 5[4]	My health is excellent.	Definitely true Mostly true Don't know Mostly false Definitely false

[1]Instructions: The following question is about activities you might do during a typical day
[2]Instructions: During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities?
[3]Instructions: This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.
[4]Instructions: How TRUE or FALSE is the following statement for you?

[0379] The Functional Assessment of Chronic Illness Therapy (FACIT) system is a collection of quality of life (QOL) questionnaires targeted to the management of cancer and other chronic illnesses. The FACIT fatigue (FACIT-F) questionnaire was developed to assess fatigue associated with anemia. It consists of 13 fatigue-related questions. The responses to the 13 items on the FACIT fatigue questionnaire are each measured on a 4-point Likert scale. The responses to the answers are the following: (i) not at all: 0 points; (ii) a little bit: 1 point; (iii) somewhat: 2 points; (iv) quite a bit: 3 points; and (v) very much: 4 points. Thus, the total score ranges from 0 to 52. High scores represent less fatigue. The FACIT-F questions and answer options are set forth below in Table 10.

Table 10: FACIT-F Questionnaire

Question	Answer Options
I feel fatigued… I feel weak all over… I feel listless ("washed out")… I feel tired… I have trouble starting things because I am tired… I have trouble finishing things because I am tired… I have energy… I am able to do my usual activities… I need to sleep during the day… I am too tired to eat… I need help doing my usual activities… I am frustrated by being too tired to do the things I want to do… I have to limit my social activity because I am tired…	0 Not at all 1 A little bit 2 Somewhat 3 Quite a bit 4 Very much

[0380] The Ulcerative Colitis Symptoms Questionnaire (UC-SQ) is a UC-specific instrument composed of 17 Likert-type items. UC-SQ was developed to assess UC related gastrointestinal and non-gastrointestinal symptoms such as frequent bowel movements, abdominal discomfort, nausea, loss of appetite, pain, and anemia along with the impact on patients' sleep. Each question can be answered using Likert-type options such as (i) Not at all: 0 points; (ii) A little bit: 1 point; (iii) Somewhat: 2 points; (iv) Quite a bit: 3 points; and (v) Very much: 4 points based on how the patient felt during the past week (i.e., 7 days). The total score ranges can vary from 0 to 68 with lower scores indicating improvement. The UC-SQ questions and answer options are set forth below in Table 11.

Table 11: UC-SQ Questionnaire

Question	Answer Options
During the past week, were your bowel movements more frequent than usual? During the past week, did you pass gas more than usual? During the past week, did you have abdominal pain? During the past week, did you have rectal pain? During the past week, did you have cramping? During the past week, have you felt tired or lacking energy? During the past week, did you feel nauseated? During the past week, did you experience loss of appetite? During the past week, did you have joint pain? During the past week, did you have difficulty sleeping? During the past week, did you experience bloating? During the past week, did you have diarrhea? During the past week, did you pass blood or have blood in your stool? During the past week, did you have mucus in your stool? During the past week, were you constipated? During the past week, did you feel that you needed to have a bowel movement - even when your bowels were empty? During the past week, did you experience a sudden or intense need to have a bowel movement?	Not at all A little bit Somewhat Quite a bit Very much

[0381] The Patient Global Impression of Change (PGIC) is a self-administered instrument that assesses change in the overall symptoms due to Ulcerative Colitis. The PGIC is one item in which subjects are asked to rate overall improvement since start of the treatment. Patients are asked the question "Compared to before your treatment began, how would you rate the change in your overall symptoms due to your ulcerative colitis?", and rate their change as "Very much improved," "Much improved," "Minimally improved", "No change," "Minimally worse," "Much worse" and "Very much worse".

[0382] In one aspect, the patient to be treated has moderately to severely active ulcerative colitis. Moderately to severely active ulcerative colitis is characterized by an Adapted Mayo score of 5 to 9 points and an endoscopy subscore of 2 to 3.

[0383] In one embodiment, the patient is a patient who had an inadequate response with, lost response, or was intolerant to a conventional therapy (e.g., aminosalicylate, corticosteroids, immunosuppressants), or to a biologic agent. In one embodiment, the patient is a patient who had an inadequate response with, lost response, or was intolerant to biologic therapies. Examples of such biologic therapies include infliximab, adalimumab, vedolizumab, golimumab, ustekinumab and certolizumab pegol. Criteria for determining if a patient has had an inadequate response to, lost response, or experienced intolerance to previous treatment with corticosteroids, immunosuppressants, and/or a biologic therapy are defined below:

Corticosteroids:

1) Signs and symptoms of persistently active disease despite a history of at least one induction regimen that included a dose equivalent to prednisone ≥ 40 mg/day orally for 3 to 4 weeks or intravenously for 1 week, or
2) Unable to taper corticosteroid to below a dose equivalent to prednisone 10 mg daily orally without recurrent active disease, or
3) History of intolerance to corticosteroids (including, but no limited to Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, infection).

Immunosuppressants:

1) Signs and symptoms of persistently active disease despite a history of at least one 90-day regimen of oral azathioprine (≥ 1.5 mg/kg/day; for subjects in Japan and China only: ≥ 1.0 mg/kg/day), 6-mercaptopurine (≥ 1 mg/kg/day [for subjects in Japan and China only: ≥ 0.6 mg/kg/day, rounded to the nearest available tablet of half tablet formulation]; or a documented 6-TGN level of 230 – 450 pmol/8 × 10^8 RBC or higher on the current dosing regimen), injectable methotrexate (MTX ≥ 15 mg/week subcutaneous [SC] or intramuscular), or tacrolimus (for subjects in Japan only: documented trough level of 5 – 10 ng/mL), or

2) History of intolerance to at least one immunosuppressant (including, but not limited to nausea/vomiting, abdominal pain, pancreatitis, liver enzyme abnormalities, lymphopenia, infection)

Biologic agents for UC:

1) Signs and symptoms of persistently active disease despite a history of any of the following:
   a. at least one 6-week induction regimen of infliximab (≥ 5 mg/kg intravenous [IV] at 0, 2 and 6 weeks),
   b. at least one 4-week induction regimen of adalimumab (one 160 mg SC dose followed by one 80 mg SC dose [or one 80 mg SC dose, in countries where this dosing regimen is allowed] followed by one 40 mg SC dose at least 2 weeks apart),
   c. at least one 2-week induction regimen of golimumab (one 200 mg SC dose followed by one 100 mg SC dose at least 2 weeks apart),
   d. at least one 6-week induction regimen of vedolizumab (300 mg IV at 0, 2 and 6 weeks), or
2) Recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify), or
3) History of intolerance to at least one biologic agent (including, but not limited to infusion-related reaction, demyelination, congestive heart failure (CHF), infection)

[0384] In one aspect, the patient is one who has previously been treated with, or is currently being treated with aminosalicylate, immunosuppressants, corticosteroids, and/or a biologic agent.

[0385] In one aspect, the Mayo Scoring System for Assessment of Ulcerative Colitis Activity or any of the evaluations described hereinbefore or in the Examples herein below is/are used to assess the efficacy of upadacitinib in the treatment of ulcerative colitis, for example moderately to severely active ulcerative colitis. In one embodiment, the evaluation used to assess the efficacy of upadacitinib in the treatment of ulcerative colitis is selected from the group consisting of the Full Mayo score, the Partial Mayo score, the Adapted Mayo score, the IBDQ, the WPAI:UC, the EQ-5D-5L, the SF-36, the FACIT-F, the UC-SQ, the PGIC, and combinations thereof.

[0386] In one embodiment, in the context of the present disclosure, the treatment of a patient having ulcerative colitis, and/or the induction of clinical remission of ulcerative colitis and/or the induction of clinical response and/or endoscopic improvement and/or endoscopic remission in a patient comprises an induction phase and a maintenance phase. In the induction phase, one or more doses of the JAK1 inhibitor, for example referred to herein as induction doses, are administered to the patient, for example, orally. In the maintenance phase, a first dose of the JAK1 inhibitor, for example referred to herein as the maintenance dose, is administered to the patient followed by at least one additional dose of the JAK1 inhibitor, for example, also referred to herein as a maintenance dose. The maintenance doses

are, for example, administered orally. The JAK1 inhibitor may be, for example, upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. Examples of induction phases and maintenance phases are described herein.

[0387] In one aspect, a certain therapeutic result is achieved by the patient during or at the end of the induction phase, for example clinical remission. In other embodiments, the therapeutic result achieved by the patient during or at the end of the induction phase is selected from the group consisting of endoscopic subscore of 0 or 1 at week 8, endoscopic subscore of 0 at week 8, fecal calprotectin below 150 mg/kg at week 8, IBDQ response (increase of IBDQ≥16 from baseline) at week 8, RBS ≥1 or absolute RBS≤1 at week 8, or RBS of 0 at week 8. In one aspect, the patient achieves clinical remission during or by the end of the induction phase. In one aspect, the patient achieves endoscopic remission during or by the end of the induction phase.

[0388] In one aspect, the patient achieves endoscopic improvement of ulcerative colitis during or by the end of the induction phase. In one aspect, the patient achieves clinical remission and endoscopic improvement of ulcerative colitis during or at the end of the induction phase.

[0389] In one embodiment, the induction phase lasts for up to 16 weeks (e.g., for up to 16 weeks following initiation of administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof). Thus, in one embodiment, the induction phase is 16 weeks. In another embodiment, the induction phase optionally lasts for less than 16 weeks, for instance, for 2 weeks, for 3 weeks, for 4 weeks, for 5 weeks, for 6 weeks, for 7 weeks, for 8 weeks, for 9 weeks, for 10 weeks, for 11 weeks, for 12 weeks, for 13 weeks, for 14 weeks, or for 15 weeks. In one aspect, the patient achieves an endoscopic remission within 8 weeks, or within 12 weeks, or within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one aspect, the patient achieves a clinical remission within 8 weeks, or within 12 weeks, or within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one aspect, the patient achieves an endoscopic improvement within 8 weeks, or within 12 weeks, or within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one aspect, the patient achieves a clinical response within 8 weeks, or within 12 weeks, or within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one aspect, the patient achieves a clinical remission within 8 weeks, or within 12 weeks, or within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof.

[0390] In one embodiment, the patient achieves clinical remission within 2 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the patient achieves clinical remission within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof.

[0391] In one embodiment, the patient achieves clinical response within 2 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one

embodiment, the patient achieves clinical response within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof.

[0392] In one embodiment, the patient achieves endoscopic improvement or endoscopic remission within 2 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the patient achieves endoscopic improvement or endoscopic remission within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the patient achieves endoscopic improvement or endoscopic remission within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the patient achieves endoscopic improvement or endoscopic remission within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof.

[0393] In one embodiment, the patient achieves corticosteroid-free remission within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the patient achieves corticosteroid-free remission within 8 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the corticosteroid-free remission is a clinical remission. In one embodiment, the corticosteroid-free remission is endoscopic remission.

[0394] In some embodiments, during or by the end of the induction phase (e.g., lasting for up to 16 weeks, including for 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks or for 16 weeks), the patient achieves at least one therapeutic result selected from the group consisting of:

1) endoscopic improvement (defined as endoscopic subscore $\leq$ 1 within 8 weeks of initiating administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof,
2) a Full Mayo score $\leq$ 2 with no subscore $>$ 1 within 8 weeks of initiating administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof,
3) clinical response (defined as decrease from baseline in the Adapted Mayo score $\geq$ 2 points and $\geq$ 30% from baseline, plus a decrease in rectal bleeding subscore (RBS) $\geq$ 1 or an absolute RBS of 0 or 1) within 8 weeks of initiating administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof,
4) clinical response within 2 weeks of initiating administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof,
5) change in Full Mayo score from Baseline to Week 8 after initiating administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof,
6) endoscopic remission (defined as endoscopic subscore of 0) within 8 weeks of initiating administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof,

7) histologic improvement (defined as a decrease from baseline in Geboes score) within 8 weeks of initiating administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof,

8) decrease in RBS≥1 or an absolute RBS ≤1 within 8 weeks of initiating administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof,

9) RBS of 0 within 8 weeks of initiating administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof,

10) endoscopic improvement (endoscopic subscore of 0 or 1) within 8 weeks of initiating administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof,

11) stool frequency subscore ≤1 within 8 weeks of initiating administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof,

12) maintenance of clinical remission at Week 52 following initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof in patients who achieved clinical remission within 8 weeks of initiating administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof,

13) endoscopic improvement within 52 weeks of initiating administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof,

14) a Full Mayo score ≤ 2 with no subscore > 1 within 52 weeks of initiating administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof,

15) clinical remission within 52 weeks of initiating administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof in patients who discontinued corticosteroid use prior to initiating administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof,

16) subjects who are taking corticosteroids at Baseline and are steroid-free at within 52 weeks of initiating administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof,

17) endoscopic improvement at Week 52 following initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof in patients who achieved clinical remission within 8 weeks of initiating administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof,

18) clinical response within 44 weeks of initiating administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof,

19) endoscopic remission within 52 weeks of initiating administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof,

20) histologic improvement within 52 weeks of initiating administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof,

21) clinical remission per Adapted Mayo score (defined as SFS≤ 1, RBS of 0, and endoscopy subscore ≤1),

and combinations thereof.

[0395] In some embodiments, the patient achieves a clinical remission within 16 weeks or within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, and further achieves any combination of additional therapeutic results selected from the group consisting of therapeutic results 1), 2), 3), 4), 5), 6), 7), 8), 9), 10), 11), 12), 13), 14), 15), 16), 17), 18), 19) 20), 21) and combinations thereof. In one such embodiment, the induction phase is 16 weeks. In one embodiment, the additional therapeutic result is achieved within 8 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, and is selected from the group consisting of therapeutic results 1), 2), 3), 4), 5), 6), 7), 8), 9), 10), 11) and combinations thereof.

[0396] In one embodiment, the induction phase is 8 weeks, and the patient achieves a clinical remission within 8 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, and further achieves any combination of additional therapeutic results selected from the group consisting of therapeutic results 1), 2), 3), 4), 5), 6), 7), 8), 9), 10), 11), 12), 13), 14), 15), 16), 17), 18), 19) 20), 21) and combinations thereof. In one embodiment, the additional therapeutic result is achieved within 8 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the additional therapeutic result is achieved within 8 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, and is selected from the group consisting of therapeutic results 1), 2), 3), 4), 5), 6), 7), 8), 9), 10), 11) and combinations thereof.

[0397] In one embodiment, the induction phase is 4 weeks, and the patient achieves a clinical remission within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, and further achieves any combination of additional therapeutic results selected from the group consisting of therapeutic results 1), 2), 3), 4), 5), 6), 7), 8), 9), 10), 11), 12), 13), 14),15), 16), 17), 18), 19) 20), 21) and combinations thereof. In one embodiment, the additional therapeutic result is achieved within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the additional therapeutic result is achieved within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, and is selected from the group consisting of endoscopic improvement, clinical remission, clinical response, endoscopic remission, histologic improvement, and combinations thereof.

[0398] In one embodiment, the patient achieves a clinical remission within 4 weeks, within 8 weeks, within 12 weeks, or within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, and/or achieves an endoscopic improvement within 4 weeks, within 8 weeks, within 12 weeks or within 16 weeks of initiating administration of

upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, and further achieves an additional therapeutic result selected from the group consisting of a decrease from baseline in Partial Mayo score ≥ 2 points and ≥30% from baseline plus a decrease in RBS ≥1 or an absolute RBS ≤ 1 over time within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; clinical response per Partial Mayo score within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a decrease from baseline in Partial Mayo score ≥ 2 points and ≥30% from baseline plus a decrease in RBS ≥1 or an absolute RBS ≤ 1 over time within 8 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a decrease from baseline in Partial Mayo score ≥ 2 points and ≥30% from baseline plus a decrease in RBS ≥1 or an absolute RBS ≤ 1 over time within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a decrease from baseline in Partial Mayo score ≥ 2 points and ≥30% from baseline plus a decrease in RBS ≥1 or an absolute RBS ≤ 1 over time within 2 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; an endoscopic remission within 16 weeks of initiating administration of pharmaceutically upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; an endoscopic remission within 12 weeks of initiating administration of upadacitinib, or an acceptable salt or solid state form thereof; an endoscopic remission within 8 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; an endoscopic remission within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a clinical response within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a clinical response within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a clinical response within 8 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a clinical response within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a Full Mayo score ≤2 with no subscore >1 within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a Full Mayo score ≤2 with no subscore >1 within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a Full Mayo score ≤2 with no subscore >1 within 8 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a Full Mayo score ≤2 with no subscore >1 within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; an endoscopic improvement within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; an endoscopic improvement within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; an endoscopic improvement within 8 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; an endoscopic improvement within 4 weeks of initiating administration of upadacitinib, or a

pharmaceutically acceptable salt or solid state form thereof; a decrease from baseline in Full Mayo score ≥ 3 points and ≥30% accompanied by a decrease in RBS of ≥1 or an absolute RBS of 0 or 1 within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a decrease from baseline in Full Mayo score ≥ 3 points and ≥30% accompanied by a decrease in RBS of ≥1 or an absolute RBS of 0 or 1 within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a decrease from baseline in Full Mayo score ≥ 3 points and ≥30% accompanied by a decrease in RBS of ≥1 or an absolute RBS of 0 or 1 within 8 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a decrease from baseline in Full Mayo score ≥ 3 points and ≥30% accompanied by a decrease in RBS of ≥1 or an absolute RBS of 0 or 1 within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; and combinations thereof. In one embodiment, the patient achieves a clinical remission within 12 weeks or within 16 weeks of initiating administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof, and/or achieves a clinical remission per Adapted Mayo score (defined as SFS≤ 1, RBS or 0, and endoscopy subscore ≤1) within 12 weeks of initiation administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the patient achieves a clinical response per Adapted Mayo score (defined as decrease from BL in the Adapted Mayo score ≥ 2 points and ≥ 30% from BL, plus a decrease in RBS ≥ 1 or an absolute RBS ≤ 1 at week 12 or 16. In one such embodiment, the induction phase is 16 weeks, and the additional therapeutic result is selected from the group consisting of a decrease from baseline in Partial Mayo score ≥ 2 points and ≥30% from baseline plus a decrease in RBS ≥1 or an absolute RBS ≤ 1 over time within 16 weeks, within 12 weeks, within 8 weeks, within 4 weeks or within 2 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; an endoscopic remission within 16 weeks, within 12 weeks, within 8 weeks, or within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a clinical response within 16 , within 12 weeks, within 8 weeks, or within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; an endoscopic improvement within 16 weeks, within 12 weeks, within 8 weeks, or within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a Full Mayo score ≤2 with no subscore >1 within 16 weeks, within 12 weeks, within 8 weeks, or within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a decrease from baseline in Full Mayo score ≥ 3 points and ≥30% accompanied by a decrease in RBS of ≥1 or an absolute RBS of 0 or 1 within 16 weeks, within 12 weeks, within 8 weeks, or within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; and combinations thereof. In one such embodiment, the induction phase is 12 weeks, and the additional therapeutic result is selected from the group consisting of a decrease from baseline in Partial Mayo score ≥ 2 points and ≥30% from

baseline plus a decrease in RBS ≥1 or an absolute RBS ≤ 1 over time within 12 weeks, within 8 weeks, within 4 weeks, or within 2 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; an endoscopic remission within 12 weeks, within 8 weeks, or within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a clinical response within 12 weeks, within 8 weeks, or within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; an endoscopic improvement within 12 weeks, within 8 weeks, or within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a Full Mayo score ≤2 with no subscore >1 within 12 weeks, within 8 weeks, or within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a decrease from baseline in Full Mayo score ≥ 3 points and ≥30% accompanied by a decrease in RBS of ≥1 or an absolute RBS of 0 or 1 within 12 weeks, within 8 weeks, or within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; and combinations thereof. In one such embodiment, the induction phase is 8 weeks, and the additional therapeutic result is selected from the group consisting of a decrease from baseline in Partial Mayo score ≥ 2 points and ≥30% from baseline plus a decrease in RBS ≥1 or an absolute RBS ≤ 1 over time within 48 weeks, 8 weeks, within 4 weeks, or within 2 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; an endoscopic remission within 8 weeks or within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a clinical response within 8 weeks or within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; an endoscopic improvement within 8 weeks or within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a Full Mayo score ≤2 with no subscore >1 within 8 weeks or within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a decrease from baseline in Full Mayo score ≥ 3 points and ≥30% accompanied by a decrease in RBS of ≥1 or an absolute RBS of 0 or 1 within 8 weeks or within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; and combinations thereof.

[0399] In one embodiment, the patient achieves clinical remission within 16 weeks, or within 12 weeks, or within 8 weeks, or within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one such embodiment, the patient is one who was taking corticosteroids at baseline but who discontinued corticosteroid use during treatment with the JAK1 inhibitor.

[0400] In one embodiment, the additional therapeutic result may be a Full Mayo score ≤2 with no subscore >1 within 16 weeks, or within 12 weeks, or within 8 weeks, or within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one such embodiment, the patient is one who was taking corticosteroids at baseline but who discontinued corticosteroid use during treatment with the JAK1 inhibitor. In another embodiment, the additional

therapeutic result may be selected from the group consisting of an endoscopic remission within 16 weeks, within 12 weeks, within 8 weeks, or within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a clinical response within 16 weeks, or 12 weeks, or 8 weeks, or 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a decrease from baseline in Partial Mayo score ≥2 points and ≥30% from baseline, plus a decrease in RBS ≥1 or an absolute RBS ≤1 over time within 16 weeks, or 12 weeks, or 8 weeks, or 4 weeks, or 2 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a decrease from baseline in Full Mayo score ≥3 points and ≥30% accompanied by a decrease in RBS of ≥1 or an absolute RBS of 0 or 1 within 16 weeks, or 12 weeks, or 8 weeks, or 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; and an endoscopic improvement within 16 weeks, or 12 weeks, or 8 weeks, or 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; and combinations thereof. In one such embodiment, the patient is one who was taking corticosteroids at baseline but who discontinued corticosteroid use during treatment with the JAK1 inhibitor.

[0401] In one embodiment, the additional therapeutic result may be an Adapted Mayo score (defined as SFS ⩽1, RBS of 0, and endoscopy subscore ⩽ 1) at 16 weeks, or within 12 weeks, or within 8 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one such embodiment, the patient is one who was taking corticosteroids at baseline but who discontinued corticosteroid use during treatment with the JAK1 inhibitor. In another embodiment, the additional therapeutic result may be selected from the group consisting of an endoscopic remission within 16 weeks, within 12 weeks, or within 8 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a clinical response within 16 weeks, or 12 weeks, or 8 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a decrease from baseline in Partial Mayo score ⩾2 points and ⩾30% from baseline, plus a decrease in RBS ⩾1 or an absolute RBS ⩽1 over time within 16 weeks, or 12 weeks, or 8 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a decrease from baseline in Full Mayo score ⩾3 points and ⩾30% accompanied by a decrease in RBS of ⩾1 or an absolute RBS of 0 or 1 within 16 weeks, or 12 weeks, or 8 weeks, or 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; and an endoscopic improvement within 16 weeks, or 12 weeks, or 8 weeks, or 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; and combinations thereof. In one such embodiment, the patient is one who was taking corticosteroids at baseline but who discontinued corticosteroid use during treatment with the JAK1 inhibitor.

[0402] In one particular embodiment, the induction phase is 8 weeks, and the patient achieves a clinical remission (SF subscore ≤ 1, RBS of 0 and endoscopic subscore ≤ 1) within 8 weeks of initiating

administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof and an endoscopic improvement (i.e., an endoscopic subscore ≤ 1) within 6 weeks or within 8 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In another embodiment, the induction phase is 4 weeks, and the patient achieves a clinical remission within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof and an endoscopic improvement within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof.

[0403] In one particular embodiment, the induction phase is 8 weeks, and the patient achieves a clinical remission within 8 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof and further achieves a full Mayo score ≤ 2, with no subscore > 1 within 8 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; an endoscopic improvement (i.e., an endoscopic subscore ≤ 1) within 6 weeks or within 8 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; or combinations thereof. In another embodiment, the induction phase is 4 weeks, and the patient achieves a clinical remission within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof and further achieves a full Mayo score ≤ 2, with no subscore > 1within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; an endoscopic improvement within 4 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; or combinations thereof.

[0404] In one embodiment, the patient is administered upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, for at least 52 weeks. The administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, may include an induction phase (e.g., an induction phase of up to 16 weeks), and additional weeks (e.g., 36 weeks or longer) of a maintenance phase (discussed hereinafter). In other embodiments, the administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, may include a shorter induction phase (e.g., up to 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, etc.), and a longer maintenance phase (e.g., a 12 week induction phase and a 40 week or longer maintenance phase).

[0405] In one embodiment, the induction phase is 8 weeks and the maintenance phase is 44 weeks. In some such embodiments, the patient may achieve at least one therapeutic result selected from the group consisting of: clinical remission within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; endoscopic remission within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; full Mayo score ≤ 2, with no subscore > 1 within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; clinical response within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; endoscopic improvement within 52 weeks of initiating administration of upadacitinib, or a

pharmaceutically acceptable salt or solid state form thereof; decrease from baseline in Partial Mayo score ≥2 points and ≥30% from baseline, plus a decrease in RBS ≥1 or an absolute RBS ≤1 over time within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a decrease from baseline in Full Mayo score ≥3 points and ≥30% accompanied by a decrease in RBS of ≥1 or an absolute RBS of 0 or 1 within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; histologic improvement within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; stool frequency subscore ≤ 1 within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a RBS of 0 within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; an endoscopic subscore ≤ 1 within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a change in IBDQ score from baseline within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; and combinations thereof.

[0406] In some embodiment when the patient is administered upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, for at least 52 weeks, the patient is one who was taking corticosteroids at baseline but who discontinued corticosteroid use during treatment with the JAK1 inhibitor, and the therapeutic result may be selected from the group consisting of clinical remission within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a endoscopic remission within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; a Full Mayo score ≤2 with no subscore >1 within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; clinical response within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; decrease from baseline in Partial Mayo score ≥2 points and ≥30% from baseline, plus a decrease in RBS ≥1 or an absolute RBS ≤1 over time within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; decrease from baseline in Full Mayo score ≥3 points and ≥30% accompanied by a decrease in RBS of ≥1 or an absolute RBS of 0 or 1 within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; an endoscopic improvement within 52 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof; and combinations thereof.

[0407] In one embodiment, in a method of the present disclosure, a patient is evaluated during or at the end of the induction phase for a therapeutic result selected from the group consisting of clinical remission, a Full Mayo score ≤2 with no subscore >1, endoscopic improvement, endoscopic remission, clinical response, decrease from baseline in Full Mayo score ≥3 points and ≥30% accompanied by a decrease in RBS of ≥1 or an absolute RBS of 0 or 1, a decrease from baseline in Partial Mayo score ≥2 points and ≥30% from baseline, plus a decrease in RBS ≥1 or an absolute RBS ≤1 over time, SF sub

score, rectal bleeding subscore, endoscopic subscore, histologic improvement, fecal calprotectin level, hs-CRP, IBDQ score, and combinations thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for clinical remission during or at the end of the induction phase. In one embodiment, in a method of the present disclosure, a patient is evaluated for endoscopic improvement during or at the end of the induction phase. In one embodiment, in a method of the present disclosure, a patient is evaluated for achievement of Full Mayo score ≤2 with no subscore >1 during or at the end of the induction phase. In one embodiment, in a method of the present disclosure, a patient is evaluated for endoscopic remission during or at the end of the induction phase. In one embodiment, in a method of the present disclosure, a patient is evaluated for clinical response during or at the end of the induction phase. In one embodiment, in a method of the present disclosure, a patient is evaluated for decrease from baseline in Partial Mayo score ≥2 points and ≥30% from baseline, plus a decrease in RBS ≥1 or an absolute RBS ≤1 over time during or at the end of the induction phase. In one embodiment, in a method of the present disclosure, a patient is evaluated for change in Full Mayo score from baseline during or at the end of the induction phase. In one embodiment, in a method of the present disclosure, a patient is evaluated for histologic improvement during or at the end of the induction phase. In one embodiment, the induction phase is 2 weeks. In one embodiment, the induction phase is 8 weeks. In one embodiment, the induction phase is 12 weeks.

[0408] In one embodiment, in a method of the present disclosure, a patient is evaluated during or at the end of the maintenance phase for a therapeutic result selected from the group consisting of endoscopic improvement, achievement of Full Mayo score ≤2 with no subscore >1, discontinuation of corticosteroid use and clinical remission per Adapted Mayo score, maintenance of clinical remission among subjects who achieved clinical remission during the induction phase, endoscopic improvement among subjects who achieved clinical remission during the induction phase, clinical response, endoscopic remission, histologic improvement, and combinations thereof.

[0409] In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by being corticosteroid-free for 44 weeks after discontinuing corticosteroids. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving clinical remission 4 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving clinical remission 8 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving clinical remission 12 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving Full Mayo score ≤2 with no subscore >1 within 52 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a

therapeutic result by achieving clinical remission defined as stool frequency subscore ≤ 1, rectal bleeding subscore of 0, and endoscopic subscore ≤ 1 with absence of friability within 52 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving a SF subscore of 0, a RBS of 0, and endoscopic subscore of 0. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving a decrease from baseline in Partial Mayo score ≥2 points and ≥30% from baseline, plus a decrease in RBS ≥1 or an absolute RBS ≤1 over time within 2 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving a decrease from baseline in Partial Mayo score ≥2 points and ≥30% from baseline, plus a decrease in RBS ≥1 or an absolute RBS ≤1 over time within 4 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving a decrease from baseline in Partial Mayo score ≥2 points and ≥30% from baseline, plus a decrease in RBS ≥1 or an absolute RBS ≤1 over time within 12 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving clinical response or a decrease from baseline in Full Mayo score ≥3 points and ≥30% accompanied by a decrease in RBS of ≥1 or an absolute RBS of 0 or 1. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving a decrease from baseline in Partial Mayo score ≥2 points and ≥30% from baseline, plus a decrease in RBS ≥1 or an absolute RBS ≤1 over time within 2 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving clinical response or a decrease from baseline in Full Mayo score ≥3 points and ≥30% accompanied by a decrease in RBS of ≥1 or an absolute RBS of 0 or 1. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving a decrease from baseline in Partial Mayo score ≥2 points and ≥30% from baseline, plus a decrease in RBS ≥1 or an absolute RBS ≤1 over time within 4 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving clinical response or a decrease from baseline in Full Mayo score ≥3 points and ≥30% accompanied by a decrease in RBS of ≥1 or an absolute RBS of 0 or 1. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving a decrease from baseline in Partial Mayo score ≥2 points and ≥30% from baseline, plus a decrease in RBS ≥1 or an absolute RBS ≤1 over time within 12 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving stool frequency subscore ≤ 1

within 2 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving stool frequency subscore ≤ 1 within 4 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving stool frequency subscore ≤ 1 within 12 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving rectal bleeding subscore of 0 over time. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving an endoscopic subscore of ≤ 1 within 12 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving an endoscopic improvement within 12 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving fecal calprotectin below 150 mg/kg within 4 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving fecal calprotectin below 150 mg/kg within 8 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving fecal calprotectin below 150 mg/kg within 12 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving an IBDQ response (increase of IBDQ ≥ 16 from Baseline) within 2 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving an IBDQ response (increase of IBDQ ≥ 16 from Baseline) within 8 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving an IBDQ response (increase of IBDQ ≥ 16 from Baseline) within 12 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving a change from Baseline in hs-CRP within 2 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving a change from Baseline in hs-CRP within 8 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving a change from Baseline in hs-CRP within 12 weeks after initial

administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving a change in Baseline in fecal calprotectin within 8 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving a change in Baseline in fecal calprotectin within 12 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving a change in corticosteroid dose within 12 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by change from Baseline in Adapted Mayo score, Full Mayo score, Partial Mayo score and/or Mayo subscores within 12 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by change form Baseline in UCEIS scores within 12 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving histologic remission (defined as Geboes score < 2) within 8 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by achieving histologic remission (defined as Geboes score < 2) within 12 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by change from Baseline in histologic score within 8 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by change from Baseline in histologic score within 8 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by change from Baseline in laboratory and nutritional parameters (e.g., hemoglobin, hematocrit, albumin, total protein concentration, and weight) within 8 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by change from Baseline in laboratory and nutritional parameters (e.g., hemoglobin, hematocrit, albumin, total protein concentration, and weight) within 12 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by change in Baseline in subject-reported stool frequency (absolute values) within 8 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic

result by change in Baseline in subject-reported stool frequency (absolute values) within 12 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by change from Baseline in IBDQ score within 8 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by change from Baseline in IBDQ score within 12 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by change from Baseline in EQ-5D-5L score within 8 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by change from Baseline in EQ-5D-5L score within 12 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by change from Baseline in WPAI:UC scores within 8 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by change from Baseline in WPAI:UC scores within 12 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by change in SF-36, PCT, MCS components and domain scores within 8 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by change in SF-36, PCT, MCS components and domain scores within 12 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by change in PGIC score within 8 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by change in PGIC score within 12 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by change from Baseline in FACIT-F score within 8 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by change from Baseline in FACIT-F score within 12 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a therapeutic result by change from Baseline in UC-SQ score within 8 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, in a method of the present disclosure, a patient is evaluated for a

therapeutic result by change from Baseline in UC-SQ score within 8 weeks after initial administration of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the patient is administered at least 14 doses, 28 doses, or at least 42 doses, or at least 56 doses of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, during the induction phase.

[0410] In one aspect, a certain therapeutic result is maintained by the patient during the maintenance phase. The maintenance phase may last for an indefinite period of time. In one embodiment, the maintenance phase is at least 36 weeks, including at least 37 weeks, at least 38 weeks, at least 39 weeks, at least 40 weeks, at least 41 weeks, at least 42 weeks, at least 43 weeks, at least 44 weeks, at least 45 weeks, at least 46 weeks, at least 47 weeks, or at least 48 weeks after the patient achieves clinical remission or clinical response after the patient achieves clinical remission or clinical response. In one embodiment, the maintenance phase is at least 40 additional weeks. In one embodiment, the maintenance phase is at least 44 additional weeks after the patient achieves clinical remission or clinical response. In one embodiment, the therapeutic result maintained by the patient during the maintenance phase is selected from the group consisting of clinical remission, a Full Mayo score ≤2 with no subscore >1, endoscopic remission, clinical response, a decrease from baseline in Partial Mayo score ≥2 points and ≥30% from baseline plus a decrease in RBS ≥1 or an absolute RBS ≤1, a decrease from baseline in Full Mayo score ≥3 points and ≥30% accompanied by a decrease in RBS of ≥1 or an absolute RBS of 0 or 1, endoscopic improvement, and combinations thereof. In one embodiment, the therapeutic result maintained by the patient during the maintenance phase is endoscopic remission. In one embodiment, the therapeutic result maintained by the patient during the maintenance phase is endoscopic response. In one embodiment, the therapeutic result maintained by the patient during the maintenance phase is clinical remission. In one embodiment, the therapeutic result maintained by the patient during the maintenance phase is corticosteroid-free remission.

[0411] In one embodiment, in a method of the present disclosure, a patient is evaluated for clinical remission during the maintenance phase. In one embodiment, a patient is evaluated for endoscopic improvement during the maintenance phase. In one embodiment, a patient is evaluated for clinical remission a Full Mayo score ≤2 with no subscore >1 during the maintenance phase. In one embodiment, in a method of the present disclosure, a patient is evaluated for endoscopic remission during the maintenance phase. In one embodiment, in a method of the present disclosure, a patient is evaluated for clinical response, or a decrease from baseline in Partial Mayo score ≥2 points and ≥30% from baseline plus a decrease in RBS ≥1 or an absolute RBS ≤1, or a decrease from baseline in Full Mayo score ≥3 points and ≥30% accompanied by a decrease in RBS of ≥1 or an absolute RBS of 0 or 1during the maintenance phase.

[0412] In one embodiment, the present disclosure provides a method for treating an inflammatory disease, in one aspect for treating ulcerative colitis, comprising (a) administering to a patient a dose of a JAK1 inhibitor (e.g., upadacitinib or a pharmaceutically acceptable salt or solid state form thereof) at week 0 and once daily (QD) thereafter for 8 weeks, wherein the dose is 45 mg QD. In

one embodiment, the method further comprises (b) administering to the patient additional doses once daily thereafter for at least 44 additional weeks, wherein the dose is 15 mg or 30 mg QD. In one embodiment the dose is administered orally.

[0413] In one embodiment, 8 weeks after initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, a patient is evaluated for clinical remission and/or for a Full Mayo score ≤2 with no subscore >1. In one embodiment, 8 weeks after initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, a patient is evaluated for clinical response and/or for a decrease from baseline in Partial Mayo score ≥2 points and ≥30% from baseline plus a decrease in RBS ≥1 or an absolute RBS ≤1, and/or for a decrease from baseline in Full Mayo score ≥3 points and ≥30% accompanied by a decrease in RBS of ≥1 or an absolute RBS of 0 or 1and/or for endoscopic improvement and/or for endoscopic remission. In one embodiment, 6 weeks after initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, a patient is evaluated for clinical remission and/or a Full Mayo score ≤2 with no subscore >1 and/or for endoscopic remission. In one embodiment, 6 weeks after initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, a patient is evaluated for a decrease from baseline in Full Mayo score ≥3 points and ≥30% accompanied by a decrease in RBS of ≥1 or an absolute RBS of 0 or 1 and/or clinical response and/or a decrease from baseline in Partial Mayo score ≥2 points and ≥30% from baseline plus a decrease in RBS ≥1 or an absolute RBS ≤1,and/or for endoscopic improvement. In one embodiment, 4 weeks after initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, a patient is evaluated for clinical remission and/or for a Full Mayo score ≤2 with no subscore >1and/or for endoscopic remission. In one embodiment, 4 weeks after initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, a patient is evaluated for a decrease from baseline in Full Mayo score ≥3 points and ≥30% accompanied by a decrease in RBS of ≥1 or an absolute RBS of 0 or 1and/or for clinical response and/or for a decrease from baseline in Partial Mayo score ≥2 points and ≥30% from baseline plus a decrease in RBS ≥1 or an absolute RBS ≤1, and/or for endoscopic improvement. In one embodiment, 2 weeks after initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, a patient is evaluated for clinical remission and/or for a Full Mayo score ≤2 with no subscore >1 and/or for endoscopic remission. In one embodiment, 2 weeks after initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, a patient is evaluated for a decrease from baseline in Full Mayo score ≥3 points and ≥30% accompanied by a decrease in RBS of ≥1 or an absolute RBS of 0 or 1 and/or for clinical response and/or for a decrease from baseline in Partial Mayo score ≥2 points and ≥30% from baseline plus a decrease in RBS ≥1 or an absolute RBS ≤1,and/or for endoscopic improvement.

[0414] In one embodiment, 48 weeks after initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, a patient is evaluated for clinical remission per Adapted Mayo score (defined sa SFS≤ 1, RBS of 0, and endoscopy subscore ≤ 1), clinical remission

per Full Mayo score (defined as a Full Mayo score ≤ 2 with no subscore > 1), clinical remission per Partial mayo score (defined as Partial Mayo score ≤ 2 iwht no subscore >1) over time; clinical remission defined as stool frequency subscore ≤1, rRBS of 0 and endoscopic subscore ≤ 1 with absence of friability and clinical response per Adapted mayo score (defined as decrease from BL in the Adapted Mayo score ≥ 2 points and ≥ 30% from BL, plus a decrease in RBS ≥ 1).

[0415] In one embodiment, the present disclosure provides a method for treating ulcerative colitis, comprising (a) administering to a patient a dose of a JAK1 inhibitor (e.g., upadacitinib or a pharmaceutically acceptable salt or solid state form thereof) at week 0 and once daily thereafter via an oral route, wherein the doses of the JAK1 inhibitor comprise 15 mg, 30 mg, or 45 mg QD, or any combination thereof.

[0416] In one embodiment, the present disclosure provides a method for treating ulcerative colitis, comprising administering to a patient 15 mg to 45 mg of a JAK1 inhibitor. In one embodiment, the present disclosure provides a method for treating ulcerative colitis, comprising administering to a patient orally 15 mg of a JAK1 inhibitor QD. In one embodiment, the present disclosure provides a method for treating ulcerative colitis, comprising administering to a patient orally 30 mg of a JAK1 inhibitor QD. In one embodiment, the present disclosure provides a method for treating ulcerative colitis, comprising administering to a patient orally 45 mg of a JAK1 inhibitor QD. In any such embodiments, the JAK1 inhibitor may be upadacitinib or a pharmaceutically acceptable salt or solid state form thereof. In any such embodiment, the JAK1 inhibitor may be in a once daily modified release formulation. In any such embodiment, the patient may have moderately to severely active ulcerative colitis prior to treatment.

[0417] In one embodiment, the administration of a JAK1 inhibitor according to the present disclosure is further described in the Examples herein below or in Figure 13.

[0418] In one embodiment, the present disclosure provides a method for treating ulcerative colitis, said method comprising a) administering at least one induction dose of a JAK1 inhibitor (e.g., upadacitinib or a pharmaceutically acceptable salt or solid state form thereof) to a patient, wherein said induction dose comprises 15 mg to 45 mg of the JAK 1 inhibitor. In one aspect, the induction dose comprises 15 mg or 30 mg or 45 mg. In one aspect, the induction dose comprises 45 mg. In one aspect, the induction dose is administered orally. In one aspect, the induction dose is administered QD. In one aspect, the induction dose is administered for 8 weeks. In one aspect the induction dose is administered for 6 weeks. In one aspect the induction dose is administered for 4 weeks. In one embodiment, the induction dose is administered for up to 12 weeks, including for 2 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, or 12 weeks.

[0419] In one embodiment, the induction dose comprises 45 mg of the JAK1 inhibitor administered QD.

[0420] In one embodiment, the induction dose comprises 30 mg of the JAK1 inhibitor administered QD.

[0421] In one embodiment, the induction dose comprises 15 mg of the JAK1 inhibitor administered QD.

[0422] In one embodiment, the JAK1 inhibitor is upadacitinib or a pharmaceutically acceptable salt or solid state form thereof.

[0423] In one embodiment, the induction dose is in a once daily modified release formulation.

[0424] In one embodiment, the method further comprises b) administering a first maintenance dose of a JAK1 inhibitor (e.g., upadacitinib, or pharmaceutically acceptable salt or solid state form thereof), to the patient after the last induction dose is administered; and c) administering at least one additional maintenance dose to the patient once daily thereafter.

[0425] In one embodiment, the first maintenance dose comprises 15 mg to 30 mg of the JAK1 inhibitor. In one aspect, the first maintenance dose comprises 15 mg or 30 mg of the JAK1 inhibitor. In one aspect, the first maintenance dose is smaller than the induction dose. In one aspect, the first maintenance dose is administered QD. In one aspect the first maintenance dose is 15 mg. In one aspect the first maintenance dose is 30 mg. In one aspect, the first maintenance dose is administered orally. In one aspect, the first maintenance dose is in a once daily modified release formulation.

[0426] In one aspect, the at least one additional maintenance dose comprises 15 mg to 30 mg of the JAK 1 inhibitor. In one aspect, the at least one additional maintenance dose comprises 15 mg or 30 mg. In one aspect, the at least one additional maintenance dose is administered orally. In one aspect, the at least one additional maintenance dose is administered QD. In one embodiment, the at least one additional maintenance dose comprises 15 mg of the JAK1 inhibitor administered QD. In one embodiment, the at least one additional maintenance dose comprises 30 mg of the JAK1 inhibitor administered QD. In one aspect, the at least one additional maintenance dose is in a once daily modified release formulation.

[0427] In any of the foregoing embodiments, the JAK1 inhibitor may be upadacitinib or a pharmaceutically acceptable salt or solid state form thereof.

[0428] In one aspect, in any of the foregoing embodiments, the patient is one who had an inadequate response to or experienced a loss of response to or intolerance to conventional treatment (e.g., aminosalicylate, corticosteroids, immunosuppressants) or to a previous treatment with a biologic agent. In one aspect, in any of the foregoing embodiments, the patient is one who had an inadequate response to, a loss of response to, or experienced intolerance to a previous treatment with an anti-TNF agent.

[0429] In one aspect, in any of the foregoing embodiments, the patient is one who is naïve to previous treatment with an aminosalicylate, a corticosteroid, an immunosuppressant, a biologic agent or an anti-TNF agent.

[0430] In one aspect, in any of the foregoing embodiments, the patient is one who had moderately to severely active ulcerative colitis prior to treatment or administration of the induction dose.

[0431] In one embodiment, the present disclosure further provides a method for inducing clinical remission of ulcerative colitis or a Full Mayo score of ≤ 2 with no subscore >1 in a patient, said

method comprising a) administering to the patient at least one induction dose of a JAK1 inhibitor as described above or herein (e.g., upadacitinib or a pharmaceutically acceptable salt or solid state form thereof). In one embodiment, the induction dose comprises 30 mg to 45 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, an induction dose is administered at week 0 and once daily (QD) thereafter for up to 12 weeks (e.g., for 4 weeks, 5 weeks, 6 weeks, 7 weeks, or 8 weeks, or 9 weeks, or 10 weeks, or 11 weeks, or 12 weeks), wherein the dose is 30 mg QD or 45 mg QD. In one embodiment, the method further comprises maintaining clinical remission of ulcerative colitis or a Full Mayo score of ≤2 with no subscore >1, said method further comprising b) administering a first maintenance dose of said JAK1 inhibitor to the patient after the last induction dose is administered and c) administering at least one additional maintenance dose to the patient thereafter as described above or herein. In one embodiment, the at least one additional maintenance dose is administered once daily. In one embodiment, the additional maintenance doses are administered once daily for at least 36 additional weeks, including for at least 36 weeks, at least 37 weeks, at least 38 weeks, at least 39 weeks, at least 40 weeks, at least 41 weeks, at least 42 weeks, at least 43 weeks, at least 44 weeks, at least 56 weeks, at least 112 weeks, at least 308 weeks, or at least 420 weeks. In one embodiment, the additional maintenance doses are administered once daily for at least 44 additional weeks. In one embodiment, the maintenance dose is 15 mg or 30 mg QD. In one embodiment the induction and maintenance doses are administered orally. In one embodiment, the patient has active ulcerative colitis with an Adapted Mayo score of 5 to 9 points and endoscopy subscore of 2 or 3 before administration of the first induction dose. In one embodiment, the patient has moderately to severely active ulcerative colitis prior to administration of the first induction dose. In one embodiment, the patient has had an inadequate response to or experienced intolerance to conventional treatment (e.g., aminosalicylates, corticosteroids, immunosuppressants) or to a previous treatment with a biologic agent and/or an anti-TNF agent. In one embodiment, the patient is naïve to previous treatment with aminosalicylates, a corticosteroid, an immunosuppressant, a biologic agent, and/or an anti-TNF agent. In one embodiment, the clinical remission or Full Mayo score of ≤2 with no subscore >1 is achieved within 4 weeks or within 8 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the clinical remission or a Full Mayo score of ≤2 with no subscore >1 is achieved within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the clinical remission or Full Mayo score of ≤2 with no subscore >1 is achieved within 10 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the clinical remission or Full Mayo score of ≤2 with no subscore >1 is achieved within 8 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the patient achieves a stool frequency subscore ≤ 1, RBS of 0 and endoscopic subscore ≤1 before administration of the first maintenance dose. In one embodiment, the patient achieves a full Mayo

score of ≤ 2 with no subscore >1 before administration of the first maintenance dose. In one embodiment, the induction and maintenance doses are in once-daily, modified release formulations.

[0432] In one embodiment, the present disclosure provides a method for inducing endoscopic remission of ulcerative colitis, the method comprising (a) administering to a patient at least one induction dose of a JAK1 inhibitor (e.g., upadacitinib or a pharmaceutically acceptable salt or solid state form thereof), wherein the induction dose comprises 30 to 45 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, an induction dose is administered at week 0 and once daily (QD) thereafter for up to 12 weeks (e.g., for 4 weeks, 5 weeks, 6 weeks, 7 weeks, or 8 weeks, or 9 weeks, or 10 weeks, or 11 weeks, or 12 weeks), wherein the dose is 30 mg QD or 45 mg QD. In one embodiment, the method further comprises maintaining endoscopic remission of ulcerative colitis, said method further comprising (b) administering to the patient a first maintenance dose of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, after the last induction dose is administered, and (c) administering at least one additional maintenance dose once daily thereafter as described above or herein. In one embodiment, the at least one additional maintenance dose is administered once daily. In one embodiment, the additional maintenance doses are administered once daily for at least 36 additional weeks, including for at least 36 weeks, at least 37 weeks, at least 38 weeks, at least 39 weeks, at least 40 weeks, at least 41 weeks, at least 42 weeks, at least 43 weeks, at least 44 weeks, at least 56 weeks, at least 112 weeks, at least 308 weeks, or at least 420 weeks. In one embodiment, the additional maintenance doses are administered once daily for at least 44 additional weeks. In one embodiment, the maintenance dose is 15 mg or 30 mg QD. In one embodiment the induction and maintenance doses are administered orally. In one embodiment, the patient has active ulcerative colitis with an Adapted Mayo score of 5 to 9 points and an endoscopy subscore of 2 or 3 before administration of the first induction dose. In one embodiment, the patient has moderately to severely active ulcerative colitis prior to administration of the first induction dose. In one embodiment, the patient has had an inadequate response to or experienced intolerance to conventional treatment (e.g., aminosalicylates, corticosteroids, immunosuppressants) or to a previous treatment with a biologic and/or an anti-TNF agent. In one embodiment, the patient is naïve to previous treatment with an aminosalicylate, a corticosteroid, an immunosuppressant, an anti-TNF agent and/or a biologic agent. In one embodiment, the endoscopic remission is achieved within 4 weeks or within 8 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the endoscopic remission is achieved within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the endoscopic remission is achieved within 10 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the endoscopic remission is achieved within 8 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the patient achieves an endoscopic subscore of 0 before

administration of the first maintenance dose. In one embodiment, the induction and maintenance doses are in once-daily, modified release formulations.

[0433] In one embodiment, the present disclosure further provides a method for inducing clinical response or inducing a decrease from baseline in Full Mayo score ≥3 points and ≥30% accompanied by a decrease in RBS of ≥1 or an absolute RBS or 0 or 1 or inducing a decrease from baseline in Partial Mayo score ⩾ 2 points and ⩾ 30%, accompanied by a decrease in RBS of ⩾ 1 or an absolute rectal bleeding subscore of ≤1in an ulcerative colitis in a patient, said method comprising a) administering to the patient at least one induction dose of a JAK1 inhibitor as described above or herein (e.g., upadacitinib or a pharmaceutically acceptable salt or solid state form thereof). In one embodiment, the induction dose comprises 30 mg to 45 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, an induction dose is administered at week 0 and once daily (QD) thereafter for up to 8 weeks (e.g., for 4 weeks, 5 weeks, 6 weeks, 7 weeks, or 8 weeks), wherein the dose is 30 mg QD or 45 mg QD. In one embodiment, the method further comprises maintaining clinical response of ulcerative colitis or maintaining a decrease from baseline in Full Mayo score ≥3 points and ≥30%, accompanied by a decrease in RBS of ≥1 or an absolute RBS or 0 or 1 or maintaining a decrease from baseline in Partial Mayo score ⩾ 2 points and ⩾ 30%, accompanied by a decrease in RBS of ⩾ 1 or an absolute rectal bleeding subscore of ≤1, said method further comprising b) administering a first maintenance dose of said JAK1 inhibitor to the patient after the last induction dose is administered and c) administering at least one additional maintenance dose to the patient thereinafter as described above or herein. In one embodiment, the at least one additional maintenance dose is administered once daily. In one embodiment, the additional maintenance doses are administered once daily for at least 36 additional weeks, including for at least 36 weeks, at least 37 weeks, at least 38 weeks, at least 39 weeks, at least 40 weeks, at least 41 weeks, at least 42 weeks, at least 43 weeks, at least 44 weeks, at least 56 weeks, at least 112 weeks, at least 308 weeks, or at least 420 weeks. In one embodiment, the additional maintenance doses are administered once daily for at least 44 additional weeks. In one embodiment, the maintenance dose is 15 mg or 30 mg QD. In one embodiment the induction and maintenance doses are administered orally. In one embodiment, the patient has active ulcerative colitis with an Adapted Mayo score of 5 to 9 points and an endoscopy subscore of 2 or 3 before administration of the first induction dose. In one embodiment, the patient has moderately to severely active ulcerative colitis prior to administration of the first induction dose. In one embodiment, the patient has had an inadequate response to or experienced intolerance to a conventional treatment (e.g., aminosalicylates, corticosteroids, immunosuppressants) or to a previous treatment with a biologic agent and/or an anti-TNF agent. In one embodiment, the patient is naïve to previous treatment with aminosalicylates, a corticosteroid, an immunosuppressant, a biologic agent and/or an anti-TNF agent. In one embodiment, the clinical response or the decrease from baseline in Full Mayo score ≥3 points and ≥ 30%, accompanied by a decrease in RBS of ≥1 or an absolute RBS or 0 or 1 or the decrease from baseline in Partial Mayo score ⩾ 2 points and ⩾ 30%, accompanied by a

decrease in RBS of ⩾ 1 or an absolute rectal bleeding subscore of ≤1 is achieved within 4 weeks or within 8 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the clinical response or the decrease from baseline in Full Mayo score ≥3 points and ≥30%, accompanied by a decrease in RBS of ≥1 or an absolute RBS or 0 or 1 is achieved within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the clinical response or the decrease from baseline in Full Mayo score ≥3 points and ≥30%, accompanied by a decrease in RBS of ≥1 or an absolute RBS or 0 or 1 or the decrease from baseline in Partial Mayo score ⩾ 2 points and ⩾ 30%, accompanied by a decrease in RBS of ⩾ 1 or an absolute rectal bleeding subscore of ≤1is achieved within 10 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the clinical response, or the decrease from baseline in Full Mayo score ≥3 points and ≥30%, accompanied by a decrease in RBS of ≥1 or an absolute RBS or 0 or 1 or the decrease from baseline in Partial Mayo score ⩾ 2 points and ⩾ 30%, accompanied by a decrease in RBS of ⩾ 1 or an absolute rectal bleeding subscore of ≤1 is achieved within 8 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the patient achieves a decrease from baseline in Adapted Mayo score ⩾ 2 points and ⩾ 30%, accompanied by a decrease in RBS of ⩾ 1 or an absolute rectal bleeding subscore of 0 or 1 before administration of the first maintenance dose. In one embodiment, the patient achieves a decrease from baseline in Partial Mayo score ⩾ 2 points and ⩾ 30%, accompanied by a decrease in RBS of ⩾ 1 or an absolute rectal bleeding subscore of ≤1 before administration of the first maintenance dose. In one embodiment, the patient achieves a decrease from baseline in Full Mayo score ⩾ 3 points and ⩾ 30%, accompanied by a decrease in RBS from baseline of ⩾ 1 or an absolute rectal bleeding subscore of 0 or 1 before administration of the first maintenance dose. In one embodiment, the induction and maintenance doses are in once-daily, modified release formulations.

[0434] In one embodiment, the present disclosure further provides a method for inducing endoscopic improvement of ulcerative colitis in a patient, said method comprising a) administering to the patient at least one induction dose of a JAK1 inhibitor as described above or herein (e.g., upadacitinib or a pharmaceutically acceptable salt or solid state form thereof). In one embodiment, the induction dose comprises 30 to 45 mg of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, an induction dose is administered at week 0 and once daily (QD) thereafter for up to 12 weeks (e.g., for 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks or 12 weeks) wherein the dose is 30 mg QD or 45 mg QD. In one embodiment, the method further comprises maintaining endoscopic improvement of ulcerative colitis, said method further comprising b) administering a first maintenance dose of said JAK1 inhibitor to the patient after the last induction dose is administered and c) administering at least one additional maintenance dose to the patient thereinafter as

described above or herein. In one embodiment, the at least one additional maintenance dose is administered once daily. In one embodiment, the additional maintenance doses are administered once daily for at least 36 additional weeks, including for at least 36 weeks, at least 37 weeks, at least 38 weeks, at least 39 weeks, at least 40 weeks, at least 41 weeks, at least 42 weeks, at least 43 weeks, at least 44 weeks, at least 56 weeks, at least 112 weeks, at least 308 weeks, or at least 420 weeks. In one embodiment, the additional maintenance doses are administered once daily for at least 44 additional weeks. In one embodiment, the maintenance dose is 15 mg or 30 mg QD. In one embodiment the induction and maintenance doses are administered orally. In one embodiment, the patient has active ulcerative colitis with an Adapted Mayo score of 5 to 9 points and an endoscopy subscore of 2 or 3 before administration of the first induction dose. In one embodiment, the patient has moderately to severely active ulcerative colitis prior to administration of the first induction dose. In one embodiment, the patient has had an inadequate response to or experienced intolerance to a conventional treatment (e.g., aminosalicylate, corticosteroids, and immunosuppressants) or to a previous treatment with a biologic agent and/or an anti-TNF agent. In one embodiment, the patient is naïve to previous treatment with an aminosalicylate a corticosteroid, an immunosuppressant, a biologic agent and/or an anti-TNF agent. In one embodiment, the endoscopic improvement is achieved within 8 weeks or within 16 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the endoscopic improvement is achieved within 12 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the endoscopic improvement is achieved within 10 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the endoscopic improvement is achieved within 8 weeks of initiating administration of upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the patient achieves an endoscopic subscore ≤ 1 before administration of the first maintenance dose. In one embodiment, the induction and maintenance doses are in once-daily, modified release formulations.

[0435] In one embodiment, the present disclosure further provides a method of maintaining clinical remission or a method of maintaining a Full Mayo score ≤ 2 with no subscore >1 of ulcerative colitis in a patient, said method comprising administering 15 mg or 30 mg of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof to the patient. In one embodiment, the upadacitinib or a pharmaceutically acceptable salt or solid state form thereof is administered once daily for at least 36 weeks, including for at least 37 weeks, at least 38 weeks, at least 39 weeks, at least 40 weeks, at least 41 weeks, at least 42 weeks, at least 43 weeks, or at least 44 weeks. In one embodiment the upadacitinib or a pharmaceutically acceptable salt or solid state form thereof is administered orally. In one embodiment, the patient has had an inadequate response to or experienced intolerance to a conventional treatment (e.g., aminosalicylates, corticosteroids, immunosuppressants) or to a previous treatment with a biologic agent and/or an anti-TNF agent. In one embodiment, the patient is naïve to previous treatment with aminosalicylates, a corticosteroid, an immunosuppressant, a biologic agent and/or

an anti-TNF agent. In one embodiment, the patient is a refractory patient. In one embodiment, the upadacitinib or a pharmaceutically acceptable salt or solid state form thereof is a in once-daily, modified release formulation.

[0436] In one embodiment, the present disclosure further provides a method of maintaining clinical response or a method of maintaining a decrease from baseline in Full Mayo score ≥3 points and ≥30%, accompanied by a decrease in RBS of ≥1 or an absolute RBS or 0 or 1 or a method of maintaining a decrease from baseline in Partial Mayo score ⩾ 2 points and ⩾ 30%, accompanied by a decrease in RBS of ⩾ 1 or an absolute rectal bleeding subscore of ≤1 in a patient, said method comprising administering 15 mg or 30 mg of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof to the patient. In one embodiment, the upadacitinib or a pharmaceutically acceptable salt or solid state form thereof is administered once daily for at least 36 weeks, including for at least 37 weeks, at least 38 weeks, at least 39 weeks, at least 40 weeks, at least 41 weeks, at least 42 weeks, at least 43 weeks, at least 44 weeks, at least 45 weeks, at least 46 weeks, at least 47 weeks, or at least 48 weeks. In one embodiment the upadacitinib or a pharmaceutically acceptable salt or solid state form thereof is administered orally. In one embodiment, the patient has had an inadequate response to or experienced intolerance to a conventional treatment (e.g., aminosalicylates, corticosteroids, immunosuppressants) or to a previous treatment with a biologic agent and/or an anti-TNF agent. In one embodiment, the patient is naïve to previous treatment with aminosalicylates, a corticosteroid, an immunosuppressant, a biologic agent and/or an anti-TNF agent. In one embodiment, the patient is a refractory patient. In one embodiment, the upadacitinib or a pharmaceutically acceptable salt or solid state form thereof is a in once-daily, modified release formulation.

[0437] In one embodiment, the present disclosure further provides a method of maintaining endoscopic improvement or endoscopic remission of ulcerative colitis in a patient, said method comprising administering 15 mg or 30 mg of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof to the patient. In one embodiment, the upadacitinib or a pharmaceutically acceptable salt or solid state form thereof is administered once daily for at least 36 weeks, including for at least 37 weeks, at least 38 weeks, at least 39 weeks, at least 40 weeks, at least 41 weeks, at least 42 weeks, at least 43 weeks, at least 44 weeks, at least 45 weeks, at least 46 weeks, at least 47 weeks, or at least 48 weeks. In one embodiment the upadacitinib or a pharmaceutically acceptable salt or solid state form thereof is administered orally. In one embodiment, the patient has had an inadequate response to or experienced intolerance to a conventional treatment (e.g., aminosalicylates, corticosteroids, immunosuppressants) or to a previous treatment with a biologic agent and/or an anti-TNF agent. In one embodiment, the patient is naïve to previous treatment with aminosalicylates, a corticosteroid, an immunosuppressant, a biologic agent and/or an anti-TNF agent. In one embodiment, the patient is a refractory patient. In one embodiment, the upadacitinib or a pharmaceutically acceptable salt or solid state form thereof is a in once-daily, modified release formulation.

[0438] In one aspect, induction doses for the methods disclosed herein are administered for 8 weeks in a dose regimen described in Table 12. In one aspect, induction doses are administered for 8 weeks in a dose regimen described in Table 12. In one aspect, maintenance doses are administered for 44 weeks or more in a dose regimen described in Table 12. In one aspect, induction doses for the methods disclosed herein are administered for 8 weeks and the maintenance doses are administered for 44 weeks in a dosing regimen as described in Table 12.

Table 12: Doses and Dosing Regimens (QD)

Induction Dose (mg)	Frequency of induction doses	Maintenance dose (mg)	Frequency of maintenance dose
7.5	QD	7.5	QD
15	QD	15	QD
30	QD	15	QD
30	QD	30	QD
45	QD	15	QD
45	QD	30	QD

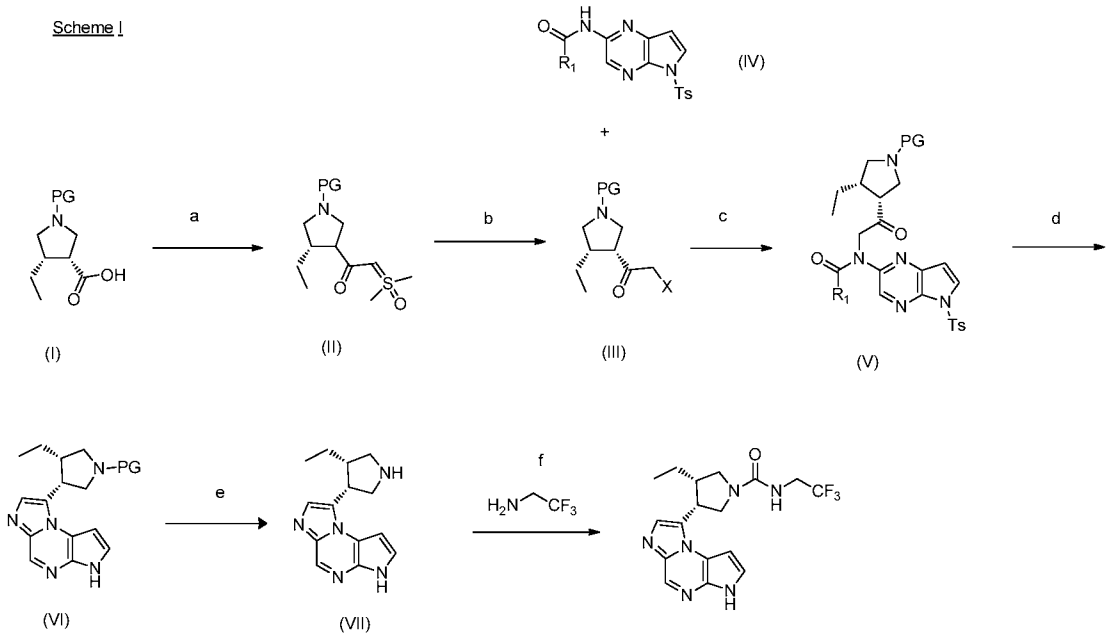
[0439] In one particular embodiment, the induction dose is 45 mg of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof administered QD, and the maintenance dose, and any additional maintenance dose administered thereafter, is 30 mg of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof administered QD. In another embodiment, the induction dose is 45 mg of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof administered QD, and the maintenance dose, and any additional maintenance dose administered thereafter, is 15 mg of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof administered QD. In one embodiment, the induction dose is 30 mg of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof administered QD, and the maintenance dose, and any additional maintenance dose administered thereafter, is 30 mg of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof administered QD. In one embodiment, the induction dose is 30 mg of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof administered QD, and the maintenance dose, and any additional maintenance dose administered thereafter, is 15 mg of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof administered QD. In one embodiment, the induction dose is 30 mg or 45 mg of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof administered QD, and the maintenance dose, and any additional maintenance dose administered thereafter, is 15 mg of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof administered QD. In one embodiment, the induction dose is 30 mg or 45 mg of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof administered QD, and the maintenance dose, and any additional maintenance dose administered thereafter, is 7.5 mg of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof administered QD.

V. Preparation of Upadacitinib

[0440] The synthesis of the compounds of the disclosure, including (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide (upadacitinib) and pharmaceutically acceptable salts thereof is provided in U.S. Patent No. 8,426,411, the entire content of which is incorporated herein by reference. In one embodiment, upadacitinib, and pharmaceutically acceptable salts thereof, may be synthesized according to the methods described in U.S. Patent Application Serial No. 15/295,561, which is herein incorporated by referenced. For example, upadacitinib may be synthesized using synthetic transformations such as those illustrated in Schemes I-IIIa. Starting materials are commercially available, may be prepared by the procedures described in U.S. Patent Application Serial No. 15/295,561, by literature procedures, or by procedures that would be well known to one skilled in the art of organic chemistry (see, for example, Larock, R.C. "Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd edition", 1999, Wiley-VCH or Greene, T.W. and Wuts, P.G.M. "Protective Groups in Organic Synthesis, 3rd Edition", 1999, Wiley-Interscience).

[0441] A process for preparing upadacitinib is illustrated in Scheme I. Reaction of protected (3R,4S)-4-ethylpyrrolidine-3-carboxylic acid (I) or a pharmaceutically acceptable salt thereof with trimethylsulfoxonium chloride gives sulfur ylide (II). Contacting sulfur ylide (II) with LiX and a sulfonic acid yields the corresponding halomethyl ketone (III). Reaction of (III) with (IV) in the presence of a base yields (V). Cyclization of (V) in the presence of a perfluoro acid anhydride and an organic base produces (VI). Removal of the protecting group and contacting the deprotected compound with an acid yields a pharmaceutically acceptable salt of (VII). Reacting the pharmaceutically acceptable salt of (VII) with 2,2,2-trifluoroethylamine produces upadacitinib.

Scheme I



wherein:

PG is a protecting group;

X is Br or Cl;

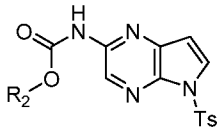
R_1 is selected from the group consisting of alkyl, aryl, and $-OR_2$;

R_2 is alkyl; and

Ts is tosyl.

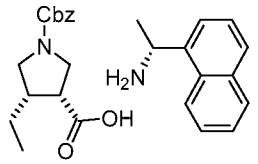
[0442] The protecting group may be any suitable protecting group known in the art. In some embodiments, the protecting group is selected from the group consisting of carboxybenzyl, *p*-methoxybenzyl carbonyl, benzyl, *p*-methoxybenzyl, and 3,4-dimethoxyenzyl. In another embodiment, the protecting group is carboxybenzyl.

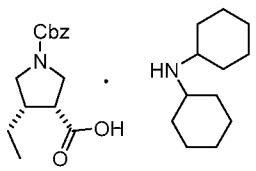
[0443] In another embodiment, R_1 is $-OR_2$, and R_2 is methyl or ethyl. In such embodiments, the compound of formula (IV) is a compound of formula (IVa):


(IVa)

wherein R_2 is methyl or ethyl.

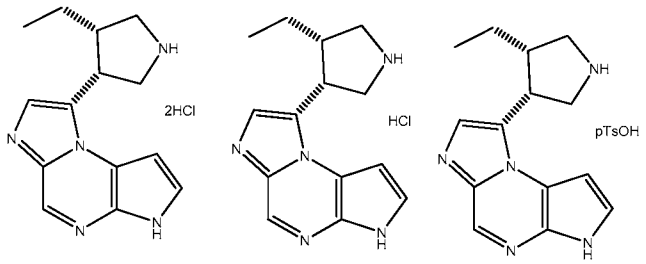
[0444] In certain embodiments, a pharmaceutically acceptable salt of a compound of the compound of formula (I) is used in the reaction of step (a). In one embodiment, the pharmaceutically acceptable salt of the compound of formula (I) is selected from the group consisting of the naphthalenethane amine salt (Ia) and the dicyclohexylamine salt (Ib)


(Ia)


(Ib)

wherein Cbz is carboxybenzyl.

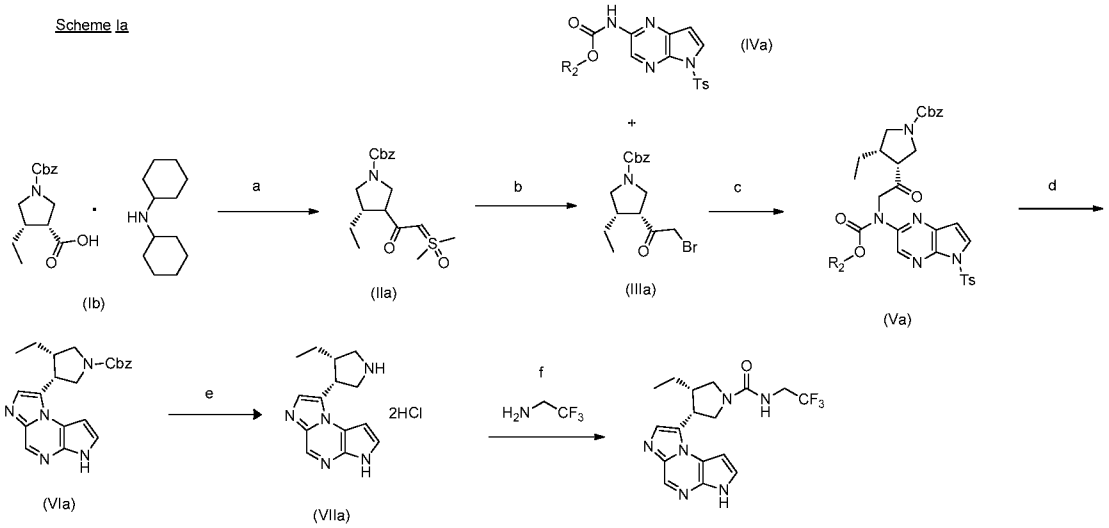
[0445] In one embodiment, the pharmaceutically acceptable salt of compound (VII) is selected from the group consisting of (VIIa), (VIIb), and (VIIc)


(VIIa), (VIIb), (VIIc).

[0446] Another process for preparing upadacitinib is illustrated in Scheme Ia. Reaction of (3R,4S)-1-((benzyloxy)carbonyl)-4-ethylpyrrolidine-3-carboxylate dicyclohexylamine salt (Ib) with trimethylsulfoxonium chloride in the presence of carbonyldiimidazole and a strong base gives sulfur ylide (IIa). Contacting sulfur ylide (IIa) with lithium bromide and a sulfonic acid yields the corresponding bromomethyl ketone (IIIa). Reaction of (IIIa) with alkyl 5-tosyl-5H-pyrrolo[2,3-b]pyrazin-2-ylcarbamate

(IVa) in the presence of lithium *tert*-butoxide yields (Va). Cyclization of (Va) in the presence of a perfluoro acid anhydride and an organic base produces (VIa). Removal of the carboxybenzyl protecting group and contacting the deprotected compound with hydrochloric acid yields the pharmaceutically acceptable salt (VIIa). Reacting the pharmaceutically acceptable salt (VIIa) with 2,2,2-trifluoroethylamine produces upadacitinib.

Scheme Ia



wherein:

Cbz is carboxybenzyl;

Ts is tosyl; and

R_2 is methyl or ethyl.

[0447] The reaction in step (a) of Schemes I and Ia is generally accomplished in the presence of a coupling agent, such as carbonyldiimidazole (CDI), and a strong base. The strong base may be, for example, potassium *tert*-butoxide, sodium *tert*-butoxide, or combinations thereof. The step (a) reaction may be conducted in any suitable solvent including, but not limited to, tetrahydrofuran, water, and methyl tert-butyl ether. In one embodiment, the reaction is conducted in the presence of carbonyldiimidazole and potassium *tert*-butoxide.

[0448] More particularly, in certain embodiments, a solution of a compound of formula (I), (Ia), or (Ib) in solvent is slowly added (e.g., over 30 minutes) to a slurry of CDI in solvent, and the resulting mixture is stirred at room temperature for 30 minutes to 12 hours, and typically for about 1 hour. The resulting solution is slowly added (e.g., over 15 minutes) to a suspension of the trimethylsulfoxonium chloride, strong base, and solvent, while maintaining the internal temperature below -1°C. In another embodiment, the reaction is quenched and the resulting compound of formula (II) or (IIa) is isolated prior to step (b).

[0449] In some embodiments, the reaction of step (a) may further involve contact of (Ia) or (Ib) with an acid prior to reaction with the trimethylsulfoxonium chloride, in order to extract the amine to obtain a compound of formula (I). Suitable acids include any mineral acid or organic acid, such as phosphoric acid, hydrochloric acid (HCl), acetic acid (HOAc), citric acid, and the like. The compound of

formula (I) may subsequently be taken up in a suitable solvent, and reacted with trimethylsulfoxonium chloride, as described herein. In one embodiment, a pharmaceutically acceptable salt of a compound of formula (I) is used in step (a), wherein the pharmaceutically acceptable salt is (Ia) or (Ib).

[0450] In step (b) of Schemes I and Ia, a compound of formula (II) or (IIa) is contacted with LiX and a sulfonic acid to form a compound of formula (III) or (IIIa), respectively. In one embodiment, the sulfonic acid is selected from the group consisting of methanesulfonic acid and p-toluenesulfonic acid. In one embodiment, the sulfonic acid is p-toluenesulfonic acid. LiX may be selected from lithium bromide and lithium chloride. In one embodiment, LiX is lithium bromide. In one embodiment, the reaction is conducted in lithium bromide and p-toluensulfonic acid. The reaction of step (b) may be conducted in any suitable solvent including, but not limited to tetrahydrofuran, ethyl acetate, heptanes, ethanol, water, and combinations thereof.

[0451] More particularly, in certain embodiments, the sulfonic acid is added to a solution of the compound of formula (II) or (IIa) and LiX in a solvent. The resulting mixture is warmed to about 35°C to about 65°C and stirred overnight. In one embodiment, the mixture is warmed to about 40°C and stirred overnight. The mixture is cooled to room temperature and washed. The compound of formula (III) or (IIIa) may be isolated, or optionally used in the next step without purification.

[0452] In step (c) of Schemes I and Ia a compound of formula (III) or (IIIa) are reacted with a compound of formula (IV) or (IVa) (prepared as described herein). The step (c) reaction is conducted in the presence of a base, such as lithium *tert*-butoxide, sodium *tert*-butoxide, or combinations thereof. In one embodiment, the base is lithium *tert*-butoxide. The reaction of step (c) may be conducted in any suitable solvent including, but not limited to dimethylacetamide, tetrahydrofuran, dichloromethane, ethyl acetate, heptanes, and combinations thereof.

[0453] More particularly, in certain embodiments, the base is added to a cooled suspension of the compound of formula (III) or (IIIa) in a solvent. The resulting solution is stirred for about 30 minutes to about 12 hours, or about 30 minutes, and cooled to about -20°C to about 0°, or about -10°C. In one embodiment, the solution is stirred for about 30 minutes and cooled to about -20°C to about 0°. A solution of a compound of formula (IV) or (IVa) in a solvent is slowly added (e.g., over 30 minutes), and the resulting mixture is stirred for about 30 minutes to about 6 hours, or about 30 minutes, at a temperature of about -20°C to about 0°C, or about -10°C. In one embodiment, following addition of the solution of the compound of formula (IV) or (IVa) in a solvent, the resulting mixture is stirred for about 30 minutes at a temperature of about -10°C. In one embodiment, the reaction is quenched, and, in some embodiments, the resulting product (V) or (Va) is isolated prior to step (d).

[0454] In step (d) of Schemes I and Ia, a compound of formula (V) or (Va) is contacted with a perfluoro acid anhydride and an organic base to form a compound of formula (VI) or (VIa), respectively. Non-limiting examples of suitable organic bases include pyridine, triethylamine, and combinations thereof. Examples of suitable perfluoro acid anhydrides include trifluoroacetic anhydride, pentafluoropropionic anhydride, heptafluorobutyric anhydride, and combinations thereof. In certain

embodiments, the organic base is pyridine and the perfluoro acid anhydride is trifluoroacetic anhydride. In other embodiments, the organic base is triethylamine, and the perfluoro acid anhydride is pentafluoropropionic anhydride. Suitable solvents for use in step (d) include, but are not limited to acetonitrile, toluene, and combinations thereof.

[0455] More particularly, in certain embodiments, the organic base and the perfluoro acid anhydride are charged into a solution of a compound of formula (V) or (Va) in solvent. The resulting mixture is warmed to about 55°C to about 75°C, or about 55°C, and stirred for about 4 hours to about 18 hours, or about 6 hours. In one embodiment, the mixture of perfluoro acid anhydride and the compound of formula (V) or (Va) is warmed to about 55°C and stirred for about 4 hours to about 18 hours. In one embodiment, the mixture is stirred for about 6 hours. Upon completion of the reaction, in some embodiments, the reaction mixture may be cooled, and concentrated prior to contacting with a hydroxide solution to quench excess reagents, and remove the tosyl protecting group. Suitable hydroxide solutions include a sodium hydroxide (NaOH) solution, a potassium hydroxide (KOH) solution, and the like. The resulting mixture may be stirred at room temperature to about 85°C, including at about 55°C, for about 30 minutes to about 8 hours. In one embodiment, the mixture is stirred for about 1 hour. Upon completion, the solvent may optionally be removed and switched to methanol, ethanol, isopropanol, or other suitable solvents prior to step (e).

[0456] In step (e) of Schemes I and Ia, a compound of formula (VI) or (VIa) is deprotected, and a pharmaceutically acceptable salt of compound (VII), such as (VIIa), (VIIb), or (VIIc) is formed. The protecting group on the compound of formula (VI) or (VIa) may be removed using any suitable means known in the art. In one embodiment, deprotection occurs by contacting the compound of formula (VI) or (VIa) with palladium on carbon (e.g., Pd/C or $Pd(OH_2)/C$) under hydrogen pressure. In other embodiments, deprotection occurs by contacting the compound of formula (VI) or (VIa) with an acid. Non-limiting examples of suitable acids include hydrochloric acid (HCl), hydrobromic acid (HBr), hydrobromic acid in acetic acid (e.g., HBr/HOAc), and the like. In other embodiments, deprotection occurs by subjecting the compound of formula (VI) or (VIa) to heating, e.g., at a temperature of from room temperature to about 85°C, including about 50°C. Upon deprotection, the compound of formula (VII) is contacted with the appropriate acid (e.g., hydrochloric acid or p-toluenesulfonic acid) to form the pharmaceutically acceptable salt.

[0457] Step (e) may occur in any suitable solvent including, but not limited to ethanol, isopropyl acetate, ethyl acetate, and combinations thereof.

[0458] More particularly, in some embodiments, palladium on carbon and the compound of formula (VI) or (VIa) in solvent are mixed under hydrogen pressure at about 1 psig to about 100 psig. In another embodiment, the hydrogen pressure is about 20 psig. The mixture is agitated for about 2 hours to about 24 hours, including about 16 hours, at about 20°C to about 85°C, including about 50 °C. In one embodiment, the mixture is agitated for about 16 hours at about 20°C to about 80°C. In one embodiment, the mixture is agitated for about 16 hours at about 50°C. Upon completion of the reaction, the reaction

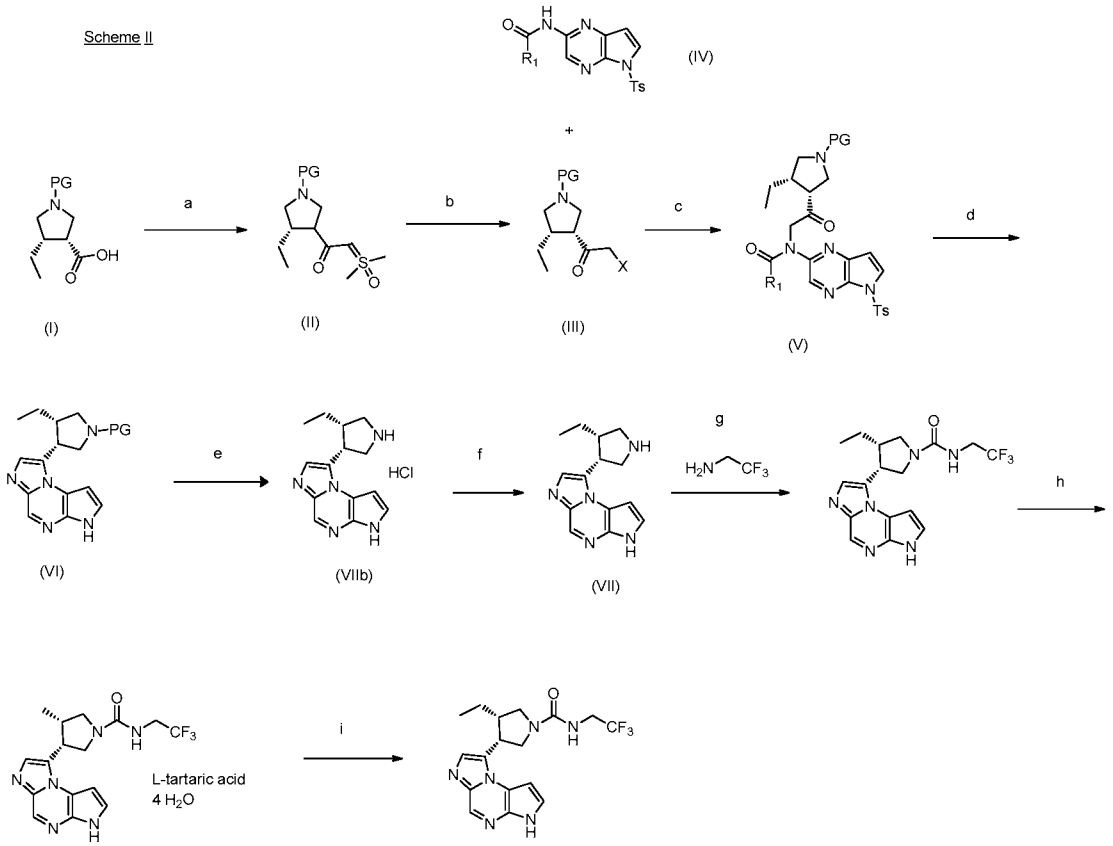
mixture is cooled and filtered, followed by addition of the appropriate acid. The resulting salt is optionally isolated prior to step (f).

[0459] In step (f), the salt produced in step (e) is reacted with 2,2,2-trifluoroethylamine to produce upadacitinib. The step (f) reaction is conducted in the presence of a coupling agent, such as carbonyldiimidazole (CDI), and optionally buffers, such as dipotassium phosphate, potassium hydroxide, and combinations thereof. In one embodiment, the step (f) reaction is conducted in the presence of CDI, dipotassium phosphate, and potassium hydroxide. The step (f) reaction may be conducted in any suitable solvent including, but not limited to, tetrahydrofuran, ethyl acetate, heptanes, ethanol, water, and combinations thereof.

[0460] More particularly, in certain embodiments, 2,2,2-trifluoroethyl amine is added slowly (e.g., over 20 minutes) to a slurry of CDI in solvent, while maintaining an internal temperature of less than 30°C. The resulting solution is stirred for about 10 minutes to about 12 hours, and in one embodiment for about 1 hour, to form an imidazolide solution. The pH of a biphasic mixture of the pharmaceutically acceptable salt from step (e) in buffer and solvent is adjusted to about 7 to about 11, and in one embodiment to about 9, by addition of a base. The imidazolide solution is added, and the resulting mixture is mixed at about 25°C while maintaining a pH of about 9 by portionwise addition of base for about 30 minutes to about 18 hours. In one embodiment, the mixture formed after addition of the imidazolide solution is mixed at about 25°C while maintaining a pH of about 9 by portionwise addition of base for about 1 hour. In one embodiment, upon completion, the reaction is quenched and the resulting product isolated.

[0461] An alternate process for preparing upadacitinib is illustrated in Scheme II. Reaction of protected (3R,4S)-4-ethylpyrrolidine-3-carboxylic acid (I) or a pharmaceutically acceptable salt thereof with trimethylsulfoxonium chloride gives sulfur ylide (II). Contacting sulfur ylide (II) with LiX and a sulfonic acid yields the corresponding halomethyl ketone (III). Reaction of (III) with (IV) in the presence of a base yields (V). Cyclization of (V) in the presence of a perfluoro acid anhydride and an organic base produces (VI). Removal of the protecting group and contacting the deprotected compound (VII) (not shown) with hydrochloric acid yields pharmaceutically acceptable salt (VIIb). The pharmaceutically acceptable salt (VIIb) is converted to the freebase (VII), which is reacted with 2,2,2-trifluoroethylamine to produce upadacitinib. Upadacitinib is contacted with L-tartaric acid to form the corresponding tartrate salt, followed by formation of the upadacitinib freebase.

Scheme II



wherein PG, Ts, X, and R1 are as defined above.

[0462] The protecting group may be any suitable protecting group known in the art. In some embodiments, the protecting group is selected from the group consisting of carboxybenzyl, *p*-methoxybenzyl carbonyl, benzyl, *p*-methoxybenzyl, and 3,4-dimethoxyenzyl. In one embodiment, the protecting group is carboxybenzyl.

[0463] In one embodiment, R_1 is $-OR_2$, and R_2 is ethyl or methyl.

[0464] In certain embodiments, a pharmaceutically acceptable salt of the compound of formula (I) is used in the reaction of step (a). In one embodiment, the pharmaceutically acceptable salt of the compound of formula (I) is selected from the group consisting of the naphthalenethane amine salt (Ia) and the dicyclohexylamine salt (Ib).

[0465] Steps (a)-(e) of Scheme II are conducted as described above for Scheme I, wherein following deprotection of the compound of formula (VI), deprotected compound (VII) is contacted with hydrochloric acid to form pharmaceutically acceptable salt (VIIb).

[0466] In step (f) of Scheme II, salt (VIIb) is contacted with a base to form the corresponding freebase (VII). Suitable bases include, but are not limited to hydroxides, such as sodium hydroxide, potassium hydroxide, and the like, and combinations thereof. In one embodiment, the base is sodium hydroxide. The reaction of step (f) may be conducted in any suitable water-containing solvent including, but not limited to, water alone or in combination with THF, 2-methyl tetrahydrofuran, ethanol, methanol, and the like.

[0467] In step (g) compound (VII) is reacted with 2,2,2-trifluoroethylamine to produce upadacitinib. The step (g) reaction is conducted in the presence of a coupling agent, such as CDI. Step (g) in Scheme II is conducted using similar reagents and under similar conditions as those set forth above for step (f) of Scheme I.

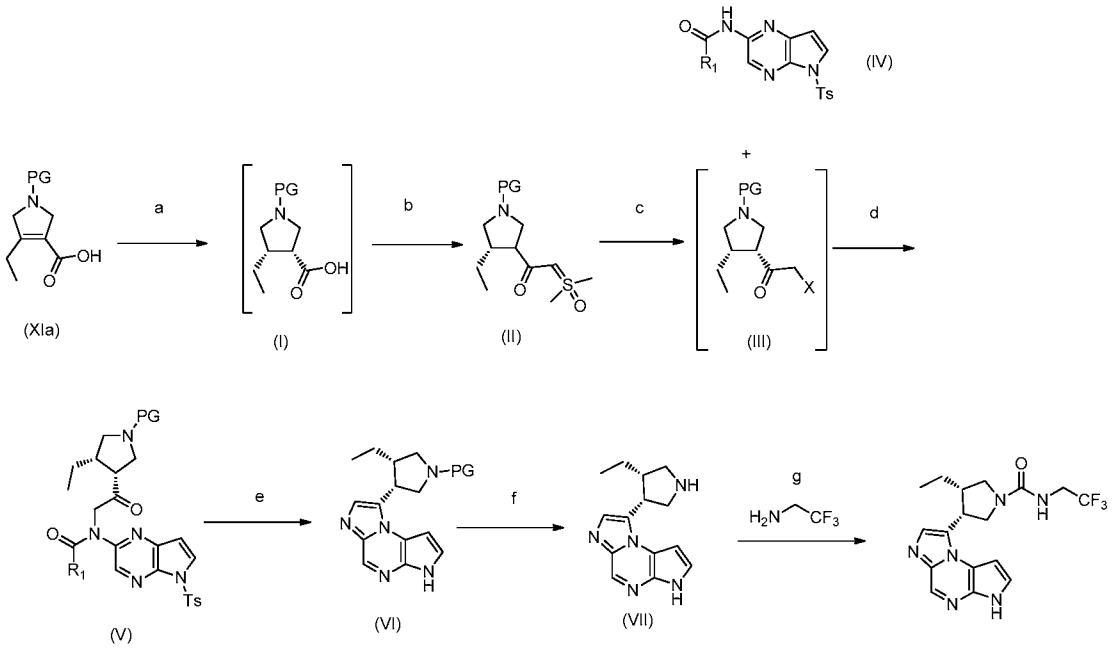
[0468] In step (h) of Scheme II, upadacitinib is contacted with L-tartaric acid to form the corresponding tartrate salt (step (h)). Formation of the tartrate salt advantageously aids in removal of impurities prior to isolation of the freebase. The tartrate salt is subsequently converted back to the freebase form (step (i)) to produce upadacitinib. In particular, in step (i) the tartrate salt may be contacted with a base, such as an inorganic base, to produce the corresponding freebase. Suitable bases include, but are not limited to, sodium bicarbonate, sodium carbonate, sodium hydroxide, potassium carbonate, potassium bicarbonate, potassium hydroxide, and the like, or combinations thereof. In one embodiment, the tartrate salt is contacted with sodium bicarbonate and sodium carbonate to produce the corresponding freebase.

[0469] Suitable solvents for use in step (h) include, but are not limited to, isopropyl acetate, methyl tert-butyl ether, water, isopropyl alcohol, and combinations thereof. Suitable solvents for use in step (i) include, but are not limited to, ethyl acetate, ethanol, water, and combinations thereof.

[0470] In some embodiments, the products of steps (d), (e), (g), and (h) of Scheme II are not isolated prior to the subsequent step.

[0471] An alternate process for preparing upadacitinib is illustrated in Scheme III. Compound (XIa) is hydrogenated to produce (I). Reaction of protected (3R,4S)-4-ethylpyrrolidine-3-carboxylic acid (I) with trimethylsulfoxonium chloride gives sulfur yilde (II). Contacting sulfur yilde (II) with an anhydrous source of HBr or HCl yields the corresponding halomethyl ketone (III). Reaction of (III) with (IV) in the presence of a base yields (V). Cyclization of (V) in the presence of a perfluoro acid anhydride and an organic base produces (VI). Removal of the protecting group and contacting the deprotected compound with an acid yields a pharmaceutically acceptable salt of (VII). Reacting the pharmaceutically acceptable salt of (VII) with 2,2,2-trifluoroethylamine produces upadacitinib.

Scheme III



wherein:

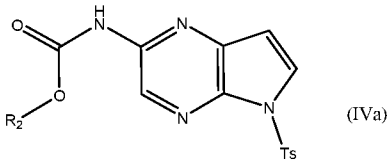
PG is a protecting group; X is Br or Cl;

R_1 is selected from the group consisting of alkyl, aryl, and $-OR_2$;

R_2 is alkyl; and Ts is tosyl.

[0472] The protecting group may be any suitable protecting group known in the art. In some embodiments, the protecting group is selected from the group consisting of carboxybenzyl, *p*-methoxybenzyl carbonyl, benzyl, *p*-methoxybenzyl, and 3,4-dimethoxyenzyl. In another embodiment, the protecting group is carboxybenzyl.

[0473] In another embodiment, R_1 is $-OR_2$, and R_2 is methyl or ethyl. In such embodiments, the compound of formula (IV) is a compound of formula (IVa):



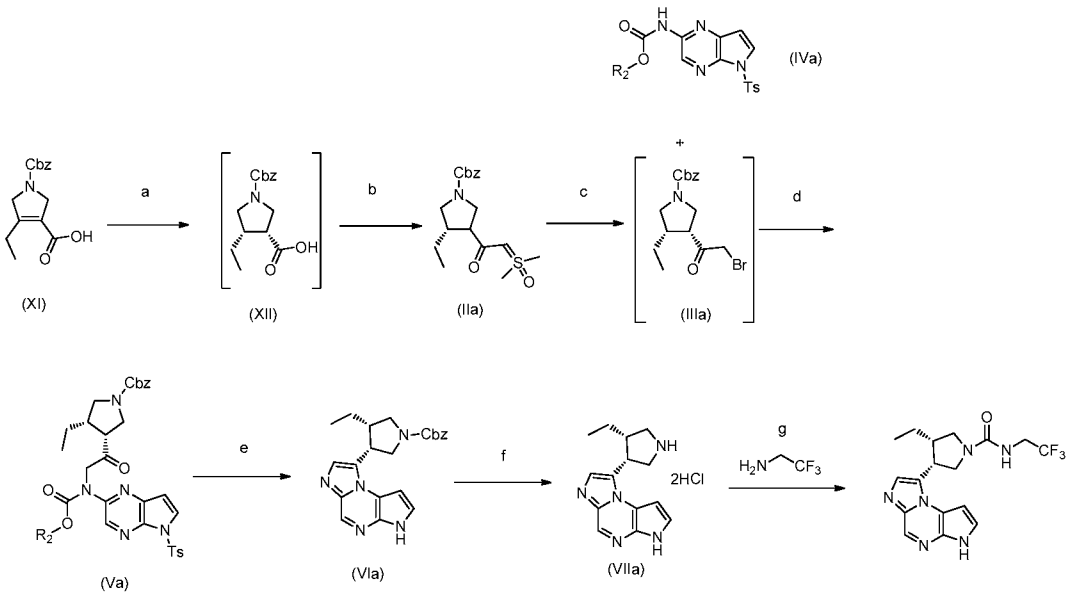
(IVa)

wherein R_2 is methyl or ethyl. It has surprisingly been discovered that when R_2 is ethyl or methyl, the compound of formula (V) and subsequent downstream compounds can be isolated as crystalline solids, which aids in purification of these intermediates. In contrast, previously known processes, which use compounds where R_2 is t-butyl, result in formation of compounds of formula (V) which are isolated as amorphous solids.

[0474] Another process for preparing upadacitinib is illustrated in Scheme IIIa. 1-((benzyloxy)carbonyl)-4-ethyl-2,5-dihydro-1H-pyrrole-3-carboxylic acid (XI) is hydrogenated to produce (XII). Reaction of (3R,4S)-1-((benzyloxy)carbonyl)-4-ethylpyrrolidine-3-carboxylate (XII) with trimethylsulfoxonium chloride gives sulfur yilde (IIa). Contacting sulfur yilde (IIa) with an anhydrous source of HBr yields the corresponding bromomethyl ketone (IIIa). Reaction of (IIIa) with alkyl 5-tosyl-

5H-pyrrolo[2,3-b]pyrazine-2-ylcarbamate (IVa) in the presence of lithium *tert*-butoxide yields (Va). Cyclization of (Va) in the presence of a perfluoro acid anhydride and an organic base produces (VIa). Removal of the carboxybenzyl protecting group and contacting the deprotected compound with hydrochloric acid yields the pharmaceutically acceptable salt (VIIa). Reacting the pharmaceutically acceptable salt (VIIa) with 2,2,2-trifluoroethylamine produces upadacitinib.

Scheme IIIa



wherein:

Cbz is carboxybenzyl; Ts is tosyl; and R_2 is methyl or ethyl.

[0475] In step (a) of Schemes III and IIIa, (XIa) or (XI) (which may be prepared as described in Scheme V) is converted to (I) or (XII), respectively. In particular, in step (a), compound (XI) or (XIa) may be contacted with a catalyst, such as a ruthenium catalyst. Any catalyst comprising a chiral phosphine may be used. One particular example of a suitable catalyst is diacetato[(S)-(-)5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole]ruthenium(II) (i.e., (S)-Segphos $Ru(OAc)_2$). Suitable solvents for use in step (a) include, but are not limited to, methanol, triethylamine, and combinations thereof.

[0476] In particular, in certain embodiments, a solution of (XI) or (XIa) and the catalyst in solvent is hydrogenated at about 30°C to about 100°C for from about 1 hour to about 18 hours. In one embodiment, the solution of (XI) or (XIa) and the catalyst in solvent is hydrogenated at about 580 psi. In one embodiment, the solution of (XI) or (XIa) and the catalyst in solvent is hydrogenated at about 200 psi gauge (psig). In one embodiment, the solution of (XI) or (XIa) and the catalyst in solvent is hydrogenated at about 80°C for from about 1 hour to about 8 hours, or for about 2 hours, or for about 4 hours. Upon completion, the reaction mixture is cooled to room temperature, filtered, and concentrated.

[0477] The reaction in step (b) of Schemes III and IIIa, is generally accomplished in the presence of a coupling agent, such as carbonyldiimidazole (CDI), and a strong base. The strong base may be, for

example, potassium *tert*-butoxide, sodium *tert*-butoxide, or combinations thereof. The step (b) reaction may be conducted in any suitable solvent including, but not limited to, tetrahydrofuran, water, and methyl tert-butyl ether. In one embodiment, the reaction is conducted in the presence of carbonyldiimidazole and potassium *tert*-butoxide.

[0478] More particularly, in certain embodiments, a suspension of trimethylsulfoxonium chloride, strong base, and solvent is heated (e.g., to about 35°C to about 65°C, or to about 45°C) for about 30 minutes to about 8 hours, or for about 1 hour, followed by cooling. In one embodiment, the suspension is cooled to a temperature of about -1°C or less, or to about -5°C or less. In some embodiments, the concentrated filtrate from step (a) is diluted with a suitable solvent (e.g., tetrahydrofuran), and to this solution is slowly added (e.g., over 30 minutes to 1 hour, or over 30 minutes) CDI. The resulting mixture is stirred at room temperature for 30 minutes to 12 hours, and typically for about 1 hour. The resulting solution is slowly added (e.g., over 15 minutes to 1 hour, or over 1 hour) to the suspension of the trimethylsulfoxonium chloride, strong base, and solvent, while maintaining the internal temperature below -1°C. In embodiments, the reaction may be stirred for about 30 minutes to about 8 hours, or for about 1 hour at a temperature of below about -1°C, or at about -5°C. In another embodiment, the reaction is quenched and the resulting compound of formula (II) or (IIa) is isolated prior to step (c).

[0479] Steps (a) and (b) of Schemes III and IIIa advantageously allow for preparation of a protected (3R,4S)-4-ethylpyrrolidine-3-carboxylic acid without formation and isolation of the naphthalenethane amine salt (Ia) or the dicyclohexylamine salt (Ib), or isolation of (I) or (XI).

[0480] In step (c) of Schemes III and IIIa, a compound of formula (II) or (IIa) is contacted with an anhydrous source of HBr or HCl to form a compound of formula (III) or (IIIa), respectively. In particular, the anhydrous source of HBr or HCl comprises no more than 0.2% water (by volume), or no more than about 0.15% water (by volume). The reaction of step (c) may be conducted in any suitable solvent including, tetrahydrofuran.

[0481] More particularly, in certain embodiments, (II) or (IIa) is combined with the HBr or HCl in a suitable solvent. In one embodiment, the solvents are tetrahydrofuran and acetic acid. In one embodiment, the solvent comprises no more than 0.2 % water (by volume). In one embodiment, (II) or (IIa) is combined with a solvent (e.g., THF) and a solution of HBr in HOAc. The resulting mixture is warmed to about 35°C to about 65°C, or about 40°C and agitated. In one embodiment, the mixture is agitated for about 4 to about 12 hours, or for about 5 hours. In one embodiment, the mixture is warmed to about 40°C and agitated (e.g., stirred) for about 5 hours. In one embodiment, the mixture is cooled to room temperature (e.g., around 20°C) and distilled, followed by washing. In one particular embodiment, the product (compound (III) or (IIIa)) is concentrated to dryness, and resuspended in a solvent (e.g., N,N-dimethylacetamide) to form a solution of (III) or (IIIa) for use in step (d).

[0482] Step (c) advantageously produces the halomethyl ketone (III) or (IIIa) in higher purity than Scheme I or Ia.

[0483] In step (d) of Schemes III and IIIa, a compound of formula (III) or (IIIa) is reacted with a compound of formula (IV) or (IVa) (prepared as described herein). The step (d) reaction is conducted in the presence of a base, such as lithium *tert*-butoxide, sodium *tert*-butoxide, or combinations thereof. In one embodiment, the base is lithium *tert*-butoxide. The reaction of step (d) may be conducted in any suitable solvent including, but not limited to dimethylacetamide, tetrahydrofuran, dichloromethane, ethyl acetate, heptanes, and combinations thereof.

[0484] More particularly, in certain embodiments, the base is slowly added (e.g., over about 30 minutes) to a cooled suspension of the compound of formula (IV) or (IVa) in a solvent. In one embodiment, the suspension of the compound of formula (IV) or (IVa) is cooled to about 0°C. The resulting solution is stirred for about 30 minutes to about 12 hours, or about 30 minutes, and cooled to about -20°C to about 0°C, or about -10°C. In one embodiment, the solution is stirred for about 30 minutes and cooled to about -20°C to about 0°C, or about -10°C. The halomethyl ketone solution prepared in step (c) is then slowly added (e.g., over about 1 hour), and the resulting mixture is agitated (e.g., stirred) for about 30 minutes to about 6 hours, or about 30 minutes, at a temperature of about -20°C to about 0°C, or about -10°C. In one embodiment, following addition of the step (c) solution, the resulting mixture is stirred for about 30 minutes at a temperature of about -10°C. In one embodiment, the reaction is quenched, and, in some embodiments, the resulting product (V) or (Va) is isolated prior to step (e).

[0485] Steps (e)-(g) of Schemes III and IIIa may be conducted as described above for steps (d)-(f) of Scheme I, respectively.

VI. Solid State Forms

[0486] The present disclosure also relates to the use of solid state forms of upadacitinib in the treatment of Crohn's disease and ulcerative colitis. Solid state forms include the Amorphous Freebase form of upadacitinib, Freebase Solvate Form A, Freebase Hydrate Form B, Freebase Hydrate Form C, Tartrate Hydrate, and Freebase Anhydrate Form D. These and other solid state forms of upadacitinib are described in U.S. Patent Application Serial No. 15/295,561, which is herein incorporated by reference. The sections below also discuss solid state forms that have been identified and selected properties of those solid state forms.

A. Amorphous Freebase

[0487] In one embodiment, the solid state form is amorphous upadacitinib (the "Amorphous Freebase"). In one aspect, the Amorphous Freebase comprises less than about 13% by weight water. In another aspect, the Amorphous Freebase comprises less than about 12% by weight water. In another aspect, the Amorphous Freebase comprises less than about 10% by weight water. In another aspect, the Amorphous Freebase comprises less than about 9% by weight water. In another aspect, the Amorphous Freebase comprises less than about 8% by weight water. In another aspect, the Amorphous Freebase

comprises less than about 7% by weight water. In another aspect, the Amorphous Freebase comprises less than about 6% by weight water. In another aspect, the Amorphous Freebase comprises less than about 5% by weight water. In another aspect, the Amorphous Freebase comprises less than about 4% by weight water. In another aspect, the Amorphous Freebase comprises less than about 3% by weight water. In another aspect, the Amorphous Freebase comprises less than about 2% by weight water. In another aspect, the Amorphous Freebase comprises less than about 1 % by weight water. In another aspect, the Amorphous Freebase has a glass transition temperature onset at about 119°C. In another aspect, the Amorphous Freebase has a glass transition temperature midpoint at about 122°C. In another aspect, the Amorphous Freebase has a glass transition temperature onset at about 119°C and a glass transition temperature midpoint at about 122°C.

[0488] The Amorphous Freebase generally has greater solubility, and increased bioavailability, relative to the corresponding crystalline forms of the compound. The Amorphous Freebase also has acceptable chemical stability. In addition, the Amorphous Freebase exhibits acceptable stability to light and peroxide. The Amorphous Freebase, however, is hygroscopic and can comprise as much as 12% by weight water at 25°C/90% relative humidity. Environmental controls potentially are required to ensure appropriate control of potency and water content during storage, dispensing, and handling of the Amorphous Freebase.

[0489] The Amorphous Freebase can be prepared, for example, using anti-solvent crystallization to prepare the Freebase Solvate Form A or Freebase Hydrate Form B (described below) followed by dehydration or desolvation to yield the Amorphous Freebase. This crystallization/dehydration/desolvation method allows for the large-scale manufacture of the Amorphous Freebase without the need for labor-intensive and expensive techniques such as spray-drying. It also provides for appropriate control of the bulk properties of the Amorphous Freebase (*i.e.*, particle size, flow properties *etc.*). When the Amorphous Freebase is prepared by desolvation of the Freebase Solvate Form A or dehydration of the Freebase Hydrate Form B, the Amorphous Freebase generally retains the morphology of the Freebase Solvate Form A or Freebase Hydrate Form B (*i.e.*, blades with hexagonal crystal faces when prepared by dehydration of Freebase Hydrate Form B, or irregular when desolvated from Freebase Solvate Form A).

[0490] The process volumes required for crystallization during the large-scale manufacture of the Freebase Solvate Form A or Freebase Hydrate Form B generally are within conventional processing volumes, but impurity rejection potentially may be lower than desired. Drying and dehydration/desolvation of the Freebase Hydrate Form B/Freebase Solvate Form A to the Amorphous Freebase generally can be carried out with standard equipment under conventional conditions and the isolated Amorphous Freebase typically can be co-milled without adversely impacting the amorphous state.

B. Crystalline Freebase Solvates and Hydrates

[0491] In another embodiment, the solid state form is a crystalline freebase of upadacitinib. In one aspect, the crystalline freebase is a solvate. In another aspect, the crystalline freebase is an isopropyl acetate/water solvate (the "Freebase Solvate Form A"). In another aspect, the crystalline freebase is a hydrate (the "Freebase Hydrate Form B"). The Freebase Solvate Form A and the Freebase Hydrate Form B are further described in the Examples of the application.

[0492] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[0493] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta, and that is further characterized by a peak at one or more of 13.7 ± 0.2, 20.8 ± 0.2 and 25.0 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[0494] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.1 ± 0.2, 9.3 ± 0.2, 12.0 ± 0.2, and 20.8 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0495] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.1 ± 0.2, 9.3 ± 0.2, 12.0 ± 0.2, and 25.0 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0496] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.1 ± 0.2, 9.3 ± 0.2, 12.0 ± 0.2, 20.8 ± 0.2, and 25.0 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0497] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.1 ± 0.2, 9.3 ± 0.2, 12.0 ± 0.2, 13.7 ± 0.2, 20.8 ± 0.2, and 25.0 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[0498] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern without a significant peak at one or more of 15.1 ± 0.2, and 21.7 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[0499] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern without a significant peak at one or more of 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[0500] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern without a significant peak at one or more of 15.1 ± 0.2, and 21.7 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0501] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta, and without a significant peak at one or more of 15.1 ± 0.2, and 21.7 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0502] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0503] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta, and without a significant peak at one or more of 15.1 ± 0.2, and 21.7 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0504] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2, 13.7 ± 0.2, 20.8 ± 0.2, and 25.0 ± 0.2 degrees two theta, and without a significant peak at one or more of 15.1 ± 0.2, and 21.7 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0505] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2, 13.7 ± 0.2, 20.8 ± 0.2, and 25.0 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0506] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2, 13.7 ± 0.2, 20.8 ± 0.2, and 25.0 ± 0.2 degrees two theta, and without a significant peak at one or more of 15.1 ± 0.2, and 21.7 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0507] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern characterized by peaks substantially at the positions listed in Table 14-A ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0508] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern characterized by peaks substantially at the positions listed in Table 14-B ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0509] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern characterized by peaks substantially at the positions listed in Table 16-B ± 0.2 degrees two theta that have a relative intensity of at least 10.0%, when measured at about 25°C with monochromatic Kα1 radiation.

[0510] In further aspects of each of the above embodiments, the significant peak values have a variation of ± 0.1 degrees two theta rather than ± 0.2 degrees two theta. In still further aspects of each of the above embodiments, the significant peak values have a variation of ± 0.05 degrees two theta rather than ± 0.2 degrees two theta.

[0511] In one embodiment, the crystalline freebase has an X-ray powder diffraction pattern substantially as shown in Figure 19.

[0512] The Freebase Solvate Form A and Freebase Hydrate Form B are not physically stable. As discussed above, they desolvate (or dehydrate) and convert to the Amorphous Freebase upon drying. Although the Freebase Solvate Form A and Freebase Hydrate Form B generally do not exhibit pharmaceutically acceptable physical stability for use as an active ingredient in a pharmaceutical dosage form, they are useful intermediates in the preparation of other solid state forms such as the Amorphous Freebase.

C. Crystalline Freebase Hydrate Form C (Hemihydrate)

[0513] In another embodiment, the solid state form is a crystalline hydrate, wherein the crystalline hydrate is a hemihydrate. In another embodiment, the solid state form is crystalline hemihydrate of upadacitinib having a powder X-ray diffraction pattern corresponding to Freebase Hydrate Form C. The Freebase Hydrate Form C is further described in the Examples of the application.

[0514] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern characterized by peaks at 13.4 ± 0.2, 15.1 ± 0.2, and 21.7 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[0515] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern characterized by peaks at 13.4 ± 0.2, 15.1 ± 0.2, and 21.7 ± 0.2 degrees two theta, and that is further characterized by a peak at one or more of 7.7 ± 0.2, 7.9 ± 0.2, 9.6 ± 0.2, 10.3 ± 0.2, 13.9 ± 0.2, 15.5 ± 0.2, 15.9 ± 0.2, 17.0 ± 0.2, 17.2 ± 0.2, 17.8 ± 0.2, 18.1 ± 0.2, 18.3 ± 0.2, 19.3 ± 0.2, 19.7 ± 0.2, 20.5 ± 0.2, 20.9 ± 0.2, 21.9 ± 0.2, 22.2 ± 0.2, 23.5 ± 0.2, 24.4 ± 0.2, 24.9 ± 0.2, 28.2 ± 0.2, and 29.5 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[0516] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern that is characterized by peaks at 13.4 ± 0.2, 15.1 ± 0.2, 15.5 ± 0.2, and 21.7 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[0517] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern that is characterized by peaks at 13.4 ± 0.2, 15.1 ± 0.2, 17.0 ± 0.2, and 21.7 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[0518] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern that is characterized by peaks at 13.4 ± 0.2, 15.1 ± 0.2, 20.9 ± 0.2, and 21.7 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[0519] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern that is characterized by peaks at 13.4 ± 0.2, 15.1 ± 0.2, 15.5 ± 0.2, 17.0 ± 0.2, 20.9 ± 0.2, and 21.7 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[0520] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern characterized by peaks at 15.5 ± 0.2, 13.4 ± 0.2, 15.1 ± 0.2, 19.3 ± 0.2, 20.5 ± 0.2, and 21.7 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[0521] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0522] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern without a significant peak at one or more of 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0523] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0524] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern characterized by peaks at 13.4 ± 0.2, 15.1 ± 0.2, and 21.7 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0525] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern characterized by peaks at 13.4 ± 0.2, 15.1 ± 0.2, and 21.7 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0526] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern characterized by peaks at 13.4 ± 0.2, 15.1 ± 0.2, and 21.7 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0527] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern characterized by peaks at 15.5 ± 0.2, 13.4 ± 0.2, 15.1 ± 0.2, 19.3 ± 0.2, 20.5 ± 0.2, and 21.7 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0528] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern characterized by peaks at 15.5 ± 0.2, 13.4 ± 0.2, 15.1 ± 0.2, 19.3 ± 0.2, 20.5 ± 0.2, and 21.7 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0529] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern characterized by peaks at 15.5 ± 0.2, 13.4 ± 0.2, 15.1 ± 0.2, 19.3 ± 0.2, 20.5 ± 0.2, and 21.7 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0530] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern characterized by peaks substantially at the positions listed in Table 14-C ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0531] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern characterized by peaks substantially at the positions listed in Table 16-C ± 0.2 degrees two theta that have a relative intensity of at least 10.0%, when measured at about 25°C with monochromatic Kα1 radiation.

[0532] In further aspects of each of the above embodiments, the significant peak values have a variation of ± 0.1 degrees two theta rather than ± 0.2 degrees two theta. In still further aspects of each of the above embodiments, the significant peak values have a variation of ± 0.05 degrees two theta rather than ± 0.2 degrees two theta.

[0533] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern substantially as shown in Figure 20 when measured at about 25°C with monochromatic Kα1 radiation.

[0534] The Freebase Hydrate Form C generally exhibits good chemical stability, physical stability, and solid state properties (including low hygroscopicity). Large-scale manufacture of the Freebase Hydrate Form C is relatively straightforward with minimal scaling, good yield, good impurity rejection, fast filtration, conventional drying, and minimal milling issues (even after subjecting the isolated material to high energy pinmilling). In addition, different particle sizes can be achieved through appropriate control of the crystallization process.

D. Crystalline Freebase Anhydrate Form D

[0535] In another embodiment, the solid state form is a crystalline anhydrate freebase of upadacitinib having a powder X-ray diffraction pattern corresponding to Freebase Anhydrate Form D. The Freebase Anhydrate Form D is further described in the Examples of the application.

[0536] In one embodiment the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, and 20.3 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[0537] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, and 20.3 ± 0.2 degrees two theta, and that is further characterized by a peak at one or more of 4.0 ± 0.2, 18.4 ± 0.2, 19.0 ± 0.2, 23.0 ± 0.2, and 24.7 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0538] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 4.0 ±0.2, 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, and 20.3 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0539] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, 18.4 ± 0.2 and 20.3 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0540] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, 19.0 ± 0.2 and 20.3 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0541] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 4.0 ± 0.2, 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, 19.0 ± 0.2 and 20.3 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0542] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, 20.3 ± 0.2, and 23.0 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0543] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, 20.3 ± 0.2, and 24.7 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0544] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 4.0 ± 0.2, 14.5 ± 0.2, and 19.0 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0545] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 4.0 ± 0.2, 14.5 ± 0.2, and 19.0 ± 0.2 degrees two theta, and that is further characterized by a peak at one or more of 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 18.4 ± 0.2, 20.3 ± 0.2, 23.0 ± 0.2, and 24.7 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0546] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 20.8 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0547] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern without a significant peak at one or more of 6.8 ± 0.2, 15.7 ± 0.2, and 21.9 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0548] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern without a significant peak at one or more of 13.4 ± 0.2, 15.5 ± 0.2, and 21.7 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0549] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern without a significant peak at one or more of 13.4 ± 0.2, 15.5 ± 0.2, and 21.7 ± 0.2 degrees two theta, and without a significant peak at one or more of 6.8 ± 0.2, 15.7 ± 0.2, and 21.9 ± 0.2 degrees two

theta, and without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 20.8 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0550] In one embodiment the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, and 20.3 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 20.8 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0551] In one embodiment the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, and 20.3 ± 0.2 degrees two theta, and without a significant peak at one or more of 6.8 ± 0.2, 15.7 ± 0.2, and 21.9 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0552] In one embodiment the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, and 20.3 ± 0.2 degrees two theta, and without a significant peak at one or more of 13.4 ± 0.2, 15.5 ± 0.2, and 21.7 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0553] In one embodiment the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, and 20.3 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 20.8 ± 0.2 degrees two theta, and without a significant peak at one or more of 6.8 ± 0.2, 15.7 ± 0.2, and 21.9 ± 0.2 degrees two theta, and without a significant peak at one or more of 13.4 ± 0.2, 15.5 ± 0.2, and 21.7 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0554] In one embodiment the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 4.0 ± 0.2, 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, 19.0 ± 0.2, and 20.3 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 20.8 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0555] In one embodiment the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 4.0 ± 0.2, 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, 19.0 ± 0.2, and 20.3 ± 0.2 degrees two theta, and without a significant peak at one or more of 6.8 ± 0.2, 15.7 ± 0.2, and 21.9 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0556] In one embodiment the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 4.0 ± 0.2, 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, 19.0 ± 0.2, and 20.3 ± 0.2 degrees two theta, and without a significant peak at one or more of 13.4 ± 0.2, 15.5 ± 0.2, and 21.7 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0557] In one embodiment the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 4.0 ± 0.2, 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, 19.0 ± 0.2, and 20.3 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 20.8 ± 0.2 degrees two theta, and without a significant peak at one or more of 6.8 ± 0.2, 15.7 ± 0.2, and 21.9 ±

0.2 degrees two theta, and without a significant peak at one or more of 13.4 ± 0.2, 15.5 ± 0.2, and 21.7 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0558] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks substantially at the positions listed in Table 14-E ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0559] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks substantially at the positions listed in Table 14-E ± 0.2 degrees two theta that have a relative intensity of at least 10.0%, when measured at about 25°C with monochromatic Kα1 radiation.

[0560] In further aspects of each of the above embodiments, the significant peak values have a variation of ± 0.1 degrees two theta rather than ± 0.2 degrees two theta. In still further aspects of each of the above embodiments, the significant peak values have a variation of ± 0.05 degrees two theta rather than ± 0.2 degrees two theta.

[0561] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern substantially as shown in Figure 22 when measured at about 25°C with monochromatic Kα1 radiation.

[0562] Freebase Anhydrate Form D is reversibly hygroscopic (up to 1.8% water at 90% RH at 25°C), and is metastable relative to Freebase Hydrate Form C at typical environmental conditions (e.g., above 2.4% RH at 23°C) used during storage for downstream processing. The manufacture of Freebase Anhydrate Form D requires strict control of water, as the Freebase Anhydrate Form D can be manufactured only when the water content of the crystallization solvent is low (e.g., less than 0.15% at 23°C, corresponding to a water activity of 2.4%), and will convert to Freebase Hydrate Form C in solutions at high water content. Freebase Anhydrate Form D is slow to crystallize, and difficult to manufacture in higher yield.

E. Crystalline Tartrate

[0563] In another embodiment, the solid state form is a tartrate of upadacitinib. In one aspect, the tartrate is amorphous. In another aspect, the tartrate is crystalline. In another aspect, the crystalline tartrate is a solvate. In another aspect, the crystalline tartrate is a hydrate. In another aspect, the tartrate is a crystalline L-tartrate. In another aspect, the crystalline L-tartrate is a hydrate. In another aspect, the crystalline tartrate is a tetrahydrate (the "Tartrate Hydrate"). The Tartrate Hydrate (a tetrahydrate) is further described in the Examples of the application.

[0564] In one embodiment, the Tartrate Hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[0565] In one embodiment, the Tartrate Hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.9 ± 0.2, 6.8 ± 0.2, 14.1 ± 0.2, 15.7 ± 0.2, 21.9 ± 0.2, and 25.9 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[0566] In one embodiment, the Tartrate Hydrate has an X-ray powder diffraction pattern without a significant peak at one or more of 13.4 ± 0.2 and 15.1 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0567] In one embodiment, the Tartrate Hydrate has an X-ray powder diffraction pattern without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0568] In one embodiment, the Tartrate Hydrate has an X-ray powder diffraction pattern without a significant peak at one or more of 13.4 ± 0.2 and 15.1 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.1 ± 0.2 and 9.3 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0569] In one embodiment, the Tartrate Hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta, and without a significant peak at one or more of 13.4 ± 0.2 and 15.1 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0570] In one embodiment, the Tartrate Hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0571] In one embodiment, the Tartrate Hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta, and without a significant peak at one or more of 13.4 ± 0.2 and 15.1 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0572] In one embodiment, the Tartrate Hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.9 ± 0.2, 6.8 ± 0.2, 14.1 ± 0.2, 15.7 ± 0.2, 21.9 ± 0.2 degrees two theta, and without a significant peak at one or more of 13.4 ± 0.2 and 15.1 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[0573] In one embodiment, the Tartrate Hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.9 ± 0.2, 6.8 ± 0.2, 14.1 ± 0.2, 15.7 ± 0.2, 21.9 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta.

[0574] In one embodiment, the Tartrate Hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.9 ± 0.2, 6.8 ± 0.2, 14.1 ± 0.2, 15.7 ± 0.2, 21.9 ± 0.2 degrees two theta, and without a significant peak at one or more of 13.4 ± 0.2 and 15.1 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta.

[0575] In further aspects of each of the above embodiments, the significant peak values have a variation of ± 0.1 degrees two theta rather than ± 0.2 degrees two theta. In still further aspects of each of the above embodiments, the significant peak values have a variation of ± 0.05 degrees two theta rather than ± 0.2 degrees two theta.

[0576] In one embodiment, the Tartrate Hydrate has an X-ray powder diffraction pattern substantially as shown in Figure 21, when measured at about 25°C with monochromatic Kα1 radiation.

[0577] The Tartrate Hydrate has acceptable chemical stability and exhibits acceptable stability to light and peroxide. The Tartrate Hydrate has good solubility (BCS Class I) and is not hygroscopic. The Tartrate Hydrate, however, potentially will convert to an amorphous tartrate below 10% relative humidity, when heated, or when compressed or under shear.

[0578] The Tartrate Hydrate can be manufactured, for example, using anti-solvent crystallization. Impurity rejection during the large-scale manufacture of the Tartrate Hydrate generally is good, but scaling may be greater than desired and specific anti-solvent addition controls and process volume restrictions potentially may be required. In addition, appropriate control of the filtration, washing, and drying steps may be required to minimize consolidation of the wet cake and formation of hard lumps in the isolated material. For example, control of the relative humidity (*e.g.*, greater than 10% and less than 100% relative humidity), temperature (*e.g.*, crystallization at about 10°C works well), and mixing rate may be required during drying to minimize the formation of hard lumps in the isolated material. Insufficient control of the drying conditions potentially will produce a consolidated, harder material that may be difficult to break up during subsequent processing. As previously noted, shearing and compression potentially will cause conversion to the amorphous tartrate. The dried material typically is milled with mechanical impact mills (*e.g.*, Fitzmills and pin mills) because shear-based mills (*e.g.*, comills) can lead to loss of crystallinity. In addition, loss of crystallinity potentially can result from pressure or compression forces during formulation (such as would be required for tableting).

F. Crystalline Purity

[0579] In additional embodiments of the solid state forms discussed above, the solid state form has a pharmaceutically acceptable crystalline purity (or a pharmaceutically acceptable amorphous purity in the case of the Amorphous Freebase). For example, in one aspect, upadacitinib comprises at least about 75% by weight of the desired solid state form. In another aspect, at least 80% by weight is the desired solid state form. In another aspect, at least 85% by weight is the desired solid state form. In another aspect, at least 90% by weight is the desired solid state form. In another aspect, at least 95% by weight is the desired solid state form. In another aspect, at least 96% by weight is the desired solid state form. In another aspect, at least 97% by weight is the desired solid state form. In another aspect, at least 98% by weight is the desired solid state form. In another aspect, at least 99% by weight is the desired solid state form. In another aspect, upadacitinib is present as the substantially crystalline pure (or amorphous pure in

the case of the Amorphous Freebase) solid state form. In a preferred aspect, the solid state form is the Amorphous Freebase. In another aspect, the solid state form is Freebase Anhydrate Form D. In a more preferred aspect, the solid state form is the Freebase Hydrate Form B. In a particularly preferred aspect, the solid state form is the Freebase Hydrate Form C. In a preferred aspect, the solid state form is the Tartrate Hydrate.

VII. Solid State Preparation

[0580] The present disclosure also relates to methods for preparing a solid state form of upadacitinib. In one aspect, the solid state form prepared is the Amorphous Freebase. In another aspect, the solid state form prepared is the Freebase Hydrate Form B. In another aspect, the solid state form prepared is the Freebase Hydrate Form C. In another aspect, the solid state form prepared is the Tartrate Hydrate. In another aspect, the solid state form prepared is the Freebase Anhydrate Form D.

A. Preparation of Amorphous Freebase

[0581] The present disclosure relates to methods for preparing the Amorphous Freebase. In one embodiment, the method comprises dehydrating the Freebase Hydrate Form B to provide the Amorphous Freebase. In another embodiment, the method comprises desolvating the Freebase Solvate Form A to provide the Amorphous Freebase. A wide range of process conditions can be employed for the dehydration/desolvation. The dehydration can be conducted, for example, under ambient conditions or in a vacuum oven. Figure 14 schematically illustrates one method of preparing the Amorphous Freebase by dehydration of the Freebase Hydrate Form B.

[0582] In another embodiment, the method comprises dissolving upadacitinib in a solvent or mixture of solvents; and adjusting the pH of the solvent or mixture of solvents to a pH greater than about 8 to initiate precipitation of the Amorphous Freebase. In one aspect, the solvent or mixture of solvents comprises water. In another aspect, the pH is adjusted to a pH greater than about 9. In another aspect, the pH is adjusted to a pH greater than about 10. In another aspect, the pH is adjusted to a pH greater than about 11. In another aspect, the pH is adjusted to a pH of at least about 9.

[0583] In still other embodiments, the method comprises preparing the Amorphous Freebase using a method selected from the group consisting of impinging jet, spray drying, and hot-melt extrusion.

B. Preparation of Crystalline Freebase Solvate Form A and Crystalline Freebase Hydrate Form B

[0584] The present disclosure additionally relates to methods for preparing the Freebase Solvate Form A and Freebase Hydrate Form B. In one embodiment, the method comprises dissolving upadacitinib in a solvent or mixture of solvents comprising an anti-solvent; and maintaining the solvent or mixture of solvents at a temperature less than about 15°C for an amount of time sufficient to initiate

crystallization of the Freebase Solvate Form A or the Freebase Hydrate Form B. The anti-solvent can comprise, for example, water. The solvent or mixture of solvents can comprise a polar solvent such as a solvent is selected from the group consisting of methanol, ethanol, n-butylamine, acetone, acetonitrile, ethyl formate, methyl acetate, ethyl acetate, methyl ethyl ketone, methyl isobutyl ketone, methyl isobutyl ketone, methyl tert-butyl ether, and isopropyl acetate. The Freebase Solvate Form A and Freebase Hydrate Form B exhibit similar PXRD patterns, and are therefore isostructural. The method generally is conducted at sub-ambient temperatures, for example, less than about 10°C, less than about 5°C, or less than about 0°C. In certain aspects, the process further comprises seeding the solvent or mixture of solvents with crystals of the Freebase Solvate Form A or the Freebase Hydrate Form B.

C. Preparation of Crystalline Freebase Hydrate Form C

[0585] The present disclosure additionally relates to methods for preparing the Freebase Hydrate Form C. In one embodiment, the method comprises dissolving upadacitinib in a solvent or mixture of solvents; and initiating crystallization to provide the Freebase Hydrate Form C. The solvent or mixture of solvents generally will comprise an anti-solvent (such as water) which can be present in the solvent or mixture of solvents before, or added to the solvent or mixture of solvents after, the upadacitinib is dissolved in the solvent or mixture of solvents. The solvent or mixture of solvents can comprise, for example, one or more polar solvents (such as polar solvent selected from the group consisting of ethanol and ethyl acetate); one or more nonpolar solvents (such as a nonpolar solvent is selected from the group consisting of hexane and heptane); or at least one polar solvent and at least one nonpolar solvent. In one aspect, the solvent or mixture of solvents is a ternary solvent mixture comprising ethyl acetate, heptane, and water. The method generally is conducted at temperatures less than about 30°C, less than about 20°C, or less than about 10°C. In certain aspects, the initiating crystallization step comprises mixing the solvent or mixture of solvents to provide sufficient agitation to initiate crystallization. In certain aspects, the initiating crystallization step comprises seeding the solvent or mixture of solvents with crystals of the Freebase Hydrate Form C. In certain aspects, the initiating crystallization step comprises both mixing the solvent or mixture of solvents and seeding the solvent or mixture of solvents with crystals of the Freebase Hydrate Form C.

[0586] In one embodiment, upadacitinib is first prepared according to any of the methods set forth herein, a reaction mixture comprising upadacitinib is filtered, and the resulting solution is suspended in a solvent or mixture of solvents. The solvent or mixture of solvents can comprise, for example, one or more polar solvents (such as polar solvent selected from the group consisting of ethanol and ethyl acetate); one or more nonpolar solvents (such as a nonpolar solvent is selected from the group consisting of hexane and heptane); or at least one polar solvent and at least one nonpolar solvent. In one particular embodiment, the solvent is ethyl acetate, or a mixture of ethyl acetate and water. In certain aspects, the initiating

crystallization step comprises seeding the solvent or mixture of solvents with crystals of the Freebase Hydrate Form C. In one particular aspect, the crystallization occurs in a wet mill.

[0587] Figure 15 schematically illustrates one method of preparing the Freebase Hydrate Form C.

D. Preparation of Crystalline Freebase Anhydrate Form D

[0588] The present disclosure additionally relates to methods for preparing the Freebase Anhydrate Form D. In one embodiment, the method comprises dissolving upadacitinib in a solvent or mixture of solvents; and initiating crystallization to provide the Freebase Anhydrate Form D. The solvent or mixture of solvents will be water-free, or close to water-free. In embodiments, the solvent or mixture of solvents will have a water content of less than about 0.15 wt%, or less than about 0.10 wt.%, or less than about 0.05 wt.%, or about 0 wt.% at 23°C. In one embodiment, the solvent or mixture of solvents will have a water activity of about 2.4% or less, or about 2.2% or less, or about 2.0% or less, or about 1.5% or less. The solvent or mixture of solvents can comprise, for example, ethyl acetate (EtOAc), heptane, and combinations thereof. In one embodiment, the solvent system comprises a mixture of heptane in ethyl acetate. In some embodiments, the solvent system comprises about 10 wt.%, or about 20 wt.%, or about 30 wt.%, or about 40 wt.% heptane in ethyl acetate. The method generally is conducted at temperatures of at least about 7°C, at least about 23°C, at least about 25°C or less, or at least about 30°C. In one embodiment, the method is conducted at about 23°C. In certain aspects, the initiating crystallization step comprises mixing the solvent or mixture of solvents to provide sufficient agitation to initiate crystallization. In certain aspects, the initiating crystallization step comprises seeding the solvent or mixture of solvents with crystals of the Freebase Anhydrate Form D. In certain aspects, the initiating crystallization step comprises both mixing the solvent or mixture of solvents and seeding the solvent or mixture of solvents with crystals of the Freebase Anhydrate Form D.

E. Preparation of Crystalline Tartrate Hydrate

[0589] The present disclosure additionally relates to methods for preparing the Tartrate Hydrate. In one embodiment, the method comprises dissolving upadacitinib and L-tartaric acid in a solvent or mixture of solvents to form a crystallization solution; and crystallizing the Tartrate Hydrate from the crystallization solution. The solvent or mixture of solvents can comprise, for example, water and/or, for example, one or more polar solvents (such as isopropyl acetate). The solvent or mixture of solvents also can comprise an anti-solvent (such as isopropyl acetate). In certain aspects, the process further comprises seeding the solvent or mixture of solvents with crystals of the Tartrate Hydrate.

[0590] The crystallization generally is conducted at a temperature less than about 40°C. When an anti-solvent is used, a moderate rate of addition is employed for the anti-solvent as a faster rate of addition typically results in the precipitation of an amorphous tartrate and a slower rate of addition allows the resulting slurry to thicken. Proper control of filtration, washing, and drying may be needed to avoid

potential issues associated with consolidation of the filter cake, including solvent entrapment, solid properties (*e.g.*, hard, chunky solids) and handing, and damage to equipment. Depending upon the properties of the dried Tartrate Hydrate material, milling may require a mechanical impact-type of mills rather than a shear-based mill (such as a co-mill).

[0591] Figure 16 schematically illustrates one method of preparing the Tartrate Hydrate.

VIII. Pharmaceutical Compositions and Routes of Administration

[0592] One or more compounds of this disclosure can be administered to a human patient by themselves or in pharmaceutical compositions where they are mixed with biologically suitable carriers or excipient(s) at doses to treat or ameliorate a disease or condition as described herein. Mixtures of these compounds can also be administered to the patient as a simple mixture or in suitable formulated pharmaceutical compositions.

[0593] The pharmaceutical compositions of the present disclosure may be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

[0594] Pharmaceutical compositions for use in accordance with the present disclosure thus may be formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

[0595] In one embodiment, the active ingredient contained in the dosage unit composition is upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof. In one embodiment, the target or label amount of active ingredient (e.g., upadacitinib) provided for inclusion in the compositions of the present disclosure refers to the amount of upadacitinib freebase. For instance, upadacitinib may be prepared in several solid state forms including Amorphous Freebase, crystalline solvates and hydrates (e.g., Freebase Solvate Form A, Freebase Hydrate Form B), crystalline hemihydrates (e.g., Freebase Hydrate Form C), crystalline anhydrate (e.g., Freebase Anhydrate Form D), and crystalline tartrate (e.g., Tartrate Hydrate). Preparation of these solid state forms is described herein and also in U.S. Patent Application Serial No. 15/295,561, which is herein incorporated by reference. It should be understood that in embodiments, where the dosage unit composition comprises, e.g., a solvate, hydrate, hemihydrate, or tartrate of upadacitinib, the amount of solvate, hydrate, hemihydrate, or tartrate of upadacitinib present in the dosage unit composition may be slightly higher than the target amount of upadacitinib (active ingredient), and preferably will be present in the dosage unit composition in an amount sufficient to deliver the target amount of upadacitinib freebase equivalent to a patient. For example, if the target amount of upadacitinib (active ingredient) in a dosage unit composition is 15 mg, a dosage unit composition comprising, for example, a hydrate of upadacitinib, may comprise the hydrate in an amount sufficient to deliver 15 mg of the upadacitinib freebase equivalent.

[0596] In one embodiment, the pharmaceutical composition is a tablet dosage form. In one aspect, the tablet is coated with a pharmaceutically acceptable polymer. In one embodiment, the pharmaceutical composition is a capsule dosage form.

[0597] In one embodiment, tablet is a controlled-release formulation, such as an extended release tablet dosage form (also referred to herein as a modified release or sustained release formulation). Such formulations permit the sustained release of the active ingredient over an extended period of time, as compared to immediate release solid dosage forms, which permit the release of most or all of the active ingredient over a short period of time (e.g., typically around 60 minutes or less). In one aspect, the tablet comprises an active ingredient (e.g., upadacitinib) and at least one additive selected from the group consisting of a release control polymer, a filler, a glidant, a lubricant (e.g., for use in compacting the granules), a pH modifier, a surfactant, and combinations thereof. In one aspect, the tablet comprises an active ingredient, a release control polymer, a filler, a glidant, and a lubricant. In one aspect, the tablet comprises an active ingredient, a release control polymer, a filler, a glidant, a lubricant, and a pH modifier.

[0598] In certain embodiments, the release control polymer will be a hydrophilic polymer. Examples of suitable release control polymers include, but are not limited to a cellulose derivative with a viscosity of between 1000 and 150,000 mPA-s, hydroxypropylmethyl cellulose (e.g., Hypromellose 2208 or controlled release grades of hydroxypropylmethyl cellulose, including the E, F, and K series), copolymers of acrylic acid crosslinked with a polyalkenyl polyether (e.g., Carbopol® polymers), hydroxypropyl cellulose, hydroxyethyl cellulose, non-ionic homopolymers of ethylene oxide (e.g., Polyox™), water soluble natural gums of polysaccharides (e.g., xanthan gum, alginate, locust bean gum, etc.), crosslinked starch, polyvinyl acetates, polyvinylpyrrolidone, mixtures of polyvinyl acetates and polyvinyl pyrrolidone, and combinations thereof. In one embodiment, the release control polymer is selected from the group consisting of hydroxypropylmethyl cellulose, copolymers of acrylic acid crosslinked with a polyalkenyl polyether (e.g., Carbopol® polymers), and combinations thereof. Examples of suitable fillers ("bulking agents") include, but are not limited to, microcrystalline cellulose (e.g., Avicel® PH 101; Avicel® PH 102;), mannitol (e.g., Pearlitol® 100 SD or Pearlitol® 200 SD), lactose, sucrose, sorbitol, and the like. In one embodiment, the filler is selected from the group consisting of microcrystalline cellulose, mannitol, and combinations thereof. Examples of suitable glidants include, but are not limited to, silicone dioxide (e.g., colloidal silicon dioxide), calcium silicate, magnesium silicate, talc, and combinations thereof. In one embodiment, the glidant is colloidal silicone dioxide. Examples of suitable lubricants include, but are not limited to, polyethylene glycol (e.g., having a molecular weight of from 1000 to 6000), magnesium stearate, calcium stearate, sodium stearyl fumarate, talc, and the like. In one embodiment, the lubricant is magnesium stearate. Examples of suitable pH modifiers include, but are not limited to, organic acids, such as tartaric acid, citric acid, succinic acid, fumaric acid; sodium citrate; magnesium or calcium carbonate or bicarbonate; and combinations thereof.

In one embodiment, the pH modifier is tartaric acid. Examples of suitable surfactants include sodium lauryl sulfate.

[0599] In one embodiment, the pharmaceutical composition comprises from about 10 w/w% to about 35 w/w% of a pH modifier, and in particular, tartaric acid, fumaric acid, citric acid, succinic acid, malic acid, or combinations thereof. In other embodiments, the formulation comprises from about 20 w/w% to about 35 w/w%, or from about 20 w/w% to about 30 w/w%, or from about 20 w/w% to about 25 w/w%, or about 10 w/w%, about 15 w/w.%, about 20 w/w%, about 25 w/w% or about 30 w/w% pH modifier. In one embodiment, the pH modifier is tartaric acid. Sustained peak plasma concentrations can theoretically be achieved by means of sustained release matrix systems. However, when such systems are made of hydrophilic polymers, such as HPMC, they seldom provide pH independent drug release of pH-dependent soluble drugs, and they are normally incapable of attaining zero-order release except for practically insoluble drugs. Is has been discovered that when a pH modifier, such as tartaric acid, fumaric acid, citric acid, succinic acid, malic acid, or combinations thereof, is used in a hydrophilic sustained release matrix system, it allows upadacitinib or a pharmaceutically acceptable salt or solid state form thereof to be released at a steady rate regardless of the pH of the environment. It has been discovered that as a tablet containing the hydrophilic polymer matrix system erodes, upadacitinib reacts with the HPMC, creating a thicker gel layer which slows the release of upadacitinib from the tablet. The resulting gel layer provides an environment suitable for upadacitinib to dissolve.

[0600] Thus, in one embodiment, the pharmaceutical composition of the present disclosure exhibits a pH-independent release of the active ingredient (upadacitinib). Advantageously, it has been discovered that including organic acids, such as a tartaric acid, in the composition as a pH modifier improves the release profile, and results in a pH independent release of the active ingredient. Without wishing to be bound to any particular theory, it is believed that the pH modifier and hydrophilic polymer create a microenvironment in which the active ingredient dissolves, and then is released. The release from the microenvironment occurs at approximately the same rate, regardless of pH. This is particularly advantageous, since the pH of the gastrointestinal tract may vary significantly from the stomach (e.g., pH of about 1.5-3), to the duodenum (e.g., pH of about 4-5), to the lower part of the small intestines (e.g., pH of about 6.5-7.5).

[0601] Thus, in one embodiment, the pharmaceutical composition is a modified release formulation comprising upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, a hydrophilic polymer, and a pH modifier, wherein the hydrophilic polymer, in contact with water, forms a gel layer that provides an environment suitable for upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, to dissolve. In some embodiments, the environment suitable for upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, to dissolve has a pH equal to or less than about 3.8 at 37°C. In some such embodiments, the environment has a pH of from about 1.5 to about 3.7, or from about 2.0 to about 3.7, or from about 2.5 to about 3.6, or from about 3.0 to about 3.6, or from about 3.0 to about 3.5.

[0602] In one such embodiment, the environment suitable for upadacitinib, or a pharmaceutically acceptable salt or solid state form thereof, to dissolve is as set forth above, and the modified release formulation comprises from about 10 w/w% to about 35 w/w% of a pH modifier, and in particular, tartaric acid, fumaric acid, citric acid, succinic acid, malic acid, or combinations thereof. In other embodiments, the formulation comprises from about 20 w/w% to about 35 w/w%, or from about 20 w/w% to about 30 w/w%, or from about 20 w/w% to about 25 w/w%, or about 10 w/w%, about 15w/w%, about 20 w/w%, about 25 w/w% or about 30 w/w% pH modifier. In any of these embodiments, the pH modifier may be selected from the group consisting of tartaric acid, fumaric acid, citric acid, succinic acid, malic acid, and combinations thereof. In one such embodiment, the pH modifier is selected from the group consisting of tartaric acid, fumaric acid, citric acid, succinic acid, and combinations thereof. In one such embodiment, the pH modifier is selected from the group consisting of tartaric acid and fumaric acid. In one embodiment, the pH modifier is tartaric acid. In one embodiment, the pH modifier is fumaric acid or citric acid. The weight % tartaric acid set forth herein is by weight of the uncoated composition (e.g., uncoated tablet). In any of the foregoing embodiments, the hydrophilic polymer may be a cellulose derivative with a viscosity of between 1000 and 150,000 mPA-s. In one embodiment, the hydrophilic polymer is selected from the group consisting of hydroxypropylmethyl cellulose, hydroxyethyl cellulose, and mixtures or combinations thereof. In one embodiment, the hydrophilic polymer is hydroxypropylmethyl cellulose. In one embodiment, the hydrophilic polymer is hydroxypropylmethyl cellulose Grade E, F, or K. In one embodiment, the hydrophilic polymer is Hypromellose 2208.

[0603] In one embodiment, the tablet is a compressed and/or milled tablet. For example, in some embodiments, the tablet is formed by blending the composition components (e.g., including the active ingredient and at least one pharmaceutically acceptable carrier). The composition can then be either directly compressed, or one or more of the composition components can be granulated prior to compression. In one embodiment, milling is performed using a mill fitted with any suitable size screen (e.g., a fitted with a screen size of from about 600 to about 1400 μm or about 610 μm or about 1397 μm). Compression can be done in a tablet press, such as in a steel die between two moving punches.

[0604] In other embodiments, the compressed and/or milled tablet is formulated using a wet granulation process. Use of wet granulation helps reduce and/or eliminate sticking that may occur when compression without wet granulation (e.g., direct compression) is used to formulate the tablets. In one embodiment, the wet granulation process may include the following steps: (a) combining the active ingredient (e.g., upadacitinib or a pharmaceutically acceptable salt or solid state form thereof or a solid state form of upadacitinib) and at least a portion of one additional composition component to form a dry granulation mixture; (b) contacting the dry granulation mixture with a granulation fluid to form a wet granulation mixture; (c) drying the wet granulation mixture to form a granulated material; (d) milling the granulated material to form a milled granulated material; (e) combining the milled granulation material with the remaining composition components; and (f) compressing the composition into the solid dosage unit (e.g., a tablet).

[0605] In step (a) of this process, the active ingredient may be combined with, for example, a portion of the release control polymer (e.g., HPMC), a portion of the filler (e.g., microcrystalline cellulose, such as Avicel® PH101), or both a portion of the release control polymer and a portion of the filler to form the dry granulation mixture. Any suitable portion of the release control polymer may be used in step (a). In one embodiment, from about 5 to 10 wt.% or from about 6 to 8 wt.% of the total amount of the release control polymer in the composition is used in step (a).

[0606] In certain embodiments, the granulation fluid used in step (b) may comprise water, a suitable solvent (e.g., ethanol, isopropanol, etc.), or combinations thereof. In one embodiment, the granulation fluid comprises water. In one embodiment, the active ingredient may be combined with a portion of the filler, while a portion of the release control polymer (e.g., HPMC) is dissolved in a liquid, such as water, to form the granulation fluid. In one embodiment, the granulation fluid is sprayed on the dry granulation mixture.

[0607] The dried granulation material may be milled using, for example, a comill fit with any suitable screen size. In one embodiment, the screen size is from about 600 to about 900 microns, or from about 610 to about 813 microns. In one embodiment, the granulated material is milled using a comill fitted with a 610 μm screen. In one embodiment, the granulated material is milled using a comill fitted with a 813 μm screen.

[0608] In step (e), the milled granulation material is combined with any remaining composition components, such as any remaining filler (e.g., microcrystalline cellulose, such as Avicel® PH102), any remaining release control polymer, glidants, lubricants, pH modifiers, surfactants, and the like. In one embodiment, the filler and/or release control polymer included in the granulated material may be the same or different than the filler and/or release control polymer added in step (e). For instance, in one embodiment, the filler included in the granulated material (e.g., Avicel®PH101) may have a smaller particle size distribution than the filler added in step (e) (e.g., Avicel®PH102).

[0609] In one embodiment, the composition may be sieved, and the sieved composition blended, for example, after step (e), and prior to compressing the composition (step (f)). In one embodiment, the formulation is sieved prior to addition of any lubricant. In one embodiment, the pH modifier (e.g., tartaric acid) is optionally milled prior to combining with the granulated material.

[0610] In some embodiments, the tablet further comprises a film coat. A film coat on the tablet further may contribute to the ease with which it can be swallowed. A film coat can also improve taste and provides an elegant appearance. In certain embodiments, the film-coat includes a polymeric film-forming material such as hydroxypropyl methylcellulose, hydroxypropylcellulose, and acrylate or methacrylate copolymers. Besides a film-forming polymer, the film-coat may further comprise a plasticizer, e.g. polyethylene glycol, a surfactant, e.g. polysorbates, and optionally a pigment, e.g. titanium dioxide or iron oxides. The film-coating may also comprise talc as anti-adhesive. In one embodiment, the film coat accounts for less than 5% by weight of a pharmaceutical composition of the present disclosure.

[0611] In another embodiment, the pharmaceutical composition is a capsule dosage form.

[0612] For the prevention or treatment of disease, the appropriate dosage of JAK1 inhibitor will depend on a variety of factors such as the type of disease to be treated, as defined above, the severity and course of the disease, whether the JAK1 inhibitor is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the antibody, and the discretion of the attending physician. The JAK1 inhibitor is suitably administered to the patient at one time or over a series of treatments.

[0613] The JAK1 inhibitor is formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being, treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the scheduling of administration, and other factors known to medical practitioners. The "therapeutically effective amount" of the JAK1 inhibitor will be governed by such considerations.

[0614] Pharmaceutical compositions suitable for use in the present disclosure include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. More specifically, a therapeutically effective amount means an amount effective to prevent development of or to alleviate the existing symptoms of the patient being treated. Determination of the effective amounts is well within the capability of those skilled in the art. In one particular embodiment, the composition will be a once-daily modified release formulation comprising 7.5 mg, 15 mg, 30 mg, or 45 mg of upadacitinib or a pharmaceutically acceptable salt or solid state form thereof.

IX. Examples

Example 1: Preparation of Amorphous Freebase

A. Method A: Precipitation From Water

[0615] Upadacitinib (approximately 300 g) was dissolved in water (10 L) and 50% sodium hydroxide (160 g) was added drop-wise over a two hour period to adjust the pH to greater than 12. Solids formed immediately. The solids were filtered, washed with two 500 mL aliquots of water, and then dried in a vacuum oven. The solids were equilibrated for a short period of time at ambient temperature prior to characterization. Conversion to Amorphous Freebase of upadacitinib was confirmed by PXRD analysis.

B. Method B: Dehydration of Freebase Hydrate Form B

[0616] A sample of the Freebase Hydrate Form B form of upadacitinib (crystallized from ethanol/water at sub-ambient temperatures as described in Example 2, Method C below) was placed in a vacuum oven at 40°C overnight. The solids removed from the vacuum oven were equilibrated for a short time at 23°C prior to characterization. Conversion to Amorphous Freebase of upadacitinib was confirmed by PXRD analysis.

Example 2: Preparation of Freebase Solvate Form A and Freebase Hydrate Form B

A. Method A: Freebase Solvate Form A (Isopropyl Acetate/Water Solvate)

[0617] A sample of the Amorphous Freebase of upadacitinib (25 mg) was added to a vial followed by isopropyl acetate (125 μL) and water (10 μL). All solids dissolved at ambient temperature. The solution was placed in a freezer at -16°C for 4 days. The liquor was decanted and the crystallized solids were isolated. The isolated crystals were analyzed by PXRD while still wet. Conversion to Freebase Solvate Form A (isopropyl acetate/water solvate) of upadacitinib was confirmed by PXRD analysis.

B. Method B: Freebase Hydrate Form B from Methanol/Water

[0618] A sample of the Amorphous Freebase of upadacitinib (164 mg) and MeOH (621 mg) were added to a vial. The components were mixed at ambient temperature until the solids dissolved. Water (approximately 680 μL) was added to the vial and the vial was placed in an ice/sodium chloride bath at approximately -3°C. Crystal seeds comprising Freebase Hydrate Form B were added to the vial and the vial was placed in a freezer at -16°C. A sample was pulled from the crystallized suspension and the solids were immediately analyzed with PXRD and TGA-MS. Conversion to Freebase Hydrate Form B of upadacitinib was confirmed by PXRD and TGA-MS analysis.

C. Method C: Freebase Hydrate Form B from Ethanol/Water

[0619] A sample of the Amorphous Freebase of upadacitinib (4.2 g) was dissolved in EtOH (15.3g) in a jacketed reactor. Water (23.3 g) was slowly added to the reactor. The reactor solution was cooled to approximately 2°C. A small portion of a seed solution comprising the Freebase Hydrate Form B was charged to the reactor. The suspension was mixed at approximately 2°C for 3 hours and water (36 g) in was charged to the reactor in small aliquots over several hours while maintaining the suspension at a temperature of approximately 2°C. The crystallized suspension was mixed at approximately 2°C and the solids were isolated via filtration. Conversion to Freebase Hydrate Form B of upadacitinib was confirmed by PXRD analysis.

[0620] The Freebase Solvate Form A and Freebase Hydrate Form B do not readily crystallize from solution. In general, sub-ambient temperatures and sufficient water activity are needed to crystallize Freebase Solvate Form A and Freebase Hydrate Form B from solution.

[0621] Crystalline freebase hydrates and solvates have been isolated from several solvent systems either through primary nucleation (without seeding) or through seeding. In addition to crystallization from isopropyl acetate/water (as described in Method A above), crystalline freebase hydrates or solvates also have been isolated through primary nucleation (without seeding) from, *e.g.*, n-butylamine/water and ethanol/water solvent systems. In addition to crystallization from methanol/water

(as described in Method B above) and ethanol/water (as described in Method C above), crystalline freebase hydrates or solvates also have been isolated through seeding from, *e.g.*, acetone/water; acetonitrile/water; ethyl formate/water; methyl acetate/water; ethyl acetate/water; methyl ethyl ketone/water; methyl isobutyl ketone/water, methyl isobutyl ketone/methyl tert-butyl ether/water; and isopropyl acetate/methyl tert-butyl ether/water solvent systems. The Freebase Solvate Form A (isopropyl acetate/water solvate) prepared in Method A above, the Freebase Hydrate Form B prepared in Methods B and C above, and these other crystalline freebase solvates or hydrates that have been prepared are isostructural and exhibit similar PXRD patterns. Notably, these crystalline freebase solvates and hydrates are distinguishable from and exhibit a different PXRD pattern than Freebase Hydrate Form C (a hemihydrate), which is described below.

[0622] The Freebase Solvate Form A and Freebase Hydrate Form B that were prepared were not stable after isolation at ambient conditions and readily dehydrated to the Amorphous Freebase.

Example 3: Preparation of Freebase Hydrate Form C

A. Method A: Freebase Hydrate Form C from Ethanol/Water

[0623] A sample of the Amorphous Freebase of upadacitinib (2 g) was transferred to a 500 mL beaker equipped with a stirring bar. EtOH (50 g) was added to the beaker and stirred until all solids dissolved. The solution was transferred to a 250 mL jacketed flask equipped with a dispersing device. The solution was cooled to 6°C. Water (150 g) was added to the solution and the solution was subjected to high shear for two hours using the dispersing device. After solid formation was observed, an additional amount of water (50 g) was added to the resulting suspension. The suspension was held overnight at ambient temperature. Solids were isolated and examined on the following day. Conversion to upadacitinib Freebase Hydrate Form C was confirmed by PXRD analysis.

B. Method B: Freebase Hydrate Form C From Ethyl Acetate/Heptane/Water

[0624] A crude reaction mixture assaying for 11.1 g of upadacitinib was taken up in 2% water in EtOAc (70 g) and seeded with Freebase Hydrate Form C (100mg). The suspension was stirred overnight and heptane (70 g) was added. The solids were collected by filtration, washed with water saturated EtOAc/heptane (1/1, 100 mL), and dried under vacuum at 50°C. Conversion to upadacitinib Freebase Hydrate Form C was confirmed by PXRD analysis.

[0625] As was observed with the Freebase Solvate Form A and the Freebase Hydrate Form B, the Freebase Hydrate Form C also does not readily crystallize from solution.

Example 4: Preparation of Tartrate Hydrate

[0626] Three methods for the preparation of upadacitinib tartrate tetrahydrate (the "Tartrate Hydrate") are described below. Method A describes an initial procedure that was used to prepare the tartrate tetrahydrate. Method B describes a modified procedure used to prepare the tartrate tetrahydrate at a larger scale. Method C describes a further modified procedure used to prepare the tartrate tetrahydrate. The modified procedure of Method C relative to the procedure of Method B further reduces solidification of the filter cake, a potential problem that potentially can impact manufacturability and downstream processing.

A. Method A

[0627] A sample of the Amorphous Freebase of upadacitinib (28.2 mg) was transferred to an amber vial. Water (200 μL) and L-tartaric acid (34.5 mg (approximately 3 equivalents)) were added to the vial. The suspension was vortexed under ambient conditions until all the solids dissolved. The solution in the vial was magnetically stirred at 0 °C. The following day, the solids were isolated from the solution and left at ambient temperature for a short period of time prior to characterization. Conversion to the upadacitinib Tartrate Hydrate (tetrahydrate) was confirmed by PXRD analysis.

B. Method B

[0628] Upadacitinib (4.6 g) was added to a jacketed reactor followed by the addition of isopropanol (6.5 mL) and IPAc (7.8 mL). The slurry was mixed at ambient condition until the solids dissolved. In a separate vial, L-tartaric acid (1.96 g) was dissolved in deionized water (3.92 mL). The L-tartaric acid solution was added to the reactor followed by the addition of tartrate tetrahydrate seed crystals (28 mg). The suspension was mixed for 30 minutes under ambient conditions. IPAc (71 mL) was added in small aliquots over 2 hours. The crystallized suspension was cooled to 5°C and equilibrated at 5°C overnight. The suspension was discharged onto a filter and the filter cake rinsed with 20 mL of water saturated IPAc. The filtered solids were air-dried for two days. Conversion to the upadacitinib Tartrate Hydrate (tetrahydrate) was confirmed by PXRD analysis.

C. Method C

[0629] Crystallization: Upadacitinib (104 g) was added to a flask together with isopropanol (222.7 g) and IPAc (375.8 g). The components were mixed under ambient conditions until the solids dissolved. In a separate flask, L-tartaric acid (61.6 g) was dissolved in water (98.3 g). The contents of the two flasks were then added to a jacketed reactor. Tartrate tetrahydrate seed crystals (1.55 g) were added to the reactor solution. The resulting suspension was mixed overnight under ambient conditions. IPAc (2542 g) was charged to the reactor suspension over an 8 hour period.

[0630] Filtration, Washing and Drying: Approximately half of the crystallized tartrate suspension was charged to a jacketed agitated filter dryer. The suspension was cooled inside the filter dryer to approximately 11°C. The suspension was filtered using positive pressure until a wet cake was obtained. Water saturated IPAc (438 g) was charged to the filter dryer and the suspension was mixed overnight at approximately 11°C. The suspension was filtered using positive pressure until a wet cake was obtained. Water saturated MTBE (110 g) was charged to the filter dryer. After 10 minutes, the suspension was filtered with positive pressure until a wet cake was obtained. Water saturated MTBE (261 g) was charged to the filter dryer and the suspension was mixed at approximately 11°C for 3.5 hours. The suspension was filtered with agitation using positive pressure until a wet cake was obtained. The wet cake was dried with constant agitation at a temperature of approximately 11°C under humidified nitrogen and positive pressure for two days. Conversion to the upadacitinib Tartrate Hydrate (tetrahydrate) was confirmed by PXRD analysis.

Example 5: Preparation of Freebase Anhydrate Form D

[0631] A sample of the Amorphous Freebase of upadacitinib was dissolved in water-free EtOAc at a concentration of 19.6% (w/w). An aliquot comprising approximately 1 mL was transferred to a 4 mL vial equipped with a magnetic stirrer. The vial was sealed with parafilm and mixed at 400 rpm on a magnetic stir plate at around 23°C for almost 8 weeks. The resulting slurry was filtered and left at ambient conditions for a short period of time prior to characterization. Conversion to Freebase Anhydrate Form D was confirmed by PXRD analysis.

Example 6: Microscopy/Crystal Morphology

[0632] The solid state forms of upadacitinib were evaluated by microscopy. Samples were examined by microscopic visual examination using a polarizing microscope (model Eclipse E-600 POL, Nikon Corp., Garden City, NY). A color video camera was used to record digital images (model DXC 390, Fryer Co., Inc., Huntley, IL). Images were captured using MetaMorph Imaging System (version 4.6R8, Universal Imaging Corporation, Downingtown, PA). Observations regarding the crystal morphology of the samples are reported in Table 13 below. Those of skill in the art will recognize that variation in crystal shape and size may be observed depending upon the specific crystallization conditions employed. The solvation states and PXRD profiles reported in Table 13 correspond to the information presented in the figures and subsequent examples of this application.

TABLE 13

Solid Form Nomenclature	Species	Solvation/Hydration State	Morphology
Amorphous Freebase	Freebase	Anhydrous	Blades (when prepared via precipitation or dehydration of Freebase Hydrate Form B)
Freebase Solvate Form A	Freebase	Isopropyl Acetate/Water Solvate	Irregular
Freebase Hydrate Form B	Freebase	Labile Hydrate	Blades
Freebase Hydrate Form C	Freebase	Hemihydrate	Prisms
Tartrate Hydrate	Tartrate	Tetrahydrate	Needles
Freebase Anhydrate Form D	Freebase	Anhydrous	Not Determined

Example 7: PXRD Analysis

[0633] The solid state forms of upadacitinib listed in Table 13 were analyzed by X-ray powder diffraction ("PXRD"). The PXRD data were collected with a G3000 diffractometer (Inel Corp., Artenay, France) equipped with a curved position sensitive detector and parallel beam optics. The diffractometer was operated with a copper anode tube (1.5 kW fine focus) at 40 kV and 30 mA. An incident beam germanium monochromator provided monochromatic Kα1 radiation $\lambda = 1.540562$ Å). The diffractometer was calibrated using the attenuated direct beam at one-degree intervals. Calibration was checked using a silicon powder line position reference standard (NIST 640c). Samples were prepared by spreading the sample powder in a thin layer on an aluminum sample holder and gently leveling with a glass microscope slide. The instrument was computer controlled using the Symphonix software (Inel Corp., Artenay, France) and the data was analyzed using the Jade software (version 6.5, Materials Data, Inc., Livermore, CA). The aluminum sample holder was mounted on the rotating sample holder of the G3000 diffractometer and the diffraction data collected at ambient conditions.

[0634] Tables 14-A through 14-E set out the significant parameters of the main peaks in terms of 2Θ values and intensities for the crystalline forms analyzed. It is known in the art that an X-ray powder diffraction pattern may be obtained which has one or more measurement errors depending on measurement conditions (such as equipment, sample preparation or machine used). In particular, it is generally known that intensities in an X-ray powder diffraction pattern may fluctuate depending on measurement conditions and sample preparation. For example, persons skilled in the art of X-ray powder diffraction will realize that the relative intensities of peaks may vary according to the orientation of the sample under testing and on the type and setting of the instrument used. The skilled person also will realize that the position of reflections can be affected by the precise height at which the sample sits in the diffractometer and the zero calibration of the diffractometer. The surface planarity of the sample also may

have an effect on the results. A person skilled in the art will appreciate that the diffraction pattern data presented below is not to be construed as absolute and any crystalline form that provides a power diffraction pattern substantially identical to those disclosed below fall within the scope of the present disclosure (for further information see Jenkins, R & Snyder, R.L. 'Introduction to X-Ray Powder Diffractometry', John Wiley & Sons, 1996).

[0635] The PXRD pattern corresponding to the Amorphous Freebase (via precipitation) and the Amorphous Freebase (via dehydration) are shown in Figures 17A and 17B, respectively.

[0636] The PXRD pattern corresponding to the Freebase Solvate Form A is shown in Figure 18. Peak listing of the experimental PXRD pattern with relative intensities is given in Table 14-A below.

Table 14-A: PXRD Peak Listing Freebase Solvate Form A (Isopropyl Acetate/Water Solvate)

PEAK POSITION (°2Θ)	RELATIVE INTENSITY
3.1	100.0
5.4	15.4
6.6	10.7
8.2	8.7
9.4	74.7
10.8	9.2
11.1	6.7
12.1	33.5
13.1	7.4
15.1	6.4
16.2	11.6
17.0	7.1
19.1	13.3
21.1	20.7
22.3	7.2
22.9	11.9
26.2	5.8
29.6	4.4

[0637] The PXRD pattern corresponding to the Freebase Hydrate Form B is shown in Figure 19. Peak listing of the experimental PXRD pattern with relative intensities is given in Table 14-B below.

Table 14-B: PXRD Peak Listing Freebase Hydrate Form B

PEAK POSITION (°2Θ)	RELATIVE INTENSITY
3.1	100.0
6.1	3.4
7.9	4.6

PEAK POSITION (°2Θ)	RELATIVE INTENSITY
9.3	54.8
10.7	3.1
12.0	27.1
12.4	6.3
13.0	3.3
13.7	4.3
14.9	7.5
15.6	4.2
16.0	3.5
17.1	3.7
18.8	7.0
20.8	13.4
22.9	6.6
23.3	4.5
24.0	6.6
24.6	4.2
25.0	12.4
26.0	4.7
26.9	5.1
28.1	3.3
28.9	2.5
29.8	4.1

[0638] The PXRD pattern corresponding to the Freebase Hydrate Form C is shown in Figure 20. Peak listing of the experimental PXRD pattern with relative intensities is given in Table 14-C below.

Table 14-C: PXRD Peak Listing Freebase Hydrate Form C

PEAK POSITION (°2Θ)	RELATIVE INTENSITY
7.7	28.8
7.9	41.1
9.6	10.2
10.3	35.0
12.4	9.8
13.4	72.5
13.9	16.9
15.1	74.6
15.5	93.7
15.9	11.7
17.0	76.1
17.2	46.8
17.8	21.6

PEAK POSITION (°2Θ)	RELATIVE INTENSITY
18.1	10.0
18.3	37.2
19.3	33.0
19.7	24.7
20.5	52.4
20.9	54.9
21.2	7.9
21.7	100.0
21.9	34.6
22.2	21.7
22.6	6.2
23.5	27.2
24.0	5.0
24.4	18
24.9	35.1
27.4	9.8
28.2	19.8
29.2	8.2
29.5	13.7
31.5	6.9

[0639] The PXRD pattern corresponding to the Tartrate Hydrate is shown in Figure 21. Peak listing of the experimental PXRD pattern with relative intensities is given in Table 14-D below. The experimental PXRD pattern is shown at the bottom of Figure 21 and the calculated PXRD pattern is shown at the top of Figure 21.

Table 14-D: PXRD Peak Listing Tartrate Hydrate

PEAK POSITION (°2Θ)	RELATIVE INTENSITY
3.9	80.3
6.8	24.6
10.4	12.8
11.8	21.6
14.1	100.0
15.7	63.3
16.1	10.4
17.1	4.5
18.0	22.1
18.4	11.6
18.8	12.4
19.7	5.2

PEAK POSITION (°2Θ)	RELATIVE INTENSITY
20.0	3.1
21.2	15.2
21.9	55.9
24.0	11.9
24.8	3.0
25.2	3.6
25.9	32.6
26.7	9.2
27.0	6.8
27.6	11.5
28.7	6.3
30.4	4.9
30.9	4.9
32.4	4.3
33.4	3.0

[0640] The PXRD pattern corresponding to the Freebase Anhydrate Form D is shown in Figure 22. Peak listing of the experimental PXRD pattern with relative intensities is given in Table 14-E below.

Table 14-E: PXRD Peak Listing Freebase Anhydrate Form D

PEAK POSITION (°2Θ)	RELATIVE INTENSITY
4.0	20.6
8.0	29.3
9.7	52.1
11.2	7.5
12.0	9.8
13.0	1.4
14.2	100.0
14.5	65.7
16.1	3.1
17.2	7.5
18.4	24.3
19.0	23.5
20.3	43.1
21.4	18.5
23.0	35.7
23.8	18.3
24.7	35.8
25.6	6.0
26.1	14.5
27.4	11.7

PEAK POSITION (°2Θ)	RELATIVE INTENSITY
28.2	9.3
28.7	5.2
30.3	6.6
31.1	1.3
31.9	3.8
32.7	1.0
33.3	5.1
34.8	0.7

Example 8: Clinical Study for Crohn's Disease

[0641] This trial was a multicenter, randomized, double-blind placebo-controlled study of upadacitinib for the induction of symptomatic and endoscopic remission in patient with moderately to severely active Crohn's disease who have inadequately responded to or are intolerant to immunosuppressants or anti-TNF therapy.

[0642] The trial consisted of a screening period of up to 30 days, a 16 week double blind induction period, re-randomization at week 16, a 36 week double blind and open label phase and a 30 day follow up period.

[0643] Approximately 220 patients with moderately to severely active Crohn's disease – defined for purposes of this study as having 1) Simplified Endoscopic Score for CD (SES-CD)≥6, (or SES-CD≥4 for patients with disease limited to the ileum), 2) a CDAI≥220 and ≤450, and 3) an average daily liquid/soft stool frequency (SF)≥ 2.5 or an average daily abdominal pain (AP) score ≥2.0) – were randomized in a 1:1:1:1:1:1 ratio to one of the schematics of the overall study design shown in Figure 1.

1. Group 1: upadacitinib 3 mg BID capsules (IR)
2. Group 2: upadacitinib 6 mg BID capsules (IR)
3. Group 3: upadacitinib 12 mg BID capsules (IR)
4. Group 4: upadacitinib 24 mg BID capsules (IR)
5. Group 5: upadacitinib 24 mg QD dose (IR) (two 12 mg capsules administered simultaneously)
6. Group 6: Placebo

[0644] The 16 week induction period began at the BL visit (week 0) and ended at the week 16 visit. The randomization at BL was stratified by endoscopic disease severity (SES-CD<15 and ≥15). Safety and efficacy evaluations were performed through the end of the study. The end of the study was defined as the date the last patient completed the last follow up visit.

[0645] At week 16, patients who had completed the induction period were re-randomized to one of four double-blinded doses of upadacitinib: 3 mg BID, 6 mg BID, 12 mg BID, or 24 mg QD (patients administered two 12 mg capsules simultaneously). The re-randomization were stratified by dose received during the first 16 weeks and overall response (responder versus non-responder) at week 16.

[0646] Each treatment group received the corresponding dose of upadacitinib or placebo orally twice daily. Patients receiving the 24 mg QD dose were administered two 12 mg capsules simultaneously orally once daily. At week 12 and week 16, patients were evaluated for clinical remission (average daily SF $\leq$ 1.5 and not worse than baseline and average daily AP $\leq$1.0 and not worse than baseline). Patients were randomly assigned (1:1) to have an endoscopy at either week 12 or at week 16, and were evaluated for endoscopic remission (SES-CD $\leq$4 and at least a two point reduction in SES-CD versus BL and no subscore >1 in any individual variable used to calculate SES-CD) at week 12 or week 16.

[0647] The central reader endoscopic score was used for calculating the endoscopic response for the evaluation of the efficacy endpoints. However, for stratification at the time of re-randomization, the endoscopic score at BL from central reader and the endoscopic score at week 12 or week 16 from site local reader were used in order to determine response status.

[0648] The co-primary endpoints for efficacy were:

- endoscopic remission at week 12 or 16
- clinical remission at week 16

[0649] Secondary endpoints to measure efficacy included:

- CDAI< 150 at week 16
- decrease in CDAI of $\geq$70 points from BL at week 16
- clinical remission at week 12
- remission at week 16 (endoscopic remission at week 12 or 16 and clinical remission at week 16)
- response at week 16 (endoscopic response at week 12 or 16 and clinical response at week 16)
- endoscopic response at week 12 or 16
- clinical response at week 16
- whether a subject with an average daily SF $\geq$2.5 and an average daily AP score $\geq$2.0 at BL achieves clinical remission at week 16
- whether a subject taking corticosteroids at BL who discontinues corticosteroid use achieves CDAI<150 at week 16
- whether a subject taking corticosteroids at BL who discontinues corticosteroid use achieves endoscopic remission at week 12 or week 16 and clinical remission at week 16
- whether a subject taking corticosteroids at BL who discontinues corticosteroid use achieves clinical remission at week 16
- whether a subject taking corticosteroids at BL who discontinues corticosteroid use achieves endoscopic remission at week 12 or week 16
- change from BL in fecal calprotectin level at week 16
- change from BL in hs-CRP (high sensitivity C-reactive protein) at week 16
- change in the Inflammatory Bowel Disease Questionnaire (IBDQ) from BL at week 16
- whether a subject with isolated ileal Crohn's Disease achieves remission at week 16

- whether a subject achieves remission at week 52
- whether a subject achieves endoscopic remission at week 52
- whether a subject achieves clinical remission at week 52
- whether a subject achieves response at week 52
- endoscopic response at week 52
- clinical response at week 52
- whether a subject taking corticosteroids at BL who discontinued corticosteroid use achieves CDAI<150 at week 52
- whether a subject taking corticosteroids at BL who discontinued corticosteroid use achieves remission at week 52
- whether a subject taking corticosteroids at BL who discontinued corticosteroid use achieves clinical remission at week 52
- whether a subject taking corticosteroids at BL who discontinued corticosteroid use achieves endoscopic remission at week 52
- CDAI <150 at week 52
- decrease in CDAI≥70 points from BL at week 52
- change from BL in fecal calprotectin level at week 52
- change from BL in hs-CRP at week 52
- change in IBDQ from BL at week 52
- whether subject with isolated ileal Crohn's Disease achieves remission at week 52
- change in extra-intestinal manifestations (EIMS) from BL at week 52

Methods

[0650] The study comprised two treatment periods: a 16 week double-blind induction period and a 36 week double-blind extension phase. In the induction period, patients with a diagnosis of ileal, colonic, or ileocolonic Crohn's disease for ≥3 months prior to BL and confirmed by endoscopy during the screening period, a CDAI ≥220 and ≤450, and who have inadequately responded to or experienced intolerance to previous treatment with an anti-TNF agent (e.g. infliximab, adalimumab or certolizumab pegol), were assigned to receive one of the following doses of upadacitinib 3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID or 24 mg QD or placebo. The co-primary endpoints were endoscopic remission at week 12 or week 16 and clinical remission at week 16. Secondary endpoints included CDAI< 150 at week 16 and endoscopic response at week 12 or 16.

[0651] Eligible patients were aged 18 to 75 years. They had a diagnosis of CD for at least three months and at screening had moderate-to-severe CD, defined as a 1) SES-CD ≥ 6 (or ≥ 4 for patients with disease limited to the ileum), 2) a CDAI of 220-450, and 3) an average daily liquid/ soft SF score ≥2.5 or an average daily AP score ≥2.0. Patients had inadequately responded to or experienced intolerance to

previous treatment with an anti-TNF agent. Patients with a current diagnosis of ulcerative colitis, collagenous colitis or indeterminate colitis as well as patients with previous exposure to a JAK inhibitor were excluded. See Table 15 below for key demographics and BL characteristics.

Table 15: Key Demographics and Baseline Characteristics

Demographics and Characteristics	PBO N = 37	3 mg BID N = 39	6 mg BID N = 37	12 mg BID N = 36	24 mg BID N = 36	24 mg QD* N = 35
Female, n (%)	24 (64.9)	19 (48.7)	21 (56.8)	17 (47.2)	25 (69.4)	19 (54.3)
Median Age, yrs	40.0	37.0	39.0	41.0	43.5	41.0
Disease duration, yrs	11.80	13.25	11.82	13.29	14.83	14.22
CDAI, mean	288.4	298.0	316.1	305.1	294.3	315.1
SF, mean	5.85	5.63	7.38	6.45	5.64	6.73
AP score, mean	1.67	1.87	1.80	1.82	1.63	1.89
SES-CD, mean	15.8	14.7	16.2	15.6	14.3	13.4
hsCRP, mean (mg/dL)	20.8	23.6	17.9	26.9	17.1	17.1
IBDQ, mean	118.0	115.2	113.7	115.2	113.8	120.7
Prior anti-TNFs, n (%)						
0	2 (5.4)	2 (5.1)	1 (2.7)	2 (5.6)	0	2 (5.7)
1	15 (40.5)	18 (46.2)	12 (32.4)	6 (16.7)	10 (27.8)	10 (28.6)
2	15 (40.5)	15 (38.5)	20 (54.1)	24 (66.7)	15 (41.7)	16 (45.7)
3	5 (13.5)	4 (10.3)	4 (10.8)	4 (11.1)	9 (25.0)	7 (20.0)
≥4	0	0	0	0	2 (5.6)	0
Steroid use at BL, n (%)	15 (40.5)	20 (51.3)	18 (48.6)	18 (50.0)	15 (41.7)	10 (28.6)
Prior non-anti-TNF biologics (%)	14(38)	15(39)	19(51)	15(42)	16(44)	14(40)
vedolilzumab, n (%)	10(27)	12(31)	14(38)	15(42)	12(33)	12(34)

*24 mg QD dose is two 12 mg doses given simultaneously

Table 16: Analysis of Primary Efficacy Endpoints

	PBO N = 37	3 mg BID N = 39	6 mg BID N = 37	12 mg BID N = 36	24 mg BID N = 36	24 mg QD* N = 35
Endoscopic Remission[1] (week 12 or16)	0 (0.0%)	4 (10.3%)	3 (8.1%)	3 (8.3%)	8 (22.2%)	5 (14.3%)
Risk Difference		10.3	8.1	8.3	22.2	14.3
P-value		0.056	0.108	0.099	0.004	0.025
94% CI		-(0.3, 201.)	(-1.6, 16.4)	(-1.5, 6.8)	(6.8, 35.2)	(1.8, 25.5)
Clinical Remission[2] (week 16)	4 (10.8%)	5 (12.8%)	10 (27.0%)	4 (11.1%)	8 (22.2%)	5 (14.3%)
Risk difference		2.0		0.3	11.4	3.5
P-value		0.740	0.082	0.952	0.205	0.607
95% CI		(-12.3, 17.3)	(-2.0, 34.3)	(-14.1, 15.0)	(-6.1, 28.5)	(-11.5, 19.6)

Note: Statistical significance was indicated by p value ≤0.10

[1]Endoscopic remission: SES-CD≤4 and at least two point reduction in SES-CD versus BL and no subscore >1 in any individual variable

[2] clinical remission: average daily liquid/very soft SF score ≤1.5 and not worse than BL AND average daily AP score ≤1.0 and not worse than BL

*24 mg QD dose is two 12 mg doses given simultaneously

Table 17: Analysis of Secondary Efficacy Endpoints (NRI)

	PBO N = 37	3 mg BID N = 39	6 mg BID N = 37	12 mg BID N = 36	24 mg BID N = 36	24 mg QD[&] N = 35
Week 16						
Clinical Response[1]	12(32.4%)	17 (43.6%)	21 (56.8%)*	17 (47.2%)	22 (61.1%)*	17 (48.6%)
Endoscopic Response (weeks 12/16)[2]	5 (13.5%)	9 (23.1%)	16 (43.2%)*	14 (38.9%)*	18 (50.0%)*	17 (48.6%)*
Clinical Remission and Endoscopic Remission	0	1 (2.6%)	2 (5.4%)	1 (2.8%)	3 (8.3%)*	2 (5.7%)
Clinical and Endoscopic Response	1 (2.7%)	6 (15.4%)*	12 (32.4%)*	10 (27.8%)*	14 (38.9%)*	12 (34.3%)*
CDAI <150	6 (16.2%)	8 (20.5%)	11 (29.7%)	14 (38.9%)*	11 (30.6%)	7 (20.0%)
CR100[5]	10(27.0%)	13(33.3%)	15 (40.5%)	16 (44.4%)	20 (55.6%)*	11 (31.4%)
CR70[6]	13(35.1%)	18 (46.2%)	20 (54.1%)	16 (44.4%)	23 (63.9%)*	17 (48.6%)
Steroid-free remisison[3]	0/15 (0%)	0/20 (0)%)	1/18 (5.6%)	1/18 (5.6%)	2/15 (13.3%)	0/10 (0%)
Steroid-free and CDAI<150[3]	0/15 (0%)	4/20 (20.0%)	4/18 (22.2%)	7/18 (38.9%)*	5/15 (33.3%)*	1/10 (10.0%)
Steroid-free and clinical response[3]	0/15 (0%)	5/20 (25%)	9/18 (50%)	8/18 (44%)	10/15 (67%)	3/10 (30%)
Week 12						
Clinical Remission[4]	4 (10.8%)	4 (10.3%)	11 (29.7%)*	5 (13.9%)	9 (25.0%)	3 (8.6%)
Clinical Response[1]	13(35.1%)	21 (53.8%)	24 (64.9%)*	19 (52.8%)	20 (55.6%)	18 (51.4%)
CDAI <150	24.3%	18.4%	41.7%	47.2%*	38.9%	22.9%
CR70[6]	35.1%	38.5%	59.5%*	47.2%	58.3%*	51.4%
CR100[5]	29.7%	30.8%	51.4%*	41.7%	52.8%*	40.0%

* Statistical significance was indicated by p value ≤ 0.10

[&] 24 mg QD dose is two 12 mg doses given simultaneously

[1] Clinical response: average daily liquid/very soft SF score ≥30% reduction from BL and average daily AP not greater than BL and/or average daily AP score ≥30% reduction from BL and average daily liquid/very soft SF score not greater than BL

[2] Endoscopic response: >25% decrease in SES-CD from BL, as scored by central reviewer

[3] Among subjects taking steroids at BL

[4] Clinical remission: average daily liquid/very soft stool frequency score ≤1.5 and not worse than BL AND average daily AP ≤1.0 and not worse than BL

[5]Decrease in CDAI score ≥100 from baseline

[6]Decrease in CDAI score ≥ 70 from baseline

Table 18: Analysis of Additional Efficacy Endpoints

Endpoints[&]	PBO N = 33	3 mg BID N = 38	6 mg BID N = 33	12 mg BID N = 34	24 mg BID N = 30	24 mg QD[**] N = 32
Modified Clinical Remission[1] (week 16)	4 (12.1%)	6 (15.8%)	10 (30.3%)*	9 (26.5%)	11 (36.7%)*	6(18.8%)
Endoscopic Improvement[2] (Week 12 or 16)	1 (3.0%)	12.8%	18.9%*	27.8%*	36.1%*	25.7%*

[&]: Includes subjects with baseline SF≥4.0 or AP≥2.0.

*: Statistical significance was indicated by p value ≤ 0.10.

**: 24 mg QD dose is two 12 mg doses given simultaneously

[1] Clinical remission: average daily SF ≤ 2.8 and not greater than Baseline AND average daily AP ≤ 1.0 and not greater than Baseline

[2] Endoscopic improvement: SES-CD > 50% reduction from BL or at least a 2 point reduction in SES-CD from BL or endoscopic remission

Results

[0652] Baseline demographics and disease characteristics were similar between study arms. In total there were 95 males and 125 females, with a mean age of 42.5 years and mean CDAI of 302.83; 96.0% percent of patients had previously been exposed to ≥1 TNF antagonists. At week 12/16, endoscopic remission was achieved by 10.3%, 8.1%, 8.3%, 22.2% and 14.3% of patients treated with 3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID and 24 mg QD, respectively, of upadacitinib, compared with 0% of patients treated with placebo (p=0.056, p=0.108, p=0.099, p=0.004, p=0.025, respectively, see Table 16). At week 16, clinical remission was achieved by 12.8%, 27.0%, 11.1%, 22.2% and 14.3% of patients treated with 3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID and 24 mg QD, respectively, of upadacitinib, compared 10.8% of patients treated with placebo (p=0.740, p=0.082, p=0.952, p=0.205, p=0.607, respectively, see Table 16). Clinical remission was observed in some patients as early as week 12. The percentage of patients achieving clinical remission at week 12 is shown in Figure 6A (patients not on baseline steroids) and Figure 6B (patients who were on steroids at baseline, and underwent mandatory taper of steroid dose starting at week 2). The steroid taper consisted of a weekly decrease by 5 mg/day of prednisone (or equivalent) for doses >10/mg/day of prednisone (or equivalent) until a 10 mg/day (or equivalent) dose was reached, then a weekly decrease by 2.5 mg/day (or equivalent) until discontinuation. Upadacitinib was shown to induce clinical remission as early as week 12.

[0653] Clinical response was achieved at week 16 by 43.6%, 56.8%, 47.2%, 61.1% and 48.6 % of patients treated with 3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID and 24 mg QD, respectively, of upadacitinib, compared with 32.4% of patients treated with placebo. Endoscopic response was achieved at week 12 or week 16 by 23.1%, 43.2%, 38.9%, 50.0% and 48.6% of patients treated with 3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID and 24 mg QD, respectively, of upadacitinib, compared with 13.5% of patients treated with placebo.

[0654] Clinical remission and endoscopic remission was achieved at week 16 by 2.6%, 5.4%, 2.8%, 8.3% and 5.7% of patients treated with 3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID and 24 mg QD, respectively, of upadacitinib, compared with 0% of patients treated with placebo. Clinical and endoscopic response was achieved at week 16 by 15.4%, 32.4%, 27.8%, 38.9% and 34.3% of patients treated with 3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID and 24 mg QD, respectively, of upadacitinib, compared with 2.7% of patients treated with placebo. Results are shown in Table 17.

[0655] Clinical remission was achieved at week 12 by 10.3%, 29.7%, 13.9%, 25.0% and 8.6% of patients treated with 3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID and 24 mg QD, respectively, of upadacitinib, compared with 10.8% of patients treated with placebo. Clinical response was achieved at week 12 by 53.8%, 64.9%, 52.8%, 55.6% and 51.4% of patients treated with 3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID and 24 mg QD, respectively, of upadacitinib, compared with 35.1% of patients treated with placebo. Results are shown in Table 17. The percentage of patients achieving clinical response at week 12 is shown in Figure 6A (patients not on baseline steroids) and Figure 6B (patients who were on steroids at baseline, and underwent mandatory taper of steroid dose starting at week 2).

[0656] Modified clinical remission was achieved at week 16 by 15.8%, 30.3%, 26.5%, 36.7%, and 18.8% of patients treated with 3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID and 24 mg QD, respectively, of upadacitinib, compared with 12.1% of patients treated with placebo. Results are shown in Table 18.

[0657] Endoscopic improvement was achieved at week 12 or week 16 by 12.8%, 18.9%, 27.8%, 36.1%, and 25.7% of patients treated with 3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID and 24 mg QD, respectively, of upadacitinib, compared with 3.0% of patients treated with placebo. Results are shown in Table 18. Of the patients who were evaluated for endoscopic improvement at week 12, 10.5%, 13.3%, 25%, 33.3%, and 12.5% of patients treated with 3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID and 24 mg QD, respectively, of upadacitinib, achieved endoscopic improvement by week 12, compared with 0% of patients treated with placebo. Of the patients who were evaluated for endoscopic improvement at week 16, 15.8%, 27.8%, 27.3%, 25%, and 31.3% of patients treated with 3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID and 24 mg QD, respectively, of upadacitinib, achieved endoscopic improvement by week 16, compared with 6.7% of patients treated with placebo. These results are shown in Table 19. These results show that endoscopic improvement was observed as early as week 12.

[0658] By week 4 of the induction period, among Crohn's patients tapering corticosteroids,13.3%, 9.5%, 11.1%,11.8%, 6.7% and 10% respectively were able to discontinue steroids with placebo, 3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID and 24 mg BID, respectively. By week 8 of the induction period, among Crohn's patients tapering corticosteroids, 26.7%, 23.8%, 44.4%,64.7%, 53.3% and 40% respectively were able to discontinue steroids 3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID and 24 mg BID, respectively. By week 12 of the induction period, among Crohn's patients were able to discontinue steroids, 33.3%, 28.6%, 55.6%,76.5%, 60% and 40% respectively were able to reduce their steroid dose by ≥50% with placebo, 3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID and 24 mg BID,

respectively. By week 16 of the induction period, among Crohn's patients tapering corticosteroids, 20%, 38.1%, 55.6%, 64.7%, 74 .3% and 40% respectively were able to reduce their steroid dose by ≥50% with placebo, 3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID and 24 mg BID, respectively.

[0659] By week 4 of the induction period, among Crohn's patients tapering corticosteroids, 20%, 42.9%, 50%,82.4%, 46.7% and 40% respectively were able to reduce their steroid dose by ≥50% with placebo, 3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID and 24 mg BID, respectively. By week 8 of the induction period, among Crohn's patients tapering corticosteroids, 55.3%, 42.9%, 66.7%,88.2%, 66.7% and 60% respectively were able to reduce their steroid dose by ≥50% with placebo, 3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID and 24 mg BID, respectively. By week 12 of the induction period, among Crohn's patients tapering corticosteroids, 46.7%, 38.1%, 61.1%,88.2%, 60% and 40% respectively were able to reduce their steroid dose by ≥50% with placebo, 3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID and 24 mg BID, respectively. By week 16 of the induction period, among Crohn's patients tapering corticosteroids, 33.3%, 38.1%, 66.7%, 88.4%, 77.3% and 40% respectively were able to reduce their steroid dose by ≥50% with placebo, 3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID and 24 mg BID, respectively.

[0660] At the end of the 16 week induction period, among Crohn's patients who discontinued corticosteroids, 11.1%, 5.9%, 20% and 10% achieved endoscopic remission with, 6 mg BID, 12 mg BID, 24 mg BID and 24 mg BID, respectively. At the end of the 16 week induction period, among patients who discontinued corticosteroids, 6.7%, 4.8%, 16.7%, 17.6%, 20% and 20% achieved endoscopic response with placebo, 3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID and 24 MG BID, respectively. At the end of the 16 week induction period, among patients who discontinued corticosteroids, 14.3%, 22.2%, 11.8%, 33.3% and 10% achieved clinical remission with 3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID and 24 MG BID, respectively. At the end of the 16 week induction period, among patients who discontinued corticosteroids 14.3%, 26.7%, 25.0%, 36.4% and 10% achieved modified clinical remission with 3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID and 24 MG BID, respectively. At the end of the 16 week induction period, among patients who discontinued corticosteroids 19.0%, 22.2%, 41.2%, 33.3% and 10% achieved CDAI<150 with 3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID and 24 MG BID, respectively. The taper consisted of a weekly decrease by 5 mg/day of prednisone (or equivalent) for doses >10/mg/day of prednisone (or equivalent) until a 10 mg/day (or equivalent) dose was reached, then a weekly decrease by 2.5 mg/day (or equivalent) until discontinuation.

Table 19: Analysis of Endoscopic Improvement by Week Evaluated

Week 12	**PBO N = 18**	**3 mg BID N = 19**	**6 mg BID N = 15**	**12 mg BID N = 12**	**24 mg BID N = 18**	**24 mg QD N = 16**
Endoscopic Improvement	**0%**	**10.5%***	**13.3%**	**25%***	**33.3%***	**12.5%**

Week 16	PBO N = 15	3 mg BID N = 19	6 mg BID N = 18	12 mg BID N = 22	24 mg BID N = 12	24 mg QD N = 16
Endoscopic Improvement	**6.7%**	**15.8%**	**27.8%**	**27.3%**	**25%**	**31.3%***

*: Statistical significance was indicated by p value ≤ 0.10.

[0661] This study included refractory patients with moderately to severely active Crohn's disease, who have had Crohn's disease for more than ten years and who have failed several treatments, including biologic treatments. Table 15 above shows the number of patients in the study that received prior anti-TNF treatment, treatment with prior non-anti-TNF biologics, treatment with vedolilzumab, and who were being treated with steroids at baseline, as well as the average duration of Crohn's disease at baseline. Typically, because refractory patients are treated with different therapeutics, the efficacy of each treatment progressively decreases. Surprisingly, however, the current study demonstrated that when treated with upadacitinib, the refractory patients showed unprecedented efficacy. The results for refractory patients in the study are shown in Figure 9.

[0662] As shown by Figure 9, refractory patients treated with upadacitinib achieved clinical remission and endoscopic response at unprecedented rates. At week 16, 15.8% of refractory patients treated with 3 mg BID of upadacitinib achieved clinical remission. At week 16, 30.3% of refractory patients treated with 6 mg BID of upadacitinib achieved clinical remission. At week 16, 26.5% of refractory patients treated with 12 mg BID of upadacitinib achieved clinical remission. At week 16, 36.7% of refractory patients treated with 24 mg QD (two 12 mg BID doses given simultaneously) achieved clinical remission.

[0663] In addition, as also shown in Figure 9, a surprising proportion of refractory patients treated with upadacitinib achieved endoscopic remission at 12 or 16 weeks. 13.2% of refractory patients treated with 3 mg BID of upadacitinib achieved endoscopic remission at 12 or 16 weeks. 21.2% of refractory patients treated with 6 mg BID of upadacitinib achieved endoscopic remission at 12 or 16 weeks. 29.4% of refractory patients treated with 2 mg BID of upadacitinib achieved endoscopic remission at 12 or 16 weeks. 33.3% of refractory patients treated with 24 mg QD (two 12 mg doses given simultaneously) of upadacitinib achieved endoscopic remission at 12 or 16 weeks.

[0664] The relationship between upadacitinib plasma concentrations and the primary endpoints and certain secondary and additional endpoints is set forth in Figures 3A-3I. Exposure-response relationships were observed for clinical response, clinical remission, CDAI remission (CDAI < 150), endoscopic response, endoscopic improvement, and endoscopic remission.

Safety

[0665] The incident of adverse events was numerically higher (~3-13%) in upadacitinib dose groups, compared to placebo, with no clear dose-relationship. Severe adverse events and treatment

discontinuations due to adverse events were lower/comparable across all upadacitinib dose groups compared to placebo except in the 12 mg BID dose group. There were no treatment emergent deaths in the study. Overall, the incidence of adverse events of special interest were low (except for infections) and similar across all treatment groups. Infections were increased in all upadacitinib BID dose groups compared to placebo. Two adjudicated major adverse cardiac events (MACE) were observed in the 12 mg BID dose group (two had an acute myocardial infarction).

[0666] The relationship between upadacitinib plasma concentration and the change from baseline in hemoglobin levels, anemia, LDL and HDL cholesterol, neutropenia, lymphopenia, and natural killer (NK) cell levels was determined, and the results shown in Figures 5A-5H. Exposure-response relationships for effects of upadacitinib on NK cells, neutrophils, LDL and HDL cholesterol in Crohn's patients were generally consistent with those previously observed in RA patients. Compared to RA patients (data not shown), subjects with Crohn's had lower decreases in hemoglobin (Figure 5A).

Example 9: Model Predicted Efficacy for Once-Daily Doses

[0667] Based on the data obtained in Example 8 for administration of an immediate release (IR) formulation of upadacitinib BID, the exposure-response relationships (simulating for 200 patients/arm) for 15 mg, 30 mg, and 45 mg modified-release QD doses of upadacitinib, for placebo, for 6 mg, 12 mg, 18 mg, and 24 mg IR BID doses of upadacitinib, and for 24 mg IR QD doses of upadacitinib was predicted. The full time-course for the different clinical endpoints was analyzed using Markov analyses. The Marko models allowed transition between response, no response, and dropouts. The models evaluated C_p, C_{ave}, C_{min}, and C_{max} as predictors for drug efficacy. The different endoscopic endpoints at Week 12/16 were analyzed using logistic regression analyses. Then, the models were used to simulate clinical response, clinical remission, CDAI <150, endoscopic response, endoscopic improvement and endoscopic remission at Weeks 12 and 16 (when applicable) for different dose regimens for both the immediate and modified release formulation by back transforming exposures to doses. The results are set forth in Figures 4A-4F.

[0668] This modelling suggests 1-3% improvements in clinical parameters between doses with the MR formulation.

Example 10: Clinical Study for Crohn's Disease: Long-term Efficacy and Safety of Upadacitinib in Moderate to Severe Crohn's Disease

[0669] In Example 10, the extension phase of the Example 8 clinical study was studied and discussed. The trial was a multicenter, randomized, double-blind placebo-controlled study of upadacitinib for the induction of symptomatic and endoscopic remission in patient with moderately to severely active Crohn's disease who have inadequately responded to or are intolerant to immunosuppressants or anti-TNF therapy.

[0670] The trial consisted of a screening period of up to 30 days, a 16 week double blind induction period, re-randomization at week 16, a 36 week double blind and open label phase and a 30 day follow up period.

[0671] Approximately 220 patients with moderately to severely active Crohn's disease – defined for purposes of this study as having 1) Simplified Endoscopic Score for CD (SES-CD)≥6, (or SES-CD≥4 for patients with disease limited to the ileum), 2) a CDAI≥220 and ≤450, and 3) an average daily liquid/soft stool frequency (SF)≥ 2.5 or an average daily abdominal pain (AP) score ≥2.0) – were randomized in a 1:1:1:1:1:1 ratio to one of the schematics of the overall study design shown in Figure 1.

1. Group 1: upadacitinib 3 mg BID capsules (IR)
2. Group 2: upadacitinib 6 mg BID capsules (IR)
3. Group 3: upadacitinib 12 mg BID capsules (IR)
4. Group 4: upadacitinib 24 mg BID capsules (IR)
5. Group 5: upadacitinib 24 mg QD dose (IR) (two 12 mg capsules administered simultaneously)
6. Group 6: Placebo

[0672] The 16 week induction period began at the BL visit (week 0) and ended at the week 16 visit. The randomization at BL was stratified by endoscopic disease severity (SES-CD<15 and ≥15). Safety and efficacy evaluations were performed through the end of the study. The end of the study was defined as the date the last patient completed the last follow up visit.

[0673] At week 16, patients who completed the 16-week induction phases were re-randomised 1:1:1 to double-blind upadacitinib at 3 mg twice daily (BID), 12 mg BID or 24 mg daily (QD) for 36 weeks. A protocol amendment stopped enrolment in the 24 mg QD arm and initiated a 6 mg BID arm. A total of 180 patients were re-randomised to one of four double-blinded doses of upadacitinib:

1. Group 1: upadacitinib 3 mg BID capsules (IR)
2. Group 2: upadacitinib 6 mg BID capsules (IR)
3. Group 3: upadacitinib 12 mg BID capsules (IR)
4. Group 4: upadacitinib 24 mg QD dose (IR) (two 12 mg capsules administered simultaneously)

[0674] The re-randomization was stratified by dose received during the first 16 weeks and overall response (responder versus non-responder) at week 16.

[0675] Each treatment group received the corresponding dose of upadacitinib orally once or twice daily. Patients receiving the 24 mg QD dose were administered two 12 mg capsules simultaneously orally once daily. At week 52, patients were evaluated for clinical remission (average daily SF ≤ 1.5 and not worse than baseline and average daily AP ≤1.0 and not worse than baseline), CDAI <150, modified clinical remission (SF ≤2.8 and AP ≤1.0, both not worse than BL in patients with SF≥4, AP≥2.0 at BL), clinical response (≥ 30% decrease in SF or AP, both not worse than BL), endoscopic remission (SES-CD ≤4 and ≥2-point reduction from BL and no subscore >1) , endoscopic response (SES-CD reduction >50%

from BL or endoscopic remission) and change from BL in C-reactive protein (CRP) and faecal calprotectin (FC).

[0676] The co-primary endpoints for efficacy were the same as the endpoints in Example 8 study.

Methods

[0677] The study comprised two treatment periods: a 16 week double-blind induction period and a 36 week double-blind extension phase. In the induction period, patients with a diagnosis of ileal, colonic, or ileocolonic Crohn's disease for ≥3 months prior to BL and confirmed by endoscopy during the screening period, a CDAI ≥220 and ≤450, and who have inadequately responded to or experienced intolerance to previous treatment with an anti-TNF agent (e.g. infliximab, adalimumab or certolizumab pegol), were assigned to receive one of the following doses of upadacitinib 3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID or 24 mg QD or placebo. The co-primary endpoints were endoscopic remission at week 12 or week 16 and clinical remission at week 16. Secondary endpoints included CDAI< 150 at week 16 and endoscopic response at week 12 or 16. In the extension phase, patients who completed the 16-week induction phases were re-randomised 1:1:1 to double-blind upadacitinib at 3 mg twice daily (BID), 12 mg BID or 24 mg daily (QD) for 36 weeks. A protocol amendment stopped enrolment in the 24 mg QD arm and initiated a 6 mg BID arm. Clinical remission (average daily stool frequency [SF] ≤1.5 and abdominal pain score [AP] ≤1.0, both not worse than Baseline [BL]), CDAI <150, modified clinical remission (SF ≤2.8 and AP ≤1.0, both not worse than BL in patients with SF≥4, AP≥2.0 at BL), clinical response (≥ 30% decrease in SF or AP, both not worse than BL), endoscopic remission (SES-CD ≤4 and ≥2-point reduction from BL and no subscore >1) , endoscopic response (SES-CD reduction >50% from BL or endoscopic remission) and change from BL in C-reactive protein (CRP) and faecal calprotectin (FC) were analysed at week 52 in patients with either both clinical and endoscopic response or clinical response at week 16. Endoscopies were evaluated at BL, 12/16 and 52 weeks by a central reader. Patients who received open label upadacitinib (escape) or prematurely discontinued prior to week 52 were considered non-responders (non-responder imputation). Adverse events were collected throughout the study up to 30 days after the last upadacitinib dose.

[0678] Eligibility, key demographics and BL characteristics of the patients were essentially the the same as those in Example 8 study.

Table 20: Analysis of Primary and Secondary Efficacy Endpoints (Clinical and endoscopic endpoints at Week 52 in the CELEST study)

Endpoint at Week 52	3mg BID N=32	6 mg BID N=14	12 mg BID N=29	24 mg QD[&] N=19
Among subjects who achieved clinical response and endoscopic response at Week 16				
Modified clinical remission[a], n (%)	7 (41.2)[b]	5 (62.5)[b]	11 (73.3)[b]	4 (40.0)[b]

Endoscopic response[c], %	10 (50.0)[d]	4 (50.0)[d]	11 (68.8)[d]	3 (30.0)[d]
Among subjects who achieved clinical response at Week 16				
Modified clinical remission, n (%)	8 (28.6)[e]	6 (42.9)[e]	14 (51.9)[e]	7 (38.9)[e]
Endoscopic response, %	11 (34.4)[f]	5 (35.7)[f]	13 (44.8)[f]	7 (36.8)[f]
Clinical remission[g], n (%)	8 (25)	4 (29)	12 (41)	6 (32)
CDAI <150, % (n)	14 (44)	7 (50)	16 (55)	7 (37)
Enhanced clinical response[h], n (%)	15 (47)	10 (71)	18 (62)	8 (42)
Clinical response[i], n (%)	16 (50)	10 (71)	18 (62)	8 (42)
Endoscopic remission[j], n (%)	5 (16)	3 (21)	7 (24)	5 (26)
Mean change from BL in hs-CRP ± SD	-2.8 ± 18.9	-2.1 ± 18.4	-13.9 ± 37.1	10.2 ± 55.7
Mean change from BL in FC ± SD	1.0 ± 2457.2	-239.3 ± 1443.1	-2617.4 ± 3232.0	-1510.3 ± 2773.9

[&] 24 mg QD dose is two 12 mg doses given simultaneously[a] Modified clinical remission: SF ≤2.8 and AP ≤1.0, both not worse than BL in patients with SF≥4 or AP≥2.0 at BL

[b] For 3, 6, and 12 mg BID and 24 mg QD, n=17, 8, 15, and 10

[c] Endoscopic response: SES-CD reduction >50% from BL or endoscopic remission. in responders and 28, 14, 27, and 18 in clinical responders, respectively

[d] For 3, 6, and 12 mg BID and 24 mg QD, n=20, 8, 16, and 10

[e] For 3, 6, and 12 mg BID and 24 mg QD, n=28, 14, 27, and 18

[f] For 3, 6, and 12 mg BID and 24 mg QD, n=32, 14, 29, and 19

[g] Clinical remission: SF ≤1.5 and AP ≤1.0 and both not worse than BL

[h] Enhanced clinical response: ≥60% reduction from induction BL in SF or ≥35% reduction from induction BL in AP and both not worse than BL or modified clinical remission

[i] Clinical response: ≥30% reduction from BL in SF or ≥30% reduction from BL in AP and both not worse than BL. [j] Endoscopic remission: SES-CD ≤ 4 and at least 2-point reduction from BL and no subscore >1

Results

[0679] Baseline demographics and disease characteristics were similar between study arms. At week 52, endoscopic remission was achieved by 16%, 21%, 24%, and 26% of patients treated with 3 mg BID, 6 mg BID, 12 mg BID, and 24 mg QD, respectively, of upadacitinib. At week 52, clinical remission was achieved by 25%, 29%, 41%, and 32% of patients treated with 3 mg BID, 6 mg BID, 12 mg BID, and 24 mg QD, respectively, of upadacitinib. Results are shown in Table 20.

[0680] Clinical response was achieved at week 52 by 50%, 71%, 62%, and 42 % of patients treated with 3 mg BID, 6 mg BID, 12 mg BID, and 24 mg QD, respectively, of upadacitinib. Enhanced clinical response was achieved at week 52 by 47%, 71%, 62%, and 42 % of patients treated with 3 mg BID, 6 mg BID, 12 mg BID and 24 mg QD, respectively, of upadacitinib. Results are shown in Table 20.

[0681] Among subjects who achieved clinical response and endoscopic response at week 16, endoscopic response was achieved at week 52 by 50.0%, 50.0%, 68.8%, and 30.0% of patients treated with 3 mg BID, 6 mg BID, 12 mg BID, and 24 mg QD, respectively, of upadacitinib. Among subjects who achieved clinical response at week 16, endoscopic response was achieved at week 52 by 34.4%, 35.7%, 44.8%, and 36.8% of patients treated with 3 mg BID, 6 mg BID, 12 mg BID, and 24 mg QD, respectively, of upadacitinib. Results are shown in Table 20. Among subjects who achieved clinical response and endoscopic response at week 16, endoscopic response was achieved at week 52 by 34.4,

35.7, 44.8 and 36.8% of patients treated with 3 mg BID, 6 mg BID, 12 mg BID and 24 mg QD, respectively.

[0682] Among subjects who achieved clinical response and endoscopic response at week 16, modified clinical remission was achieved at week 52 by 41.2%, 62.5%, 73.3%, and 40.0% of patients treated with 3 mg BID, 6 mg BID, 12 mg BID, and 24 mg QD, respectively, of upadacitinib. Among subjects who achieved clinical response at week 16, modified clinical remission was achieved at week 52 by 28.6%, 42.9%, 51.9%, and 38.9% of patients treated with 3 mg BID, 6 mg BID, 12 mg BID, and 24 mg QD, respectively, of upadacitinib. Results are shown in Table 20.

Safety

[0683] The incident of adverse events (AEs) was numerically higher with upadacitinib 3 and 12 mg BID (45 [75.0%] and 43 [72.9%]) than that with 6 mg BID and 24 mg QD (14 [60.9%] and 23 [63.9%]), respectively. Serious AEs were numerically higher with 3 mg BID and infections with 3 and 12 mg BID than that in the other arms. Two malignancies occurred with 12 mg BID.

Conclusion

[0684] Dose-dependent improvements in clinical and endoscopic outcomes and markers of inflammation were observed with 36-week upadacitinib treatment in patients who responded to a 16-week induction regimen. The overall safety profile of upadacitinib is consistent with other studies in rheumatoid arthritis.

Example 11: Clinical Study for Crohn's Disease: Rapidity of Clinical and Laboratory Improvements Following Upadacitinib Induction Treatment

[0685] This analysis evaluates the rapidity of clinical remission, clinical response, and changes in markers of inflammation during the induction phase of the clinical study discussed in Example 8.

Methods

[0686] Adult patients with Crohn's Disease Activity Index (CDAI) 220-450, average daily liquid/very soft stool frequency (SF) ≥2.5 or daily abdominal pain score (AP) ≥2.0, and Simplified Endoscopic Score for CD (SES-CD) ≥6 [or ≥4 for those with isolated ileal disease), were randomized to double-blind therapy with placebo (PBO) or immediate release formulation of upadacitinib at 3, 6, 12, 24 mg twice daily (BID) or 24 mg once daily (QD) for 16 weeks. Patients were randomized at baseline for follow-up ileocolonoscopy at either Week 12 or 16. Proportion of patients with modified clinical remission and enhanced clinical response, both defined in Figure, mean change from baseline in C-reactive protein (CRP) and faecal calprotectin (FC) were assessed over time in all patients unless otherwise mentioned. Comparisons between each upadacitinib dose with PBO was tested by Cochran-

Mantel-Haenszel test stratified by SES-CD at BL. Non-responder imputation was applied to patients who received open-label upadacitinib or prematurely discontinued prior to Week 16 or initiated corticosteroids or had dose increase higher than baseline.

Results

[0687] Baseline demographics and disease characteristics were similar between study arms. A total of 220 patients were enrolled (mean age 40.7±12.9 years, CDAI 302.7±63.4, disease duration 13.2±10.0 years). Overall, patients receiving upadacitinib achieved modified clinical remission as early as week 4 and enhanced clinical response at week 8. Over time, there were sustained clinical improvements in several upadacitinib dosage groups for up to 16 weeks (Figures 10A-10E and Figures 11A-11E). Mean C-reactive protein (CRP) levels significantly decreased in all upadacitinib doses at week 4 and were sustained for up to 16 weeks in the 12 and 24 mg BID and 24 mg QD arms (Figure 12). Statistically significant decrease in mean faecal calprotectin (FC) from baseline was observed with upadacitinib at 12 and 24 mg BID at week 4 and 24 mg BID at week 16.

Conclusions

[0688] Early and significant effects of upadacitinib in clinical parameters were demonstrated in a refractory patient population with active Crohn's disease, concurrent with rapid and sustainable decrease in the markers of inflammation hsCRP and faecal calprotectin.

Example 12: Clinical Study for Ulcerative Colitis

[0689] This trial is a multicenter, randomized, double-blind placebo-controlled study of upadacitinib for the induction and maintenance of clinical remission (using the Mayo Scoring System for Assessment of Ulcerative Colitis Activity, excluding Physician's Global Assessment [i.e., Adapted Mayo score]) in patients with moderately to severely active ulcerative colitis.

[0690] The trial consists of a screening period of up to 35 days, an 8 week double blind induction period (Substudy 1), a second 8 week double blind and open label induction period (Substudy 2), re-randomization at week 8, a 44 week double blind and open label maintenance phase (Substudy 3), and a 30 day follow up period.

[0691] Approximately 250 patients with moderately to severely active ulcerative colitis are randomized in a 1:1:1:1:1 ratio for Substudy 1 to one of the treatment arms of the overall study design shown in Figure 13.

1. Group 1: upadacitinib 7.5 mg QD MR capsules
2. Group 2: upadacitinib 15 mg QD MRcapsules
3. Group 3: upadacitinib 30 mg QD MR capsules
4. Group 4: upadacitinib 45 mg QD MR capsules

5. Group 5: Placebo QD dose

[0692] The first 8 week induction period begins at the BL visit (week 0) and ends at the week 8 visit. Once the 250 randomized patients have completed an 8 week induction, an analysis of efficacy and safety of upadacitinib versus placebo will be performed. Based on this analysis, one induction dose of upadacitinib (Dose A) will be identified for further evaluation in Substudy 2. During the analysis period, approximately 100 additional subjects will continue to be randomized into Groups 3 and 4 of Substudy 1 to receive either 30 mg QD or 45 mg QD treatment (50 patients per dose group).

[0693] Substudy 2 consists of two parts. In Part 1, approximately 375 patients with moderately to severely active ulcerative colitis are randomized in a 2:1 ratio to one of the double-blinded induction treatment arms as shown in Figure 13: upadacitinib Dose A mg QD or placebo QD. Dose A is the dose determined in Substudy 1 for further evaluation. Part 2 of Substudy 2 is open label. Approximately 330 subjects will be enrolled in Part 2 of Substudy 2 to receive open-label upadacitinib Dose A QD. This second 8 week induction period begins at the BL visit (week 0) and ends at the week 8 visit.

[0694] Approximately 450 patients who received the 15, 30 or 45 mg QD of upadacitinib in Substudy 1 and those who received the selected induction dose in Substudy 2 and who also achieved a clinical response (i.e., a decrease from baseline in the Adapted Mayo score $\geq$2 points and $\geq$30% from baseline accompanied by a decrease in RBS$\geq$1 or an absolute RBS $\leq$1) will be re-randomized in the maintenance portion of the study (Substudy 3). This period will begin at the baseline visit (Week 8 of Substudy 1 or Substudy 2) and will end at the Week 44 visit. The treatment assignment in Substudy 3 will depend on the treatment received in Substudies 1 and 2, as follows:

[0695] Placebo: continue placebo

[0696] 7.5 mg QD upadacitinib: continue 7.5 mg QD upadacitinib

[0697] 15 mg QD upadacitinib: randomized 1:1 to receive either upadacitinib 15 mg QD or matching placebo

[0698] 30 mg QD or 45 mg QD upadacitinib: randomized 1:1:1 to receive either upadacitinib 15 mg QD, upadacitinib 30 mg QD, or matching placebo.

[0699] During Substudy 3, subjects who meet the criteria for loss of response after at least 4 weeks of follow up will have the option receive open label upadacitinib. Loss of response is defined as follows: a subject who presents with an stool frequency subscore and RBS score at least 1 point greater than the end-of-induction value (Week 8 of Substudy 1 or 2) on two consecutive visits at least 14 days apart. The schematics of the overall study design are shown in Figure 13.

[0700] The primary endpoints for efficacy for Substudy 1 and Substudy 2 are the proportion of patients who achieve clinical remission per Adapted Mayo score (defined as stool frequency subscore $\leq$ 1, rectal bleeding subscore of 0, and endoscopic subscore $\leq$1) at week 8. The primary efficacy endpoint for Substudy 3 is the proportion of patients who achieve clinical remission per Adapted Mayo score at week 44. Secondary efficacy endpoints for both Substudy 1 and Substudy 2 are:

- endoscopic improvement (defined as endoscopic subscore ≤1)
- achieving Full Mayo score ≤2 with no subscore > 1) at week 8
- Clinical response (i.e., decrease from baseline in the Adapted Mayo score ≥2 points and ≥30% from baseline, plus a decrease in rectal bleeding subscore (RBS) ≥1 or an absolute RBS ≤1) at week 8
- decrease from baseline in the Partial Mayo score ≥2 points and ≥30% from baseline plus a decrease in rectal bleeding subscore (RBS) ≥1 or an absolute RBS ≤1) at week2
- Change in Full Mayo score from Baseline to Week 8
- Endoscopic remission (defined as endoscopic subscore of 0) at Week 8
- Histologic improvement (defined as decrease from baseline in Geboes score) at week 8

[0701] Secondary efficacy endpoints for Substudy 3 maintenance are:

- Endoscopic improvement at week 44
- Full Mayo score ≤2 with no subscore >1) at week 44
- Subjects who discontinued corticosteroid use and achieved clinical remission per Adapted Mayo score at week 44
- Subjects who maintain clinical remission at Week 44 among subjects who achieved clinical remission per Adapted Mayo score in Substudy 1 or 2
- Subjects who are taking corticosteroids at baseline and are corticosteroid-free at week 44
- Subjects with endoscopic improvement at week 44 among subjects who achieved clinical remission in Substudy 1 or 2
- Subjects achieving clinical response (i.e., decrease from baseline in the Adapted Mayo score ≥2 points and ≥30% from baseline accompanied by a decrease in RBS≥1 or an absolute RBS ≤1) at week 44
- Subjects with endoscopic remission at week 44
- Subjects who achieved histologic improvement at week 44

Methods

[0702] The study comprised three treatment periods: Substudy 1 comprising an 8 week double-blind induction period; Substudy 2 comprising two parts: Part 1 is an 8 week double-blind induction period and Part 2 is an 8 week open-label option of the substudy; Substudy 3 evaluates patients from Substudy 1 and Substudy 2 who achieved clinical response.

[0703] Eligible patients are aged 18 to 75 years. They have a diagnosis of ulcerative colitis for 90 days or greater prior to baseline, confirmed by colonoscopy during the screening period, with exclusion of current infection, colonic dysplasia and/or malignancy. Patients have active ulcerative colitis with an Adapted Mayo score of 5 to 9 points and an endoscopic subscore of 2 to 3 at baseline. Eligible

patients are those who have demonstrated an inadequate response to or experienced intolerance to corticosteroids, immunosuppressants and/or biologic therapies, as defined below:

- Corticosteroids:
  - Signs and symptoms of persistently active disease despite a history of at least one induction regimen that included a dose equivalent to prednisone ≥40 mg/day orally for 3 to 4 weeks or intravenously for 1 week or
  - Unable to taper corticosteroids to below a doses equivalent to prednisone 10 mg daily orally without recurrent active disease or
  - History of intolerance to corticosteroids (including, but not limited to Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, infection)
- Immunosuppressants:
  - Signs and symptoms of persistently active disease despite a history of at least one 90-day regimen of oral azathioprine (≥1.5 mg/kg/day; for subjects in Japan and China only: ≥1.0 mg/kg/day), 6-mercaptopurine (≥1 mg/kg/day; for subjects in Japan and China only: ≥0.6 mg/kg/day) or a documents 6-TGN level of 230-450 pmol/8 x 10^8 RBC or higher on the current dosing regimen), injectable methotrexate (MTX≥15 mg/week subcutaneously or intramuscular), or tacrolimus or
  - History of intolerance to at least one immunosuppressant (including, but not limited to nausea/vomiting, abdominal pain, pancreatitis, liver enzyme abnormalities, lymphopenia, infection)
- Biologic agents for UC:
  - Signs and symptoms of persistently active disease despite a history of any of the following:
    - At least one 6-week induction regimen of infliximab (≥5 mg/kg intravenous at 0, 2 and 6 weeks),
    - At least one 4-week induction regimen of adalimumab (one 160 mg subcutaneous dose followed by 80 mg subcutaneous dose [or one 80 mg subcutaneous dose) followed by one 40 mg subcutaneous dose at least 2 weeks apart),
    - At least one 2-week induction regimen of golimumab (one 200 mg subcutaneous dose followed by one 100 mg subcutaneous dose at least two weeks apart),
    - At least one 6-week induction regimen of vedolizumab (300 mg intravenous at 0, 2 and 6 weeks), or
  - Recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify) or
  - History of intolerance to at least one biologic agent (including, but not limited to infusion-related reaction, demyelination, congestive heart failure CHF), infection)

[0704] Oral MTX use is allowed during the study, however prior or current use of oral MTX is not sufficient for inclusion into the study unless these subjects were previously treated with corticosteroids or immunosuppressants (azathioprine or 6-MP) and in the judgment of the investigator have failed to respond to or could not tolerate their treatment.

Examples 13-16: Modified Release Tablets

[0705] Modified release tablets containing either 7.5 mg (Example 13) 15 mg (Example 14), 30 mg (Example 15), or 45 mg (Example 16) of upadacitinib were prepared using a wet granulation process.

[0706] Upadacitinib (hemi-hydrate), microcrystalline cellulose (MCC), and hydroxypropyl methylcellulose (HPMC) were added to a granulator and mixed. Water was sprayed to granulate. The granulated material was then dried and milled using a comill fitted with a 610 micron screen to form a granulate composition containing 25% drug load. The granulate composition is summarized in Table 21.

Table 21: Granulate Composition (25% Drug Load)

Component	Function	Amount in Granulation Composition (%)
Upadacitinib freebase (hemi-hydrate)[1]	Active	25.0%
Microcrystalline cellulose (Avicel® PH 101)	Filler	67.0%
HPMC (Hypromellose 2208)	Release control polymer	8.0%

[1]Upadacitinib used in Examples 13-16 was a hemi-hydrate (Freebase Hydrate Form C, as described herein and in U.S. Patent Application No. 15/295,561). As used herein, the amount of upadacitinib present in the Examples 13-16 formulations refers to the amount of upadacitinib freebase equivalent provided by the hemi-hydrate.

[0707] The granulation composition was combined with the remaining formulation components other than magnesium stearate, and sieved using a comill fitted with a 1397 micron screen, followed by blending. The magnesium stearate was then added to the bin and blended. The lubricated granulation was compressed into tablets using a rotary tablet press. The tablets were coated using a film coater, which sprayed a solution containing the Opadry® II Yellow film coat and purified water until the desired amount of coating had been applied to the tablets.

[0708] The formulations of the tablets are set forth in Table 22.

Table 22: Modified Release Tablets

Component	Function	Ex. 13 (mg)	Ex. 14 (mg)	Ex. 15 (mg)	Ex. 16 (mg)
Tablet Core					
Granulation composition (25% drug load)	Active	30.7[1]	61.4[2]	122.8[3]	184.3[4]
Microcrystalline cellulose (Avicel® PH 102)	Filler	149.5	121.3	64.8	8.3
Mannitol (Pearlitol® 100SD)	Filler	100.6	100.6	100.6	100.6

Component	Function	Ex. 13 (mg)	Ex. 14 (mg)	Ex. 15 (mg)	Ex. 16 (mg)
Tartaric acid (crystalline or powder)	pH modifier	96.0	96.0	96.0	96.0
HPMC (Hypromellose 2208)	Release control polymer	93.5	91.1	96.2	81.3
Colloidal silicon dioxide	Glidant	2.4	2.4	2.4	2.4
Magnesium stearate	Lubricant	7.2	7.2	7.2	7.2
Uncoated weight of tablet		479.9	480.0	480.0	480.1
Opadry® II Yellow	Film coat	14.4	14.4	14.4	14.4
Purified Water[5]	Processing aid	n/a	n/a	n/a	n/a
Total weight of tablet		494.3	494.4	494.4	494.5

[1]Provides 7.5 mg of upadacitinib freebase equivalent.

[2]Provides 15 mg of upadacitinib freebase equivalent.

[3]Provides 30 mg of upadacitinib freebase equivalent.

[4]Provides 45 mg of upadacitinib freebase equivalent.

[5]Processing aid removed during coating.

Example 17: Observed Steady State Exposures for 15 mg Modified Release Tablets and 6 mg Immediate Release Capsules Under Fasting Conditions

[0709] The steady state pharmacokinetic profile of a 15 mg once daily modified release (MR) tablet (comprising upadacitinib hemi-hydrate) under fasting conditions was evaluated, and compared to that of a 6 mg immediate release (IR) twice daily (BID) capsule comprising upadacitinib (tartrate tetrahydrate) as the active. The 15 mg MR tablet had the following formulation set forth in Table 23.

Table 23: 15 mg Modified Release Tablet

Component	Function	Amount (mg) (ER7)
Upadacitinib (hemi-hydrate)[1]	Active	15.4
Microcrystalline cellulose (Avicel® PH 102)	Filler	162.4
Mannitol (Pearlitol® 100 SD)	Filler	52.6
Tartaric acid	pH modifier	144.0
HPMC (Hypromellose 2208)	Release control polymer	96.0
Colloidal silicon dioxide	Glidant	2.4
Magnesium stearate impalpable powder	Lubricant	7.2
Uncoated weight of tablet		480.0
Opadry® II Yellow (PVA based)	Film coat	14.40
Total weight of tablet		494.39

[1]Upadacitinib was a hemi-hydrate (Freebase Hydrate Form C, as described herein and in U.S. Patent Application No. 15/295,561). The hemi-hydrate provides about 15 mg of upadacitinib freebase equivalent.

[0710] The tablet was prepared by first milling the tartaric acid through a Fitz mill Model M5A, fitted with a 1512-0027 screen. The upadacitinib hemi-hydrate, microcrystalline cellulose, mannitol (when present), milled tartaric acid, release control polymer, and colloidal silicone dioxide (when present) were combined and blended. The blend was milled using a Mobil Mill fitted with a 610 or 1397 micron screen. The magnesium stearate was screened through mesh #30 and was then added to the bin and

blended. The lubricated granulation was compressed into about 480 mg weight tablets using a rotary tablet press. The tablet was coated using a film coater, which sprayed a solution containing the Opadry® II Yellow film coat and purified water until 14.40 mg of coating had been applied to the tablets.

[0711] Healthy human subjects were assigned to one of two regimens under fasting conditions in a randomized, two-period, cross-over study design. Subjects in Regimen K (n=12 at onset; n=11 on Day 7) were administered the 6 mg IR capsule twice daily for seven days under fasting conditions. Subjects in Regimen L (n=12) were administered the 15 mg MR tablet once daily for seven days under fasting conditions. On days one and seven, serial blood samples were collected from each subject prior to the daily dosing and up to 24 hours after dosing. Blood samples were also collected at 48, 72, 96 and 120 hours after initial dosing. Upon collection, the samples were promptly placed in an ice bath, and within 2 hours after sample collection they were centrifuged at about 4°C. The resulting plasma samples were placed in clean polypropylene-tubes and stored in a freezer until analysis. The plasma samples were assayed for upadacitinib using appropriate liquid chromatography mass spectrometry procedures. Pharmacokinetic parameters were estimated using non-compartmental methods, and summary statistics were computed for each parameter by regimen.

[0712] The results are summarized in Table 24. The mean plasma concentration of upadacitinib at each time point measured for each of the two regimens is set forth in Figure 7.

Table 24: Mean (%CV)[e] Pharmacokinetic Parameters for Upadacitinib Following Administration of 6 mg BID (IR) Capsules and 15 mg QD (MR) Tablets for Seven Days (Fasting Conditions)

PK Parameter	Units	Regimen K (6 mg IR Capsules (BID))		Regimen L (15 mg MR Tablet (QD))	
		Day 1	Day 7	Day 1	Day 7
C_{max}	ng/mL	36.5 (25)	33.9 (26)	31.7 (40)	31.9 (35)
T_{max}[a]	hours	1.0 (1.0 – 13)	1.0 (0.5 – 14)	3.0 (1.5 – 6.0)	2.5 (1.5– 4.0)
AUC_{24}	ng•h/mL	289 (21)	288 (22)	249 (29)	279 (26)
C_{12}	ng/mL	2.0 (30)	2.8 (24)	--	--
C_{24}	ng/mL	3.2 (36)	3.6 (23)	1.9 (42)	3.1 (37)
C_{min}	ng/mL	--	2.7 (26)	--	3.1 (37)
Fluctuation Index	%	303 (13)	259 (13)	299 (22)	246 (21)
$t_{1/2}$[b]	hours	--	14.7 (77)	--	10.3 (76)
C_{max} to C_{24} ratio[a]	---	12 (7.7 – 19)	8.8 (7.4 – 13)	22 (5.8 – 43)	12 (4.2 -20)
C_{max} to C_{min} ratio[a]	---	--	13 (8.3 – 18)	--	12 (4.2–20)
AUC_{24}/Dose	(ng•h/mL)/mg	24.8 (23)	24.0 (22)	16.6 (29)	18.6 (26)
R_{AUC}[c]	---	--	1.02 (0.88 – 1.09)	--	1.11 (0.87 – 1.99)
R_{Cmax}[d]	---	--	0.97 (0.68 – 1.17)	--	1.01 (0.65 – 3.01)

[a] – Median (minimum-maximum)

[b] – Harmonic mean (pseudo-%CV)

[c] – R_{AUC} = AUC_{24}Day7/AUC_{24}Day 1; median (range)

[d] – R_{Cmax} = C_{max}Day 7/C_{max}Day 1; median (range)

[e] – Data in parentheses is the coefficient of variance of the PK parameter (% CV), unless otherwise indicated

[0713] The relative bioavailability for the once-daily (MR) tablet formulation (Regimen L) relative to the twice daily (IR) capsule formulation (Regimen K) at steady state was also determined based on analysis of the natural logarithms of C_{max}, AUC_{24}, C_{min}, and C_{24}. The results are summarized in Table 25 below.

Table 25: Relative Bioavailability Estimates and 90% Confidence Intervals for 15 mg QD Tablets Relative to 6 mg BID Capsules at Steady State under Fasting Conditions

	Relative Bioavailability	
PK Parameter	**Point Estimate**	**90% Confidence Interval**
C_{max}	0.909	0.736 - 1.122
AUC_{24}	0.939	0.837 - 1.053
C_{min}	1.090	0.852 - 1.395

[0714] The ratio of steady-state AUC for the 15 mg QD tablets relative to the 6 mg BID capsules was approximately 1, with the 90% confidence intervals within the equivalence boundaries. The ratio of the steady-state C_{min} was approximately 1 for the 15 mg QD tablet relative to the 6 mg BID capsules.

[0715] As can be seen from this data, at steady state under fasting conditions, the 15 mg QD tablets provided equivalent AUC_{24} and comparable C_{max} and C_{min} relative to the 6 mg BID capsules. The steady state C_{max} was 10% lower for the 15 mg QD tablet compared to the 6 mg BID capsule.

Example 18: Observed Steady State Exposures for 30 mg Modified Release Tablets and 12 mg Immediate Release Capsules Under Fasting Conditions

[0716] The steady state pharmacokinetic profile of a 30 mg once daily modified release (MR) tablet (comprising upadacitinib hemi-hydrate) under fasting conditions was evaluated, and compared to that of a 12 mg immediate release (IR) twice daily (BID) capsule comprising upadacitinib (tartrate tetrahydrate) as the active. The 30 mg MR tablet had the following formulation set forth in Table 26.

Table 26: 30 mg Modified Release Tablet

Component	**Function**	**Amount (mg) (ER8)**
Upadacitinib (hemi-hydrate)[1]	Active	30.7
Microcrystalline cellulose (Avicel® PH 102)	Filler	147.1
Mannitol (Pearlitol® 100 SD)	Filler	52.6
Tartaric acid	pH modifier	144.0
HPMC (Hypromellose 2208)	Release control polymer	96.0
Colloidal silicon dioxide	Glidant	2.4
Magnesium stearate impalpable powder	Lubricant	7.2

Uncoated weight of tablet		480.0
Opadry® II Yellow (PVA based)	Film coat	14.40
Total weight of tablet		494.43

[1]Upadacitinib was a hemi-hydrate (Freebase Hydrate Form C, as described in U.S. Patent Application No. 15/295,561). The hemi-hydrate provides about 30 mg of upadacitinib freebase equivalent.

[0717] The tablet was prepared by first milling the tartaric acid through a Fitz mill Model M5A, fitted with a 1512-0027 screen. The upadacitinib hemi-hydrate, microcrystalline cellulose, mannitol (when present), milled tartaric acid, release control polymer, and colloidal silicone dioxide (when present) were combined and blended. The blend was milled using a Mobil Mill fitted with a 610 or 1397 micron screen. The magnesium stearate was screened through mesh #30 and was then added to the bin and blended. The lubricated granulation was compressed into about 480 mg weight tablets using a rotary tablet press. The tablet was coated using a film coater, which sprayed a solution containing the Opadry® II Yellow film coat and purified water until 14.40 mg of coating had been applied to the tablets.

[0718] Healthy human subjects were assigned to one of two regimens under fasting conditions in a randomized, two-period, cross-over study design. Subjects in Regimen M (n=11) were administered the 12 mg IR capsule twice daily for seven days under fasting conditions. Subjects in Regimen N (n=12 at onset; n=11 at Day 7) were administered the 30 mg MR tablet once daily for seven days under fasting conditions. On days one and seven, serial blood samples were collected from each subject prior to the daily dosing and up to 24 hours after dosing. Blood samples were also collected at 48, 72, 96 and 120 hours after initial dosing. Upon collection, the samples were promptly placed in an ice bath, and within 2 hours after sample collection they were centrifuged at about 4°C. The resulting plasma samples were placed in clean polypropylene-tubes and stored in a freezer until analysis. The plasma samples were assayed for upadacitinib using appropriate liquid chromatography mass spectrometry procedures. Pharmacokinetic parameters were estimated using non-compartmental methods, and summary statistics were computed for each parameter by regimen.

[0719] The results are summarized in Table 27. The mean plasma concentration of upadacitinib at each time point measured for each of the two regimens is set forth in Figure 8.

Table 27: Mean (%CV)[e] Pharmacokinetic Parameters for Upadacitinib Following Administration of 12 mg BID (IR) Capsules and 30 mg QD (MR) Tablets for Seven Days (Fasting Conditions)

PK Parameter	**Units**	**Regimen M (12 mg IR Capsules (BID))**		**Regimen N (30 mg MR Tablet (QD))**	
		Day 1	**Day 7**	**Day 1**	**Day 7**
	ng/mL	80.8 (23)	73.9 (19)	65.7 (22)	68.2 (30)
T_{max}[a]	hours	1.0 (0.5 – 13)	1.0 (0.5 – 1.5)	2.5 (1.5 – 4.0)	3.0 (2.0 – 4.0)
AUC_{24}	ng•h/mL	497 (15)	534 (18)	454 (23)	525 (23)
C_{12}	ng/mL	3.0 (46)	4.1 (55)	--	--
C_{24}	ng/mL	6.5 (54)	6.9 (37)	2.8 (37)	4.4 (39)
C_{min}	ng/mL	--	3.8 (58)	--	3.8 (43)
Fluctuation Index	%	388 (15)	317 (14)	349 (12)	291 (17)

$t_{1/2}$[b]	hours	--	7.3 (60)	--	14.4 (64)
C_{max} to C_{24} ratio[a]	---	15 (5.4 – 20)	12 (5.9 – 16)	29 (13 – 38)	17 (4.1 – 33)
C_{max} to C_{min} ratio[a]	---	--	19 (8.4 – 31)	--	17 (11 – 37)
AUC_{24}/Dose	(ng•h/mL)/mg	21.1 (15)	22.3 (18)	15.1 (22)	17.5 (23)
R_{AUC}[c]	---	--	1.08 (0.97 – 1.18)	--	1.11 (0.79 – 1.67)
R_{Cmax}[d]	---	--	0.98 (0.65 – 1.18)	--	1.03 (0.40 – 1.82)

[a] – Median (minimum-maximum)

[b] – Harmonic mean (pseudo-%CV)

[c] – R_{AUC} = AUC_{24}Day7/AUC_{24}Day 1; median (range)

[d] – R_{Cmax} = C_{max}Day 7/C_{max}Day 1; median (range)

[e] – Data in parentheses is the coefficient of variance of the PK parameter (% CV), unless otherwise indicated

[0720] The relative bioavailability for a single dose of the once-daily (MR) tablet formulation (Regimen N) relative to the twice daily (IR) capsule formulation (Regimen M) was also determined based on analysis of the natural logarithms of C_{max}, AUC_{24}, C_{min}, and C_{24}. The results are summarized in Table 28 below.

Table 28: Relative Bioavailability Estimates and 90% Confidence Intervals for 30 mg QD Tablets Relative to 12 mg BID Capsules at Steady State under Fasting Conditions

	Relative Bioavailability	
PK Parameter	**Point Estimate**	**90% Confidence Interval**
C_{max}	0.900	0.732 - 1.107
AUC_{24}	0.974	0.869 - 1.092
C_{min}	0.874	0.747 - 1.022

[0721] The ratio of steady-state AUC for the 30 mg QD tablets relative to the 12 mg BID capsules was approximately 1, with the 90% confidence intervals within the equivalence boundaries. The steady-state C_{min} for the 30 mg QD tablet was approximately 13% lower than for the 12 mg BID capsules. Outliers with high C_{min} in the 12 mg BID dose may have contributed to this difference.

[0722] As can be seen from this data, at steady state under fasting conditions, the 30 mg QD tablets provided equivalent AUC_{24} and comparable C_{max} and C_{min} relative to the 12 mg BID capsules. The steady state C_{max} was 10% lower for the 30 mg QD tablet compared to the 12 mg BID capsules.

[0723] This written description uses examples to disclose the invention, including the best mode, and also to enable any person skilled in the art to practice the invention, including making and using any devices or systems and performing any incorporated methods. The patentable scope of the invention is defined by the claims, and may include other examples that occur to those skilled in the art. Such other examples are intended to be within the scope of the claims if they have structural elements that

do not differ from the literal language of the claims, or if they include equivalent structural elements with insubstantial differences from the literal languages of the claims.

WHAT IS CLAIMED IS:

1. A method of inducing clinical remission of ulcerative colitis in an adult patient having moderately to severely active ulcerative colitis, the method comprising orally administering to the patient a 45 mg induction dose of upadacitinib once a day for 8 weeks, wherein the patient achieves clinical remission per Adapted Mayo score at 8 weeks after the administration of the initial said 45 mg induction dose of upadacitinib; and administering a first maintenance dose of 15 mg or 30 mg upadacitinib to the patient after the last induction dose is administered, and administering at least one additional maintenance dose of 15 mg or 30 mg upadacitinib to the patient once daily thereafter, whereby the clinical remission is maintained.

2. The method of claim 1, wherein the patient has had an inadequate response or intolerance to conventional therapy.

3. The method of claim 2, wherein the conventional therapy comprises an aminosalicylate, corticosteroid or immunosuppressant.

4. The method of claim 1, wherein the patient has had an inadequate response or intolerance to biologic therapy.

5. The method of claim 4, wherein the biologic therapy comprises an anti-TNF agent.

6. A method of inducing endoscopic improvement of ulcerative colitis in an adult patient having moderately to severely active ulcerative colitis, the method comprising orally administering to the patient a 45 mg induction dose of upadacitinib once a day for 8 weeks, wherein the patient achieves endoscopic improvement at 8 weeks after the administration of the initial said 45 mg induction dose of upadacitinib; and administering a first maintenance dose of 15 mg or 30 mg upadacitinib to the patient after the last induction dose is administered, and administering at least one additional maintenance dose of 15 mg or 30 mg upadacitinib to the patient once daily thereafter, whereby the endoscopic improvement is maintained.

7. The method of claim 6, wherein the patient has had an inadequate response or intolerance to conventional therapy.

8. The method of claim 7, wherein the conventional therapy comprises an aminosalicylate, corticosteroid or immunosuppressant.

9. The method of claim 6, wherein the patient has had an inadequate response or intolerance to biologic therapy.

10. The method of claim 9, wherein the biologic therapy comprises an anti-TNF agent.

11. A method of inducing histologic-endoscopic mucosal remission of ulcerative colitis in an adult patient having moderately to severely active ulcerative colitis, the method comprising orally administering to the patient a 45 mg induction dose of upadacitinib once a day for 8 weeks, wherein the patient achieves histologic-endoscopic mucosal remission at 8 weeks after the administration of the initial said 45 mg induction dose of upadacitinib; and administering a first maintenance dose of 15 mg or 30 mg upadacitinib to the patient after the last induction dose is administered, and administering at least one additional maintenance dose of 15 mg or 30 mg upadacitinib to the patient once daily thereafter, whereby the histologic-endoscopic mucosal remission is maintained.

12. The method of claim 11, wherein the patient has had an inadequate response or intolerance to conventional therapy.

13. The method of claim 12, wherein the conventional therapy comprises an aminosalicylate, corticosteroid or immunosuppressant.

14. The method of claim 11, wherein the patient has had an inadequate response or intolerance to biologic therapy.

15. The method of claim 14, wherein the biologic therapy comprises an anti-TNF agent.

16. A method of inducing clinical response of ulcerative colitis in an adult patient having moderately to severely active ulcerative colitis, the method comprising orally administering to the patient a 45 mg induction dose of upadacitinib once a day for 16

weeks, wherein the patient achieves clinical response at 16 weeks after the administration of the initial said 45 mg induction dose of upadacitinib; and administering a first maintenance dose of 15 mg or 30 mg upadacitinib to the patient after the last induction dose is administered, and administering at least one additional maintenance dose of 15 mg or 30 mg upadacitinib to the patient once daily thereafter, whereby the clinical response is maintained.

17. The method of claim 16, wherein the patient has had an inadequate response or intolerance to conventional therapy.

18. The method of claim 17, wherein the conventional therapy comprises an aminosalicylate, corticosteroid or immunosuppressant.

19. The method of claim 16, wherein the patient has had an inadequate response or intolerance to biologic therapy.

20. The method of claim 19, wherein the biologic therapy comprises an anti-TNF agent.

21. A method of inducing clinical response of ulcerative colitis in an adult patient having moderately to severely active ulcerative colitis, the method comprising:

a) orally administering to the patient a 45 mg induction dose of upadacitinib once a day for 8 weeks;

b) evaluating the patient for clinical response at 8 weeks after the administration of the initial said 45 mg induction dose of upadacitinib, and if the patient has not achieved clinical response per Adapted Mayo score at 8 weeks after the administration of the initial said 45 mg induction dose of upadacitinib;

c) continuing to orally administer to the patient a 45 mg dose of upadacitinib once a day for an additional 8 weeks, wherein the patient achieves clinical response per Adapted Mayo score at 16 weeks after the administration of the initial said 45 mg induction dose of upadacitinib; and

d) administering a first maintenance dose of 15 mg or 30 mg upadacitinib to the patient after the last induction dose is administered, and administering at least one additional maintenance dose of 15 mg or 30 mg upadacitinib to the patient once daily thereafter, whereby the clinical response is maintained.

22. The method of claim 21, wherein the patient has had an inadequate response or intolerance to conventional therapy.

23. The method of claim 22, wherein the conventional therapy comprises an aminosalicylate, corticosteroid or immunosuppressant.

24. The method of claim 21, wherein the patient has had an inadequate response or intolerance to biologic therapy.

25. The method of claim 24, wherein the biologic therapy comprises an anti-TNF agent.

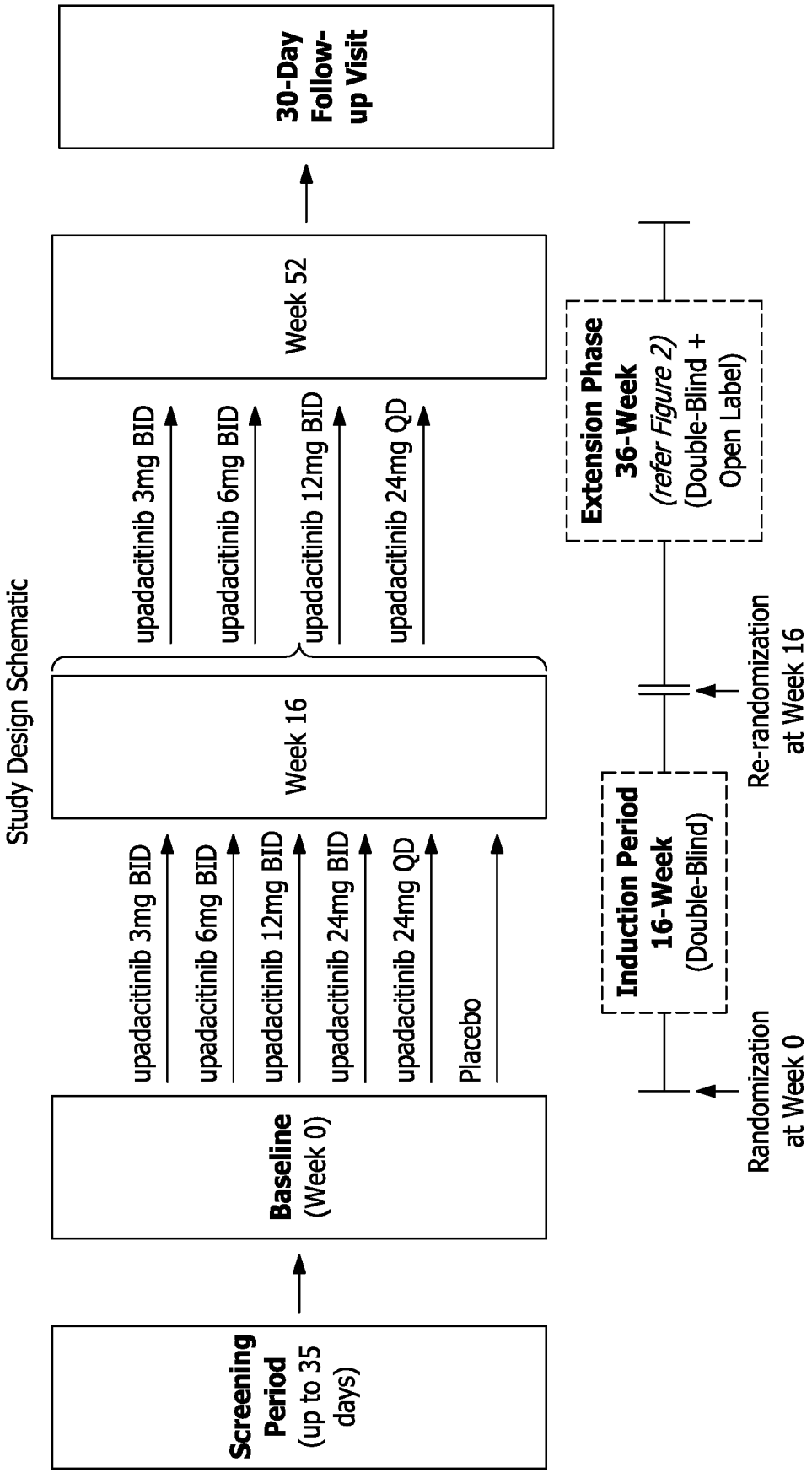

Study Design Schematic
Screening Period (up to 35 days)
Baseline (Week 0)
upadacitinib 3mg BID
upadacitinib 6mg BID
upadacitinib 12mg BID
upadacitinib 24mg BID
upadacitinib 24mg QD
Placebo
Week 16
upadacitinib 3mg BID
upadacitinib 6mg BID
upadacitinib 12mg BID
upadacitinib 24mg QD
Week 52
30-Day Follow-up Visit
Randomization at Week 0
Induction Period 16-Week (Double-Blind)
Re-randomization at Week 16
Extension Phase 36-Week (refer Figure 2) (Double-Blind + Open Label)

FIG. 1

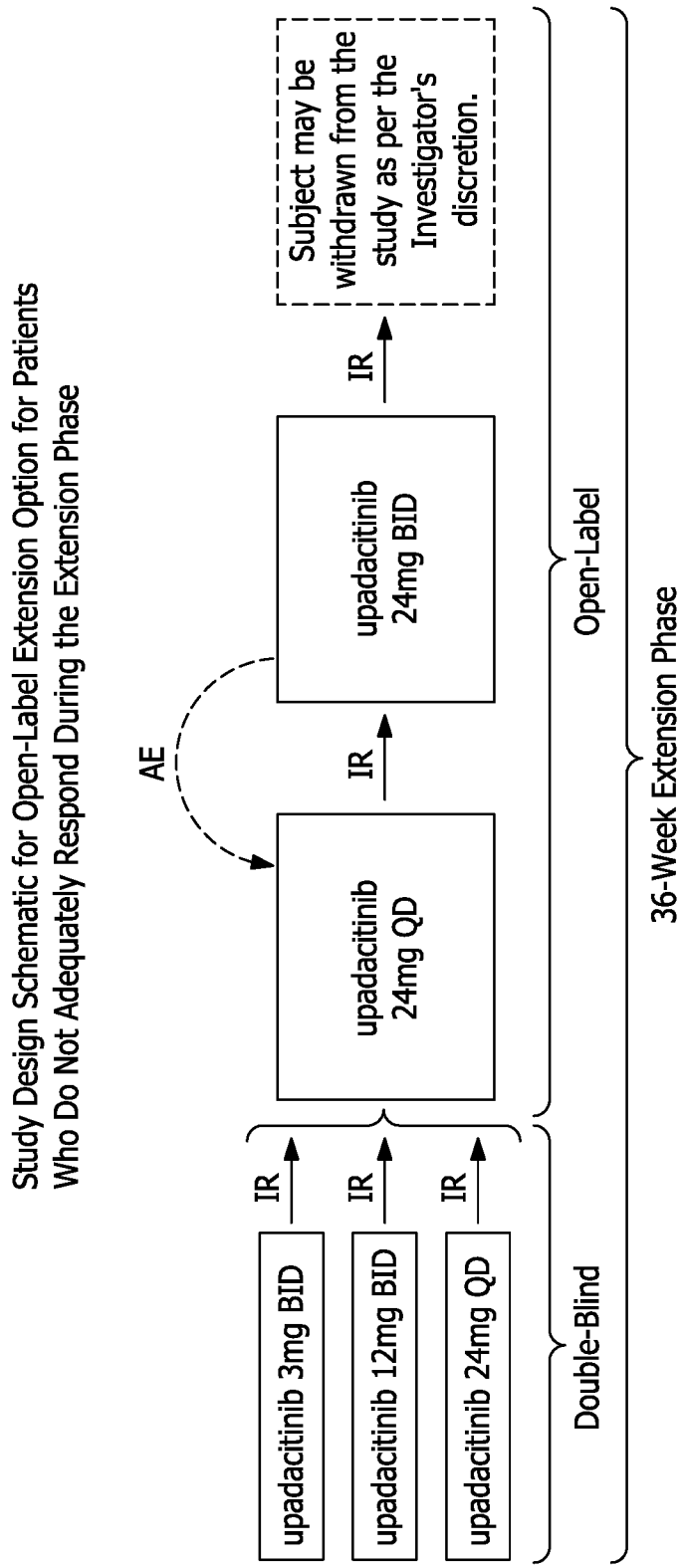

Study Design Schematic for Open-Label Extension Option for Patients Who Do Not Adequately Respond During the Extension Phase
upadacitinib 3mg BID
upadacitinib 12mg BID
upadacitinib 24mg QD
IR
IR
IR
upadacitinib 24mg QD
upadacitinib 24mg BID
AE
IR
Subject may be withdrawn from the study as per the Investigator's discretion.
Double-Blind
Open-Label
36-Week Extension Phase
IR: Inadequate Response

FIG. 2

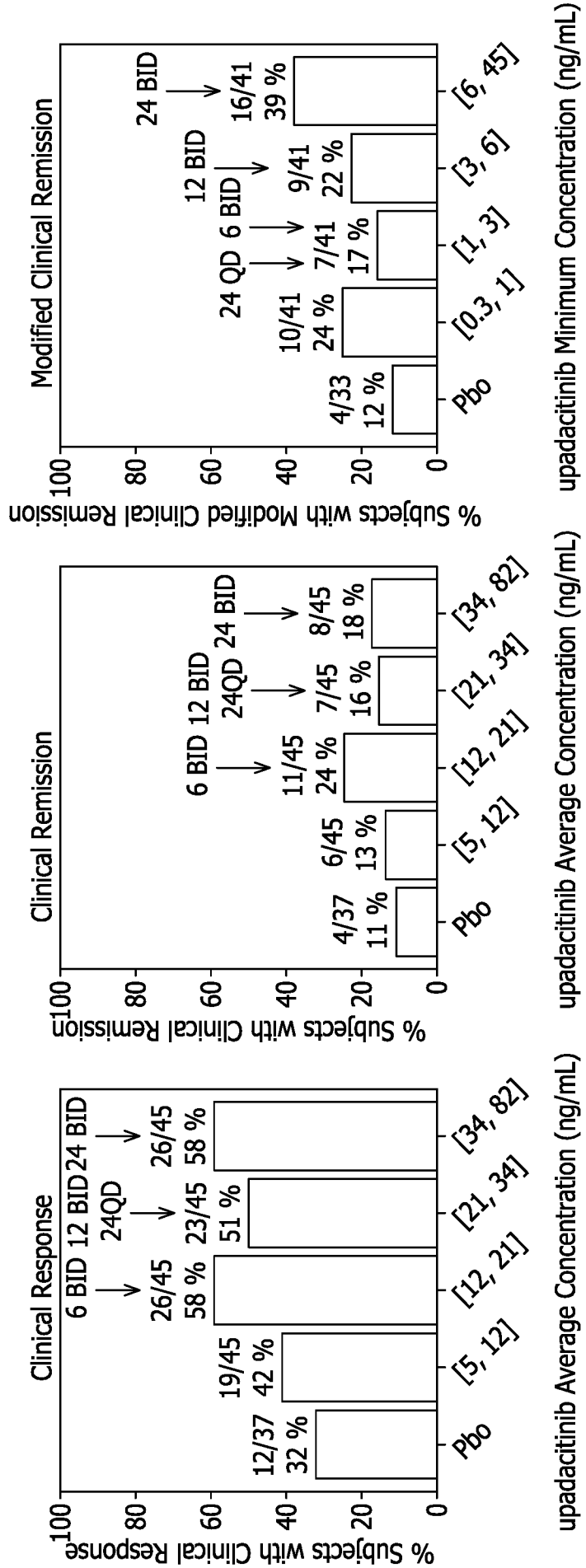


FIG. 3A FIG. 3B FIG. 3C

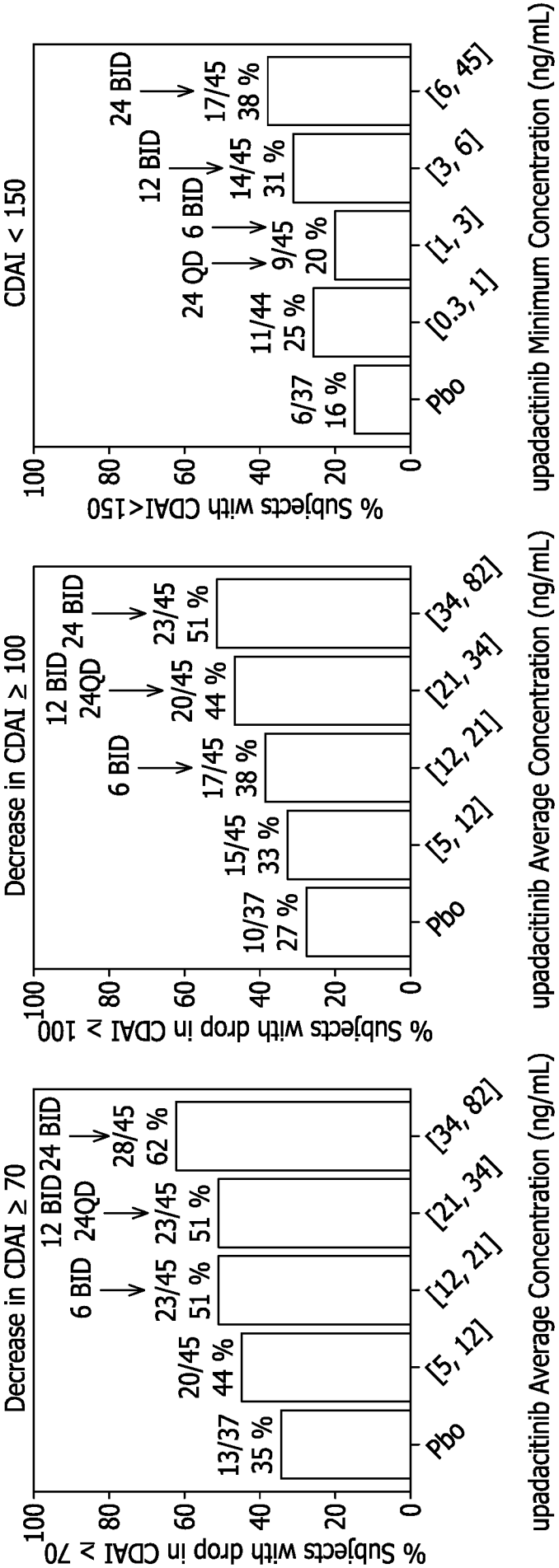


FIG. 3D FIG. 3E FIG. 3F

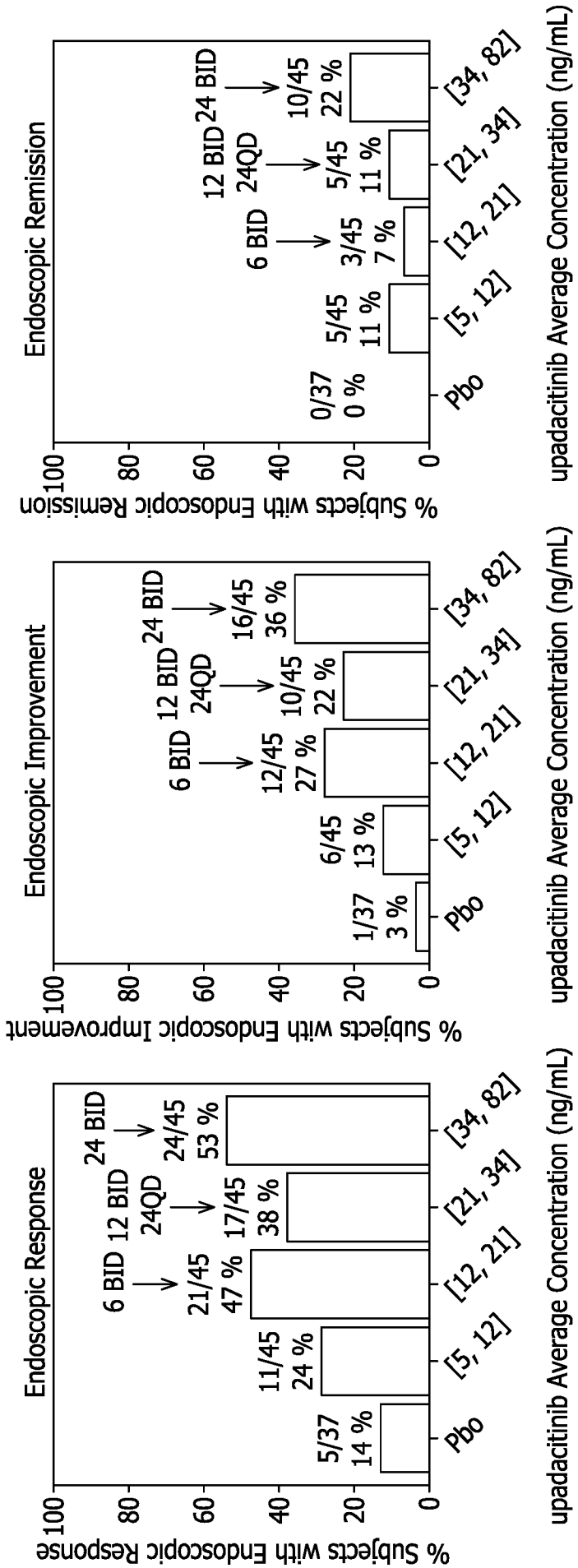


FIG. 3G

FIG. 3H

FIG. 3I

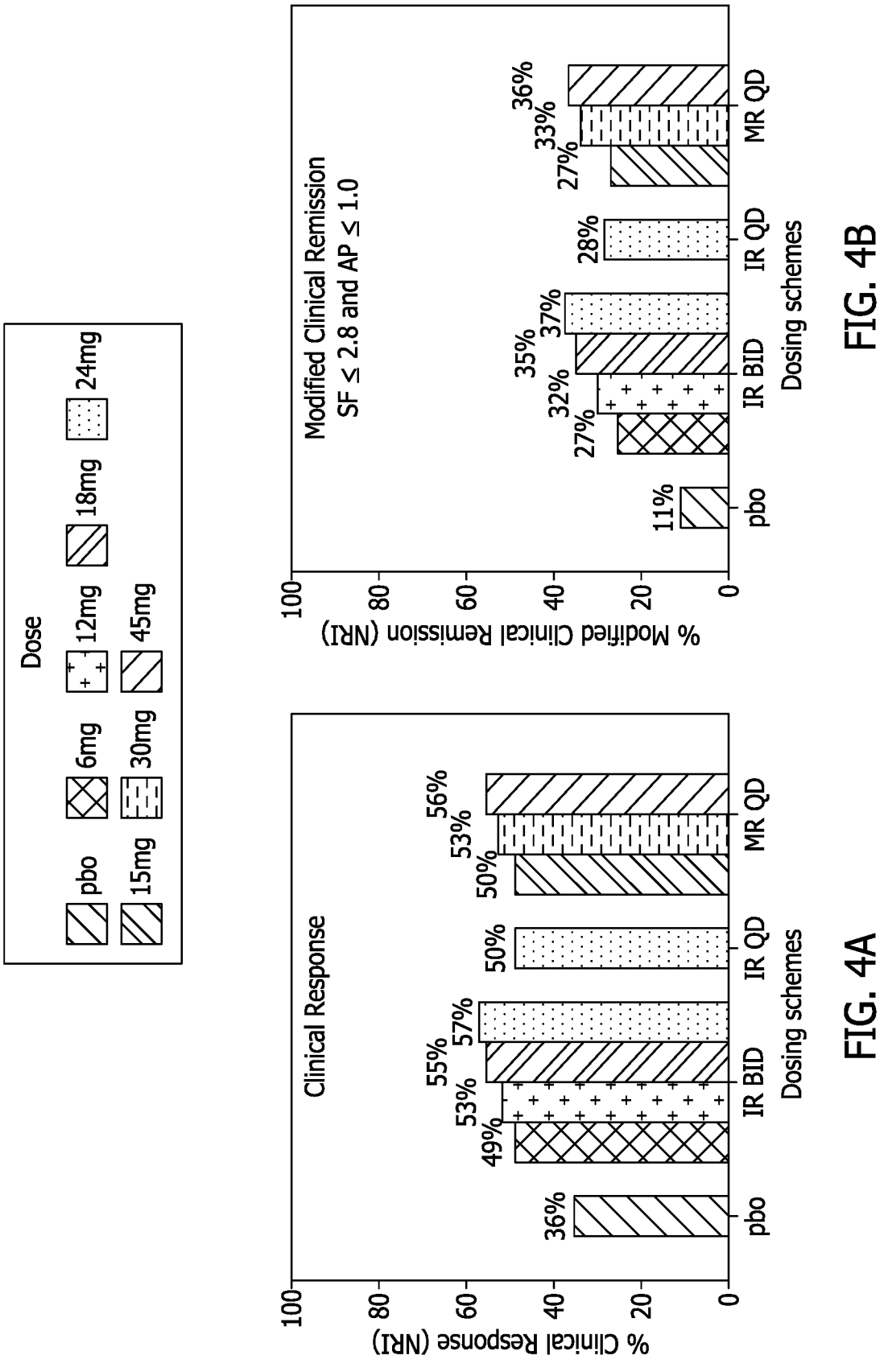

Dose
pbo
6mg
12mg
18mg
24mg
15mg
30mg
45mg
Clinical Response
% Clinical Response (NRI)
100
80
60
40
20
0
36%
49%
53%
55%
57%
50%
50%
53%
56%
pbo
IR BID
IR QD
MR QD
Dosing schemes
Modified Clinical Remission
SF ≤ 2.8 and AP ≤ 1.0
% Modified Clinical Remission (NRI)
11%
27%
32%
35%
37%
28%
27%
33%
36%

FIG. 4A

FIG. 4B

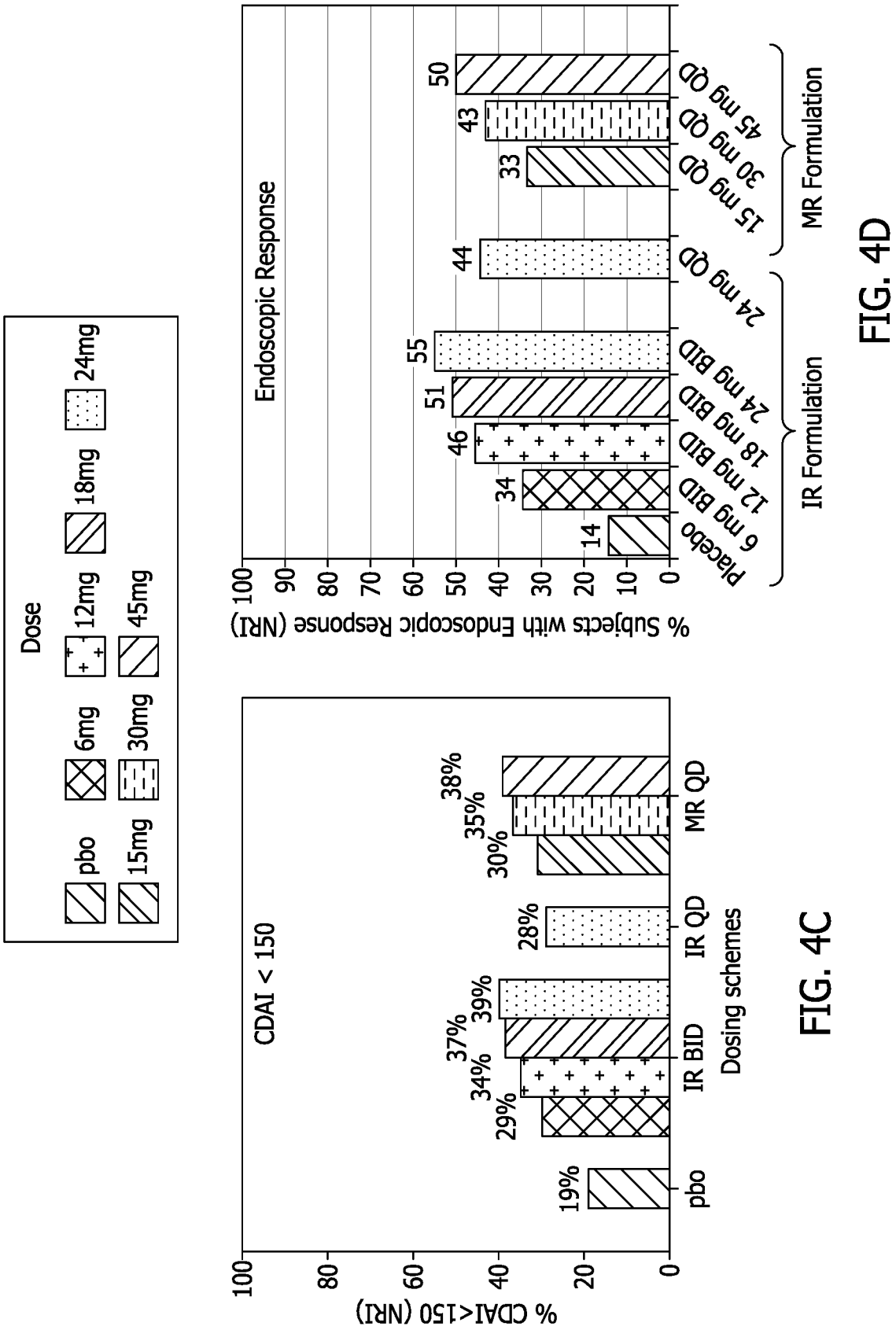

Dose
pbo
6mg
12mg
18mg
24mg
15mg
30mg
45mg
% CDAI<150 (NRI)
CDAI < 150
19%
29%
34%
37%
39%
28%
30%
35%
38%
pbo
IR BID
IR QD
MR QD
Dosing schemes
% Subjects with Endoscopic Response (NRI)
Endoscopic Response
14
34
46
51
55
44
33
43
50
Placebo
6 mg BID
12 mg BID
18 mg BID
24 mg BID
24 mg QD
15 mg QD
30 mg QD
45 mg QD
IR Formulation
MR Formulation

FIG. 4C

FIG. 4D

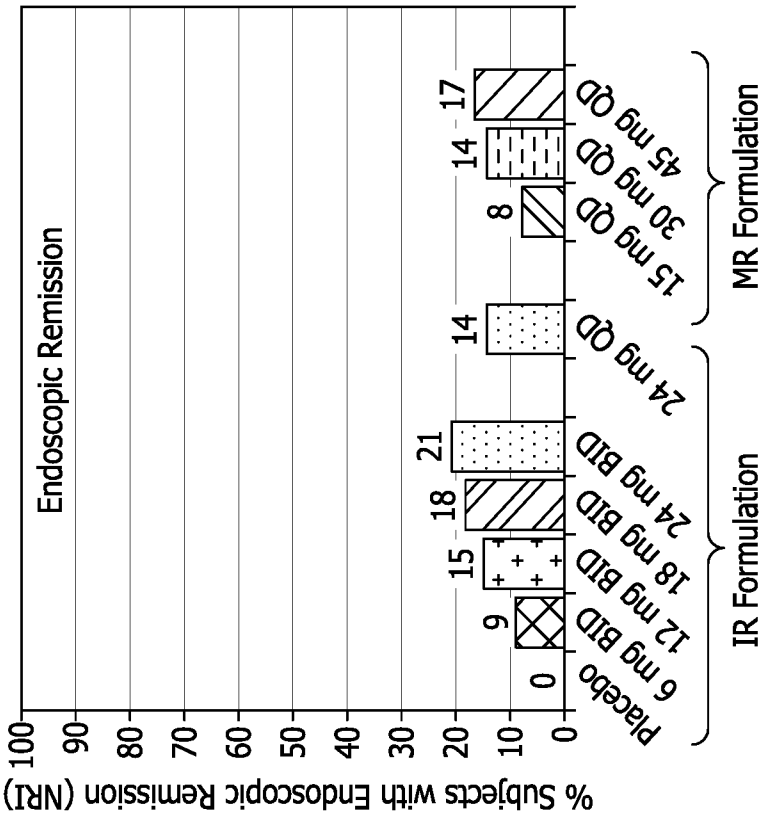

% Subjects with Endoscopic Remission (NRI)
Endoscopic Remission
0
10
20
30
40
50
60
70
80
90
100
Placebo
6 mg BID
12 mg BID
18 mg BID
24 mg BID
24 mg QD
15 mg QD
30 mg QD
45 mg QD
0
9
15
18
21
14
8
14
17
IR Formulation
MR Formulation

FIG. 4F

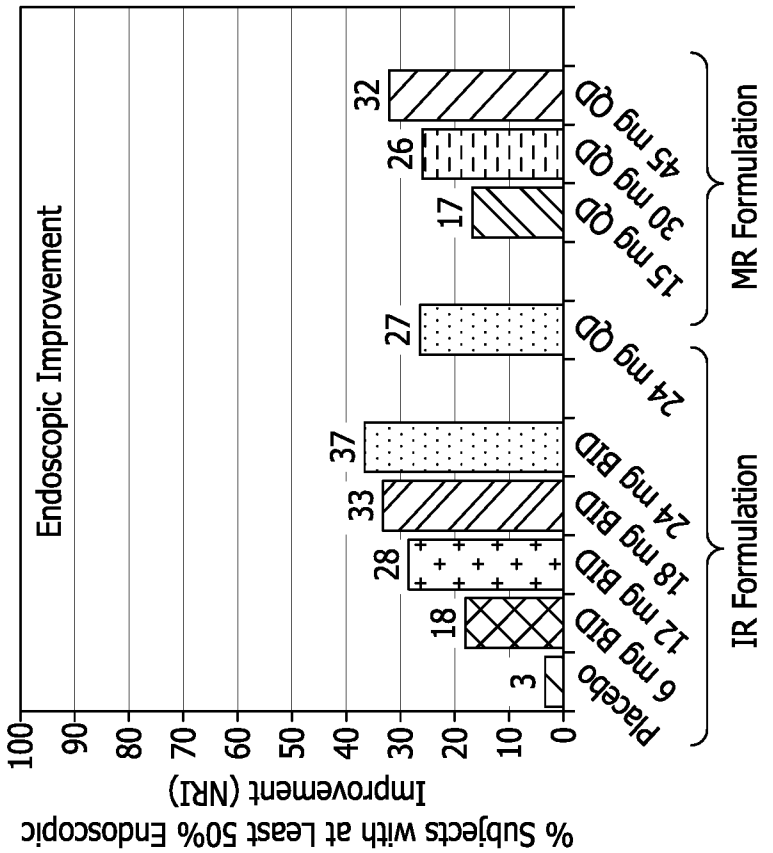

% Subjects with at Least 50% Endoscopic Improvement (NRI)
Endoscopic Improvement
0
10
20
30
40
50
60
70
80
90
100
Placebo
6 mg BID
12 mg BID
18 mg BID
24 mg BID
24 mg QD
15 mg QD
30 mg QD
45 mg QD
3
18
28
33
37
27
17
26
32
IR Formulation
MR Formulation

FIG. 4E

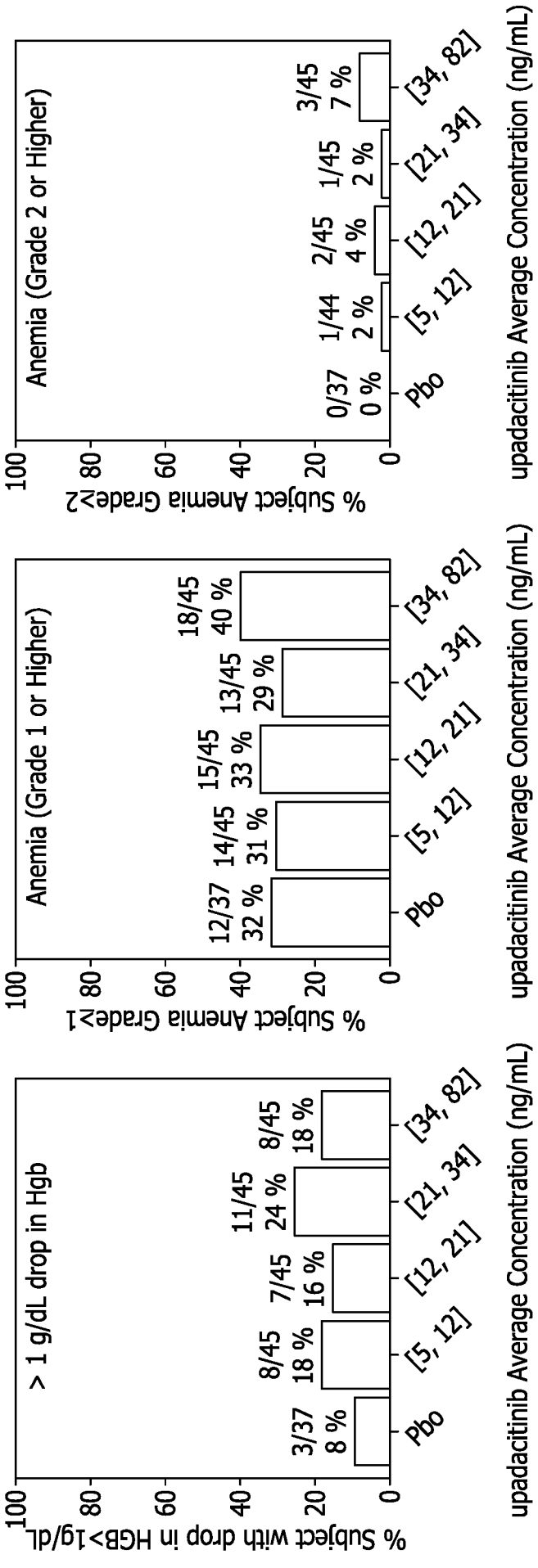


FIG. 5A

FIG. 5B

FIG. 5C

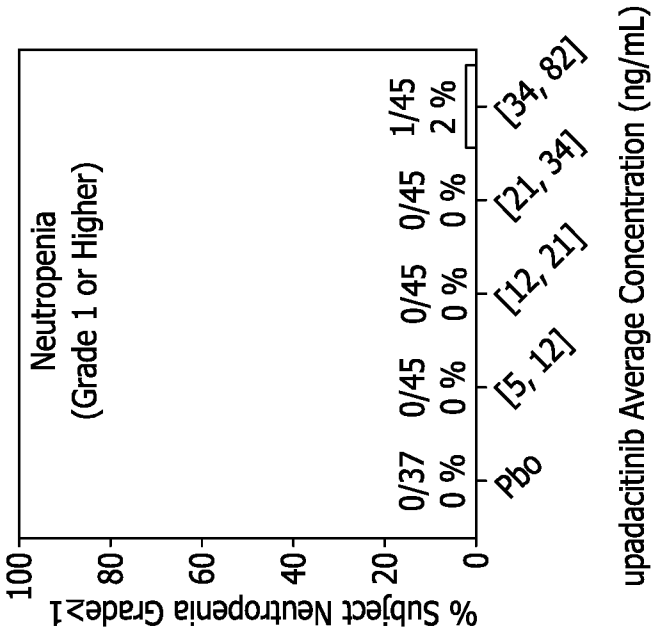


FIG. 5F

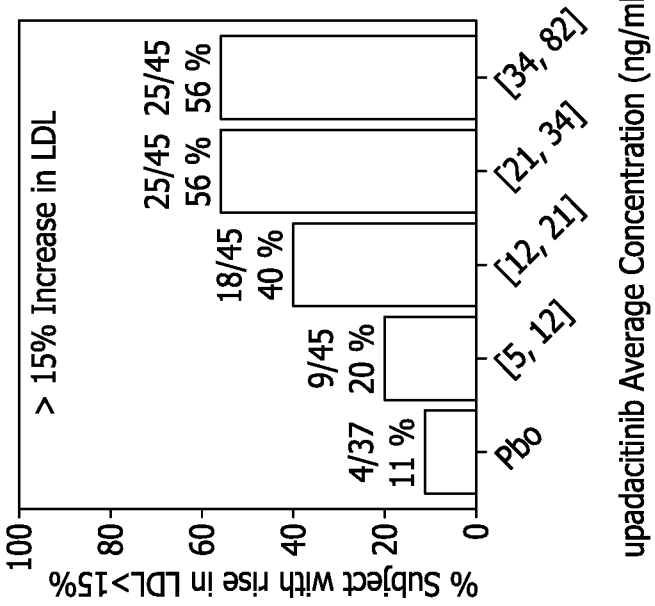


FIG. 5E

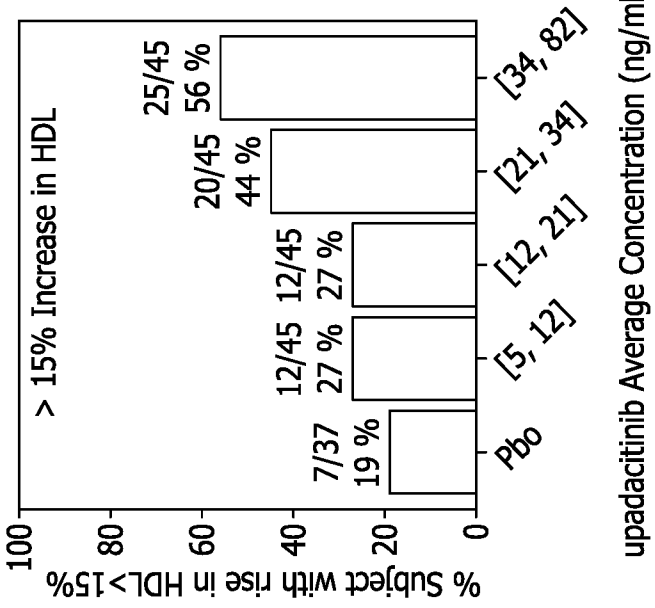


FIG. 5D

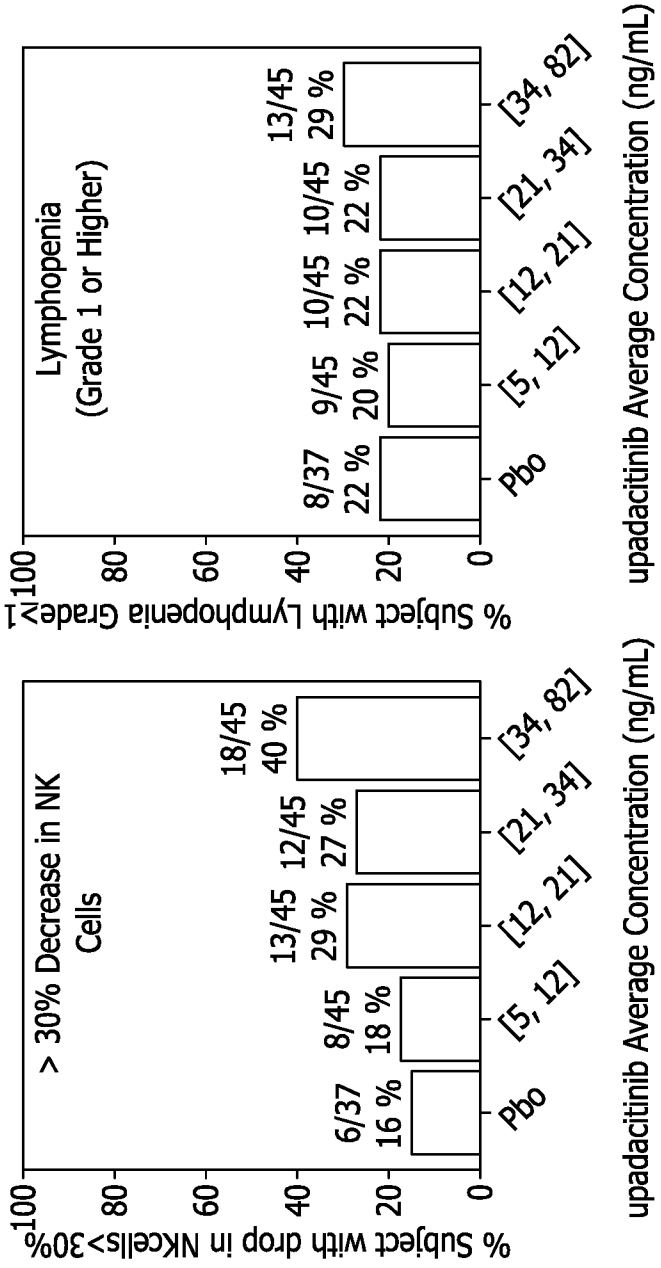

> 30% Decrease in NK Cells
% Subject with drop in NKcells>30%
100
80
60
40
20
0
6/37
16 %
8/45
18 %
13/45
29 %
12/45
27 %
18/45
40 %
Pbo
[5, 12]
[12, 21]
[21, 34]
[34, 82]
upadacitinib Average Concentration (ng/mL)
Lymphopenia
(Grade 1 or Higher)
% Subject with Lymphopenia Grade≥1
8/37
22 %
9/45
20 %
10/45
22 %
10/45
22 %
13/45
29 %
Pbo
[5, 12]
[12, 21]
[21, 34]
[34, 82]
upadacitinib Average Concentration (ng/mL)

FIG. 5G

FIG. 5H

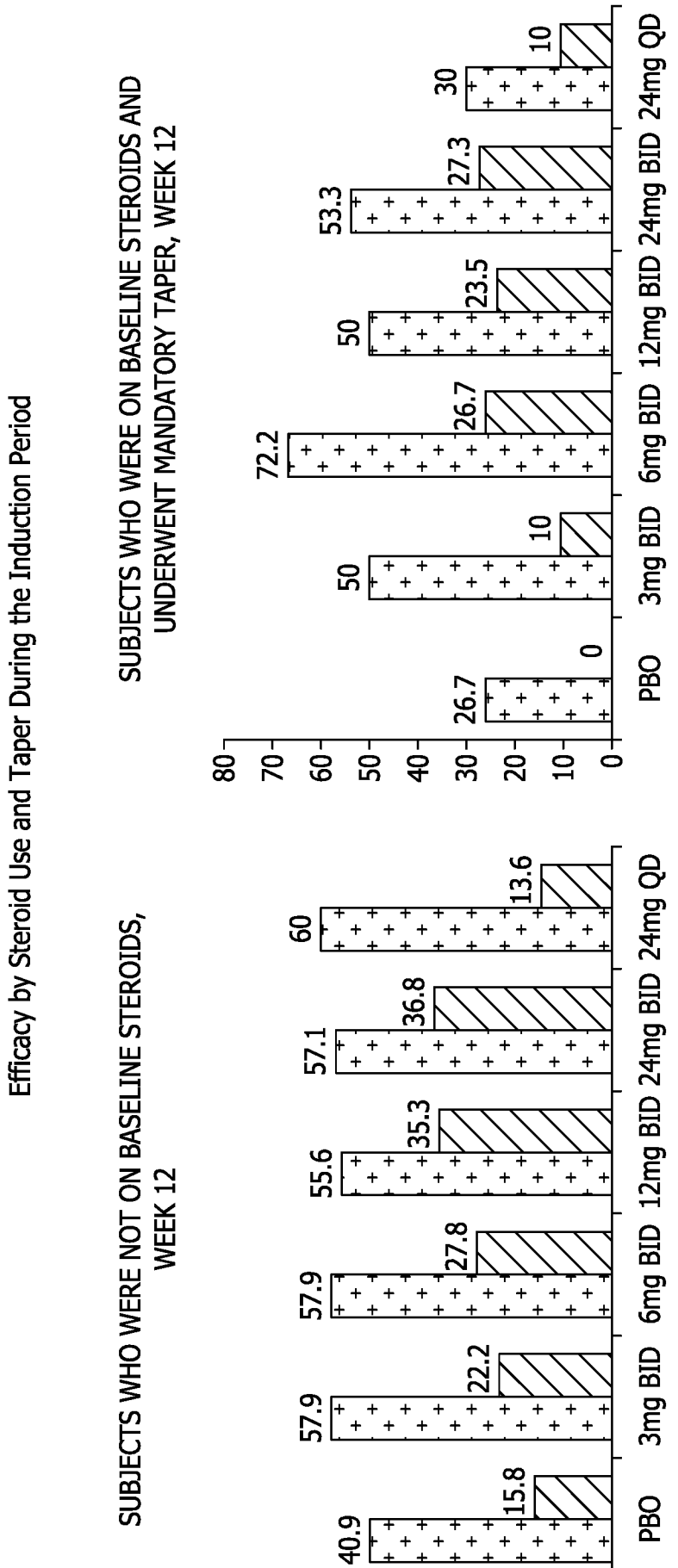

Efficacy by Steroid Use and Taper During the Induction Period
SUBJECTS WHO WERE NOT ON BASELINE STEROIDS, WEEK 12
SUBJECTS WHO WERE ON BASELINE STEROIDS AND UNDERWENT MANDATORY TAPER, WEEK 12
Clinical Response
Clinical Remission
PBO
3mg BID
6mg BID
12mg BID
24mg BID
24mg QD
40.9
15.8
57.9
22.2
57.9
27.8
55.6
35.3
57.1
36.8
60
13.6
26.7
0
50
10
72.2
26.7
50
23.5
53.3
27.3
30
10

FIG. 6A

FIG. 6B

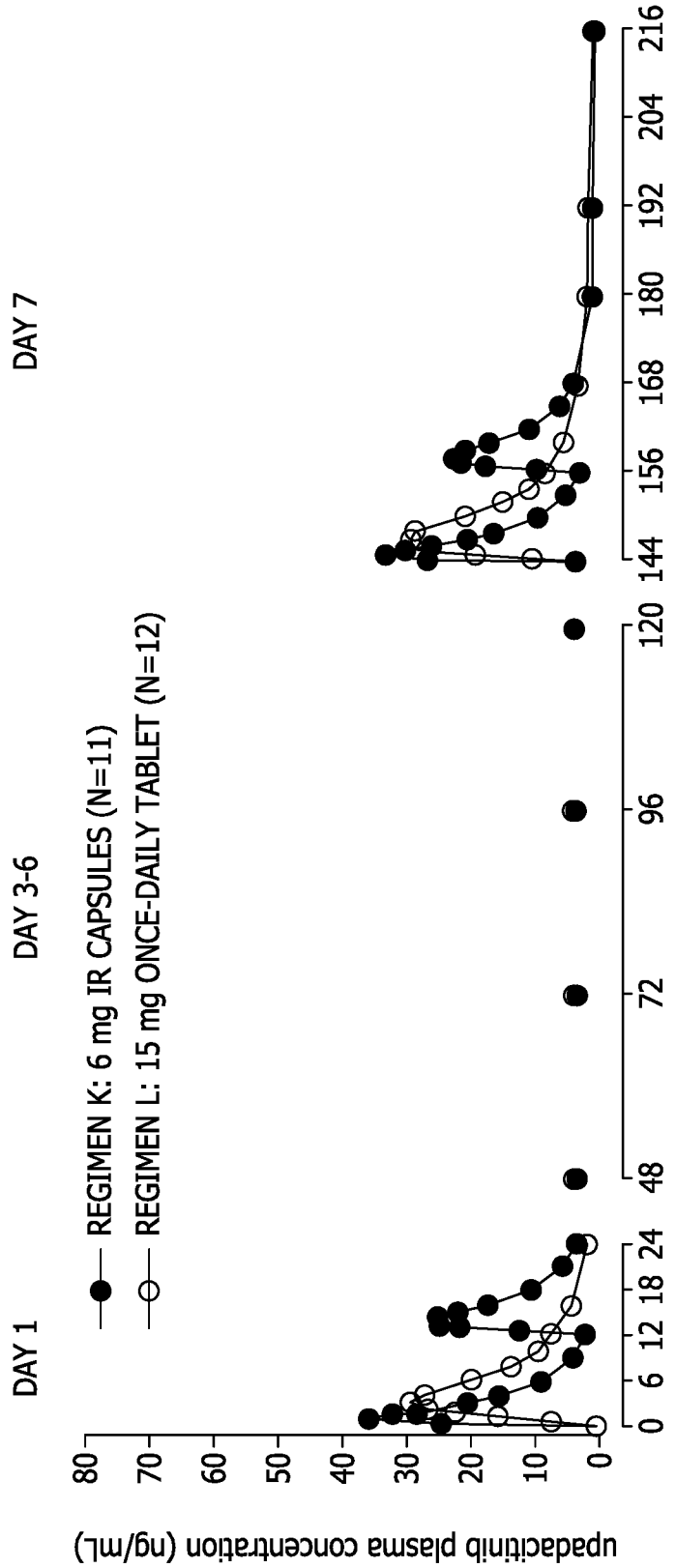

DAY 1
DAY 3-6
DAY 7
REGIMEN K: 6 mg IR CAPSULES (N=11)
REGIMEN L: 15 mg ONCE-DAILY TABLET (N=12)
upadacitinib plasma concentration (ng/mL)
0
10
20
30
40
50
60
70
80
0
6
12
18
24
48
72
96
120
144
156
168
180
192
204
216
TIME (hr)

FIG. 7

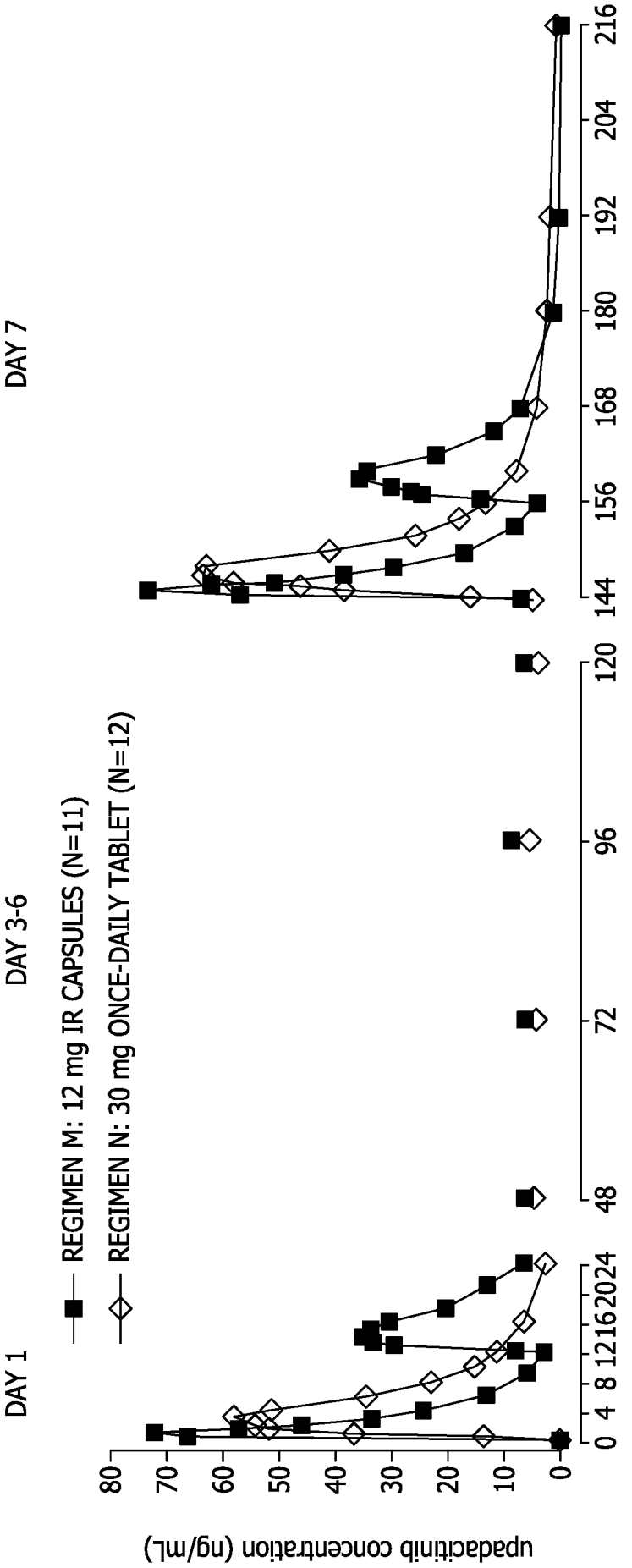

upadacitinib concentration (ng/mL)
80
70
60
50
40
30
20
10
0
DAY 1
DAY 3-6
DAY 7
REGIMEN M: 12 mg IR CAPSULES (N=11)
REGIMEN N: 30 mg ONCE-DAILY TABLET (N=12)
0 4 8 12 16 20 24
48
72
96
120
144
156
168
180
192
204
216
TIME (hr)

FIG. 8

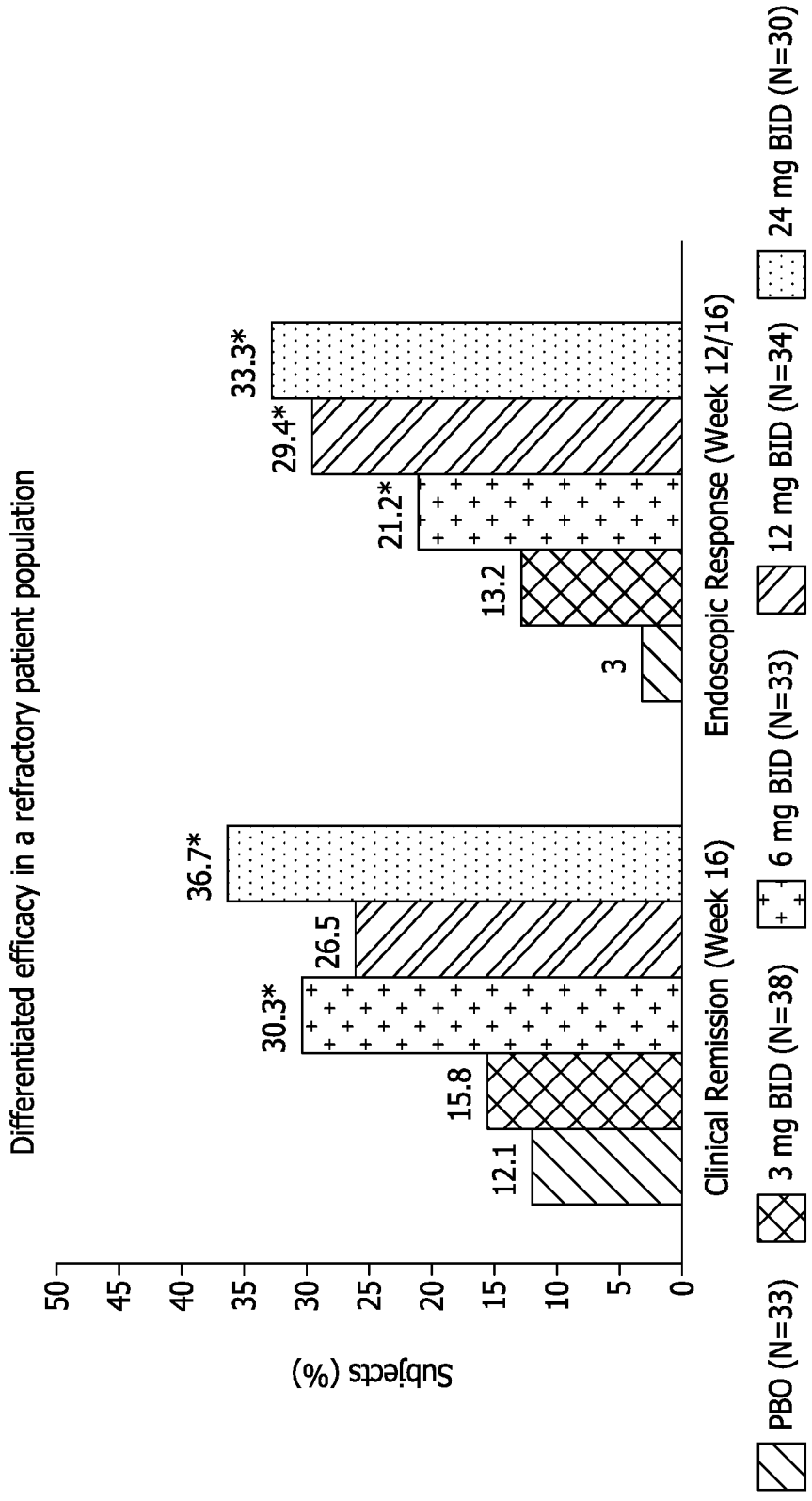

Differentiated efficacy in a refractory patient population
Subjects (%)
50
45
40
35
30
25
20
15
10
5
0
12.1
15.8
30.3*
26.5
36.7*
3
13.2
21.2*
29.4*
33.3*
Clinical Remission (Week 16)
Endoscopic Response (Week 12/16)
PBO (N=33)
3 mg BID (N=38)
6 mg BID (N=33)
12 mg BID (N=34)
24 mg BID (N=30)
*Statistically significant at 2-sided alpha of 0.10

FIG. 9

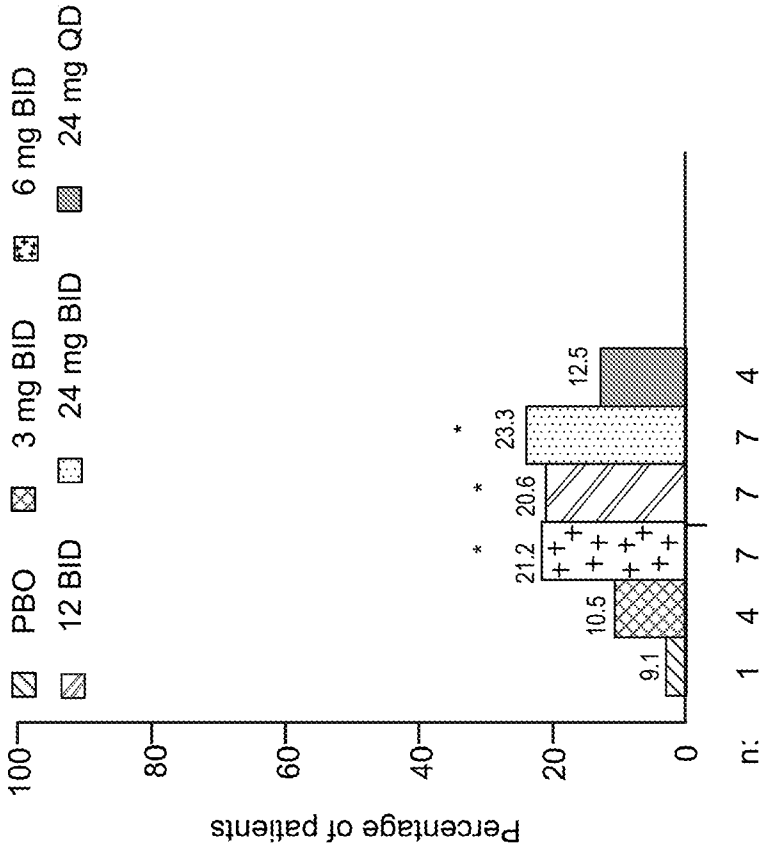


FIG. 10B

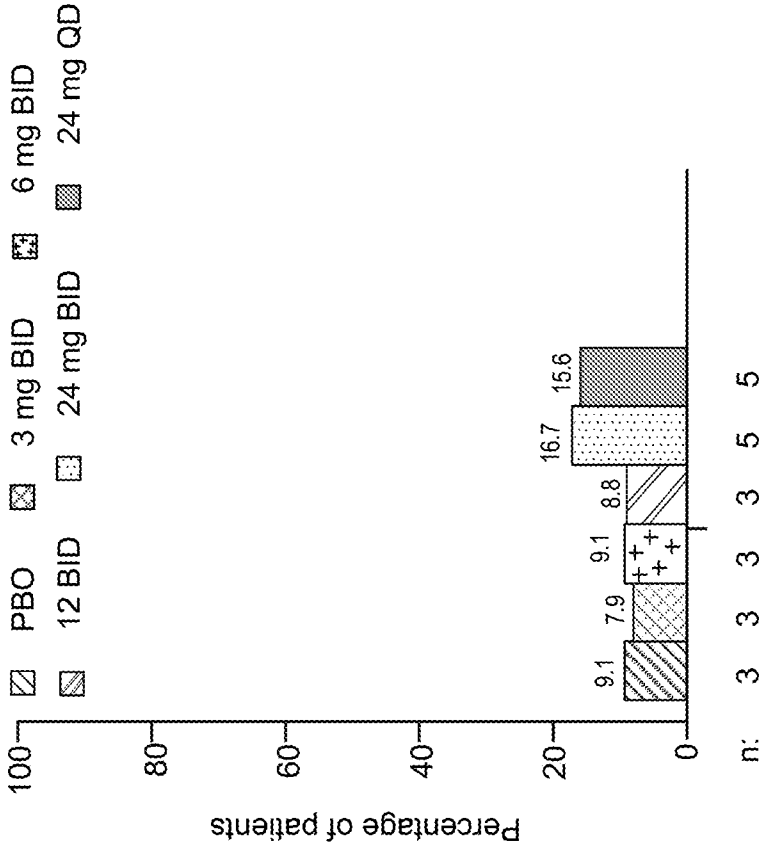
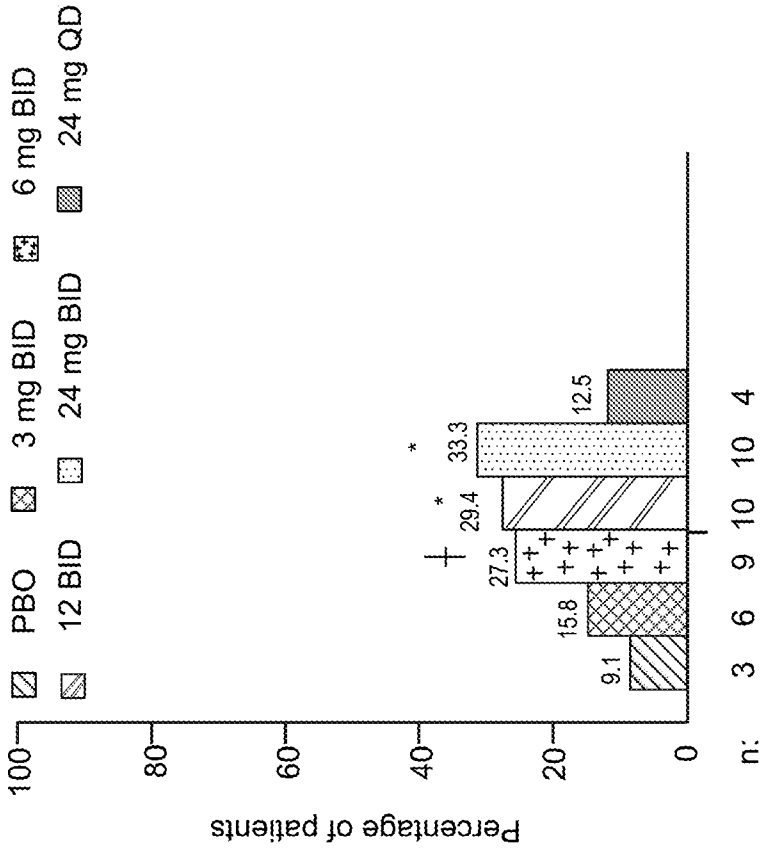
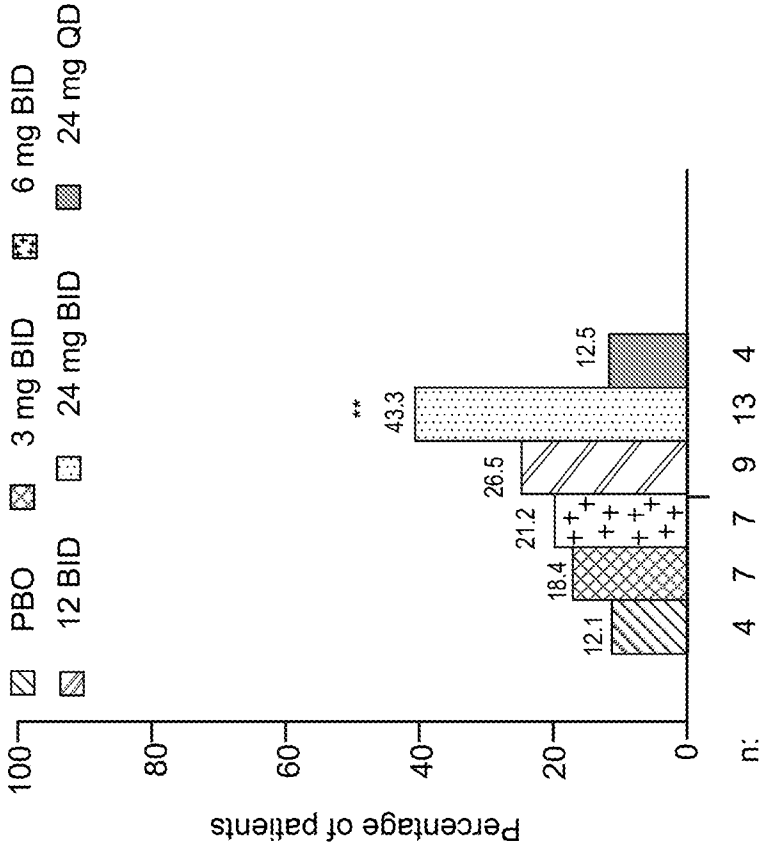


FIG. 10A



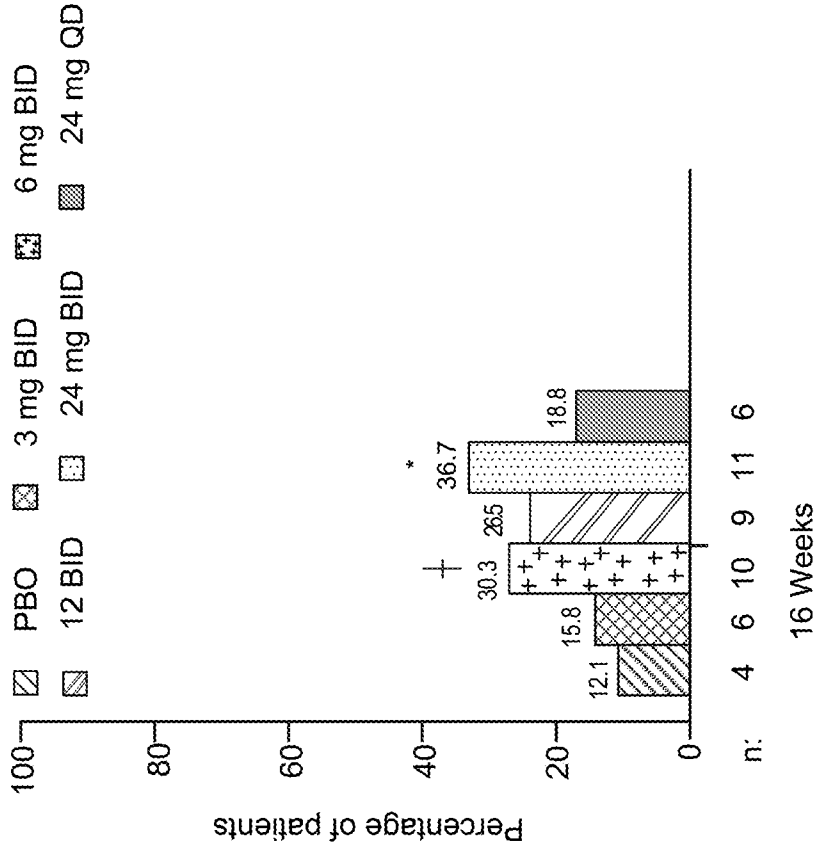
*, † statistically significant at ≤0.05, and ≤0.1 level

FIG. 10D



** statistically significant at ≤0.01 level

FIG. 10C



*, † statistically significant at ≤0.05, and ≤0.1 level

FIG. 10E

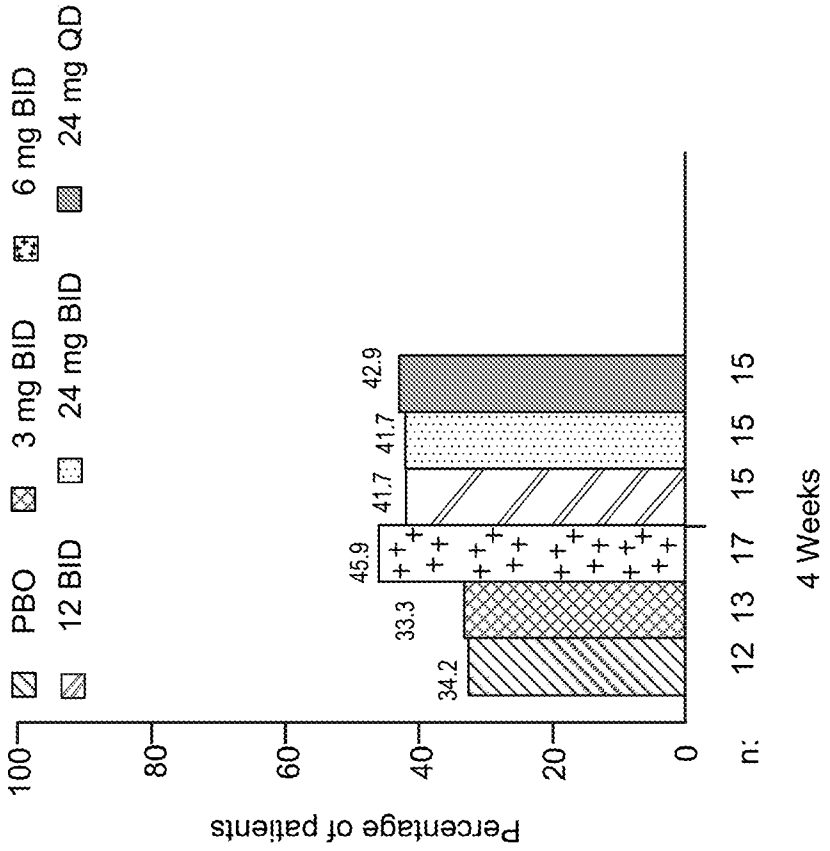


FIG. 11B

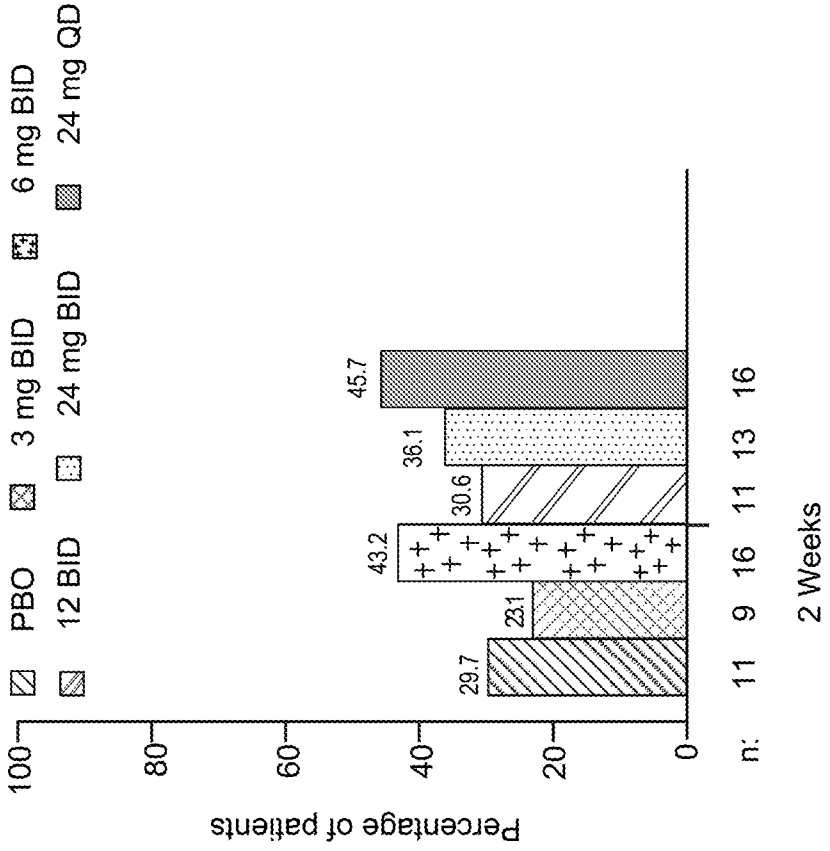
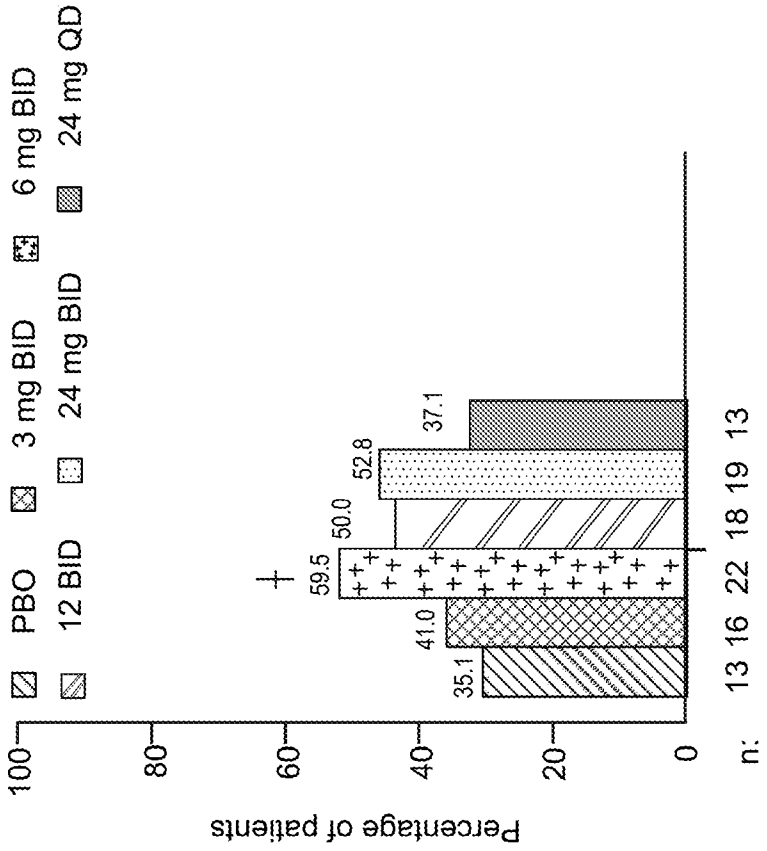
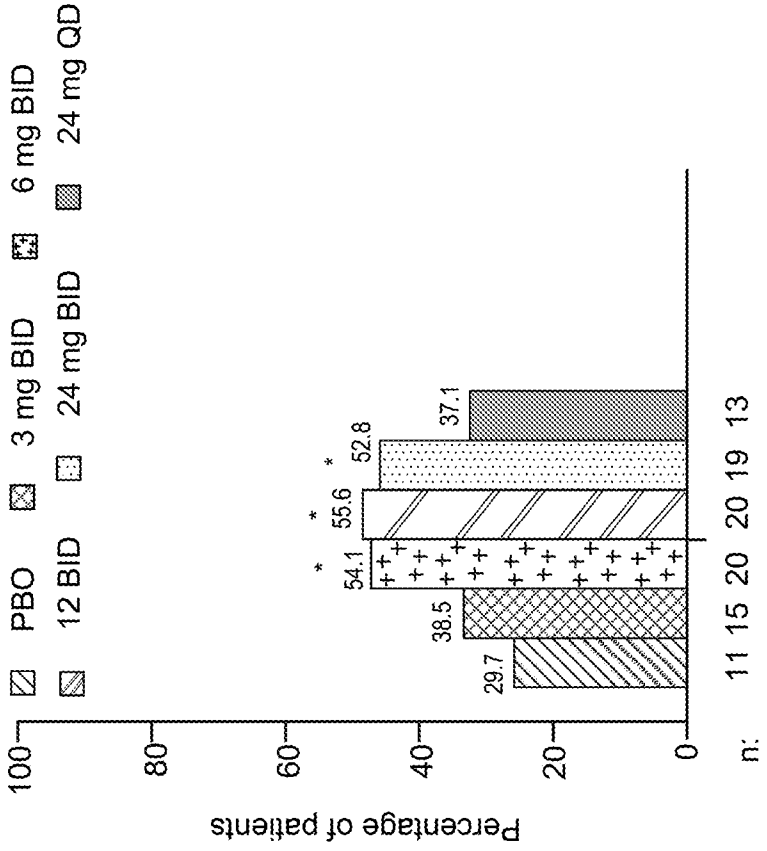


FIG. 11A



† statistically significant at ≤0.1 level

FIG. 11D



* statistically significant at ≤0.05 level

FIG. 11C

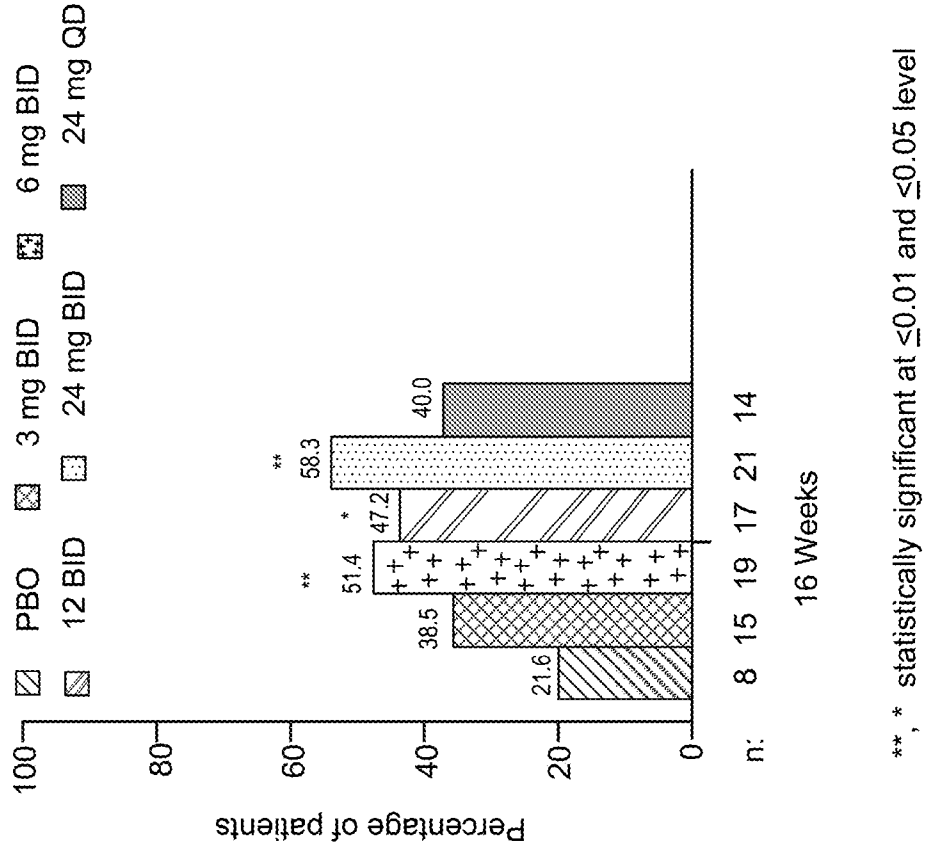

PBO
12 BID
3 mg BID
24 mg BID
6 mg BID
24 mg QD
Percentage of patients
100
80
60
40
20
0
21.6
38.5
51.4
47.2
58.3
40.0
**
*
**
n: 8 15 19 17 21 14
16 Weeks
**, * statistically significant at ≤0.01 and ≤0.05 level

FIG. 11E

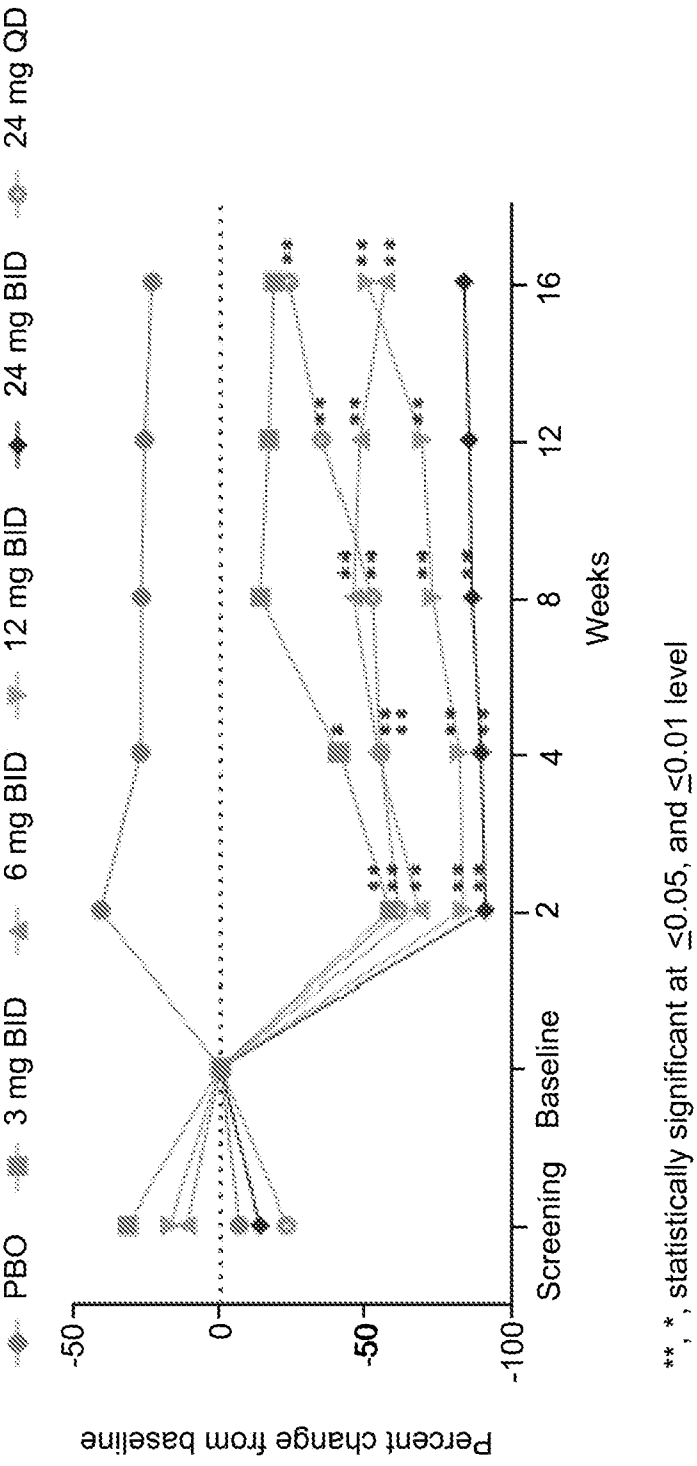
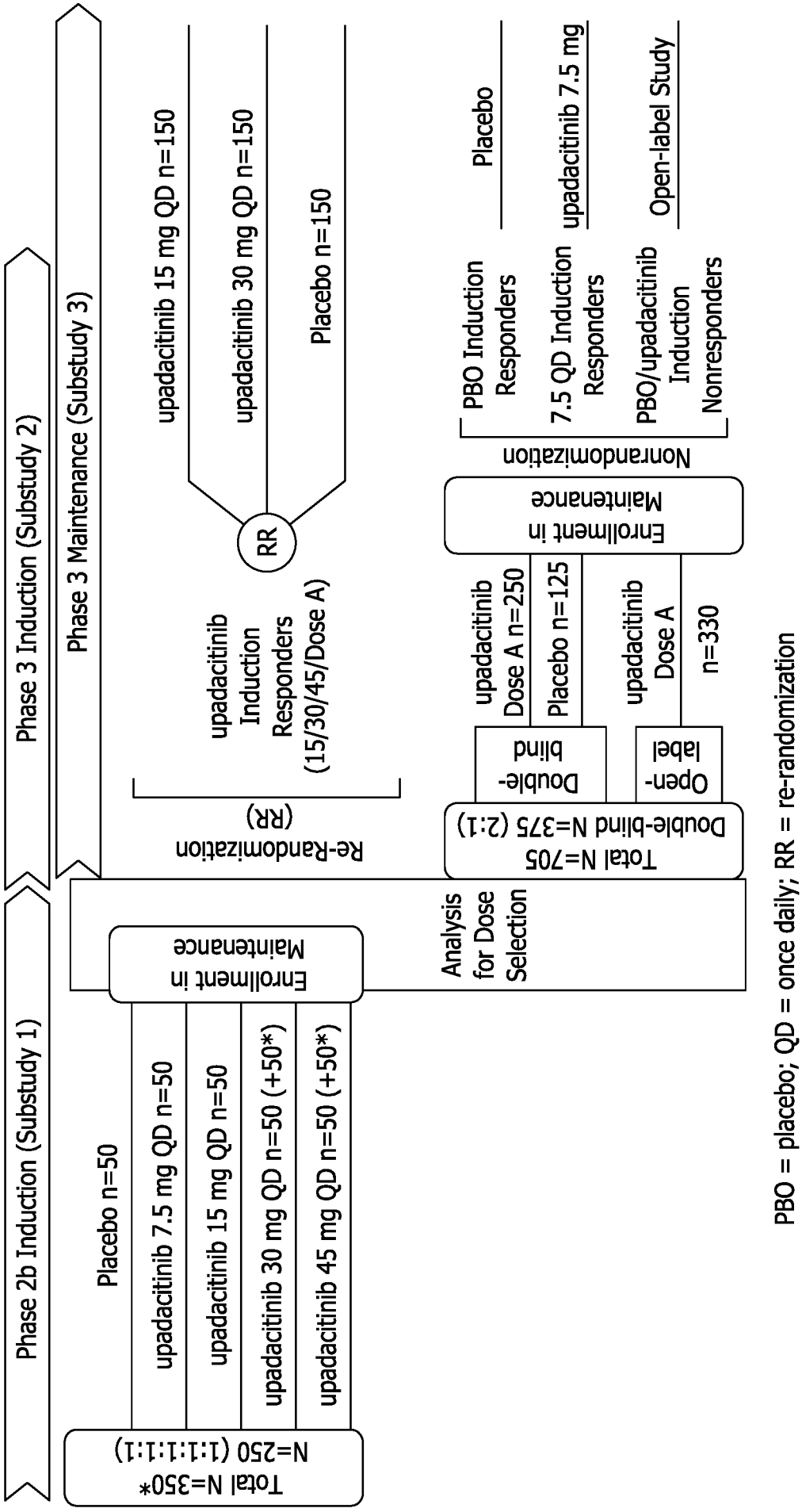

PBO
3 mg BID
6 mg BID
12 mg BID
24 mg BID
24 mg QD
Percent change from baseline
-50
0
-50
-100
Screening
Baseline
2
4
8
12
16
Weeks
**, *, statistically significant at ≤0.05, and ≤0.01 level

FIG. 12



PBO = placebo; QD = once daily; RR = re-randomization

FIG. 13

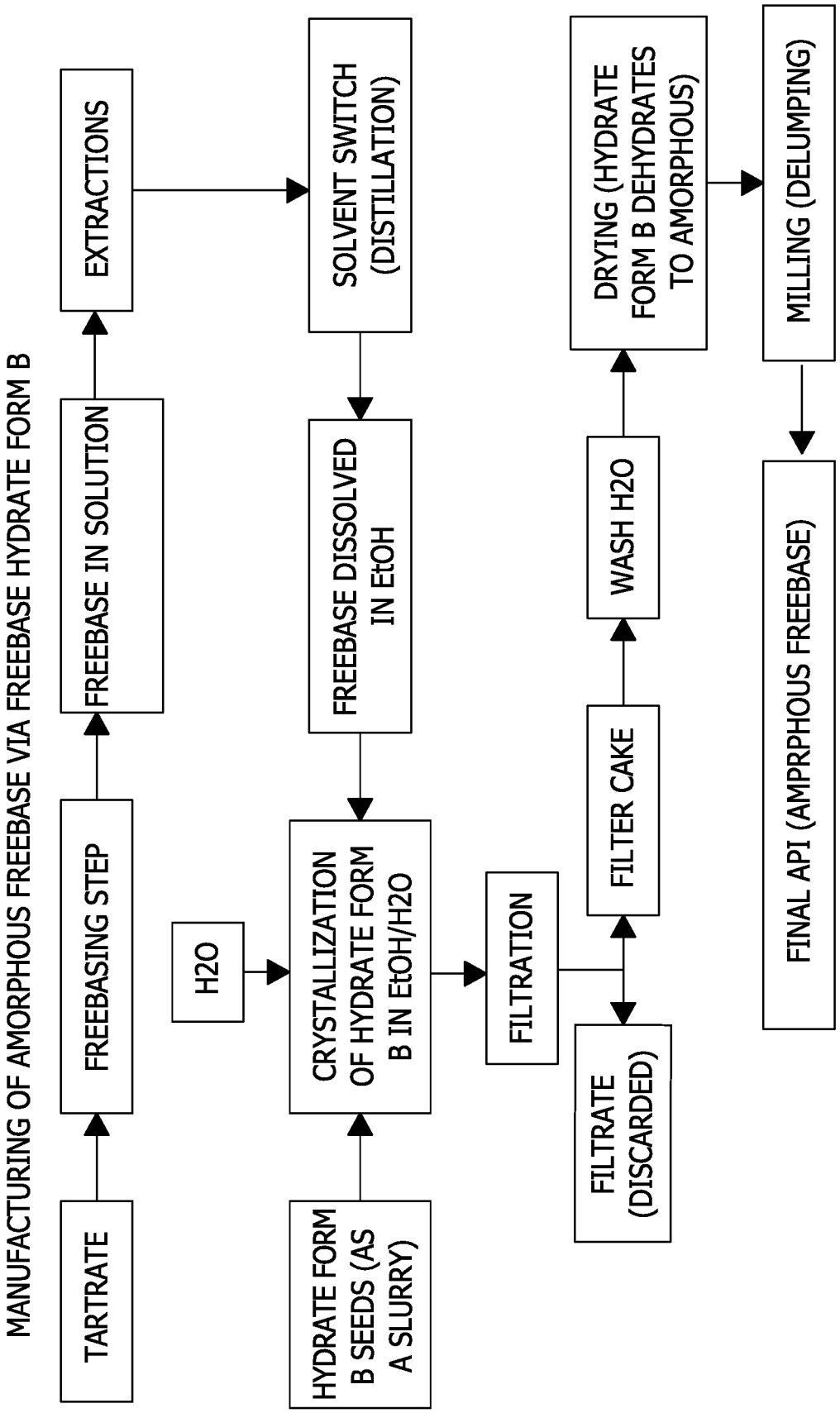

MANUFACTURING OF AMORPHOUS FREEBASE VIA FREEBASE HYDRATE FORM B
TARTRATE
FREEBASING STEP
FREEBASE IN SOLUTION
EXTRACTIONS
SOLVENT SWITCH (DISTILLATION)
FREEBASE DISSOLVED IN EtOH
H2O
HYDRATE FORM B SEEDS (AS A SLURRY)
CRYSTALLIZATION OF HYDRATE FORM B IN EtOH/H2O
FILTRATION
FILTRATE (DISCARDED)
FILTER CAKE
WASH H2O
DRYING (HYDRATE FORM B DEHYDRATES TO AMORPHOUS)
MILLING (DELUMPING)
FINAL API (AMPRPHOUS FREEBASE)

FIG. 14

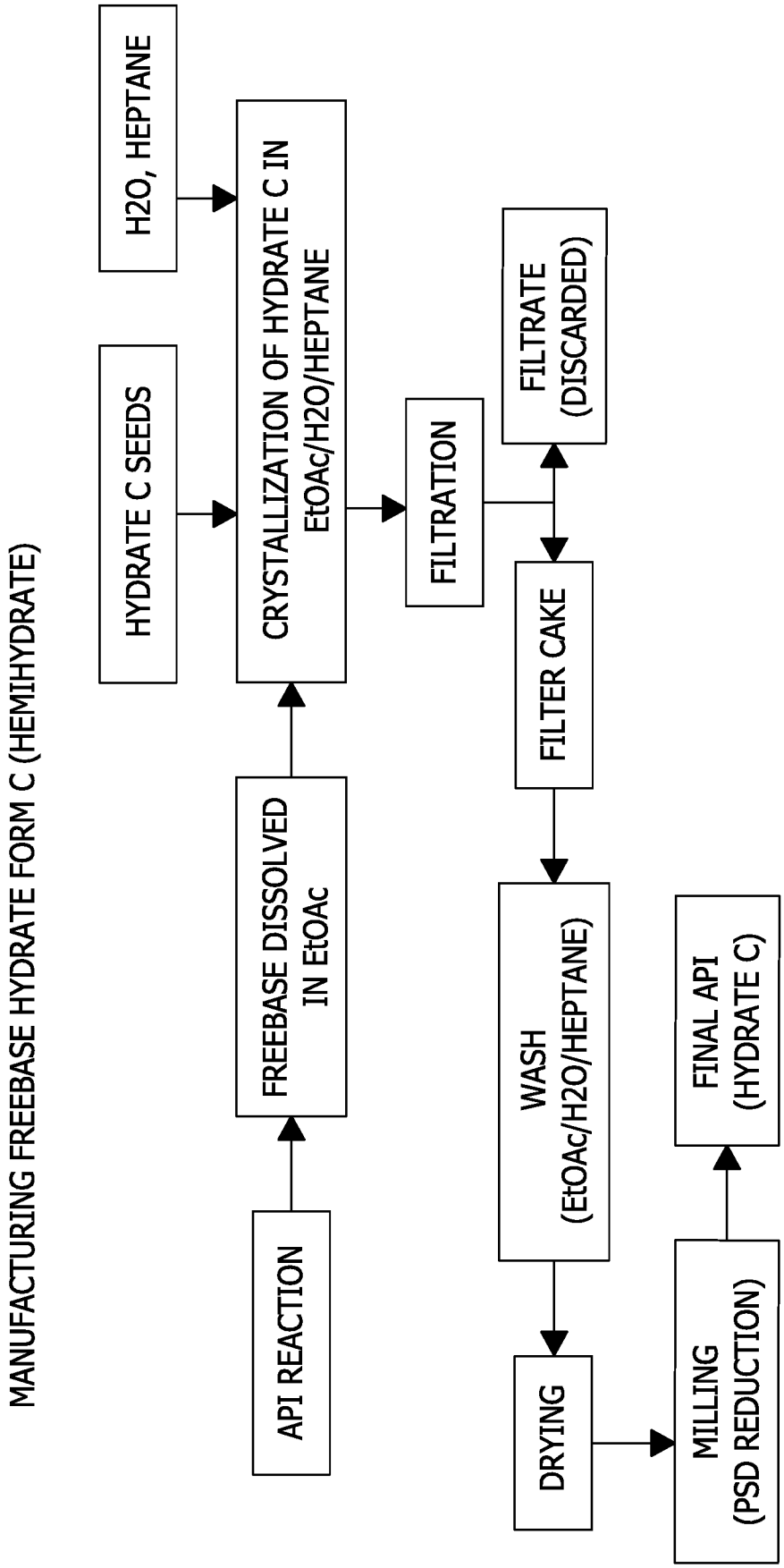

MANUFACTURING FREEBASE HYDRATE FORM C (HEMIHYDRATE)
API REACTION
FREEBASE DISSOLVED IN EtOAc
H2O, HEPTANE
HYDRATE C SEEDS
CRYSTALLIZATION OF HYDRATE C IN EtOAc/H2O/HEPTANE
FILTRATION
FILTRATE (DISCARDED)
FILTER CAKE
WASH (EtOAc/H2O/HEPTANE)
DRYING
MILLING (PSD REDUCTION)
FINAL API (HYDRATE C)

FIG. 15

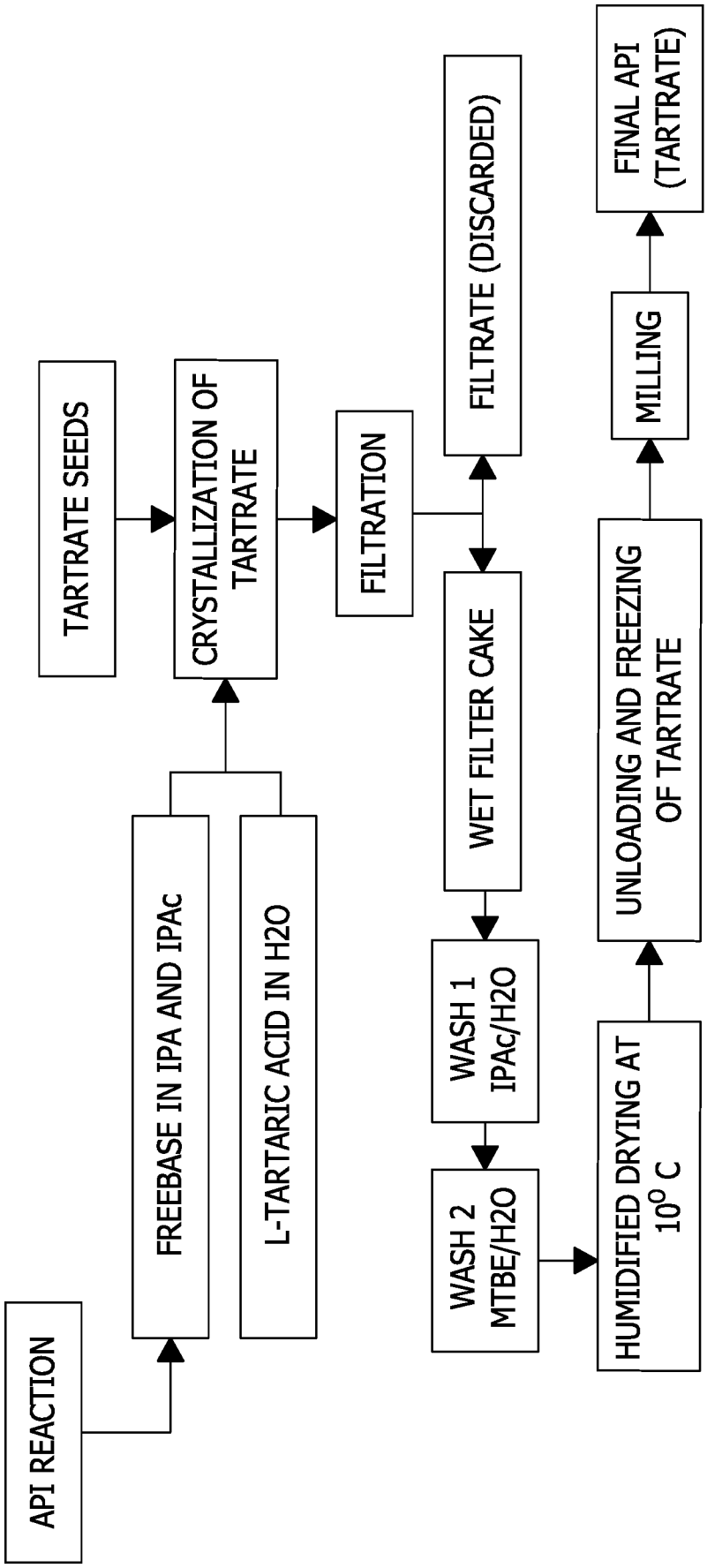

API REACTION
FREEBASE IN IPA AND IPAc
L-TARTARIC ACID IN H2O
TARTRATE SEEDS
CRYSTALLIZATION OF TARTRATE
FILTRATION
FILTRATE (DISCARDED)
WET FILTER CAKE
WASH 1 IPAc/H2O
WASH 2 MTBE/H2O
HUMIDIFIED DRYING AT 10° C
UNLOADING AND FREEZING OF TARTRATE
MILLING
FINAL API (TARTRATE)

FIG. 16

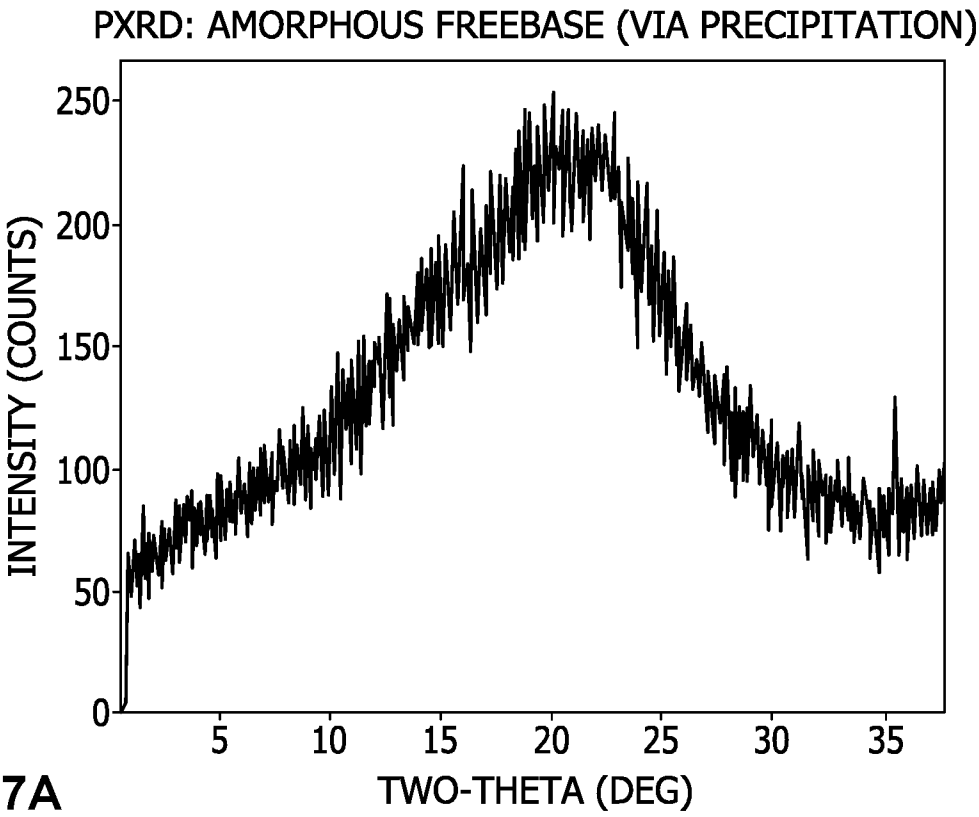


FIG. 17A

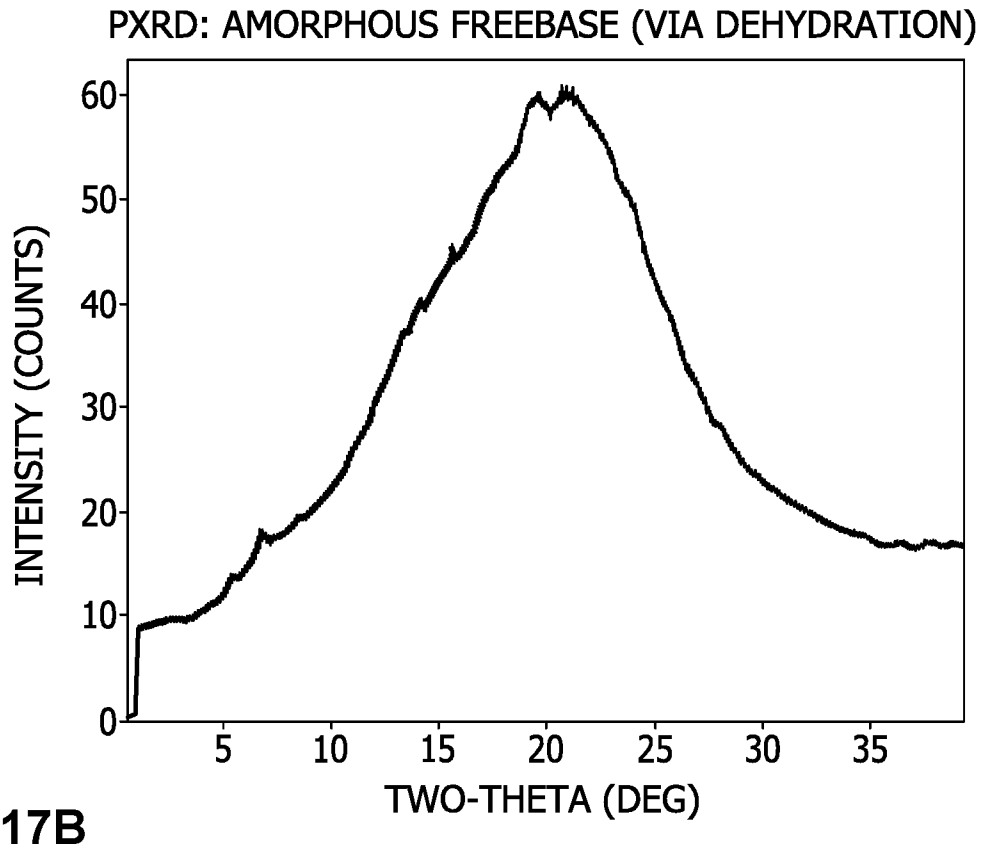


FIG. 17B

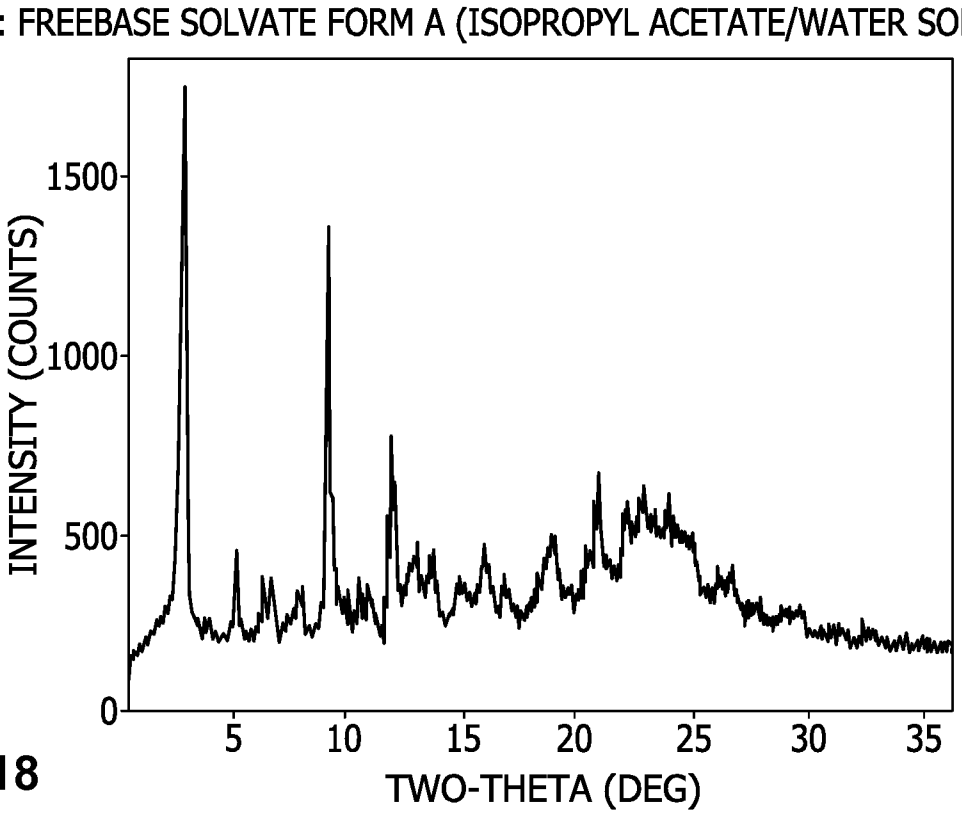

PXRD: FREEBASE SOLVATE FORM A (ISOPROPYL ACETATE/WATER SOLVATE)
INTENSITY (COUNTS)
1500
1000
500
0
5
10
15
20
25
30
35
TWO-THETA (DEG)

FIG. 18

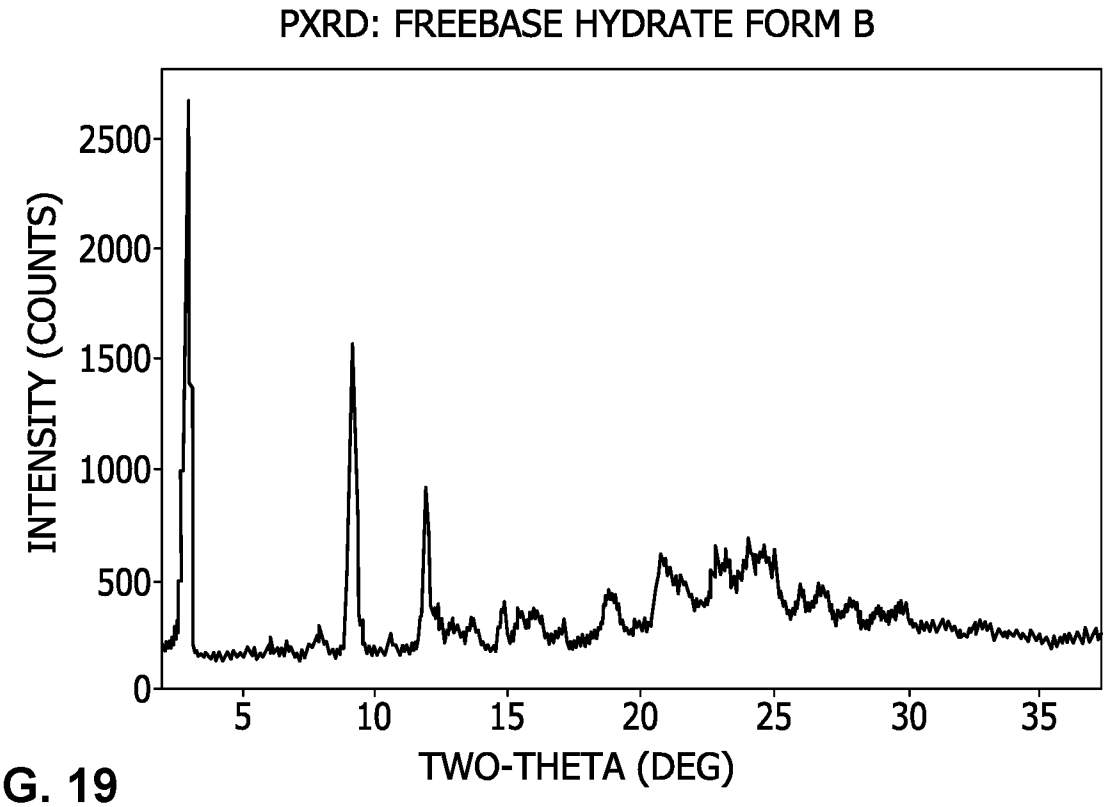

PXRD: FREEBASE HYDRATE FORM B
INTENSITY (COUNTS)
2500
2000
1500
1000
500
0
5
10
15
20
25
30
35
TWO-THETA (DEG)

FIG. 19

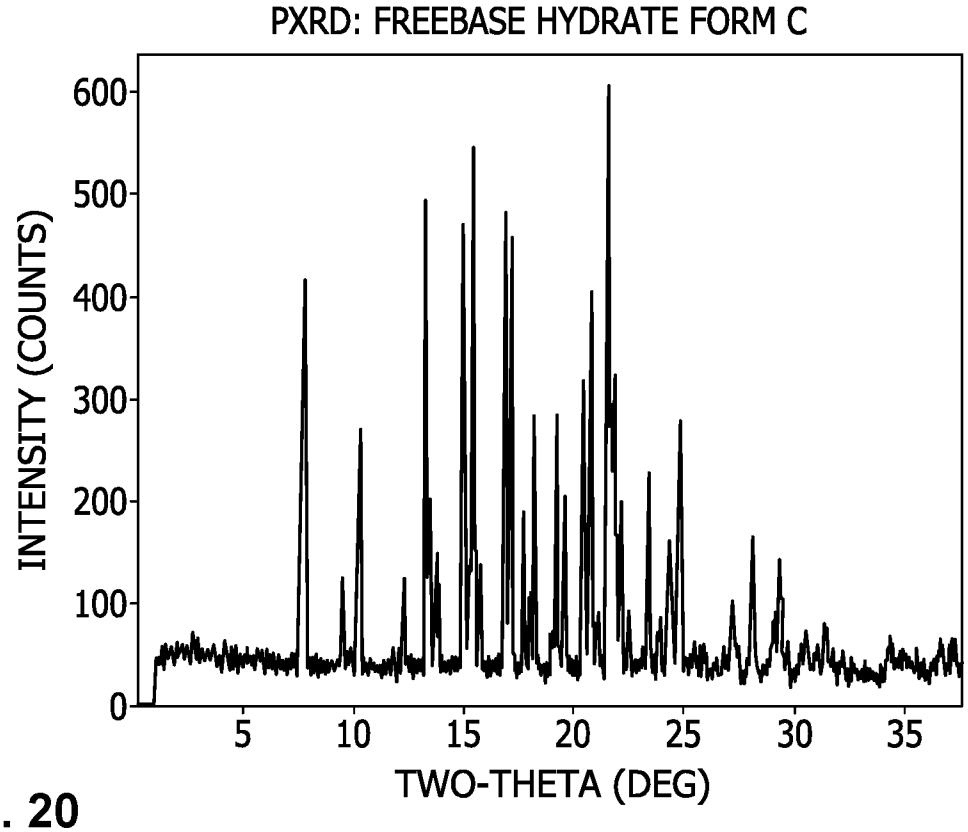

PXRD: FREEBASE HYDRATE FORM C
INTENSITY (COUNTS)
600
500
400
300
200
100
0
5
10
15
20
25
30
35
TWO-THETA (DEG)

FIG. 20

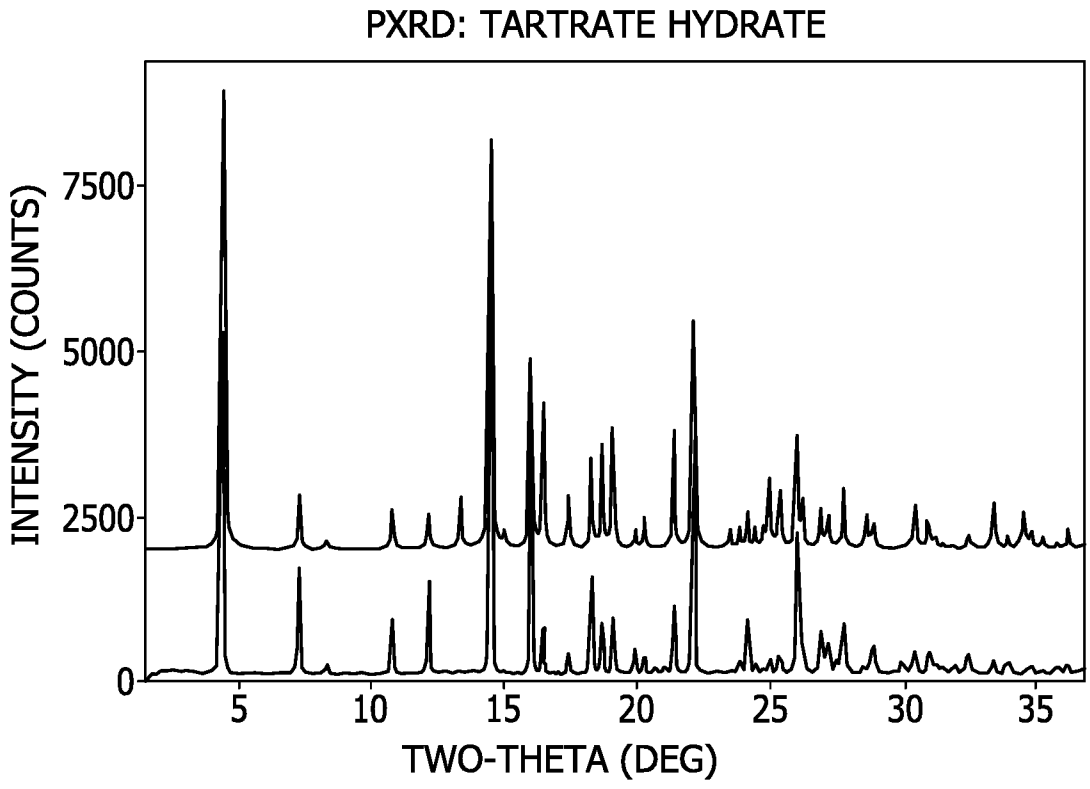

PXRD: TARTRATE HYDRATE
INTENSITY (COUNTS)
7500
5000
2500
0
5
10
15
20
25
30
35
TWO-THETA (DEG)

FIG. 21

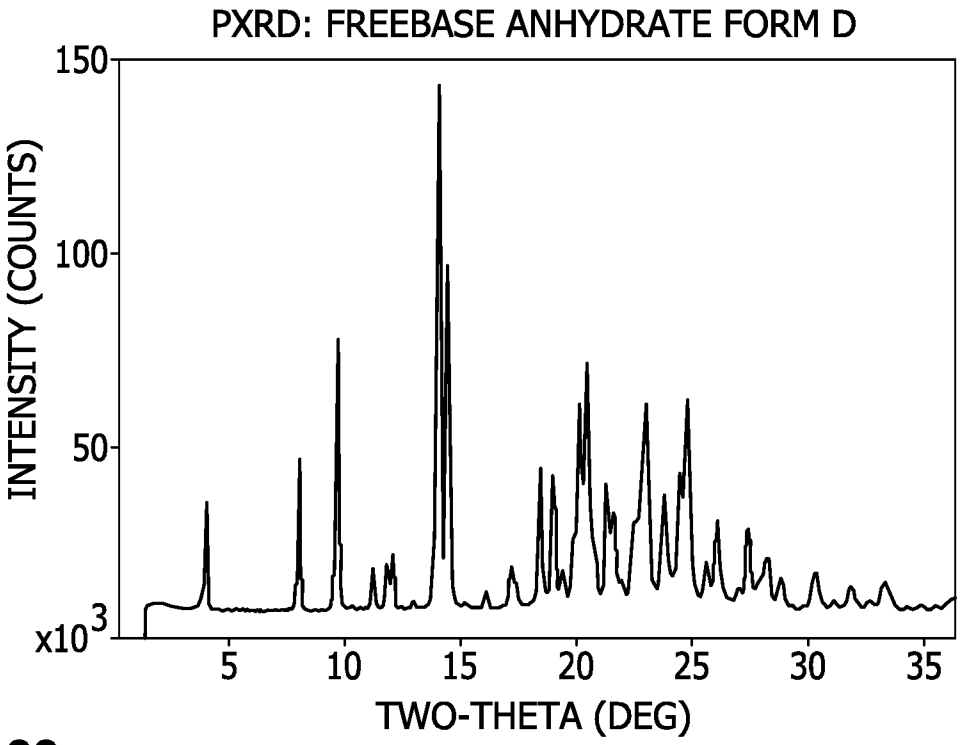

PXRD: FREEBASE ANHYDRATE FORM D
INTENSITY (COUNTS)
150
100
50
x10^3
5
10
15
20
25
30
35
TWO-THETA (DEG)

FIG. 22

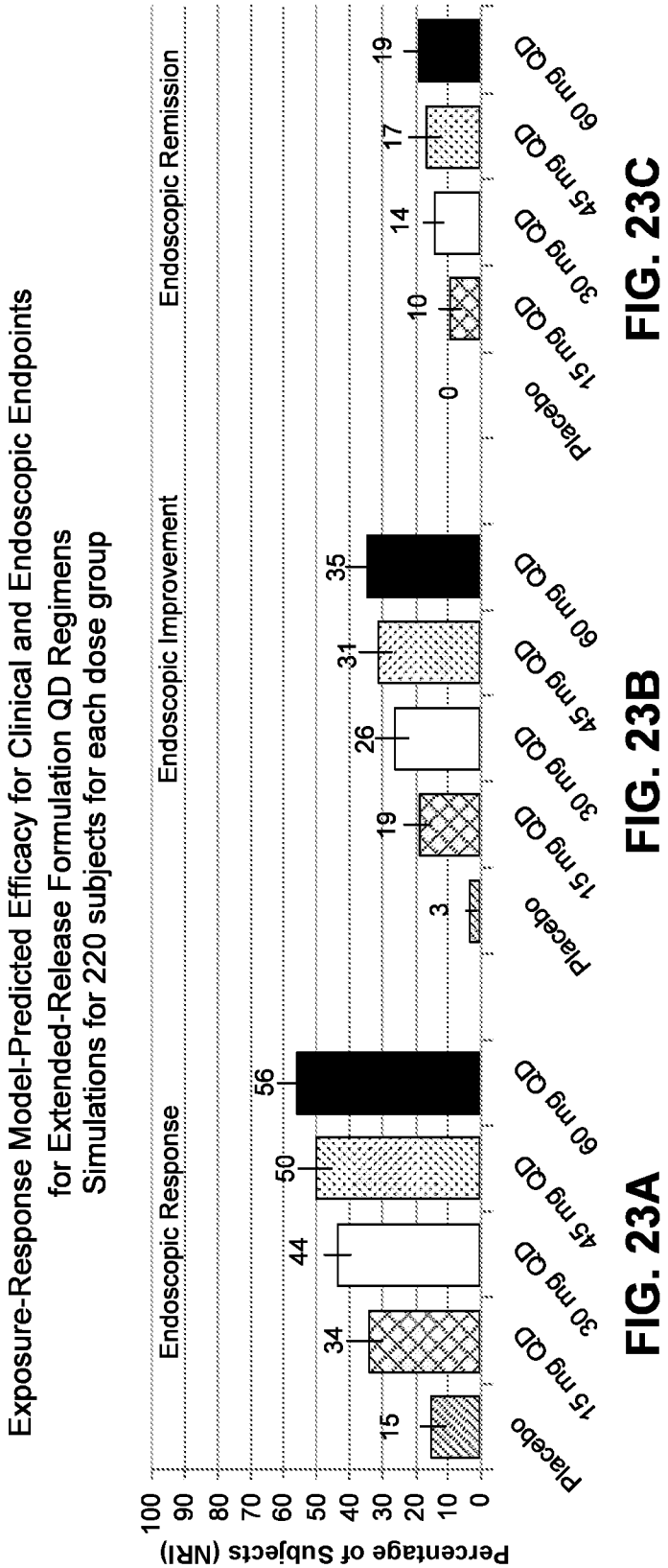


FIG. 23A

FIG. 23B

FIG. 23C

FIG. 23D

FIG. 23E

FIG. 23F