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Clinical Trial for the Treatment of Skin EIM with Compound 1

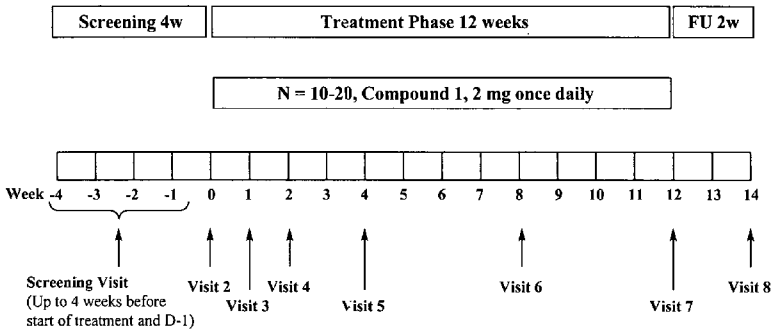


FIGURE 1

(57) **Abstract:** The present invention relates to, *inter alia*, methods of treatment and combinations of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1) useful for the treatment of extra-intestinal manifestations (EIM) in an individual with inflammatory bowel disease (BBD) and for the treatment of pyoderma gangrenosum (PG). In some embodiments, the methods further comprise administering Compound 1, or a harmaceutically salt, solvate, or hydrate thereof, in combination with a therapeutically effective amount of a compound selected from the group consisting of: a corticosteroid, a 5-aminosalicylic acid derivative, and a TNF-alpha inhibitor; or a corticosteroid, an immunosuppressant, a biologic, an anti-inflammatory agent, and an antibiotic.

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COMPOUNDS AND METHODS FOR TREATMENT OF INFLAMMATORY BOWEL DISEASE WITH EXTRA-INTESTINAL MANIFESTATIONS

FIELD OF THE INVENTION

The present invention relates to, *inter alia*, methods of treatment and combinations of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1) useful for the treatment of extra-intestinal manifestations (EIM) in an individual with inflammatory bowel disease (IBD) and for the treatment of pyoderma gangrenosum (PG). In some embodiments, the methods further comprise administering Compound 1, or a pharmaceutically salt, solvate, or hydrate thereof, in combination with a therapeutically effective amount of a compound selected from the group consisting of: a corticosteroid, a 5-aminosalicylic acid derivative, and a TNF-alpha inhibitor; or a corticosteroid, an immunosuppressant, a biologic, an anti-inflammatory agent, and an antibiotic.

BACKGROUND OF THE INVENTION

The sphingosine-1-phosphate (S1P) receptors 1-5 constitute a family of G protein-coupled receptors with a seven-transmembrane domain. These receptors, referred to as $S1P_1$ to $S1P_5$ (formerly termed endothelial differentiation gene (EDG) receptor-1, -5, -3, -6, and -8, respectively; Chun *et. al.*, Pharmacological Reviews, 54:265-269, 2002), are activated *via* binding by sphingosine-1-phosphate, which is produced by the sphingosine kinase-catalyzed phosphorylation of sphingosine. $S1P_1$, $S1P_4$, and $S1P_5$ receptors activate Gi but not Gq, whereas $S1P_2$ and $S1P_3$ receptors activate both Gi and Gq. The $S1P_3$ receptor, but not the $S1P_1$ receptor, responds to an agonist with an increase in intracellular calcium.

The compound (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (**Compound 1**) is a potent (EC_{50} cAMP, 0.093 nM (human)) and selective (EC_{50} β-arrestin, 6.10 nM ($S1P_1$), >10,000 nM ($S1P_2$), >10,000 nM, ($S1P_3$), 147 nM ($S1P_4$), and 24.4 nM ($S1P_5$)), orally available investigational drug candidate for the $S1P_1$ receptor.

In preclinical studies, Compound 1 showed calculated lymphocyte lowering IC_{50} values in four different species: 0.101 μM (mouse), 0.051 μM (rat), 0.058 μM (dog), and 0.098 μM (monkey). Notably, the calculated lymphocyte lowering IC_{50} values reflect total plasma concentration wherein Compound 1 is highly protein bound (97.8% human, 98.0% rat). Compound 1 was shown to be efficacious in the murine experimental autoimmune encephalomyelitis (EAE) model that mimics multiple sclerosis. Prophylactically, Compound 1 prevented the onset and severity of disease relative to vehicle up to day 25, at which time dosing was discontinued. All treatment arms went on to develop severe disease. Therapeutic administration of Compound 1 was also examined. Treatment began at day 18, by which time all animals had developed severe disease. Compound 1 was administered from day 18 to day 37 and showed to reverse the disease relative to vehicle and was similar to the efficacy observed with fingolimod

(*i.e.*, GILENYA® was approved in September 2010 for the treatment of individuals with relapsing forms of multiple sclerosis). Similarly, Compound 1 was efficacious in a collagen induced arthritis (CIA) model. Prophylactic oral administration in female Lewis rats resulted in a significant reduction in ankle diameters on day 17 following a daily oral dose and was similar to that observed in rats treated with fingolimod or methotrexate. Improvement in histological parameters in the knees and ankles of CIA rats was also observed, suggesting that inhibiting lymphocyte entry into arthritic joints with Compound 1 treatment suppresses CIA in rodents. Additional details can be found in the following, PCT application, serial number PCT/US2009/004265, filed 22 July 2009 (International Publication Number WO2010/011316); PCT application, serial number PCT/US2011/000153, filed 27 January2011 (International Publication Number WO2011/094008); and Buzard: D. J., *et. al.*, *ACS Med. Chem. Lett.* 2014, 5, 1313−1317; each hereby incorporated by reference in its entirety.

S1P is a signaling sphingolipid required by lymphocytes to exit the lymphoid tissue and enter the bloodstream via a chemotactic gradient. The S1P1 receptor is a physiological mediator which has been shown to regulate lymphocyte recirculation between lymphoid tissue and blood. Binding and internalization of the S1P1 receptor may result in lymphocyte retention within lymphoid tissue, with subsequent reduction in peripheral lymphocyte count and lymphocyte availability for recruitment to sites of inflammation. S1P1 receptor surface expression is required for S1P gradient-mediated lymphocyte migration out of lymphoid tissue into the circulation (Brinkmann V., *Nat Rev Drug Discov 2010 November*; 9(11):883-97).

Compound 1 is an orally available, selective, sphingosine 1-phosphate receptor (S1P) agonist. The S1P1 receptor is a physiological mediator which has been shown to regulate lymphocyte recirculation between lymphoid tissue and blood. Binding and internalization of the S1P1 receptor may result in lymphocyte retention within lymphoid tissue, with subsequent reduction in peripheral lymphocyte count and lymphocyte availability for recruitment to sites of inflammation. S1P1 receptor surface expression is required for S1P gradient-mediated lymphocyte migration out of lymphoid tissue into the circulation (Brinkmann V., *et. al.*, Nat Rev *Drug Discov 2010 November*; 9 (11):883-97).

Compound 1 is being developed to treat autoimmune diseases. Initial investigations will focus on Inflammatory Bowel Disease (IBD), which is a broad term that describes conditions with chronic or recurring immune response and inflammation of the gastrointestinal tract (Centers for Disease Control and Prevention. Inflammatory bowel disease (IBD). http://www.cdc.gov/ibd/. Accessed January 8, 2015). There are two major types of IBD: Crohn's disease (CD) and ulcerative colitis (UC). These are chronic remittent or progressive inflammatory conditions that may affect the entire gastrointestinal tract (CD) and the colonic mucosa (UC), and are associated with an increased risk for colon cancer.11 Collectively, individuals with IBD suffer from a multitude of GI symptoms, including diarrhea, rectal bleeding and abdominal pain.

The causes of these IBDs are not completely understood, but three characteristics define their etiology: (1) genetic predisposition; (2) an altered, dysregulated immune response; and (3) an altered response to gut microorganisms.2 The triggering event for the activation of the immune response in IBD has yet to be identified, but possible factors related to this event include a pathogenic organism (as yet unidentified) or an inappropriate response to a normally innocuous microbial or other antigen (perhaps due to failure to downgrade the inflammatory response, and/or to repeated exposure to such antigen from an alteration in barrier function) (Centers for Disease Control and Prevention. Inflammatory bowel disease (IBD). http://www.cdc.gov/ibd/. Accessed January 8, 2015). Once the inflammation has been triggered, it may be difficult for the IBD individual's immune system to turn off the response (Danese S. and Fiocchi C., *N Engl J Med. 2011 Nov*;365;18:1713-1725).

The number of individuals diagnosed with IBD has dramatically increased worldwide over the past 50 years.5 In 2014, The Crohn's and Colitis Foundation of American estimated that approximately 1.6 million people are affected by IBD in the United States (US) alone, (Crohn's and Colitis Foundation of America. The Facts About Inflammatory Bowel Diseases. November 2014, New York, NY 10017. http://www.ccfa.org/assets/pdfs/ibdfactbook.pdf. Accessed January 7, 2015) with as many as 70,000 new cases diagnosed in the US each year (Loftus E.V., *Gastroenterology*, 2004; 126:1504-17). In Europe, an estimated 2.5 – 3 million people are affected by IBD, (Burisch J, *et. al., J Crohns Colitis. 2013 May*;7(4):322-37) and as many as 5 million may be affected worldwide (World IBD Day. http://www.worldibdday.org/index.html. Accessed January 7, 2015). Universally, incidence rates for both Crohn's disease and ulcerative colitis were highest among individuals between 20 and 40 years old. Thus, IBD affects individuals in the healthiest and productive years of life, resulting in long-term cost to the individual, health-care system and society (American Gastroenterological Assoc. IBD emerges as a global disease, 2012 January 5, ScienceDaily. www.sciencedaily.com/releases/2012/01/120104135402.htm. Accessed January 7, 2015).

Treatment for individuals with IBD is generally for symptomatic care (relief of symptoms) and mucosal healing and includes 5 major classes of medications: aminosalicylates (5-ASA), antibiotics, corticosteroids, immunomodulators, and biologic therapies. These drugs are generally prescribed in a "step-up" approach, with escalation of the medical regimen until a response is achieved (Medscape. Inflammatory Bowel Disease: Practice Essentials. http://emedicine.medscape.com/article/179037-overview#aw2aab6b2b4. Accessed January 8, 2015).

A single ascending dose study and a multiple ascending dose study, conducted in healthy subjects, have demonstrated the lymphocyte lowering capabilities of **Compound 1**. Lymphocyte trafficking agents such as natalizumab and vedolizumab, both injectable or infused therapies, have demonstrated efficacy in IBD indications. More recently, ozanimod, an S1P1 oral receptor modulator showed promising results in a Phase 2 study for UC. The availability of oral lymphocyte trafficking agents such as **Compound 1** would offer individuals an additional, more convenient treatment for IBD.

Inflammatory bowel diseases are associated with various extra-intestinal manifestations (EIMs). The prevalence of IBD with EIMs as co-morbidities varies from 25% to 40% depending on the clinical presentation (Taverela V. F., *Aliment Pharmacol Ther* 2004; Suppl 4:50-53). Specifically, IBD with EIMs could have a negative impact on disease prognosis and quality of life, and in most cases their clinical course becomes independent of gut disease activity.

IBD with skin EIMs is common, occurring in 2% to 34% of the IBD population (Taverela V. F., *Aliment Pharmacol Ther* 2004; Suppl 4:50-53). Specifically, erythema nodosum and pyoderma gangrenosum are the most common skin manifestations of IBD, while psoriasis is the active dermatological comorbidity disease observed most often, affecting 7%-11% of the IBD population (Danese S., *et. al.*, *Br J Dermatol*, 1982;106: 323-330). IBD and these major skin EIMs in IBD share some common pathogenic mechanisms including neutrophil and lymphocyte infiltration (Marzano A. V., *et. al.*, *Inflamm. Bowel Dis.* 2014; 20:213-227). To this point, targeted immunosuppressive therapies have demonstrated efficacy in IBD with skin EIMs. For example, TNF-alpha inhibitors are known to reduce intestinal inflammation and induce clinical remission in individuals with IBD, and are also known to reduce EIMs of IBD. However, a small percentage of individuals with IBD taking TNF-alpha inhibitors experience de novo paradoxical psoriasis (reporting a rate ranging from 1.6 to 8.8%) despite beneficial intestinal effects while on treatment (Freling E., *et. al.*, *Am J Gastroenterol* 2015; 110:1186-1196). The pathophysiology of the paradoxical disease is not understood, but the leading hypothesis is that decreased TNF-alpha induces the activation of autoreactive T cells and an increased interferon activity as well as other pro-inflammatory cytokines, such as IL-12, IL-17, IL-23. Recently, interferon-alpha (IFN-alpha) production by dermal plasmacytoid dendritic cells (DCs) has been identified as a key element in the early phase of psoriatic skin lesion induction. Plasmacytoid DCs, the natural IFN-alpha producing cells, have recently been shown to infiltrate the skin of individuals with psoriasis and to produce IFN-alpha. IFN-alpha induces the expression of CXCR3 on T cells, facilitating homing to the skin (Nestle F.O., *et. al.*, *J Exp Med.* 2005 Jul 4;202(1):135-43).

It is clear that existing treatments for IBD, and IBD skin EIMs, including TNF-alpha inhibitors, have limitations and a need remains for therapies with sustained efficacy, improved safety, and convenient administration (Paul C., *et. al.*, *J Eur Acad Dermatol Venereol* 2012; 26 (suppl 3): 1-10).

Spingosine-1-phosphate (S1P) is a spingolipid required by lymphocytes to exit the lymphoid tissue and enter the bloodstream via a chemotactic gradient. Agonists of the S1P receptor-1 (S1P1) block lymphocyte migration out of the lymph tissue through internalization of the receptor, resulting in a sequestration of lymphocytes (Brinkmann V., *et. al.*, *J Biol Chem* 2002; 277:21453-57). Recent clinical development of S1P1 agonists and the resulting lymphocyte sequestration have potential for treating multiple autoimmune and chronic inflammatory diseases including multiple sclerosis, IBD and psoriasis. Fingolimod was the first drug in this class to be approved the treatment of multiple sclerosis (Kappos L, *et. al.*, *N Engl J Med.* 2010 Feb 4; 362(5):387-401). More recently the S1P1 receptor agonist ponesimod

was observed to reduce the severity of chronic plaque psoriasis after chronic oral administration in a phase 2 randomized clinical trial (Vaclavkova A., *et. al.*, *Lancet* 2014; 384: 2036-45). In this study, ponesimod was associated with dyspnea, elevated liver enzymes, bradycardia, headache and dizziness. Furthermore, S1P1 agonists (FTY720, SEW2871) have been observed to have an anti-inflammatory impact on the production of IL-12 family cytokines, indicating therapeutic potential for S1P treatment of several inflammatory diseases like psoriasis (Schaper K., *et. al.*, *Mol Immunol.* 2014 May;59(1):10-8). Importantly, a recent report demonstrating S1P4 agonists inhibit plasmacytoid dendritic cell activation and interferon-alpha production suggest a potential therapeutic role for S1P1/S1P4 agonists like **Compound 1** in paradoxical psoriasis (Dillmann C., *et. al.*, *J Immunol.* 2016 Feb 15;196(4):1579-90).

Pyoderma gangrenosum (PG) is considered to be a rare disorder associated with inflammation, mainly characterized by large skin ulcers (Cohen, P.R., *Am J Clin Dermatol. 2009;10(5):301-12*; Marzano A.V., *et. al.*, *Clinical and Experimental Immunology, 2010;162: 1–11*). The ulcers are known to break down at a rapid rate and are painful, often turning necrotic (Su W., *et. al.*, *J Cut. Path*; 1986;13: 323-330). Other inflammatory diseases such as inflammatory bowel disorder (IBD), ulcerative colitis (UC) and Bechet's disease are indicated to share the same clinicopathophysiology (Gameiro A, *et. al.*, *Clin. Cos. Inv. Dermatol; 2015;8: 285-293*). PG was considered to have a parallel relationship with other underlying diseases (*e.g.*, UC, IBD) with PG being the cutaneous manifestation (Brunsting LA, *et. al. Arch Dermatol Syph; 1930;22:655-680*), however this hypothesis was drawn into question by Driesch (Von den Driesch P., *Br. J. Dermatol; 1997;137(6):1000-5*) and published data suggesting consideration of PG as an independent disease, irrespective of underlying disorders.

Based upon U.S. Department of Health and Human Services' National Institutes of Health's Office of Rare Disease Research, the incidence of PG has been estimated that each year in the United States, 1 person per 100,000 people is affected (U.S. Department of Health & Human Services National Institutes of Health, https://rarediseases.info.nih.gov/diseases/7510/pyoderma-gangrenosum). The incidence peak occurs between the ages of 20 to 50 years, with women being more often affected than men (Wollina U., *Orphanet Journal of Rare Diseases*; 2007, 2:19).

Diagnosis of PG is reliant on clinical signs, exclusion principle and supported by histopathology of the biopsy (Wollina U., *Orphanet Journal of Rare Diseases*; 2007, 2:19; Weenig R.H., *et. al.*, *N Engl J Med*; 2002; 347:1412-1418). The histopathology can differ dependent on the timing (early stage-mild to moderate perivascular lymphocytic infiltrate; late-stage necrosis with dense lymphocytic infiltration along with involvement of blood vessels) and site of biopsy (Su W., *et. al.*, *J Cut. Path*; 1986;13: 323-330). The diagnosis using clinical signs alone has been shown historically to lead to misdiagnoses as PG for at least 6 categories including vascular occlusive or venous disease, vasculitis, cancer, infectious disease, exogenous tissue injury and drug reactions (Weenig R.H., *et. al.*, *N Engl J Med*; 2002;347:1412-1418), and support of exclusion and histopathology is recommended for diagnosis.

The documented treatments for PG include, for example, systemic corticosteroids and cyclosporin A. Combinations of steroids with cytotoxic drugs are used in resistant cases. The combination of steroids with sulfa drugs or immunosuppressants has been used as steroid sparing modalities. In some cases, anti-TNF therapy was reported to be beneficial which suggests that inhibition of TNF may help.

Gevokizumab is a potent IL-1 beta monoclonal antibody with unique allosteric modulating properties and has the potential to treat individuals with a wide variety of inflammatory and other diseases. Gevokizumab binds strongly to interleukin-1 beta (IL-1 beta), a pro-inflammatory cytokine, and modulates the cellular signaling events that produce inflammation. This agent was being developed as a potential treatment for PG; however, development was discontinued in 2016.

Agonists of the S1P1 receptor block lymphocyte migration out of the lymph tissue through internalization of the receptor, resulting in a sequestration of lymphocytes (Brinkmann V., *et. al., J Biol Chem*; 2002; 277:21453-57). Recent clinical development of S1P1 receptor agonists and the resulting lymphocyte sequestration have potential for treating multiple autoimmune and chronic inflammatory diseases including multiple sclerosis, IBD and psoriasis. Fingolimod was the first drug in this class to be approved for the treatment of multiple sclerosis (Kappos L., *et. al., N Engl J Med.*; 2010 Feb 4; 362(5):387-401). More recently the S1P1 receptor agonist ponesimod was observed to reduce the severity of chronic plaque psoriasis after chronic oral administration in a Phase 2 randomized clinical trial (Vaclavkova A., *et. al., Lancet*; 2014; 384: 2036-45). In this study, ponesimod was associated with dyspnea, elevated liver enzymes, bradycardia, headache and dizziness. Furthermore, S1P1 agonists (FTY720, SEW2871) have been observed to have an anti-inflammatory impact on the production of IL-12 family cytokines, indicating therapeutic potential for S1P treatment of several inflammatory diseases like psoriasis (Schaper K., *et. al., Mol Immunol.*; 2014 May;59(1):10-8). Importantly, a recent report demonstrating S1P4 agonists inhibition of plasmacytoid dendritic cell activation and interferon-alpha production suggest a potential therapeutic role for S1P1/S1P4 agonists like Compound 1in paradoxical psoriasis (Dillmann C., *et. al., Cells. J Immunol.*; 2016 Feb 15;196(4):1579-90).

Histopathology of ulcerative pyoderma gangrenosum (PG) is characterized by a dense dermal infiltrate composed mainly of neutrophils in biopsy from the central area of ulceration, and a mainly lymphocytic infiltrate with thrombosis of vessels and extravasated erythrocytes in biopsy from the border of the ulcer (Cohen, P.R., *Am J Clin Dermatol.*; 2009;10(5):301-12). In individuals with ulcerative PG the number of T-lymphocytes are significantly higher at the wound edge compared to the wound bed. In contrast, neutrophils were significantly more numerous in the wound bed than the wound edge (Marzano A.V., *et. al., Experimental Immunology*, 2010;162: 1–11). This suggests that activated T-lymphocytes at the wound edge could promote ulcer formation. Further support for T-cell involvement in the disease comes from observations in individuals with PG that are characterized by an over-expression in the blood of the CD4+CCR5+ and CD4+CCR6+ and a down-regulation of CD4+CCR4+ counts with respect to healthy subjects (Quaglino P, *et. al., J Eur Acad Dermatol Venereol*; 2016;30: 655-8).

In addition to the potential anti-inflammatory benefits of systemic lymphocyte immunomodulation, S1P is known to exert anti-proliferative effects in human keratinocytes (Schuppel M., *et. al.*, *J Invest Dermatol* 2008; 128:1747-56), and inhibits dendritic cell migration (Reines I., *et. al.*, *J Clin Invest Dermatol* 2009; 129:1954-62). Thus, the potential role of S1P receptor modulation in skin EIMs of IBD might involve both systemic and local epidermal mechanisms.

Further, a differentiated profile for Compound 1 compared to other S1P modulators for the treatment of PG could arise from the hypothesis that S1P4 as well as S1P1 receptor modulation could aid in neutrophil trafficking (Allende M. L., *J Biol Chem*; 2011; 286: 7348-58).

Next generation S1P modulators, such as, (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (**Compound 1**), or a pharmaceutically acceptable salt, hydrate, or solvate thereof, would offer a novel therapy for IBD individuals with skin EIMs.

Further, the evidence suggests that T-lymphocytes can play a role in PG and that reduction of lymphocytes by S1P1 receptor modulators represent a novel therapeutic approach in PG. The availability of lymphocyte trafficking agents, such as, (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt, hydrate, or solvate thereof, would offer individuals a novel therapy for pyoderma gangrenosum.

SUMMARY OF THE INVENTION

In its various embodiments, the present invention is directed to, *inter alia*, methods of treating active skin extra-intestinal manifestations (EIM) in an individual with inflammatory bowel disease (IBD) in need thereof comprising administering a therapeutically effective amount of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

In other embodiments, the present invention is directed to uses of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt, hydrate, or solvate thereof, in the manufacture of a medicament for the treatment of active skin extra-intestinal manifestations (EIM) in an individual with inflammatory bowel disease (IBD).

In some embodiments, the individual has at least one condition selected from the group consisting of: psoriasis, erythema nodosum (EN), and pyoderma gangrenosum (PG).

In some embodiments, the individual has psoriasis.

In some embodiments, the individual has erythema nodosum (EN).

In some embodiments, the individual has pyoderma gangrenosum (PG).

In some embodiments, the individual has at least one condition selected from the group consisting of: psoriasis, erythema nodosum (EN), and pyoderma gangrenosum (PG).

In some embodiments, the skin extra-intestinal manifestations (EIM) is psoriasis.

In some embodiments, the skin extra-intestinal manifestations (EIM) is erythema nodosum (EN).

In some embodiments, the skin extra-intestinal manifestations (EIM) is pyoderma gangrenosum (PG).

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is in an amount equivalent to about 1 mg to about 5 mg of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is in an amount equivalent to about 2 mg of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is selected from: Compound 1, a calcium salt of Compound 1, and an L-arginine salt of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is an L-arginine salt of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is an anhydrous, non-solvated crystalline form of the L-arginine salt of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is a crystalline free-plate habit of the non-solvated L-arginine salt of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is an anhydrous, non-solvated crystalline form of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is administered orally.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is formulated as a capsule or tablet suitable for oral administration.

In some embodiments, the methods further comprise administering Compound 1, or a pharmaceutically salt, solvate, or hydrate thereof, in combination with a therapeutically effective amount of a compound selected from the group consisting of: a corticosteroid, a 5-aminosalicylic acid derivative, and a TNF-alpha inhibitor.

In some embodiments, the corticosteroid is cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone, and fludrocortisone.

In some embodiments, the 5-aminosalicylic acid derivative is selected from the group consisting of: balsalazide, mesalamine, olsalazine, and sulfasalazine.

In some embodiments, the TNF-alpha inhibitor is selected from the group consisting of: as infliximab (Remicade®), adalimumab (Humira®), certolizumab pegol (Cimzia®), and golimumab (Simponi®), and etanercept (Enbrel®).

In further embodiments, the present invention is directed to, *inter alia*, methods of treating pyoderma gangrenosum (PG) in an individual in need thereof comprising administering a therapeutically effective amount of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-

tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

In other embodiments, the present invention is directed to uses of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt, hydrate, or solvate thereof, in the manufacture of a medicament for the treatment of pyoderma gangrenosum (PG).

In some embodiments, the individual has at least one condition selected from the group consisting of: an inflammatory bowel disease, arthritis, a hematological disease, and an autoinflammatory disease.

In some embodiments, the individual has at least one condition selected from the group consisting of: ulcerative colitis and Crohn's disease.

In some embodiments, the individual has at least one condition selected from the group consisting of: rheumatoid arthritis and seronegative arthritis.

In some embodiments, the individual has at least one condition selected from the group consisting of: myelocytic leukemia, hairy cell leukemia, myelofibrosis, myeloid metaplasia, and monoclonal gammopathy.

In some embodiments, the individual has at least one condition selected from the group consisting of: PAPA syndrome and granulomatosis with polyangiitis.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is in an amount equivalent to about 1 mg to about 5 mg of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is in an amount equivalent to about 2 mg of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is selected from: Compound 1, a calcium salt of Compound 1, and an L-arginine salt of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is an L-arginine salt of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is an anhydrous, non-solvated crystalline form of the L-arginine salt of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is a crystalline free-plate habit of the non-solvated L-arginine salt of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is an anhydrous, non-solvated crystalline form of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is administered orally.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is formulated as a capsule or tablet suitable for oral administration.

In some embodiments, the methods further comprise administering Compound 1, or a pharmaceutically salt, solvate, or hydrate thereof, in combination with a therapeutically effective amount of a compound selected from the group consisting of: a corticosteroid, an immunosuppressant, a biologic, an anti-inflammatory agent, and an antibiotic.

In some embodiments, the corticosteroid is cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone, and fludrocortisone.

In some embodiments, the immunosuppressant is selected from the group consisting of: cyclosporin A, tacrolimus, and mycophenolic acid.

In some embodiments, the immunosuppressant is cyclosporin A.

In some embodiments, the biologic is selected from the group consisting of: abatacept, adalimumab, adalimumab-atto, anakinra, certolizumab pegol, etanercept, etanercept-szzs, golimumab, infliximab, infliximab-dyyb, rituximab, tocilizumab, tofacitinib, vedolizumab, and natalizumab.

In some embodiments, the anti-inflammatory agent is selected from the group consisting of: aceclofenac, vedolizumab, aspirin, celecoxib, clonixin, dexibuprofen, dexketoprofen, diclofenac, diflunisal, droxicam, enolic acid, etodolac, etoricoxib, fenoprofen, flufenamic acid, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, licofelone, lornoxicam, loxoprofen, meclofenamic acid, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, parecoxib, phenylbutazone, piroxicam, salicylic acid, salsalate, sulindac, tenoxicam, tolfenamic acid, and tolmetin.

In some embodiments, the antibiotic is selected from the group consisting of: ceftobiprole, ceftaroline, clindamycin, dalbavancin, daptomycin, fusidic acid, linezolid, mupirocin, oritavancin, tedizolid, telavancin, tigecycline, vancomycin, amikacin, gentamicin, kanamycin, neomycin, netilmicin, tobramycin, and paromomycin.

In some embodiments, the antibiotic is selected from the group consisting of: mupirocin and gentamicin.

These and other aspects of the invention disclosed herein will be set forth in greater detail as the patent disclosure proceeds.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a clinical protocol for the treatment of IBD with skin EIMs with Compound 1.

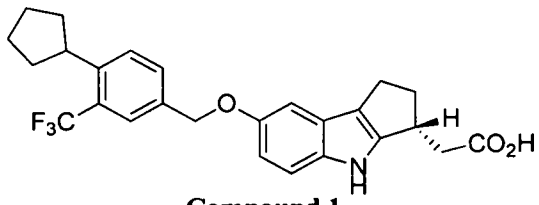
Figure 2 shows a clinical protocol for the treatment of pyoderma gangrenosum (PG) with Compound 1.

Figure 3 shows a PXRD Pattern overlay for the L-arginine salt of Compound 1 showing the peak intensity differences between plates and spherulites indicating a higher degree of crystallinity for the plates compared to the spherulites. Also shown is the lower sample-related background scatter (*i.e.*, a lower amorphous halo contribution) for the plates. However, the plates and spherulites are observed to show the same crystal phase.

Figure 4 shows a flowchart for the preparation of core tablets of the L-arginine salt of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (**Compound 1**).

DETAILED DESCRIPTION OF THE INVENTION

In its various embodiments, the present invention is directed to, *inter alia*, methods of treating active skin extra-intestinal manifestations (EIM) in an inflammatory bowel disease (IBD) individual in need thereof comprising administering a therapeutically effective amount of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt, hydrate, or solvate thereof.



Compound 1

In other embodiments, the present invention is directed to uses of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt, hydrate, or solvate thereof, in the manufacture of a medicament for the treatment of extra-intestinal manifestations (EIM) in an individual with inflammatory bowel disease (IBD).

In other embodiments, the present invention is directed to (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt, hydrate, or solvate thereof, for use in the treatment of extra-intestinal manifestations (EIM) in an individual with inflammatory bowel disease (IBD).

In some embodiments, the EIM is a dermal EIM. In some embodiments, the EIM is an active skin EIM.

The present invention further provides, *inter alia*, methods of treating pyoderma gangrenosum (PG) in an individual in need thereof comprising administering a therapeutically effective amount of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

In other embodiments, the present invention is directed to uses of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt, hydrate, or solvate thereof, in the manufacture of a medicament for the treatment of pyoderma gangrenosum (PG) in an individual.

In other embodiments, the present invention is directed to (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1), or a

pharmaceutically acceptable salt, hydrate, or solvate thereof, for use in the treatment of pyoderma gangrenosum.

Certain processes for the preparation of Compound 1 and the L-arginine salt of Compound 1 have been previously described; see WO2010/011316 and WO2011/094008. In addition, the novel crystalline plate habit for the L-arginine salt of Compound 1 has been previously described and is referred to herein as, "crystalline free-plate habit of the non-solvated L-arginine salt of Compound 1"; see WO2016/209809.

The following is a list of abbreviations: ACS (acute coronary syndrome); ADL (activities of daily living); AE (adverse event); ALB (albumin); ALK-P (alkaline phosphatase); ALT (alanine aminotransferase (SGPT)); AST (aspartate aminotransferase (SGOT)); bpm (beats per minute); BUN (blood urea nitrogen); Ca (calcium); CBC (complete blood count); CFR (Code of Federal Regulations); CI (confidence interval); CIA (collagen-induced arthritis); Cl (chloride); CL/F (apparent oral clearance); CMO (contract manufacturing organization); CRF (case report form); CRF (case report form); CRO (contract research organization); CRP (C-reactive protein); D (day); DLQI (Dermatology Life Quality Index); EAE (experimental autoimmune encephalomyelitis); ECG (electrocardiogram); ED50 (median effective dose); EIM (extra-intestinal manifestation); ELISA (enzyme-linked immunosorbent assay); EOS (end of study); EOT (end of treatment); FDA (Food and Drug Administration); FEF25-75% (mean forced expiratory flow between 25 and to 75% of FVC); FEV1 (forced expiratory volume in the first second); FU (follow-up); FVC (forced vital capacity); GCP (Good Clinical Practice); GGT (gamma glutamyl transferase); h (hour); Hb (hemoglobin); HBsAg (hepatitis B surface antigen); hCG (human chorionic gonadotropin); Hct (hematocrit); HCV (hepatitis C virus); HDPE (High-density polyethylene); HIV (human immunodeficiency virus); HR (heart rate); HREC (human resource ethics committee (AUS)); IBD (Inflammatory Bowel Disease); IBDQ (Inflammatory Bowel Disease Questionnaire); IBDQ (Inflammatory Bowel Disease Questionnaire); ICF (informed consent form); ICH (International Conference on Harmonization); IEC (Independent Ethics Committee); IND (Investigational New Drug); INR (international normalized ratio); IRB (Institutional Review Board); IUD (intrauterine device); IUS (hormone-releasing system); kg (kilogram); LDH (lactate dehydrogenase); MCH (mean corpuscular hemoglobin); MCV (mean corpuscular volume); MedDRA (Medical Dictionary for Regulatory Activities); mg (milligram); MI (myocardial infarction); mL (milliliter); mm (millimeter); mmHg (millimeters of mercury); MRSD (maximum recommended starting dose); Na (sodium); NOAEL (no observed adverse effect level); OCT (optical coherence tomography); OTC (over-the-counter); PA (Posteroanterior); PASI (Psoriasis Area and Severity Index); PBL (peripheral blood lymphocyte); PFT (pulmonary function test); PG (pyoderma gangrenosum); PGA (Physicians Global Assessments); PI (Principal Investigator); PPD (A CRO responsible for SAE processing in this study); PPD PVG (A Pharmacovigilance department of PPD); PRO (patient reported outcome); PRO (patient reported outcome); PT (prothrombin time); PTT (partial thromboplastin time); PV (pharmacovigilance); q.d.

(quaque die (once daily)); RBC (red blood cell (count)); RT-PCR (real-time polymerase chain reaction); S1P (sphingosine 1-phosphate receptor); S1P(1-5) (sphingosine 1-phosphate (1-5) receptor); SAE (serious adverse event); SAP (statistical analysis plan); SBP (systolic blood pressure); SD (standard deviation); sec (second); SOP(s) (standard operating procedure(s)); $t_{1/2}$ (elimination half-life); TEM (T effector memory cells); TIA (Transient Ischemic Attack); TIA (transient ischemic attack); tmax (the median time to reach maximum plasma concentration); UC (ulcerative colitis); ULN (upper limit of normal); VAS (visual analogue scale); VS (vital signs); VZV (varicella zoster virus); WBC (white blood cell); WHO (World Health Organization); and WHODRUG (World Health Organization Drug Dictionary).

CRYSTALLINE L-ARGININE SALT OF COMPOUND 1

The crystalline free-plate habit or morphology and processes useful in the preparation of a crystalline free-plate habit of L-arginine salt of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)-benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid are described in WO2016/209809. The plates were discovered from the novel synthetic methods and were shown to be thin hexagonal-like plates with two opposite sides of the plate being longer that the other sides (*i.e.*, elongated hexagonal plate). However, due to the thin characteristic of the plates, a complete unbroken plate is rarely seen. Instead, what is generally observed are large to small broken pieces of the thin hexagonal-like plates. It is understood by those skilled in the art that microscopy is one of the more useful techniques to distinguish two crystalline habits or morphologies. This is particularly useful when 2 or more morphologies are associated with the same or substantially the same crystal phase as is the case with the L-arginine salt of **Compound 1**. Comparing the PXRD patterns of the habit prepared previously (*i.e.*, WO2011/094008 and **Example 2** *infra*) and the plate habit prepared as described in WO2016/209809 (*i.e.*, see **Figure 3**, PXRD overlay between spherulites and plates) it was observed that the two PXRD patterns were the same or substantially the same, thus the two habits represented the same crystal phase.

Although the two habits revealed the same or substantially the same PXRD pattern, a higher degree of crystallinity was observed for the plate habit as indicated by substantially higher peak intensities and yet lower sample-related background scatter (*i.e.*, a lower amorphous halo contribution). Since sample size and sample preparation can affect peak intensities and sample-related background scatter, and since the two habits share the same crystal phase, PXRD may not be considered the most appropriate test method to distinguish between two habits. However, PXRD does allow for determining whether two habits have the same crystal phase or different crystal phases. For determining different habits, microscopy is one of the more useful methods. Accordingly, the skilled person would be capable of reviewing a micrograph for a crystal habit and readily determine the crystal habit.

In addition to the techniques recognized in the art, specific surface can also be used to characterize a habit, such as the free-plates. Accordingly, the specific surface area values disclosed in the

present invention have been obtained by means of a specific surface area analysis technique based on the BET (Brunauer, Emmett and Teller) theory, which is a well-accepted theory known in the art for the calculation of surface areas of solids by means of measuring their physical adsorption of gas molecules (see: Brunauer, S.; Emmett, P. H.; and Teller, E.; *J. Am. Chem. Soc.*, *1938*, **60**, 309). In particular, the specific surface area values measured in the present invention have been calculated from the BET surface area plot obtained by measuring the quantity of nitrogen gas molecules adsorbed by a weighted amount of solid at different relative pressures (P/P_0) within the range 0.05-0.3 (P/P_0), at 77.3 K. The measurement of the adsorption of gas molecules was carried out by means of a Micromeritics™ TriStar II BET surface analyzer having the characteristics as set out below in **Example 4**. Namely, nitrogen gas was used for the adsorption measurement. The sample for each analysis was degassed at 25°C for 960 minutes under vacuum (*i.e.*, 100 mm/Hg). The determination of the adsorption of nitrogen was measured at 77.3 K at eleven relative pressures (P/P_0) sufficiently dispersed within the range of about 0.05 to about 0.30 (*i.e.* eleven absolute pressures in the range of about 36 mm Hg to about 223 mm Hg relative to the saturated pressure at the time of measurement that ranged from about 738 mmHg to about 743 mmHg).

One aspect of the present invention relates to a novel crystalline plate morphology of L-arginine salt of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclo-penta[b]indol-3-yl)acetic acid as described herein.

One aspect of the present invention relates to a crystalline free-plate habit of L-arginine salt of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid.

In some embodiments, the crystalline free-plate habit has a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 16.4° ± 0.2°, and 20.5° ± 0.2°. In some embodiments, the crystalline free-plate habit has a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 20.5° ± 0.2°, and 24.6° ± 0.2°. In some embodiments, the crystalline free-plate habit has a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 16.4° ± 0.2°, 20.5° ± 0.2°, and 24.6° ± 0.2°. In some embodiments, the crystalline free-plate habit has a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 16.4° ± 0.2°, 20.5° ± 0.2°, 24.6° ± 0.2°, and 28.8° ± 0.2°. In some embodiments, the crystalline free-plate habit has a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 16.4° ± 0.2°, 20.5° ± 0.2°, 24.6° ± 0.2°, 28.8° ± 0.2°, and 37.3° ± 0.2°.

In some embodiments, the crystalline free-plate habit has a differential scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 205.0°C to 208.5°C at a scan rate of 10°C/minute. In some embodiments, the crystalline free-plate habit has a differential scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 205.0°C to 208.1°C at a scan rate of 10°C/minute. In some embodiments, the crystalline free-plate habit has a differential

scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 205.5°C to 208.5°C at a scan rate of 10°C/minute. In some embodiments, the crystalline free-plate habit has a differential scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 206.0°C to 208.5°C at a scan rate of 10°C/minute. In some embodiments, the crystalline free-plate habit has a differential scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 206.5°C to 208.5°C at a scan rate of 10°C/minute. In some embodiments, the crystalline free-plate habit has a differential scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 205.5°C to 208.1°C at a scan rate of 10°C/minute. In some embodiments, the crystalline free-plate habit has a differential scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 206.5°C to 208.1°C at a scan rate of 10°C/minute. In some embodiments, the crystalline free-plate habit has a differential scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 207.0°C to 208.1°C at a scan rate of 10°C/minute.

In some embodiments, the crystalline free-plate habit has a dynamic moisture sorption (DMS) profile with an adsorption phase from 30% RH to 90% RH wherein the crystalline free-plate habit gains about 0.3% weight or less at 90% RH. In some embodiments, the crystalline free-plate habit has a dynamic moisture sorption (DMS) profile with an adsorption phase from 30% RH to 90% RH wherein the crystalline free-plate habit gains about 0.2% weight or less at 90% RH.

One aspect of the present invention relates to a crystalline free-plate habit of L-arginine salt of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid having a BET specific surface area of about 0.05 m^2/g, about 0.1 m^2/g, about 0.15 m^2/g, about 0.2 m^2/g, about 0.25 m^2/g, about 0.3 m^2/g, about 0.35 m^2/g, about 0.4 m^2/g, about 0.45 m^2/g, about 0.5 m^2/g, about 0.55 m^2/g, about 0.6 m^2/g, about 0.65 m^2/g, or about 0.7 m^2/g to about 2.0 m^2/g, about 2.5 m^2/g, about 3.0 m^2/g, about 3.5 m^2/g, about 4.0 m^2/g, about 4.5 m^2/g, about 5.0 m^2/g, about 5.5 m^2/g, about 6.0 m^2/g, about 6.5 m^2/g, about 7.0 m^2/g, about 7.5 m^2/g, about 8.0 m^2/g, about 8.5 m^2/g, about 9.0 m^2/g, or about 9.5 m^2/g.

In some embodiments, the crystalline free-plate habit has a BET specific surface area of about 0.1 m^2/g to about 5.0 m^2/g. In some embodiments, the crystalline free-plate habit has a BET specific surface area of about 0.1 m^2/g to about 4.0 m^2/g. In some embodiments, the crystalline free-plate habit has a BET specific surface area of about 0.3 m^2/g to about 4.0 m^2/g. In some embodiments, the crystalline free-plate habit has a BET specific surface area of about 0.5 m^2/g to about 4.0 m^2/g. In some embodiments, the crystalline free-plate habit has a BET specific surface area of about 0.6 m^2/g to about 4.0 m^2/g. In some embodiments, the crystalline free-plate habit has a BET specific surface area of about 0.3 m^2/g to about 3.0 m^2/g. In some embodiments, the crystalline free-plate habit has a BET specific surface area of about 0.4 m^2/g to about 2.0 m^2/g. In some embodiments, the crystalline free-plate habit has a BET specific

surface area of about 0.5 m^2/g to about 1.8 m^2/g. In some embodiments, the crystalline free-plate habit has a BET specific surface area of about 0.6 m^2/g to about 1.6 m^2/g.

In some embodiments, the crystalline free-plate habit has:

1) a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 16.4° ± 0.2°, 20.5° ± 0.2°, 24.6° ± 0.2°, 28.8° ± 0.2°, and 37.3° ± 0.2°;

2) a differential scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 205.0°C to 208.5°C at a scan rate of 10°C/minute; and/or

3) a dynamic moisture sorption (DMS) profile with an adsorption phase from 30% RH to 90% RH wherein the crystalline free-plate habit gains about 0.3% weight or less at 90% RH.

In some embodiments, the crystalline free-plate habit has:

1) a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 16.4° ± 0.2°, 20.5° ± 0.2°, and 24.6° ± 0.2°;

2) a differential scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 206.5°C to t 208.5°C at a scan rate of 10°C/minute; and/or

3) a dynamic moisture sorption (DMS) profile with an adsorption phase from 30% RH to 90% RH wherein the crystalline free-plate habit gains about 0.3% weight or less at 90% RH.

In some embodiments, the crystalline free-plate habit has:

1) a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 20.5° ± 0.2°, and 24.6° ± 0.2°;

2) a differential scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 205.5°C to 208.5°C at a scan rate of 10°C/minute; and/or

3) a dynamic moisture sorption (DMS) profile with an adsorption phase from 30% RH to 90% RH wherein the crystalline free-plate habit gains about 0.2% weight or less at 90% RH.

In some embodiments, the crystalline free-plate habit has:

1) a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 16.4° ± 0.2°, and 20.5° ± 0.2°;

2) a differential scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 207.1°C to 208.1°C at a scan rate of 10°C/minute; and/or

3) a dynamic moisture sorption (DMS) profile with an adsorption phase from 30% RH to 90% RH wherein the crystalline free-plate habit gains about 0.2% weight or less at 90% RH.

In some embodiments, the crystalline free-plate habit has:

1) a differential scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 205.0°C to 208.5°C at a scan rate of 10°C/minute; and/or

2) a dynamic moisture sorption (DMS) profile with an adsorption phase from 30% RH to 90% RH wherein the crystalline free-plate habit gains about 0.3% weight or less at 90% RH.

In some embodiments, the crystalline free-plate habit has:

1) a differential scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 206.5°C to t 208.5°C at a scan rate of 10°C/minute; and/or

2) a dynamic moisture sorption (DMS) profile with an adsorption phase from 30% RH to 90% RH wherein the crystalline free-plate habit gains about 0.3% weight or less at 90% RH.

In some embodiments, the crystalline free-plate habit has:

1) a differential scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 205.5°C to 208.5°C at a scan rate of 10°C/minute; and/or

2) a dynamic moisture sorption (DMS) profile with an adsorption phase from 30% RH to 90% RH wherein the crystalline free-plate habit gains about 0.2% weight or less at 90% RH.

In some embodiments, the crystalline free-plate habit has:

1) a differential scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 207.1°C to 208.1°C at a scan rate of 10°C/minute; and/or

2) a dynamic moisture sorption (DMS) profile with an adsorption phase from 30% RH to 90% RH wherein the crystalline free-plate habit gains about 0.2% weight or less at 90% RH. In some embodiments, the crystalline free-plate habit has:

1) a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 16.4° ± 0.2°, and 20.5° ± 0.2°;

2) a differential scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 205.0°C to 208.5°C at a scan rate of 10°C/minute;

3) a dynamic moisture sorption (DMS) profile with an adsorption phase from 30% RH to 90% RH wherein said crystalline free-plate habit gains about 0.3% weight or less at 90% RH; and/or

4) a BET specific surface area of about 0.1 m^2/g to about 5.0 m^2/g. In some embodiments, the crystalline free-plate habit has:

1) a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 20.5° ± 0.2°, and 24.6° ± 0.2°;

2) a differential scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 205.5°C to t 208.5°C at a scan rate of 10°C/minute;

3) a dynamic moisture sorption (DMS) profile with an adsorption phase from 30% RH to 90% RH wherein said crystalline free-plate habit gains about 0.3% weight or less at 90% RH; and/or

4) a BET specific surface area of about 0.1 m^2/g to about 4.0 m^2/g.

In some embodiments, the crystalline free-plate habit has:

1) a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 20.5° ± 0.2°, and 24.6° ± 0.2°;

2) a differential scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 205.5°C to t 208.5°C at a scan rate of 10°C/minute;

3) a dynamic moisture sorption (DMS) profile with an adsorption phase from 30% RH to 90% RH wherein said crystalline free-plate habit gains about 0.3% weight or less at 90% RH; and/or

4) a BET specific surface area of about 0.3 m^2/g to about 3.0 m^2/g.

In some embodiments, the crystalline free-plate habit has:

1) a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 16.4° ± 0.2°, 20.5° ± 0.2°, and 24.6° ± 0.2°;

2) a differential scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 205.5°C to 208.5°C at a scan rate of 10°C/minute;

3) a dynamic moisture sorption (DMS) profile with an adsorption phase from 30% RH to 90% RH wherein said crystalline free-plate habit gains about 0.3% weight or less at 90% RH; and/or

4) a BET specific surface area of about 0.6 m^2/g to about 4.0 m^2/g.

In some embodiments, the crystalline free-plate habit has:

1) a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 16.4° ± 0.2°, 20.5° ± 0.2°, and 24.6° ± 0.2°;

2) a differential scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 206.5°C to t 208.5°C at a scan rate of 10°C/minute;

3) a dynamic moisture sorption (DMS) profile with an adsorption phase from 30% RH to 90% RH wherein said crystalline free-plate habit gains about 0.3% weight or less at 90% RH; and/or

4) a BET specific surface area of about 0.4 m^2/g to about 2.0 m^2/g.

In some embodiments, the crystalline free-plate habit has:

1) a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 16.4° ± 0.2°, 20.5° ± 0.2°, 24.6° ± 0.2°, and 28.8° ± 0.2°;

2) a differential scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 206.5°C to 208.1°C at a scan rate of 10°C/minute;

3) a dynamic moisture sorption (DMS) profile with an adsorption phase from 30% RH to 90% RH wherein said crystalline free-plate habit gains about 0.2% weight or less at 90% RH; and/or

4) a BET specific surface area of about 0.5 m^2/g to about 1.8 m^2/g.

In some embodiments, the crystalline free-plate habit has:

1) a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 16.4° ± 0.2°, 20.5° ± 0.2°, 24.6° ± 0.2°, 28.8° ± 0.2°, and 37.3° ± 0.2°;

2) a differential scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 205.5°C to 208.1°C at a scan rate of 10°C/minute;

3) a dynamic moisture sorption (DMS) profile with an adsorption phase from 30% RH to 90% RH wherein said crystalline free-plate habit gains about 0.2% weight or less at 90% RH; and/or

4) a BET specific surface area of about 0.6 m2/g to about 4.0 m2/g.

In some embodiments, the crystalline free-plate habit has:

1) a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 16.4° ± 0.2°, 20.5° ± 0.2°, 24.6° ± 0.2°, 28.8° ± 0.2°, and 37.3° ± 0.2°;

2) a differential scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 207.1°C to 208.1°C at a scan rate of 10°C/minute;

3) a dynamic moisture sorption (DMS) profile with an adsorption phase from 30% RH to 90% RH wherein said crystalline free-plate habit gains about 0.2% weight or less at 90% RH; and/or

4) a BET specific surface area of about 0.6 m^2/g to about 1.6 m^2/g.

One aspect of the present invention relates to a crystalline free-plate habit of L-arginine salt of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid having a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 16.4° ± 0.2°, and 20.5° ± 0.2°. In some embodiments, the crystalline free-plate habit has a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 20.5° ± 0.2°, and 24.6° ± 0.2°. In some embodiments, the crystalline free-plate habit has a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 16.4° ± 0.2°, 20.5° ± 0.2°, and 24.6° ± 0.2°. In some embodiments, the crystalline free-plate habit has a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 16.4° ± 0.2°, 20.5° ± 0.2°, 24.6° ± 0.2°, and 28.8° ± 0.2°. In some embodiments, the crystalline free-plate habit has a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 16.4° ± 0.2°, 20.5° ± 0.2°, 24.6° ± 0.2°, 28.8° ± 0.2°, and 37.3° ± 0.2°.

One aspect of the present invention relates to a crystalline free-plate habit of L-arginine salt of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid having a differential scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 205.0°C to 208.5°C when scanned at 10°C per minute. In some embodiments, the crystalline free-plate habit has a differential scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 205.0°C to 208.1°C at a scan rate of 10°C/minute. In some embodiments, the crystalline free-plate habit has a differential scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 205.5°C to 208.5°C at a scan rate of 10°C/minute. In some embodiments, the crystalline free-plate habit has a differential scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 205.5°C to 208.1°C at a scan rate of 10°C/minute. In some embodiments, the crystalline free-plate habit has a differential scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 206.0°C to 208.5°C at a scan rate of 10°C/minute. In some embodiments, the crystalline free-plate habit has a differential

scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 206.5°C to 208.5°C at a scan rate of 10°C/minute. In some embodiments, the crystalline free-plate habit has a differential scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 206.5°C to 208.1°C at a scan rate of 10°C/minute. In some embodiments, the crystalline free-plate habit has a differential scanning calorimetry trace comprising an endotherm with an extrapolated onset temperature of 207.0°C to 208.1°C at a scan rate of 10°C/minute. In some embodiments, the crystalline free-plate habit has a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 16.4° ± 0.2°, and 20.5° ± 0.2°. In some embodiments, the crystalline free-plate habit has a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 20.5° ± 0.2°, and 24.6° ± 0.2°. In some embodiments, the crystalline free-plate habit has a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 16.4° ± 0.2°, 20.5° ± 0.2°, and 24.6° ± 0.2°. In some embodiments, the crystalline free-plate habit has a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 16.4° ± 0.2°, 20.5° ± 0.2°, 24.6° ± 0.2°, and 28.8° ± 0.2°. In some embodiments, the crystalline free-plate habit has a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 16.4° ± 0.2°, 20.5° ± 0.2°, 24.6° ± 0.2°, 28.8° ± 0.2°, and 37.3° ± 0.2°.

One aspect of the present invention relates to a crystalline free-plate habit of L-arginine salt of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid having a dynamic moisture sorption (DMS) profile with an adsorption phase from 30% RH to 90% RH wherein the crystalline free-plate habit gains about 0.3% weight or less at 90% RH. In some embodiments, the crystalline free-plate habit has a dynamic moisture sorption (DMS) profile with an adsorption phase from 30% RH to 90% RH wherein the crystalline free-plate habit gains about 0.2% weight or less at 90% RH. In some embodiments, the crystalline free-plate habit has a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 16.4° ± 0.2°, and 20.5° ± 0.2°. In some embodiments, the crystalline free-plate habit has a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 20.5° ± 0.2°, and 24.6° ± 0.2°. In some embodiments, the crystalline free-plate habit has a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 16.4° ± 0.2°, 20.5° ± 0.2°, and 24.6° ± 0.2°. In some embodiments, the crystalline free-plate habit has a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 16.4° ± 0.2°, 20.5° ± 0.2°, 24.6° ± 0.2°, and 28.8° ± 0.2°. In some embodiments, the crystalline free-plate habit has a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 16.4° ± 0.2°, 20.5° ± 0.2°, 24.6° ± 0.2°, 28.8° ± 0.2°, and 37.3° ± 0.2°.

One aspect of the present invention relates to a crystalline free-plate habit of L-arginine salt of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid having a BET specific surface area of about 0.1 m^2/g to about 5.0 m^2/g. In some embodiments, the crystalline free-plate habit has a BET specific surface area of about 0.1 m^2/g to about 4.0 m^2/g. In some

embodiments, the crystalline free-plate habit has a BET specific surface area of about 0.3 m^2/g to about 4.0 m^2/g. In some embodiments, the crystalline free-plate habit has a BET specific surface area of about 0.5 m^2/g to about 4.0 m^2/g. In some embodiments, the crystalline free-plate habit has a BET specific surface area of about 0.6 m^2/g to about 4.0 m^2/g. In some embodiments, the crystalline free-plate habit has a BET specific surface area of about 0.3 m^2/g to about 3.0 m^2/g. In some embodiments, the crystalline free-plate habit has a BET specific surface area of about 0.4 m^2/g to about 2.0 m^2/g. In some embodiments, the crystalline free-plate habit has a BET specific surface area of about 0.5 m^2/g to about 1.8 m^2/g. In some embodiments, the crystalline free-plate habit has a BET specific surface area of about 0.6 m^2/g to about 1.6 m^2/g. In some embodiments, the crystalline free-plate habit has a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 16.4° ± 0.2°, and 20.5° ± 0.2°. In some embodiments, the crystalline free-plate habit has a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 20.5° ± 0.2°, and 24.6° ± 0.2°. In some embodiments, the crystalline free-plate habit has a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 16.4° ± 0.2°, 20.5° ± 0.2°, and 24.6° ± 0.2°. In some embodiments, the crystalline free-plate habit has a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 16.4° ± 0.2°, 20.5° ± 0.2°, 24.6° ± 0.2°, and 28.8° ± 0.2°. In some embodiments, the crystalline free-plate habit has a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 8.2° ± 0.2°, 16.4° ± 0.2°, 20.5° ± 0.2°, 24.6° ± 0.2°, 28.8° ± 0.2°, and 37.3° ± 0.2°.

CERTAIN EMBODIMENTS

In its various embodiments, the present invention is directed to, *inter alia*, methods of treating active skin extra-intestinal manifestations (EIM) in an inflammatory bowel disease (IBD) individual in need thereof comprising administering a therapeutically effective amount of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

In other embodiments, the present invention is directed to uses of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt, hydrate, or solvate thereof, in the manufacture of a medicament for the treatment of active skin extra-intestinal manifestations (EIM) in an individual with inflammatory bowel disease (IBD).

In some embodiments, the individual has at least one condition selected from the group consisting of: psoriasis, erythema nodosum (EN), and pyoderma gangrenosum (PG).

In some embodiments, the individual has psoriasis.

In some embodiments, the individual has erythema nodosum (EN).

In some embodiments, the individual has pyoderma gangrenosum (PG).

In some embodiments, the skin extra-intestinal manifestations (EIM) is psoriasis.

In some embodiments, the skin extra-intestinal manifestations (EIM) is erythema nodosum (EN).

In some embodiments, the skin extra-intestinal manifestations (EIM) is pyoderma gangrenosum (PG).

In some embodiments, the skin extra-intestinal manifestations (EIM) is pyoderma gangrenosum (PG).

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is in an amount equivalent to about 1 mg to about 5 mg of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is in an amount equivalent to about 1 mg to about 2 mg.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is in an amount equivalent to about 1 mg or about 2 mg.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is in an amount equivalent to about 1 mg of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is in an amount equivalent to about 2 mg of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is selected from: Compound 1, a calcium salt of Compound 1, and an L-arginine salt of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is an L-arginine salt of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is an anhydrous, non-solvated crystalline form of the L-arginine salt of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is a crystalline free-plate habit of the non-solvated L-arginine salt of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is an anhydrous, non-solvated crystalline form of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is administered orally.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is formulated as a capsule or tablet suitable for oral administration.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is administered once daily.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is administered without food.

In some embodiments, the methods further comprise administering Compound 1, or a pharmaceutically salt, solvate, or hydrate thereof, in combination with a therapeutically effective amount of a compound selected from the group consisting of: a corticosteroid, a 5-aminosalicylic acid derivative, and a TNF-alpha inhibitor.

In some embodiments, Compound 1 or a pharmaceutically salt, solvate, or hydrate thereof is administered to an individual who is also being administered a therapeutically effective amount of a compound selected from the group consisting of: a corticosteroid, a 5-aminosalicylic acid derivative, and a TNF-alpha inhibitor.

In some embodiments, when administered with Compound 1, an individual is administered a reduced amount of the compound selected from the group consisting of: a corticosteroid, a 5-aminosalicylic acid derivative, and a TNF-alpha inhibitor.

In some embodiments, the corticosteroid is cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone, and fludrocortisone.

In some embodiments, the 5-aminosalicylic acid derivative is selected from the group consisting of: balsalazide, mesalamine, olsalazine, and sulfasalazine.

In some embodiments, the TNF-alpha inhibitor is selected from the group consisting of: as infliximab (Remicade®), adalimumab (Humira®), certolizumab pegol (Cimzia®), and golimumab (Simponi®), and etanercept (Enbrel®).

In still other embodiments, the present invention is directed to, *inter alia*, methods of treating pyoderma gangrenosum (PG) in an individual in need thereof comprising administering a therapeutically effective amount of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

In some embodiments, the individual has at least one condition selected from the group consisting of: an inflammatory bowel disease, arthritis, a hematological disease, and an autoinflammatory disease.

In some embodiments, the individual has at least one condition selected from the group consisting of: ulcerative colitis and Crohn's disease.

In some embodiments, the individual has at least one condition selected from the group consisting of: rheumatoid arthritis and seronegative arthritis.

In some embodiments, the individual has at least one condition selected from the group consisting of: myelocytic leukemia, hairy cell leukemia, myelofibrosis, myeloid metaplasia, and monoclonal gammopathy.

In some embodiments, the individual has at least one condition selected from the group consisting of: PAPA syndrome and granulomatosis with polyangiitis.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is in an amount equivalent to about 1 mg to about 5 mg of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is in an amount equivalent to about 1 mg to about 2 mg.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is in an amount equivalent to about 1 mg or about 2 mg.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is in an amount equivalent to about 1 mg of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is in an amount equivalent to about 2 mg of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is selected from: Compound 1, a calcium salt of Compound 1, and an L-arginine salt of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is an L-arginine salt of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is an anhydrous, non-solvated crystalline form of the L-arginine salt of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is a crystalline free-plate habit of the non-solvated L-arginine salt of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is an anhydrous, non-solvated crystalline form of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is administered orally.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is formulated as a capsule or tablet suitable for oral administration.

In some embodiments, the methods further comprise administering Compound 1, or a pharmaceutically salt, solvate, or hydrate thereof, in combination with a therapeutically effective amount of a compound selected from the group consisting of: a corticosteroid, an immunosuppressant, a biologic, an anti-inflammatory agent, and an antibiotic.

In some embodiments, the corticosteroid is cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone, and fludrocortisone.

In some embodiments, the immunosuppressant is selected from the group consisting of: cyclosporin A, tacrolimus, and mycophenolic acid.

In some embodiments, the immunosuppressant is cyclosporin A.

In some embodiments, the biologic is selected from the group consisting of: abatacept, adalimumab, adalimumab-atto, anakinra, certolizumab pegol, etanercept, etanercept-szzs, golimumab, infliximab, infliximab-dyyb, rituximab, tocilizumab, tofacitinib, vedolizumab, and natalizumab. Additional names, such as their marketed names for the biologics include: abatacept (Orencia®),

adalimumab (Humira®), adalimumab-atto (Amjevita®) a biosimilar to Humira, anakinra (Kineret®), certolizumab pegol (Cimzia®), etanercept (Enbrel®, etanercept-szzs (Erelzi®) a biosimilar to Enbrel, golimumab (Simponi®, Simponi Aria®), infliximab (Remicade®), infliximab-dyyb (Inflectra®) a biosimilar to Remicade, rituximab (Rituxan®), tocilizumab (Actemra®), tofacitinib (Xeljanz®), vedolizumab (Entyvio®), and natalizumab (Tysabri®).

In some embodiments, the anti-inflammatory agent is selected from the group consisting of: aceclofenac, vedolizumab, aspirin, celecoxib, clonixin, dexibuprofen, dexketoprofen, diclofenac, diflunisal, droxicam, enolic acid, etodolac, etoricoxib, fenoprofen, flufenamic acid, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, licofelone, lornoxicam, loxoprofen, meclofenamic acid, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, parecoxib, phenylbutazone, piroxicam, salicylic acid, salsalate, sulindac, tenoxicam, tolfenamic acid, and tolmetin.

In some embodiments, the antibiotic is selected from the group consisting of: ceftobiprole, ceftaroline, clindamycin, dalbavancin, daptomycin, fusidic acid, linezolid, mupirocin, oritavancin, tedizolid, telavancin, tigecycline, vancomycin, amikacin, gentamicin, kanamycin, neomycin, netilmicin, tobramycin, and paromomycin.

In some embodiments, the antibiotic is selected from the group consisting of: mupirocin and gentamicin.

In other embodiments, the present invention is directed to uses of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt, hydrate, or solvate thereof, in the manufacture of a medicament for the treatment of pyoderma gangrenosum (PG) in an individual.

In some embodiments, the individual has at least one condition selected from the group consisting of: an inflammatory bowel disease, arthritis, a hematological disease, and an autoinflammatory disease.

In some embodiments, the individual has at least one condition selected from the group consisting of: ulcerative colitis and Crohn's disease.

In some embodiments, the individual has at least one condition selected from the group consisting of: rheumatoid arthritis and seronegative arthritis.

In some embodiments, the individual has at least one condition selected from the group consisting of: myelocytic leukemia, hairy cell leukemia, myelofibrosis, myeloid metaplasia, and monoclonal gammopathy.

In some embodiments, the individual has at least one condition selected from the group consisting of: PAPA syndrome and granulomatosis with polyangiitis.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is in an amount equivalent to about 1 mg to about 5 mg of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is in an amount equivalent to about 2 mg of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is selected from: Compound 1, a calcium salt of Compound 1, and an L-arginine salt of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is an L-arginine salt of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is an anhydrous, non-solvated crystalline form of the L-arginine salt of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is a crystalline free-plate habit of the non-solvated L-arginine salt of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is an anhydrous, non-solvated crystalline form of Compound 1.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is administered orally.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is formulated as a capsule or tablet suitable for oral administration.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is administered once daily.

In some embodiments, the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is administered without food.

In some embodiments, the methods further comprise administering Compound 1, or a pharmaceutically salt, solvate, or hydrate thereof, in combination with a therapeutically effective amount of a compound selected from the group consisting of: a corticosteroid, an immunosuppressant, a biologic, an anti-inflammatory agent, and an antibiotic.

In some embodiments, the corticosteroid is cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone, and fludrocortisone.

In some embodiments, the immunosuppressant is selected from the group consisting of: cyclosporin A, tacrolimus, and mycophenolic acid.

In some embodiments, the immunosuppressant is cyclosporin A.

In some embodiments, the biologic is selected from the group consisting of: abatacept, adalimumab, adalimumab-atto, anakinra, certolizumab pegol, etanercept, etanercept-szzs, golimumab, infliximab, infliximab-dyyb, rituximab, tocilizumab, tofacitinib, vedolizumab, and natalizumab. Additional names, such as their marketed names for the biologics include: abatacept (Orencia®), adalimumab (Humira®), adalimumab-atto (Amjevita®) a biosimilar to Humira, anakinra (Kineret®), certolizumab pegol (Cimzia®), etanercept (Enbrel®, etanercept-szzs (Erelzi®) a biosimilar to Enbrel, golimumab (Simponi®, Simponi Aria®), infliximab (Remicade®), infliximab-dyyb (Inflectra®) a

biosimilar to Remicade, rituximab (Rituxan®), tocilizumab (Actemra®), tofacitinib (Xeljanz®), vedolizumab (Entyvio®), and natalizumab (Tysabri®).

In some embodiments, the anti-inflammatory agent is selected from the group consisting of: aceclofenac, vedolizumab, aspirin, celecoxib, clonixin, dexibuprofen, dexketoprofen, diclofenac, diflunisal, droxicam, enolic acid, etodolac, etoricoxib, fenoprofen, flufenamic acid, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, licofelone, lornoxicam, loxoprofen, meclofenamic acid, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, parecoxib, phenylbutazone, piroxicam, salicylic acid, salsalate, sulindac, tenoxicam, tolfenamic acid, and tolmetin.

In some embodiments, the antibiotic is selected from the group consisting of: ceftobiprole, ceftaroline, clindamycin, dalbavancin, daptomycin, fusidic acid, linezolid, mupirocin, oritavancin, tedizolid, telavancin, tigecycline, vancomycin, amikacin, gentamicin, kanamycin, neomycin, netilmicin, tobramycin, and paromomycin.

In some embodiments, the antibiotic is selected from the group consisting of: mupirocin and gentamicin.

In some embodiments, the pyoderma gangrenosum is classic pyoderma gangrenosum.

In some embodiments, the individual is experiencing an inflammatory episode of pyoderma gangrenosum.

In some embodiments, the individual has at least one ulcer located on their leg.

In some embodiments, the individual has at least one ulcer located on their hand.

In some embodiments, the pyoderma gangrenosum is selected from at least one of the following: peristomal pyoderma gangrenosum, bullous pyoderma gangrenosum, pustular pyoderma gangrenosum, and vegetative pyoderma gangrenosum.

In some embodiments, the individual has at least one active pyoderma gangrenosum ulcer.

In some embodiments, the individual has at least one active, non-healing pyoderma gangrenosum ulcer.

In some embodiments, the individual does not have inflammatory bowel disease.

In some embodiments, the individual does not have ulcerative colitis.

In some embodiments, the individual does not have Crohn's disease.

In some embodiments, Compound 1 is administered without food.

In some embodiments, the individual is administered the therapeutically effective amount of Compound 1 once daily.

PHARMACEUTICAL COMPOSITIONS

A further aspect of the present invention pertains to pharmaceutical compositions comprising one or more compounds as described herein and one or more pharmaceutically acceptable carriers. Some

embodiments pertain to pharmaceutical compositions comprising a compound of the present invention and a pharmaceutically acceptable carrier.

Some embodiments of the present invention include a method of producing a pharmaceutical composition comprising admixing at least one compound according to any of the compound embodiments disclosed herein and a pharmaceutically acceptable carrier.

Formulations may be prepared by any suitable method, typically by uniformly mixing the active compound(s) with liquids or finely divided solid carriers, or both, in the required proportions and then, if necessary, forming the resulting mixture into a desired shape.

Conventional excipients, such as binding agents, fillers, acceptable wetting agents, tabletting lubricants and disintegrants may be used in tablets and capsules for oral administration. Liquid preparations for oral administration may be in the form of solutions, emulsions, aqueous or oily suspensions and syrups. Alternatively, the oral preparations may be in the form of dry powder that can be reconstituted with water or another suitable liquid vehicle before use. Additional additives such as suspending or emulsifying agents, non-aqueous vehicles (including edible oils), preservatives and flavorings and colorants may be added to the liquid preparations. Parenteral dosage forms may be prepared by dissolving the compound of the invention in a suitable liquid vehicle and filter sterilizing the solution before filling and sealing an appropriate vial or ampule. These are just a few examples of the many appropriate methods well known in the art for preparing dosage forms.

A compound of the present invention can be formulated into pharmaceutical compositions using techniques well known to those in the art. Suitable pharmaceutically acceptable carriers, outside those mentioned herein, are known in the art; for example, see Remington, *The Science and Practice of Pharmacy*, 20th Edition, 2000, Lippincott Williams & Wilkins, (Editors: Gennaro *et al.*)

While it is possible that, for use in the prophylaxis or treatment, a compound of the invention may, in an alternative use, be administered as a raw or pure chemical, it is preferable however to present the compound or active ingredient as a pharmaceutical formulation or composition further comprising a pharmaceutically acceptable carrier.

The invention thus further provides pharmaceutical formulations comprising a compound of the invention or a pharmaceutically acceptable salt, solvate, hydrate or derivative thereof together with one or more pharmaceutically acceptable carriers thereof and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not overly deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation, insufflation or by a transdermal patch. Transdermal patches dispense a drug at a controlled rate by presenting the drug for absorption in an efficient manner with a minimum of degradation of the drug. Typically, transdermal patches comprise an

impermeable backing layer, a single pressure sensitive adhesive and a removable protective layer with a release liner. One of ordinary skill in the art will understand and appreciate the techniques appropriate for manufacturing a desired efficacious transdermal patch based upon the needs of the artisan.

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical formulations and unit dosages thereof and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, gels or capsules filled with the same, all for oral use; in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are capsules, tablets, powders, granules or suspensions, with conventional additives such as lactose, mannitol, corn starch or potato starch; with binders such as crystalline cellulose, cellulose derivatives, acacia, corn starch or gelatins; with disintegrators such as corn starch, potato starch or sodium carboxymethyl-cellulose; and with lubricants such as talc or magnesium stearate. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable pharmaceutically acceptable carrier.

Compounds of the present invention or a salt, solvate, hydrate or physiologically functional derivative thereof can be used as active ingredients in pharmaceutical compositions, specifically as S1P1 receptor modulators. The term "active ingredient" is defined in the context of a "pharmaceutical composition" and is intended to mean a component of a pharmaceutical composition that provides the primary pharmacological effect, as opposed to an "inactive ingredient" which would generally be recognized as providing no pharmaceutical benefit.

The dose when using the compounds of the present invention can vary and as is customary and known to the physician, it is to be tailored to the individual conditions in each individual case. It depends, for example, on the nature and severity of the illness to be treated, on the condition of the individual, on the compound employed or on whether an acute or chronic disease state is treated or prophylaxis is conducted or on whether further active compounds are administered in addition to the compounds of the present invention. Representative doses of the present invention include, but are not limited to, about 1 mg to about 5 mg, about 1 mg, about 1.25 mg, about 1.5 mg, about 1.75 mg, about 2 mg, about 2.25 mg, about 2.5 mg, about 2.75 mg, about 3 mg, about 3.25 mg, about 3.5 mg, about 3.75 mg, about 4 mg, about 4.25 mg, about 4.5 mg, about 4.75 mg, and about 5 mg. Multiple doses may be administered during the

day, especially when relatively large amounts are deemed to be needed, for example 2, 3 or 4 doses. Depending on the individual and as deemed appropriate by the individual's physician or caregiver it may be necessary to deviate upward or downward from the doses described herein.

The amount of active ingredient or an active salt, solvate or hydrate derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the individual and will ultimately be at the discretion of the attendant physician or clinician. Representative factors include the type, age, weight, sex, diet and medical condition of the individual, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized, whether an acute or chronic disease state is being treated or prophylaxis is conducted or whether further active compounds are administered in addition to the compounds of the present invention and as part of a drug combination. The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety factors including those cited above. Thus, the actual dosage regimen employed may vary widely and therefore may deviate from a preferred dosage regimen and one skilled in the art will recognize that dosage and dosage regimens outside these typical ranges can be tested and, where appropriate, may be used in the methods of this invention.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as 2, 3, 4 or more sub-doses per day. The sub-dose itself may be further divided, *e.g.*, into a number of discrete loosely spaced administrations. The daily dose can be divided, especially when relatively large amounts are administered as deemed appropriate, into several, for example 2, 3 or 4 part administrations. If appropriate, depending on individual behavior, it may be necessary to deviate upward or downward from the daily dose indicated.

For preparing pharmaceutical compositions from the compounds of the present invention, the suitable pharmaceutically acceptable carrier can be either solid, liquid or a mixture of both. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or encapsulating materials.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted to the desired shape and size.

The powders and tablets may contain varying percentage amounts of the active compound. A representative amount in a powder or tablet may be from 0.5 to about 90 percent of the active compound. However, an artisan would know when amounts outside of this range are necessary. Suitable carriers for

powders and tablets include magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as an admixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein (*e.g.*, by stirring). The molten homogenous mixture is then poured into convenient sized molds, allowed to cool and thereby to solidify.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Liquid form preparations include solutions, suspensions and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution. Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds according to the present invention may thus be formulated for parenteral administration (*e.g.* by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The pharmaceutical compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, *e.g.* sterile, pyrogen-free water, before use.

Aqueous formulations suitable for oral use can be prepared by dissolving or suspending the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents and the like.

For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch.

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising the active agent in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multi-dose form. In the latter case of a dropper or pipette, this may be achieved by the individual administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomizing spray pump.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurized pack with a suitable propellant. If the compounds of the present invention or pharmaceutical compositions comprising them are administered as aerosols (*e.g.*, nasal aerosols, by inhalation), this can be carried out, for example, using a spray, a nebulizer, a pump nebulizer, an inhalation apparatus, a metered inhaler or a dry powder inhaler. Pharmaceutical forms for administration of the compounds of the present invention as an aerosol can be prepared by processes well known to the person skilled in the art. Solutions or dispersions of the compounds of the present invention or a pharmaceutically acceptable salt, solvate, hydrate or derivative thereof in water, water/alcohol mixtures or suitable saline solutions, for example, can be employed using customary additives (*e.g.*, benzyl alcohol or other suitable preservatives), absorption enhancers for increasing the bioavailability, solubilizers, dispersants and others and, if appropriate, customary propellants (*e.g.*, carbon dioxide, CFCs, such as, dichlorodifluoromethane, trichlorofluoromethane,

dichlorotetrafluoroethane and the like). The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

In formulations intended for administration to the respiratory tract, including intranasal formulations, the compound will generally have a small particle size for example of the order of 10 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. When desired, formulations adapted to give sustained release of the active ingredient may be employed.

Alternatively, the active ingredients may be provided in the form of a dry powder (*e.g.*, a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP)). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form (*e.g.*, capsules, cartridges) as for gelatin or blister packs from which the powder may be administered by means of an inhaler.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

In some embodiments, the compositions are tablets or capsules for oral administration.

In some embodiments, the compositions are liquids for intravenous administration.

The compounds according to the invention may optionally exist as pharmaceutically acceptable salts including pharmaceutically acceptable acid addition salts prepared from pharmaceutically acceptable non-toxic acids including inorganic and organic acids. Representative acids include, but are not limited to, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, dichloroacetic, formic, fumaric, gluconic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, oxalic, pamoic, pantothenic, phosphoric, succinic, sulfiric, tartaric, oxalic, p-toluenesulfonic and the like, such as those pharmaceutically acceptable salts listed by Berge *et al.*, *Journal of Pharmaceutical Sciences*, 66:1-19 (1977), incorporated herein by reference in its entirety.

The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent. The compounds of this invention may form solvates with standard low molecular weight solvents using methods known to the skilled artisan.

Compounds of the present invention can be converted to "pro-drugs." The term "pro-drugs" refers to compounds that have been modified with specific chemical groups known in the art and that

when administered into an individual undergo biotransformation to give the parent compound. Pro-drugs can thus be viewed as compounds of the invention containing one or more specialized non-toxic protective groups used in a transient manner to alter or to eliminate a property of the compound. In one general aspect, the "pro-drug" approach is utilized to facilitate oral absorption. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems Vol. 14 of the A.C.S. Symposium Series; and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are hereby incorporated by reference in their entirety.

Some embodiments of the present invention include a method of producing a pharmaceutical composition for "combination-therapy" comprising admixing at least one compound according to any of the compound embodiments disclosed herein, together with at least one known pharmaceutical agent as described herein and a pharmaceutically acceptable carrier.

As will be recognized, the steps of the methods of the present invention need not be performed any particular number of times or in any particular sequence. Additional objects, advantages and novel features of this invention will become apparent to those skilled in the art upon examination of the following examples thereof, which are intended to be illustrative and not intended to be limiting.

EXAMPLES

Example 1: Preparation of Compounds

The preparation of Compound 1, including certain crystal forms of Compound 1 are described in International Patent Application No. PCT/US2009/004265, published as International Publication No. WO2010/011316, and International Patent Application No. PCT/US2011/000153, published as International Publication No. WO2011/094008, the entire contents of each are incorporated herein by reference in their entirety.

The preparation of the crystalline free-plate habit of the non-solvated L-arginine salt of Compound 1 is described in International Patent Application No. PCT/US2016/038506, published as International Publication No. WO2016/209809, the entire contents of which are incorporated herein by reference in their entirety.

Example 2: Clinical Trial for Skin Extra-Intestinal Manifestation (EIM) with Compound 1

A clinical trial is conducted in 10-20 individuals with IBD and active skin extra-intestinal manifestations.

All visits in the study are ambulatory visits. A screening period of up to four weeks is followed by a 12-week treatment period. During the treatment period, individuals take one 2 mg tablet of **Compound 1** once per day. The last dose is taken one day before the last treatment visit at week 12. A follow-up visit takes place two weeks after the end of treatment (**Figure 1**).

Screening Visit:

Individuals visit the study site for screening assessments up to four weeks prior to the planned start of treatment.

Individuals start the 24-hour ambulatory pre-dose Holter (ECG) monitoring procedure at D-1.

Treatment Visits:

Visit (week 0, day 1):

Individuals return to the study site to receive the first dose of Compound 1 and remain at the study site for six hours for safety evaluation. Holter monitoring continues for another 18 hours.

Visits at week 1, week 2, week 4, week 8, and week 12:

Individuals return to the study site and undergo examinations at weeks 1, 2, 4, 8, and 12. The last dose of Compound 1 is administered one day before the last treatment visit at week 12.

Follow up Visits / End of Study Visit:

Week 14 (two weeks after end of treatment):

Individuals return to the study site for the final visit.

Premature Discontinuation:

Procedures planned for week 14 are performed for all individuals that discontinue the study prematurely.

Inclusion Criteria

1. Men or women of age 18 to 80 years, inclusive.

2. Able to give signed informed consent and willing and able to comply with the study requirements.

3. Considered to be in stable health in the opinion of the investigator as determined by:

a.) A pre-study physical examination with no clinically significant abnormalities unrelated to IBD.

b.) Vital signs (VS) at screening: pulse rate $\geq$ 55 bpm, systolic blood pressure (SBP) $\geq$ 90, and diastolic blood pressure (DBP) $\geq$ 55 mmHg.

c.) Liver function tests (ALT/AST, bilirubin and alkaline phosphatase) < 2x the upper limit of normal [ULN].

d.) All other pre-study clinical laboratory findings within normal range, or if outside of the normal range not deemed clinically significant in the opinion of the investigator.

e.) 12-lead electrocardiogram (ECG) showing no clinically significant abnormalities in the opinion of the investigator.

f.) A chest x- ray showing no evidence of active pulmonary disease (a chest x-ray taken within the previous 12 months from the screening visit may also be used).

g.) Ophthalmology evaluation (by an ophthalmologist) without evidence of macular edema, supported with OCT where available (dependent on site capability) no later than three months prior to screening.

4. Individuals receiving stable treatment for IBD and EIM.

5. Diagnosis of active psoriasis, erythema nodosum or pyoderma gangrenosum by physician assessments.

6. Diagnosis of ulcerative colitis (UC) or Crohn's disease (CD) established prior to screening by clinical and endoscopic evidence.

Permitted Medications for the Treatment of IBD (UC and CD)

Oral 5-ASA treatment is permitted for the treatment of IBD, provided that the individual is receiving the medication(s) at baseline, and that the dose(s) has been stable. These medications are to remain stable throughout the study.

Oral corticosteroids that the individual is receiving at baseline are continued, provided that the dose has been stable for two weeks prior to baseline. These medications are to remain stable at least eight weeks.

TNF-alpha inhibitor treatment is permitted provided that the dose remains stable throughout the study.

Probiotics (e.g., Culturelle, Saccharomyces boulardii) are permitted provided that the dose has been stable for the two weeks immediately prior to randomization.

Antidiarrheals are allowed throughout the study as necessary for control of chronic diarrhea.

Azathioprine or 6-mercaptopurine are permitted, provided that the dose has been stable for the eight weeks immediately prior to screening (these immunosuppressive agents are discontinued at the time of randomization).

Dermatological medications that the individual is receiving at baseline are continued, provided that these are stable for two weeks prior to baseline and remain stable throughout the study.

Physician's Global Assessment (PGA)

1) Disease activity score for CD

Patient reported outcomes (liquid stools, abdominal pain and general wellbeing) are captured in a daily diary by the individual. Patient reported outcomes can be reviewed by site personnel during screening and (prior to dosing, if applicable) at weeks 0, 1, 2, 4, 8 and 12 and at any unscheduled visit(s) due to disease exacerbation. Presence of extra-intestinal manifestation (arthritis/anthralgia, iritis/uveitis, skin/mouth lesion, peri-anal disease, other fistula, fever > 37.8°C), use of anti-diarrheals, abdominal mass, haematocrit and weight are captured weekly or at each visit. The investigator or designee calculates the disease activity scores taking into consideration the above data and the individual reported outcomes.

2) Physician Global Assessments for active skin extra-intestinal manifestations

The Physician Global Assessment (PGA) is used as an instrument to measure skin disease activity (e.g., for EG, EN or psoriasis).

Patients Global Assessment for active skin extra-intestinal manifestations.

The Patients Global Assessment will be used to measure how individuals rate the severity and pain of their skin disease.

3) Dermatology Life Quality Index (DLQI)

This questionnaire measures how much of the individual's life is affected by their skin problems.

4) Psoriasis Area and Severity Index (PASI)

The PASI is a tool for the measurement of severity of psoriasis. PASI combines the assessment of the severity of lesions and the area affected into a single score in the range 0 (no disease) to 72 (maximum disease).

5) Inflammatory Bowel Disease Questionnaire (IBDQ)

The IBDQ is used to measure how the individual has felt during the last two weeks. The IBDQ is used during screening and at weeks 2, 4, 8, and 12.

6) Skin Punch Biopsies

Skin punch biopsies (from healthy skin and from target lesion) are collected before treatment and at week 8 or 12. Immunohistochemistry and other analysis methods (such as RT-PCR) are performed to evaluate immune cell infiltration, cytokine expression in the skin and other inflammatory parameters.

7) C-reactive Protein (CRP)

Blood samples for analysis of C-reactive protein (CRP) are collected at screening; at weeks 0, 1, 2, 4, 8, and 12; and at the two-week follow-up.

Efficacy Endpoints

- UC endpoint: Change from baseline in stool frequency, rectal bleeding, PGA (Physicians Global Assessments) at weeks 1, 2, 4, 8 and 12.
- CD endpoint: Change from baseline in disease activity score at week 1, 2, 4, 8 and 12.
- Change from baseline in endoscopic improvement/histologic healing using endoscopy or flexible proctosigmoidoscopy (only if there are signs of inflammation at screening another evaluation is performed at week 12).
- Change from baseline in level of fecal calprotectin at week 4, 8 and 12. Change from baseline in Physician Global Assessments for active skin extra-intestinal manifestations (PG, EN and psoriasis) at week 1, 2, 4, 8 and 12.
- Change from baseline in Patients Global Assessments for active skin extra-intestinal manifestations (PG, EN and psoriasis) at week 1, 2, 4, 8 and 12.

- Change from baseline in the Dermatology Life Quality Index (DLQI) score at week 1, 2, 4, 8 and 12.
- Psoriasis endpoint only (all other endpoints are for all skin manifestations): Change from baseline in Psoriasis Area and Severity Index (PASI) score at week 1, 2, 4, 8 and 12.
- Change from baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) score at week 2, 4, 8 and 12.
- Skin punch biopsies (from healthy skin and from target lesion) are collected before treatment and at week 8 or 12. Immunohistochemistry and other analyzing methods such as RT-PCR are performed to evaluate immune cell infiltration, cytokine expression in the skin and other inflammatory parameters.
- Change from baseline in C-reactive protein (CRP) at weeks 1, 2, 4, 8 and 12.
- Change from baseline in leucocyte characterization.
- Change from baseline in lymphocyte counts at weeks 1, 2, 4, 8 and 12.

Example 3: Clinical Trial for Pyoderma Gangrenosum with Compound 1

A clinical trial is conducted in individuals aged 18 to 80 years old (inclusive) who have active pyoderma gangrenosum (PG) ulcers. All visits in the study are ambulatory visits. The screening period lasts up to four weeks and is followed by a 12-week treatment period. During the treatment period, individuals take one 2 mg tablet of Compound 1 once per day. The last dose is taken one day before the end of the treatment period (week 12). A follow-up visit takes place two weeks after the end of treatment.

Screening Visit

Each individual visits the study site for screening assessment within 4 weeks of the planned start of the treatment (Day 1). Individuals then undergo screening procedures to determine eligibility.

Individuals return to the study site at Day-1 for confirmation of eligibility, and start the 24-hour ambulatory pre-dose Holter (ECG) monitoring procedure.

Treatment Visits

Baseline Visit (Day 1): Individuals return to the study site to receive the first dose of Compound 1. Individuals are instructed to take the tablet first thing in the morning on an empty stomach. Individuals are advised not to crush, break, chew, or dissolve the tablet and to take study medication with an adequate amount of water. The individuals remain at the study site for at least six hours for safety evaluation. Holter monitoring continues to allow for an overall continuous 24-hour pre- and a 24-hour post-dose monitoring.

Visits at week 2, week 4, week 8, and week 12: Individuals return to the study site and tests are conducted. The last dose of Compound 1 is planned 1 day before the end of the treatment visit at week 12.

Follow up Visit/End of Study Visit

Visit at week 14 (two weeks after end of treatment): Individuals return to the study site for the final visit.

Permitted Medications

- Oral corticosteroids
- TNF-alpha inhibitor (etanercept, infliximab, adalimumab or other)
- Oral 5-ASA medication
- Antidiarrheal treatment
- OTC analgesics (paracetamol / acetaminophen, NSAIDs)

Efficacy Endpoints

- Change from baseline (Day 1 pre-dose) to week 12 in Physician Global Assessments for active skin manifestations. Assessment of target lesion/ulceration:
  - **0**: Total resolution of target ulcer with no signs of active PG
  - **1**: Almost completely healed target ulcer with only minimal signs of active PG
  - **2**: Evidence of target ulcer healing which involves at least 50% of ulcer/ulcer margin
  - **3**: Evidence of target ulcer healing which involves less than 50% of ulcer/ulcer margin
  - **4**: No evidence of target ulcer healing
- Change from baseline (Day 1 pre-dose) to week 12 in Patient Global Assessments for active skin manifestations: visual analog scale (VAS) for assessment of severity of the disease and severity of pain by patient.
- Change from baseline (Day 1 pre-dose) to week 12 in Dermatology Life Quality Index (DLQI).
- Change from baseline (Day 1 pre-dose) to week 12 in CRP levels.

The following measures are also assessed:

- Imaging (digital photos) of the target lesion.
- Evaluation of the changes in surface area of target lesion.
- Punch biopsy (histology).

Example 4: BET (Brunauer, Emmett, and Teller) Specific Surface Area Method (Plate Habit)

In general, the specific surface areas for crystalline free-plate habit of the non-solvated L-arginine salt of Compound 1 were determined by physical adsorption of nitrogen gas on the surface of the sample from each lot using the well-established technique based on the Brunauer, Emmett, and Teller theory.

The BET surface areas for the samples were measured by Micromeritics Pharmaceutical Services using a Micromeritics™ TriStar II BET surface area analyzer (MicroActive for TriStar II Plus 2.02 Software™). The samples were degassed at 25°C for 960 minutes under vacuum (*i.e.*, 100 mm/Hg). The determination of the adsorption of N_2 at 77.3 K was measured using a BET surface area eleven-point method with relative pressures in the range of about 0.05 to about 0.3 (P/P_0) for a weighed amount of each sample, see **Table 1** below. The analysis was performed per ISO9277.

TABLE 1

Arena Lot	Lot Number	Sample (g)	Correlation Coefficient	BET Surface Area (m^2/g)
5015-12-12	A1	0.6163	0.99916	0.7
5015-12-13	A2	1.5270	0.99945	0.7
5015-12-14	A3	0.4465	0.99922	1.5
5015-12-15	A4	0.5709	0.99939	1.0
5015-12-16	A5	0.9582	0.99940	0.8
04GSp	A6	0.4332	0.99921	2.4
05GSp	A7	0.3652	0.99910	1.9
06GSp	A8	0.6866	0.99984	3.0
07GSp	A9	0.2754	0.99914	3.1

Example 5: Formulations for L-Arginine Salt of (R)-2-(7-(4-Cyclopentyl-3-(trifluoromethyl)-benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic Acid.

Core tablets were manufactured using the formulation as described in **Table 2** and using substantially the same process as described in **Figure 4**. The L-arginine salt of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid is 72.42% free acid (Compound 1) and 27.58% L-arginine (*i.e.*, 1.381 mg of the L-arginine salt of Compound 1 corresponds to 1 mg of active/free acid).

Table 2

Tablet Strength	**1 mg**	**2 mg**
L-Arg Salt of **Compound 1**	1.381	2.762
Mannitol Pearlitol® 100SD	54.119	52.738
Microcrystalline cellulose – Avicel®	40	40
Sodium Starch Glycolate – Explotab®	4	4
Magnesium Stearate	0.5	0.5
Opadry® II Blue	4	4
Total tablet target weight	104	104

Those skilled in the art will recognize that various modifications, additions, substitutions, and variations to the illustrative examples set forth herein can be made without departing from the spirit of the invention and are, therefore, considered within the scope of the invention.

CLAIMS

What is claimed is:

1. A method of treating a skin extra-intestinal manifestation (EIM) in an individual with inflammatory bowel disease (IBD) in need thereof, comprising administering a therapeutically effective amount of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

2. The method according to claim 1, wherein the skin extra-intestinal manifestation (EIM) is psoriasis.

3. The method according to claim 1, wherein skin extra-intestinal manifestation (EIM) is erythema nodosum (EN).

4. The method according to claim 1, wherein the skin extra-intestinal manifestation (EIM) is pyoderma gangrenosum (PG).

5. The method according to any one of claims 1 to 4, further comprising administering Compound 1, or a pharmaceutically salt, solvate, or hydrate thereof, in combination with a therapeutically effective amount of a corticosteroid selected from the group consisting of: dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone, and fludrocortisone.

6. The method according to any one of claims 1 to 4, further comprising administering Compound 1, or a pharmaceutically salt, solvate, or hydrate thereof, in combination with a therapeutically effective amount of a 5-aminosalicylic acid derivative selected from the group consisting of: balsalazide, mesalamine, olsalazine, and sulfasalazine.

7. The method according to any one of claims 1 to 4, further comprising administering Compound 1, or a pharmaceutically salt, solvate, or hydrate thereof, in combination with a therapeutically effective amount of a TNF-alpha inhibitor selected from the group consisting of: as infliximab (Remicade®), adalimumab (Humira®), certolizumab pegol (Cimzia®), and golimumab (Simponi®), and etanercept (Enbrel®).

8. Use of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt, hydrate, or solvate thereof, in the manufacture of a medicament for the treatment of extra-intestinal manifestations (EIM) in an inflammatory bowel disease (IBD) individual.

9. The use according to claim 8, wherein the skin extra-intestinal manifestation (EIM) is psoriasis.

10. The use according to claim 8, wherein the skin extra-intestinal manifestation (EIM) is erythema nodosum (EN).

11. The use according to claim 8, wherein the skin extra-intestinal manifestation (EIM) is pyoderma gangrenosum (PG).

12. The method according to any one of claims 1 to 7, or the use according to any one claims 8 to 11, wherein the skin EIM is an active skin EIM.

13. The method according to any one of claims 1 to 7, or the use according to any one claims 8 to 11, wherein the therapeutically effective amount of Compound 1 is therapeutically effective for both the skin EIM and the IBD.

14. A method of treating pyoderma gangrenosum (PG) in an individual in need thereof comprising administering a therapeutically effective amount of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

15. The method according to claim 14, wherein the individual has at least one condition selected from the group consisting of: an inflammatory bowel disease, arthritis, a hematological disease, and an autoinflammatory disease.

16. The method according to claim 14, wherein the individual has at least one condition selected from the group consisting of: ulcerative colitis and Crohn's disease.

17. The method according to claim 14, wherein the individual has at least one condition selected from the group consisting of: rheumatoid arthritis and seronegative arthritis.

18. The method according to claim 14, wherein the individual has at least one condition selected from the group consisting of: myelocytic leukemia, hairy cell leukemia, myelofibrosis, myeloid metaplasia, and monoclonal gammopathy.

19. The method according to claim 14, wherein the individual has at least one condition selected from the group consisting of: PAPA syndrome and granulomatosis with polyangiitis.

20. The method according to any one of claims 14 to 19, further comprising administering Compound 1, or a pharmaceutically salt, solvate, or hydrate thereof, in combination with a therapeutically effective amount of a compound selected from the group consisting of: a corticosteroid, an immunosuppressant, a biologic, an anti-inflammatory agent, and an antibiotic.

21. Use of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt, hydrate, or solvate thereof, in the manufacture of a medicament for the treatment of pyoderma gangrenosum (PG) in an individual.

22. The use according to claim 21, wherein the individual has at least one condition selected from the group consisting of: an inflammatory bowel disease, arthritis, a hematological disease, and an autoinflammatory disease.

23. The use according to claim 21, wherein the individual has at least one condition selected from the group consisting of: ulcerative colitis and Crohn's disease.

24. The use according to claim 21, wherein the individual has at least one condition selected from the group consisting of: rheumatoid arthritis and seronegative arthritis.

25. The use according to claim 21, wherein the individual has at least one condition selected from the group consisting of: myelocytic leukemia, hairy cell leukemia, myelofibrosis, myeloid metaplasia, and monoclonal gammopathy.

26. The use according to claim 21, wherein the individual has at least one condition selected from the group consisting of: PAPA syndrome and granulomatosis with polyangiitis.

27. The use according to any one of claims 21 to 26, further comprising administering Compound 1, or a pharmaceutically salt, solvate, or hydrate thereof, in combination with a therapeutically

effective amount of a compound selected from the group consisting of: a corticosteroid, an immunosuppressant, a biologic, an anti-inflammatory agent, and an antibiotic.

28. The method according to any one of claims 14 to 20, or the use according to any one of claims 21 to 27, wherein the pyoderma gangrenosum is classic pyoderma gangrenosum.

29. The method according to any one of claims 14 to 20, or the use according to any one of claims 21 to 27, wherein the individual is experiencing an inflammatory episode of pyoderma gangrenosum.

30. The method according to any one of claims 14 to 20, or the use according to any one of claims 21 to 27, wherein the individual has at least one ulcer located on their leg.

31. The method according to any one of claims 14 to 20, or the use according to any one of claims 21 to 27, wherein the individual has at least one ulcer located on their hand.

32. The method according to any one of claims 14 to 20, or the use according to any one of claims 21 to 27, wherein the pyoderma gangrenosum is selected from at least one of the following: peristomal pyoderma gangrenosum, bullous pyoderma gangrenosum, pustular pyoderma gangrenosum, and vegetative pyoderma gangrenosum.

33. The method according to any one of claims 14 to 20, or the use according to any one of claims 21 to 27, wherein the individual has at least one active pyoderma gangrenosum ulcer.

34. The method according to any one of claims 14 to 20, or the use according to any one of claims 21 to 27, wherein the individual has at least one active, non-healing pyoderma gangrenosum ulcer.

35. The method according to any one of claims 14 to 20, or the use according to any one of claims 21 to 27, wherein the individual does not have inflammatory bowel disease.

36. The method according to any one of claims 14 to 20, or the use according to any one of claims 21 to 27, wherein the individual does not have ulcerative colitis.

37. The method according to any one of claims 14 to 20, or the use according to any one of claims 21 to 27, wherein the individual does not have Crohn's disease.

38. The method according to any one of claims 1 to 7, 12 to 20, and 28 to 37, or the use according to any one of claims 8 to 13 and 21 to 37, wherein the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is in an amount equivalent to about 1 mg to about 5 mg of Compound 1.

39. The method according to any one of claims 1 to 7, 12 to 20, and 28 to 37, or the use according to any one of claims 8 to 13 and 21 to 37, wherein the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is in an amount equivalent to about 1 mg to about 2 mg.

40. The method according to any one of claims 1 to 7, 12 to 20, and 28 to 37, or the use according to any one of claims 8 to 13 and 21 to 37, wherein the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is in an amount equivalent to about 1 mg of Compound 1.

41. The method according to any one of claims 1 to 7, 12 to 20, and 28 to 37, or the use according to any one of claims 8 to 13 and 21 to 37, wherein the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is in an amount equivalent to about 2 mg of Compound 1.

42. The method according to any one of claims 1 to 7, 12 to 20, and 28 to 41, or the use according to any one of claims 8 to 13 and 21 to 41, wherein the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is selected from: Compound 1, a calcium salt of Compound 1, and an L-arginine salt of Compound 1.

43. The method according to any one of claims 1 to 7, 12 to 20, and 28 to 41, or the use according to any one of claims 8 to 13 and 21 to 41, wherein the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is an L-arginine salt of Compound 1.

44. The method according to any one of claims 1 to 7, 12 to 20, and 28 to 41, or the use according to any one of claims 8 to 13 and 21 to 41, wherein the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is an anhydrous, non-solvated crystalline form of the L-arginine salt of Compound 1.

45. The method according to any one of claims 1 to 7, 12 to 20, and 28 to 41, or the use according to any one of claims 8 to 13 and 21 to 41, wherein the Compound 1, or a pharmaceutically

acceptable salt, hydrate, or solvate thereof, is a crystalline free-plate habit of the non-solvated L-arginine salt of Compound 1.

46. The method according to any one of claims 1 to 7, 12 to 20, and 28 to 41, or the use according to any one of claims 8 to 13 and 21 to 41, wherein the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is an anhydrous, non-solvated crystalline form of Compound 1.

47. The method according to any one of claims 1 to 7, 12 to 20, and 28 to 46, or the use according to any one of claims 8 to 13 and 21 to 46, wherein the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is administered orally.

48. The method according to any one of claims 1 to 7, 12 to 20, and 28 to 46, or the use according to any one of claims 8 to 13 and 21 to 46, wherein the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is formulated as a capsule or tablet suitable for oral administration.

49. The method according to any one of claims 1 to 7, 12 to 20, and 28 to 46, or the use according to any one of claims 8 to 13 and 21 to 46, wherein the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is administered once daily.

50. The method according to any one of claims 1 to 7, 12 to 20, and 28 to 49, or the use according to any one of claims 8 to 13 and 21 to 49, wherein the Compound 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, is administered without food.

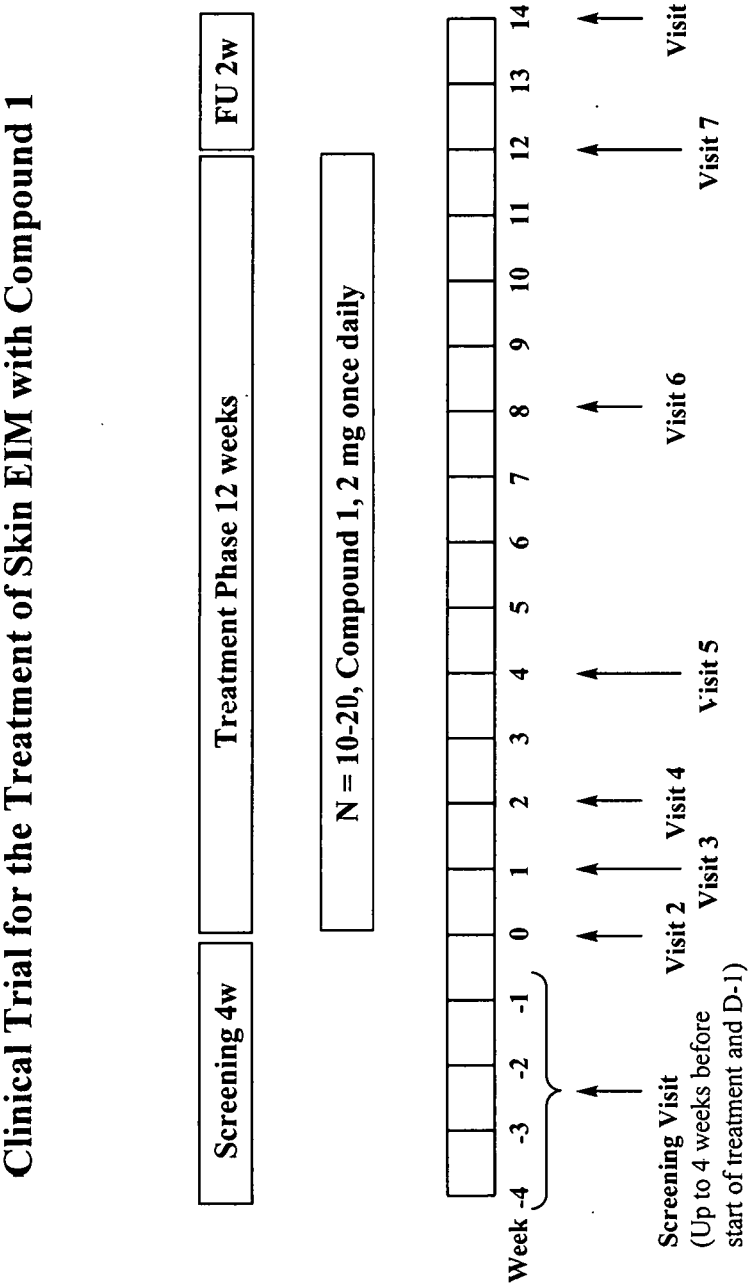

Clinical Trial for the Treatment of Skin EIM with Compound 1
Screening 4w
Treatment Phase 12 weeks
FU 2w
N = 10-20, Compound 1, 2 mg once daily
Week -4 -3 -2 -1 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Screening Visit
(Up to 4 weeks before
start of treatment and D-1)
Visit 2
Visit 3
Visit 4
Visit 5
Visit 6
Visit 7
Visit 8

FIGURE 1

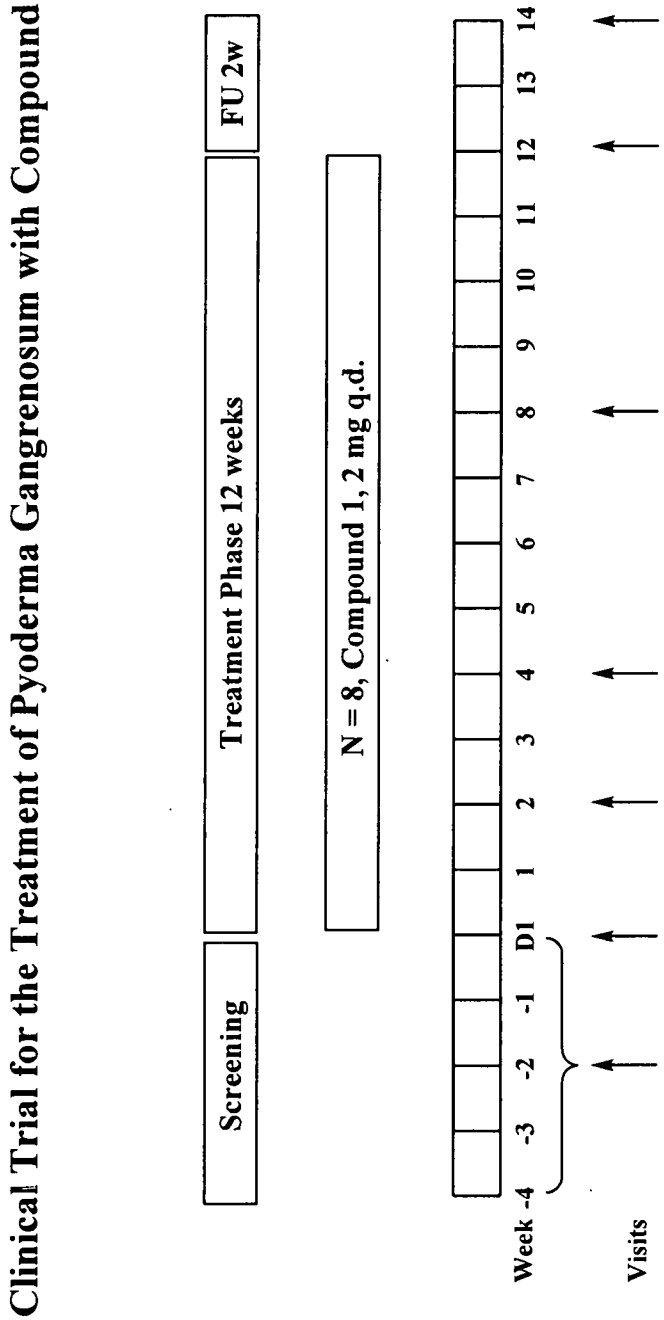

Clinical Trial for the Treatment of Pyoderma Gangrenosum with Compound 1
Screening
Treatment Phase 12 weeks
FU 2w
N = 8, Compound 1, 2 mg q.d.
Week -4 -3 -2 -1 D1 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Visits
Up to 4 weeks before start of treatment

FIGURE 2

PXRD Pattern for the L-arginine Salt of Compound 1 Showing the Peak Intensity Differences Spherulites and Plates

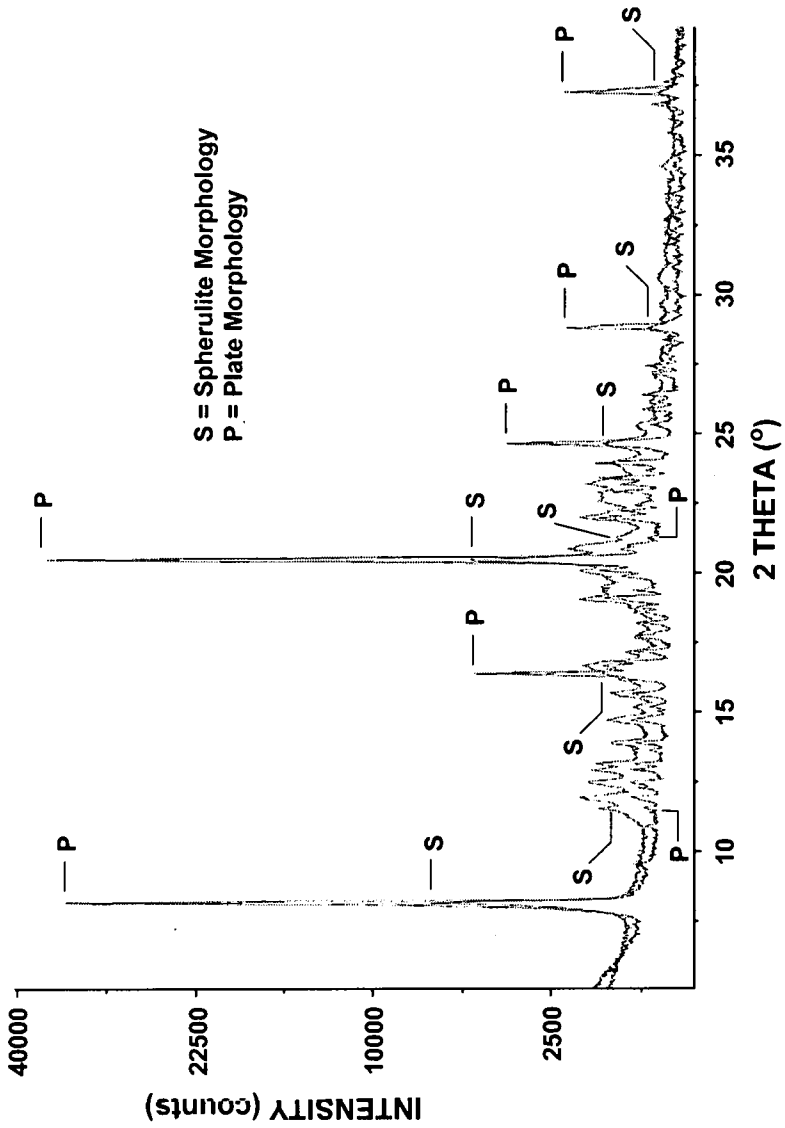


FIGURE 3

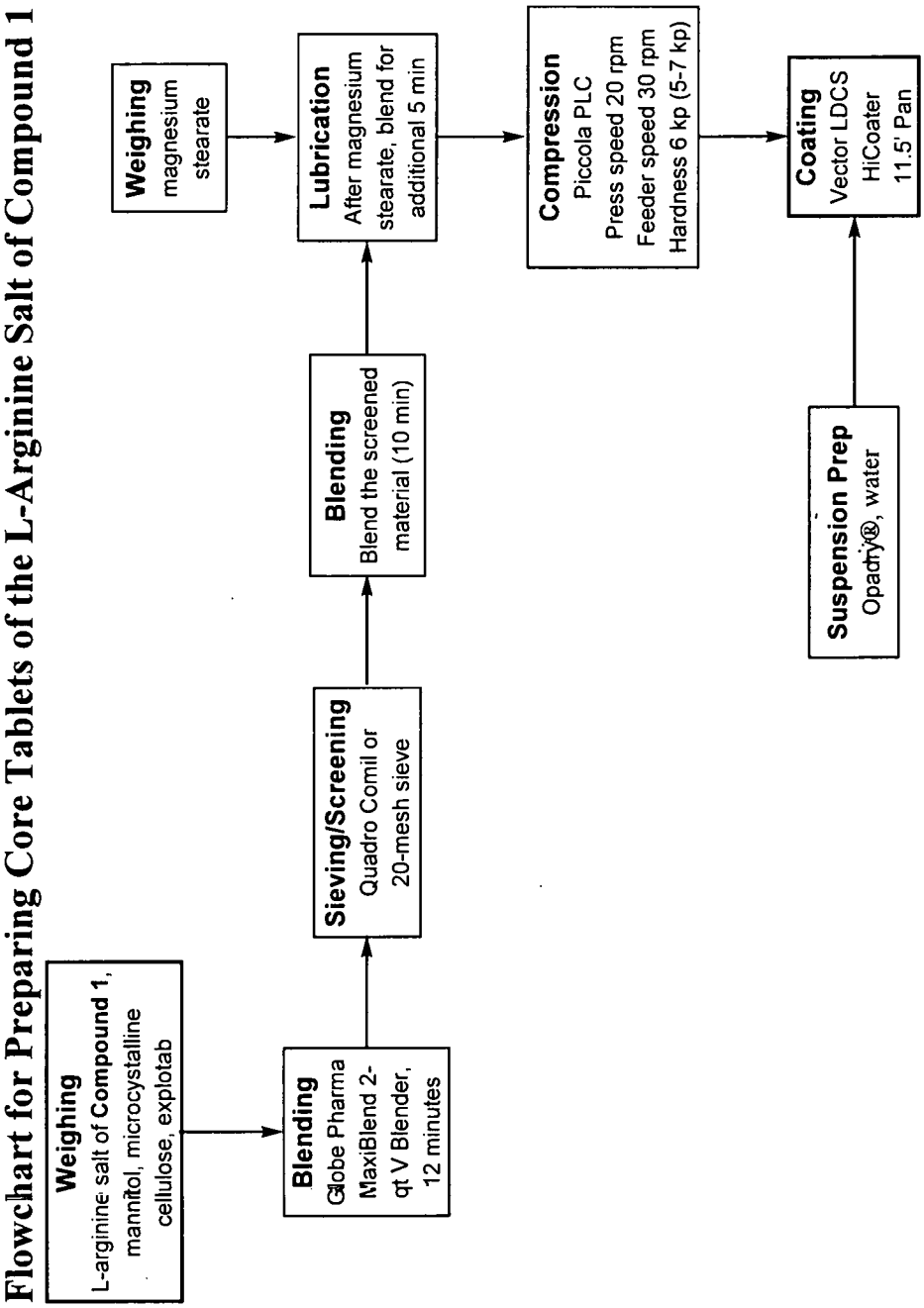

Flowchart for Preparing Core Tablets of the L-Arginine Salt of Compound 1
Weighing
L-arginine salt of Compound 1, mannitol, microcystalline cellulose, explotab
Blending
Globe Pharma MaxiBlend 2-qt V Blender, 12 minutes
Sieving/Screening
Quadro Comil or 20-mesh sieve
Blending
Blend the screened material (10 min)
Weighing
magnesium stearate
Lubrication
After magnesium stearate, blend for additional 5 min
Compression
Piccola PLC
Press speed 20 rpm
Feeder speed 30 rpm
Hardness 6 kp (5-7 kp)
Coating
Vector LDCS HiCoater 11.5' Pan
Suspension Prep
Opadry®, water

Figure 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/000048

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K45/06 A61K31/404 A61P1/00 A61P17/02 A61P37/00
A61P17/00 A61P1/04 A61K9/20
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	STEPHAN R. VAVRICKA ET AL: "Extraintestinal Manifestations of Inflammatory Bowel Disease :", INFLAMMATORY BOWEL DISEASES, vol. 21, no. 8, 1 August 2015 (2015-08-01) , pages 1982-1992, XP055477312, US ISSN: 1078-0998, DOI: 10.1097/MIB.0000000000000392 p. 1986, 1987, chapter "EIM of the skin"; Table 3	1-50
Y	WO 2016/112075 A1 (ARENA PHARM INC [US]) 14 July 2016 (2016-07-14) p. 34, l. 24-27; Example 2; claims 44, 45, 49, 52, 55, 56	1-50

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 May 2018	30/05/2018

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/000048

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	TOSHIYUKI YAMAMOTO: "Crohn's Disease and Mucocutaneous Conditions", JOURNAL OF CLINICAL & EXPERIMENTAL DERMATOLOGY RESEARCH, vol. 4, no. 2, 1 January 2014 (2014-01-01) , XP055477332, ISSN: 2155-9554, DOI: 10.4172/2155-9554.S2-001 the whole document -----	1-50

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2018/000048

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2016112075 A1	14-07-2016	AU 2016205361 A1	17-08-2017
		CA 3002540 A1	14-07-2016
		CN 107405332 A	28-11-2017
		EP 3242666 A1	15-11-2017
		JP 2018504398 A	15-02-2018
		KR 20170109578 A	29-09-2017
		WO 2016112075 A1	14-07-2016