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(71) Applicant: CELGENE CORPORATION [US/US]; 86
Morris Avenue, Summit, NJ 07901 (US).

(72) Inventors: HOUGH, Douglas; 14 Hillcrest Road, Martins-
ville, NJ 08836 (US). STEVENS, Randall; 2 Straitsmouth
Way, Rockport, MA 01966 (US).

(74) Agents: HUGUES, Colin, O. et al.; Jones Day, 222 East
41st Street, New York, NY 10017-6702 (US).

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(54) Title: APREMILAST FOR THE TREATMENT OF A LIVER DISEASE OR A LIVER FUNCTION ABNORMALITY

(57) Abstract: Methods of treating, managing or preventing liver disease are disclosed. Specific methods encompass the administra-
tion of apremilast, alone or in combination with additional active agents or treatment regimens.



APREMILAST FOR THE TREATMENT OF A LIVER DISEASE OR A LIVER FUNCTION ABNORMALITY

1. FIELD

[0001] Provided herein are methods for treating, preventing and/or managing a liver disease or a liver function abnormality by the administration of apremilast, alone or in combination with other therapeutics or treatment regimens. Also provided herein are pharmaceutical compositions and dosage forms comprising specific amounts of apremilast suitable for use in methods of treating, preventing and/or managing a liver disease or a liver function abnormality.

2. BACKGROUND

[0002] Fatty liver disease (FLD), whether it is alcoholic FLD (AFLD) or nonalcoholic FLD (NAFLD), encompasses a morphological spectrum of hepatic steatosis (fatty liver) and steatohepatitis. Alcohol is a well-known cause of fatty liver disease in adults, and can manifest histologically as steatosis, steatohepatitis, and cirrhosis. In recent years it has become evident that another entity, nonalcoholic fatty liver disease (NAFLD), can mimic the entire spectrum of hepatic changes typically associated with alcohol abuse. NAFLD is associated with insulin resistance, obesity, diabetes mellitus, hypertension, and dyslipidemias, collectively called the metabolic syndrome. The morphologic changes of alcoholic and nonalcoholic fatty liver disease are indistinguishable (Kumar, Abbas, Aster, *Robbins Basic Pathology*, 9th Ed.; Elsevier; 2013).

[0003] NAFLD is a condition defined by excessive fat accumulation in the form of triglycerides (steatosis) in the liver (> 5% of hepatocytes histologically). A subgroup of NAFLD patients have liver cell injury and inflammation in addition to excessive fat (steatohepatitis). The latter condition, designated nonalcoholic steatohepatitis (NASH), is virtually indistinguishable histologically from alcoholic steatohepatitis (ASH). While the simple steatosis seen in NAFLD does not correlate with increased short-term morbidity or mortality, progression of this condition to that of NASH dramatically increases the risks of cirrhosis, liver failure, and hepatocellular carcinoma (HCC). Cirrhosis due to NASH is an increasingly frequent reason for liver transplantation (Global Guidelines - Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis, World Gastroenterology Organisation, June 2012).

[0004] NASH is widely considered to be the liver expression of the metabolic syndrome. There is at present a worldwide epidemic of diabetes and obesity. At least 1.46 billion adults were overweight

or obese and 170 million of the world's children were overweight or obese in 2008. The numbers are continuing to rise, indicating that NASH will become an increasingly common liver problem in both rich and poor countries, increasing the global burden of liver disease, and affecting public health and health-care costs globally.

[0005] Over the past couple of decades, it has become increasingly clear that NAFLD and NASH are now the number one cause of liver disease in Western countries. The prevalence of NAFLD has doubled during last 20 years, whereas the prevalence of other chronic liver diseases has remained stable or even decreased. More recent data confirm that NAFLD and NASH play an equally important role in the Middle East, Far East, Africa, the Caribbean, and Latin America.

[0006] PDE4 inhibitors have been evaluated in NAFLD with mixed results. Pentoxifylline appears to improve Liver Function Tests abnormalities by decreasing levels of alanine aminotransferase and/or aspartate aminotransferase (ALT and AST respectively) in both animal models and human studies without effecting cytokines such as TNF- α (Chae MK et al. *Exp Diabetes Res* 2012; 762565). However, in a Phase 1 clinical trial of ASP9831 by Astellas, after 12 weeks of treatment neither a 50 mg nor 100 mg daily dose demonstrated any significant difference in percentage change from baseline for either AST or ALT (Ratzu V, et al. *Clin Gastroenterol Hepatol.* 2014 Feb 12. pii: S1542-3565). Thus, there remains a clear and unmet need to develop therapeutics for more effective treatment of liver disease and liver function abnormalities.

[0007] Other liver diseases having liver function abnormalities include inherited liver disorders (e.g. porphyria, Wilson's disease, and hemochromatosis); acute hepatitis (viral or bacterial infection, toxin exposure, and drug-induced hepatitis); autoimmune liver disease (e.g. primary biliary cirrhosis and lupus hepatitis); and biliary tract disease (e.g. sclerosing cholangitis). These diseases and pruritus associated with liver disease may benefit from treatment with a selective PDE4 inhibitor.

3. SUMMARY

[0008] Provided herein are methods for treating, preventing and/or managing a liver disease or a liver function abnormality in humans in need thereof. Liver diseases having liver function abnormalities include, but are not limited to, inherited liver disorders (e.g. porphyria, Wilson's disease, and hemochromatosis); acute hepatitis (viral or bacterial infection, toxin exposure, and drug-induced hepatitis); autoimmune liver disease (e.g. primary biliary cirrhosis and lupus hepatitis); and biliary tract disease (e.g. sclerosing cholangitis). Additionally, herein are methods for treating pruritus associated with liver disorders and jaundice. The methods comprise administering to a patient

in need of such treatment, prevention or management with a therapeutically or prophylactically effective amount of apremilast, or a pharmaceutically acceptable prodrug, metabolite, polymorph, salt, solvate (*e.g.*, hydrate) or clathrate thereof. Also provided herein is a therapeutically or prophylactically effective amount of a compound being apremilast, or a pharmaceutically acceptable prodrug, metabolite, polymorph, salt, solvate (*e.g.*, hydrate) or clathrate thereof for use in methods as described above, wherein the methods comprise administering to a patient in need of such treatment, prevention or management the compound.

[0009] In some embodiments, provided herein is a method of treating, preventing and/or managing a liver disease or a liver function abnormality, which comprises orally administering to a patient having a liver disease or a liver function abnormality an effective amount of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminisoindoline-1,3-dione, or a pharmaceutically acceptable prodrug, polymorph, salt, or solvate thereof. In some embodiments, provided herein is an effective amount of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminisoindoline-1,3-dione, or a pharmaceutically acceptable prodrug, polymorph, salt, or solvate thereof, for use in a method of treating, preventing and/or managing a liver disease or a liver function abnormality, which comprises orally administering to a patient having a liver disease or a liver function abnormality an effective amount of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminisoindoline-1,3-dione, or a pharmaceutically acceptable prodrug, polymorph, salt, or solvate thereof. In some embodiments, the compound of the invention is administered once daily. In some embodiments, the compound of the invention is administered twice daily.

[0010] In some embodiments, the patient is administered about 10 mg twice daily (BID) of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminisoindoline-1,3-dione, or a pharmaceutically acceptable prodrug, polymorph, salt, or solvate thereof. In some embodiments, the dose is about 20 mg BID. In other embodiments, the dose is about 30 mg BID. In some embodiments, the dose is about 40 mg BID or 80 mg once daily (QD).

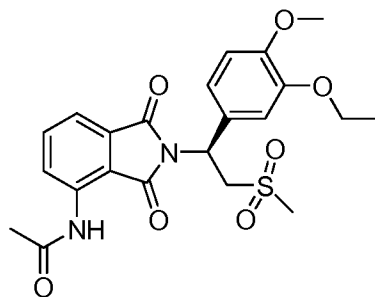
[0011] In some embodiments, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminisoindoline-1,3-dione, or a pharmaceutically acceptable prodrug, polymorph, salt, or solvate thereof is administered orally in a dosage form such as a tablet or a capsule.

4. DETAILED DESCRIPTION

4.1 Definitions

[0012] As used herein, the term “apremilast” refers to (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisindoline-1,3-dione, also known as N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isindol-4-yl]acetamide.

Apremilast has the following structure:



[0013] Without being limited by theory or mechanism of action, apremilast is an inhibitor of phosphodiesterase 4 (PDE4), and works intracellularly to modulate a network of pro- and anti-inflammatory mediators. Phosphodiesterase 4 is a cyclic adenosine monophosphate (cAMP)-specific phosphodiesterase (PDE) and the dominant PDE in inflammatory cells. Inhibition of PDE4 elevates intracellular cAMP levels, which in turn down regulates the inflammatory response by modulating the expression of tumor necrosis factor-alpha (TNF- α), interleukin (IL)-23, and other inflammatory cytokines. Elevation of cAMP also increases anti inflammatory cytokines such as IL-10. These pro- and anti-inflammatory mediators have been implicated in psoriasis and psoriatic arthritis. *See, e.g.,* Schafer *et al.*, “Apremilast, a cAMP phosphodiesterase-4 inhibitor, demonstrates anti-inflammatory activity in vitro and in a model of psoriasis,” *Br. J. Pharmacol.*, 2010,159(4):842-55.

[0014] Apremilast is under clinical development for the treatment of adult inflammatory autoimmune disorders that involve elevated cytokine levels, such as psoriasis, psoriatic arthritis, rheumatoid arthritis, Behçet’s disease and ankylosing spondylitis.

[0015] As used herein and unless otherwise indicated, the term “pharmaceutically acceptable salt” includes, but is not limited to, salts prepared from pharmaceutically acceptable non-toxic acids or bases including inorganic acids and bases and organic acids and bases. Suitable pharmaceutically acceptable base addition salts provided herein include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from lysine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Suitable non-toxic acids include, but are not limited to, inorganic and

organic acids such as acetic, alginic, anthranilic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, formic, fumaric, furoic, galacturonic, gluconic, glucuronic, glutamic, glycolic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phenylacetic, phosphoric, propionic, salicylic, stearic, succinic, sulfanilic, sulfuric, tartaric acid, and p-toluenesulfonic acid. Specific non-toxic acids include hydrochloric, hydrobromic, phosphoric, sulfuric, and methanesulfonic acids. Examples of specific salts thus include hydrochloride and mesylate salts.

[0016] As used herein and unless otherwise indicated, the term “hydrate” means a compound provided herein or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

[0017] As used herein and unless otherwise indicated, the term “solvate” means a solvate formed from the association of one or more solvent molecules to a compound provided herein. The term “solvate” includes hydrates (*e.g.*, mono-hydrate, dihydrate, trihydrate, tetrahydrate and the like).

[0018] As used herein and unless otherwise indicated, the term “polymorph” means solid crystalline forms of a compound provided herein or complex thereof. Different polymorphs of the same compound can exhibit different physical, chemical and /or spectroscopic properties.

[0019] As used herein and unless otherwise specified, the term “prodrug” means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (*in vitro* or *in vivo*) to provide the compound. Examples of prodrugs include, but are not limited to, derivatives and metabolites of apremilast that include biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. Prodrugs can typically be prepared using well-known methods, such as those described by *Burger's Medicinal Chemistry and Drug Discovery*, 172-178, 949-982 (Manfred E. Wolff *ed.*, 5th ed. 1995).

[0020] As used herein, and unless otherwise specified, the term “enantiomer,” “isomer” or “stereoisomer” encompasses all enantiomerically/stereomerically pure and enantiomerically/stereomerically enriched compounds provided herein.

[0021] As used herein, and unless otherwise indicated, the term “stereomerically pure” or “enantiomerically pure” means that a compound comprises one stereoisomer and is substantially free of its counter stereoisomer or enantiomer. For example, a compound is stereomerically or enantiomerically pure, when the compound contains greater than or equal to 80%, 90%, 95%, 96%, 97%, 98% or 99% of one stereoisomer, and 20%, 10%, 5%, 4%, 3%, 2%, 1% or less of the counter

stereoisomer. “Substantially free of its (R) enantiomer” is encompassed by the term stereomerically pure or enantiomerically pure.

[0022] As used herein, term “adverse effect” includes, but is not limited to gastrointestinal, renal and hepatic toxicities, leukopenia, increases in bleeding times due to, *e.g.*, thrombocytopenia, and prolongation of gestation, nausea, vomiting, somnolence, asthenia, dizziness, teratogenicity, extra-pyramidal symptoms, akathisia, cardiotoxicity including cardiovascular disturbances, inflammation, male sexual dysfunction, and elevated serum liver enzyme levels. The term “gastrointestinal toxicities” includes but is not limited to gastric and intestinal ulcerations and erosions. The term “renal toxicities” includes but is not limited to such conditions as papillary necrosis and chronic interstitial nephritis.

[0023] As used herein, the term “patient” refers to a mammal, particularly a human. In some embodiments, the patient is a female. In further embodiments, the patient is a male. In further embodiments, the patient is a child or adolescent.

[0024] As used herein, and unless otherwise specified, the term “liver function abnormality” includes, but is not limited to, a liver disease or abnormality that can result in an abnormal liver function test. An abnormal liver function test may indicate abnormal levels of bilirubin, albumin, total protein, lactic dehydrogenase, alkaline phosphatase, 5'-nucleotidase, gamma glutamyltranspeptidase, aminotransferases and other enzymes in the blood. Liver function tests are known in the art, see *e.g.*, Lee, *Basic Skills in Interpreting Laboratory Data*, 5th Ed., American Society of Health-System Pharmacists 2013.

[0025] As used herein, and unless otherwise specified, the terms “treat,” “treating” and “treatment” contemplate an action that occurs while a patient is suffering from the specified disease or disorder, which reduces the severity or symptoms of the disease or disorder, or retards or slows the progression of symptoms of the disease or disorder.

[0026] As used herein, unless otherwise specified, the terms “prevent,” “preventing” and “prevention” contemplate an action that occurs before a patient begins to suffer from the specified disease or disorder, which inhibits or reduces the severity or symptoms of the disease or disorder.

[0027] As used herein, and unless otherwise indicated, the terms “manage,” “managing,” and “management” encompass preventing the recurrence of the specified disease or disorder in a patient who has already suffered from the disease or disorder, and/or lengthening the time that a patient who has suffered from the disease or disorder remains in remission. The terms encompass modulating the

threshold, development and/or duration of the disease or disorder, or changing the way that a patient responds to the disease or disorder.

4.2 Methods of Treatment

[0028] Provided herein are methods of treating, managing and/or preventing a liver disease or a liver function abnormality, which comprise administering to a patient in need of such treatment, management or prevention a therapeutically or prophylactically effective amount of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione, or a pharmaceutically acceptable prodrug, metabolite, polymorph, salt, solvate or clathrate thereof. Liver diseases having liver function abnormalities include, but are not limited to, inherited liver disorders (*e.g.* porphyria, Wilson's disease, and hemochromatosis); acute hepatitis (viral or bacterial infection, toxin exposure, and drug-induced hepatitis); autoimmune liver disease (*e.g.* primary biliary cirrhosis and lupus hepatitis); and biliary tract disease (*e.g.* sclerosing cholangitis).

[0029] In some embodiments, the methods also encompass inhibiting or averting symptoms of a liver disease or a liver function abnormality as well as addressing the disease itself, prior to the onset of symptoms by administering stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione, or a pharmaceutically acceptable prodrug, metabolite, polymorph, salt, solvate or clathrate thereof.

[0030] In one embodiment provided herein is a method of treating or managing a liver disease or a liver function abnormality, which comprises orally administering to a patient having a liver disease or a liver function abnormality an effective amount of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione, or a pharmaceutically acceptable prodrug, polymorph, salt, or solvate thereof.

[0031] In one embodiment provided herein is a method of treating or managing pruritus associated with a liver disease or a liver function abnormality, which comprises orally administering to a patient having a liver disease or a liver function abnormality an effective amount of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione, or a pharmaceutically acceptable prodrug, polymorph, salt, or solvate thereof.

[0032] In one embodiment, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione is administered once daily. In one embodiment, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione is administered twice daily. In some embodiments, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-

dione is administered in an amount of about 10 mg, 20 mg, 30 mg, or 40 mg once daily. In certain embodiments, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione may be used alone in doses of 10, 20 mg, 30 mg, or 40 mg once daily, or in combination with other treatment measures. In some embodiments, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione is administered in an amount of about 10 mg, 20 mg, 30 mg, or 40 mg twice daily. In certain embodiments, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione may be used alone in doses of 10, 20 mg, 30 mg, or 40 mg twice daily (BID), or in combination with other treatment measures.

[0033] In one embodiment, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione is administered in an amount of about 100 mg once daily. In one embodiment, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione is administered in an amount of about 90 mg once daily. In one embodiment, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione is administered in an amount of about 80 mg once daily. In one embodiment, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione is administered in an amount of about 70 mg once daily. In one embodiment, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione is administered in an amount of about 60 mg once daily. In one embodiment, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione is administered in an amount of about 50 mg once daily.

[0034] In one embodiment, the patient is administered about 10 mg BID of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione, or a pharmaceutically acceptable prodrug, polymorph, salt, or solvate thereof. In some embodiments, the dose is about 20 mg BID. In other embodiments, the dose is about 30 mg BID. In other embodiments, the dose is about 40 mg BID.

[0035] In one embodiment, the patient is administered about 10 mg QD of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione, or a pharmaceutically acceptable prodrug, polymorph, salt, or solvate thereof. In some embodiments, the dose is about 20 mg QD. In other embodiments, the dose is about 30 mg QD. In other embodiments, the dose is about 40 mg QD. In other embodiments, the dose is about 50 mg QD. In other

embodiments, the dose is about 60 mg QD. In other embodiments, the dose is about 70 mg QD. In other embodiments, the dose is about 80 mg QD.

[0036] In one embodiment, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, or a pharmaceutically acceptable prodrug, polymorph, salt, or solvate thereof is administered orally in a dosage form such as a tablet or a capsule.

[0037] In one embodiment, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, or a pharmaceutically acceptable prodrug, polymorph, salt, or solvate thereof is administered orally in a tablet form. In some embodiments, the tablet comprises a 10 mg, 20 mg, 30 mg, or 40 mg dose of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione.

[0038] In one embodiment, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione is orally administered to a patient having a liver disease or a liver function abnormality at a starting dose of about 10 mg, 20 mg, 30 mg, or 40 mg twice daily. In some embodiments, the maximum daily dose is about 20 mg to about 40 mg. In some embodiments, the maximum daily dose is about 30 mg to about 60 mg. In some embodiments, the maximum daily dose is about 40 mg to about 100 mg.

[0039] In one embodiment, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione is orally administered to a patient having a liver disease or a liver function abnormality at a starting dose of about 10 mg, 20 mg, 30 mg, or 40 mg once daily. In some embodiments, the maximum daily dose is about 20 mg to about 40 mg. In some embodiments, the maximum daily dose is about 30 mg to about 60 mg. In some embodiments, the maximum daily dose is about 40 mg to about 100 mg.

[0040] In one embodiment, the stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione comprises greater than about 90% by weight of (+) isomer based on the total weight percent of the compound.

[0041] In one embodiment, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione comprises greater than about 95% by weight of (+) isomer based on the total weight percent of the compound.

[0042] In one embodiment, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione comprises greater than about 96% by weight of (+) isomer based on the total weight percent of the compound.

[0043] In one embodiment, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione comprises greater than about 97% by weight of (+) isomer based on the total weight percent of the compound.

[0044] In one embodiment, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione comprises greater than about 98% by weight of (+) isomer based on the total weight percent of the compound.

[0045] In one embodiment, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione comprises greater than about 99% by weight of (+) isomer based on the total weight percent of the compound.

[0046] In one embodiment, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione is administered in an amount of about 20 mg twice a day following the initial titration schedule.

[0047] In one embodiment, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione is administered in an amount of about 30 mg twice a day following the initial titration schedule.

[0048] In one embodiment, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione is administered in an amount of about 40 mg twice a day following the initial titration schedule.

[0049] In one embodiment, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione is administered once daily.

[0050] In one embodiment, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione is administered twice daily.

[0051] In one embodiment, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione is administered in a tablet form. In some embodiments, the tablet comprises a 10 mg, 20 mg, 30 mg, 40 mg or 80 mg dose of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione.

[0052] In one embodiment, the tablet further comprises lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc. In one embodiment, the tablet further comprises iron oxide red. In one embodiment, the tablet further comprises iron oxide yellow. In one embodiment, the tablet further comprises iron oxide black.

[0053] In one embodiment, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione is administered in a tablet form comprising a 10 mg dose of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide red.

[0054] In one embodiment, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione is administered in a tablet form comprising a 20 mg dose of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide red, and iron oxide yellow.

[0055] In one embodiment, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione is administered in a tablet form comprising a 30 mg dose of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide red, iron oxide yellow, and iron oxide black.

[0056] In one embodiment provided herein, the method further comprises administering to the patient a therapeutically effective amount of one or more second active agents. In one embodiment, one or more second active agents are medications for treating a liver disease or liver function abnormality.

[0057] In one embodiment, the liver disease is fatty liver disease.

[0058] In one embodiment, the liver disease is hepatic fibrosis.

[0059] In one embodiment, the liver disease is hepatic steatosis.

[0060] In one embodiment, the liver disease is nonalcoholic steatohepatitis.

[0061] In one embodiment, the liver disease is alcoholic steatohepatitis.

[0062] In one embodiment, the liver disease is relapsed or refractory to a prior treatment.

[0063] In one embodiment, the fatty liver disease is nonalcoholic fatty liver disease.

[0064] In one embodiment, the fatty liver disease is alcoholic fatty liver disease.

[0065] In one embodiment, the nonalcoholic fatty liver disease is pediatric nonalcoholic fatty liver disease.

- [0066] In one embodiment, the liver function abnormality comprises an elevated level of alanine aminotransferase or aspartate aminotransferase in the patient.
- [0067] In one embodiment, the liver disease is viral hepatitis.
- [0068] In one embodiment, the liver disease is bacterial hepatitis.
- [0069] In one embodiment, the liver disease is acute hepatitis.
- [0070] In one embodiment, the liver disease is primary biliary cirrhosis.
- [0071] In one embodiment, the liver disease is lupus hepatitis.
- [0072] In one embodiment, the liver disease is Wilson's disease.
- [0073] In one embodiment, the liver disease is drug-induced hepatitis.
- [0074] In one embodiment, the liver disease is toxin exposure hepatitis.
- [0075] In one embodiment, the liver disease is hemochromatosis.
- [0076] In one embodiment, the liver disease is acute porphyria.
- [0077] In one embodiment, the liver disease is autoimmune hepatitis.
- [0078] In one embodiment, the liver disease is sclerosis cholangitis.
- [0079] In one embodiment, the liver disease is acute cholestatic jaundice.
- [0080] In one embodiment, the liver disease is associated with pruritus.
- [0081] In one embodiment, a normal range of aspartate aminotransferase is from 10 to 35 IU/L. In one embodiment, an elevated or high level of aspartate aminotransferase is greater than 35 IU/L. In one embodiment, a low level of aspartate aminotransferase is less than 10 IU/L.
- [0082] In one embodiment, a normal range of alanine aminotransferase is from 10 to 40 IU/L. In one embodiment, an elevated or high level of alanine aminotransferase is greater than 40 IU/L. In one embodiment, a low level of alanine aminotransferase is less than 10 IU/L.
- [0083] In one embodiment provided herein, the method comprises administering stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, substantially free of any salt, solvate, or prodrug forms of (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione.
- [0084] In one embodiment provided herein, the method comprises administering a pharmaceutically acceptable salt of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione.
- [0085] In one embodiment provided herein, the method comprises administering a pharmaceutically acceptable solvate of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione.

[0086] In one embodiment provided herein, the method decreases the level of alanine aminotransferase in the patient.

[0087] In one embodiment provided herein, the method decreases the level of aspartate aminotransferase in the patient.

[0088] In one embodiment, the methods further comprises the administration of a therapeutically or prophylactically effective amount of one or more second active agents, including but not limited to, an analgesic, an anti-inflammatory agent, a COX-2 inhibitor, an opioid, a corticosteroid, a biologic agent, and an immunosuppressant. In one embodiment, the second active agent is a non-steroidal anti-inflammatory drug (*i.e.*, NSAID such as celecoxib, diclofenac, ibuprofen, indomethacin, meloxicam, naproxen, and piroxicam). In one embodiment, the second active agent is a disease-modifying antirheumatic drug (*i.e.*, DMARD such as methotrexate, leflunomide, sulfasalazine and hydroxychloroquine).

[0089] In one embodiment, the patient has received prior treatment for a liver disease or a liver function abnormality. In some embodiments, the patient is relapsed or refractory to prior treatment.

4.2.1 Combination Therapy

[0090] In particular methods encompassed by this embodiment, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminoisindoline-1,3-dione is administered in combination with another drug ("second active agent") for treating, managing and/or preventing a liver disease or a liver function abnormality.

[0091] In particular methods encompassed by this embodiment, stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminoisindoline-1,3-dione is administered in combination with an additional treatment for treating, managing and/or preventing a liver disease or a liver function abnormality.

[0092] In one embodiment, the additional treatment is surgical correction of the liver disease or a liver function abnormality.

[0093] In one embodiment, the additional treatment is a liver transplant.

[0094] In certain embodiments, the methods encompass synergistic combinations for the treatment, prevention and/or management of a liver disease or liver function abnormality.

Stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminoisindoline-1,3-dione may also be used to alleviate adverse effects associated with some second active agents.

[0095] One or more second active agents can be used in the methods together with stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione. Second active agents can be administered before, after or simultaneously with stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione. In some embodiments, the methods comprise the administration of a therapeutically effective amount of medications for treating a liver disease or liver function abnormality.

[0096] In one embodiment, the second active agent is selected from the group consisting of a thiazolidinedione, a statin, a fibrate, a lipid lowering agent, or a medication for weight loss. In one embodiment, the second active agent is a thiazolidinedione. In one embodiment, the second active agent is a statin. In one embodiment, the second active agent is a fibrate. In one embodiment, the second active agent is a lipid lowering agent. In one embodiment, the second active agent is a medication for weight loss.

[0097] In one embodiment, the second active agent is selected from the group consisting of an anti-inflammatory agent, an immunosuppressant, mycophenolate mofetil, a biologic agent, or a Cox-2 inhibitor. In one embodiment, the second active agent is an anti-inflammatory agent. In one embodiment, the second active agent is an immunosuppressant. In one embodiment, the second active agent is mycophenolate mofetil. In one embodiment, the second active agent is a biologic agent. In one embodiment, the second active agent is a Cox-2 inhibitor.

[0098] In some embodiments, the second active agents may include, but are not limited to, anti-inflammatories such as NSAIDs including, but not limited to, diclofenac (*e.g.*, ARTHROTEC[®]), diflunisal (*e.g.*, DOLOBID[®]), etodolac (*e.g.*, LODINE[®]), fenoprofen (*e.g.*, NALFON[®]), ibuprofen (*e.g.*, ADVIL, CHILDREN'S ADVIL/MOTRIN, MEDIPREN, MOTRIN, NUPRIN or PEDIACARE FEVER[®]), indomethacin (*e.g.*, ARTHREXIN[®]), ketoprofen (*e.g.*, ORUVAIL[®]), ketorolac (*e.g.*, TORADOL[®]), fosfomycin tromethamine (*e.g.*, MONURAL[®]), meclofenamate (*e.g.*, Meclomen[®]), nabumetone (*e.g.*, RELAFEN[®]), naproxen (*e.g.*, ANAPROX[®], ANAPROX[®] DS, EC-NAPROSYN[®], NAPRELAN[®] or NAPROSYN[®]), oxaprozin (*e.g.*, DAYPRO[®]), piroxicam (*e.g.*, FELDENE[®]), sulindac (*e.g.*, CLINORIL[®]), and tolmetin (*e.g.*, TOLECTIN[®] DS or TOLECTIN[®]).

[0099] In other embodiments, the second active agents may include, but are not limited to, disease-modifying antirheumatic drugs (DMARDs) or immunosuppressants such as, but not limited to, methotrexate (Rheumatrex[®]), sulfasalazine (Azulfidine[®]), leflunomide (Arava[®]), and cyclosporine (Sandimmune[®] or Neral[®]).

[00100] In other embodiments, the second active agent is an oral corticosteroid, such as, but not limited to, budesonide (Entocort®), dexamethazone, fludrocortisone (Florinef®, Florinef® acetate), hydrocortisone, methylprednisone, prednisolone, and prednisone.

[00101] In other embodiments, second active agents may include, but are not limited to, mycophenolate mofetil (CellCept®), an immunosuppressive agent widely used in organ transplantation and gaining favor in treating autoimmune and inflammatory skin disorders.

[00102] In further embodiments, second active agents may include, but are not limited to, biologic agents such as etanercept (Enbrel®), infliximab (Remicade®) and adalimumab (Humira®).

[00103] In further embodiments, second active agents may include, but are not limited to, Cox-2 inhibitors such as celecoxib (Celebrex®), valdecoxib (Bextra®) and meloxicam (Mobic®).

[00104] In some embodiments, one or more selective active agents are selected from the group consisting of acitretin, adalimumab, alclometasone, alefacept, aloe vera, amcinonide, ammonium lactate/urea, ammonium lactate/halobetasol, anthralin, benzocaine/pyrilamine/zinc oxide, betamethasone, betamethasone/calcipotriene, calcipotriene, clobetasol, clocortolone, coal tar, coal tar/salicylic acid, corticotropin, cyclosporine, desonide, desoximetasone, diflorasone, fluocinonide, flurandrenolide, halcinonide, halobetasol, hydrocortisone, hydrocortisone/pramoxine, hydroxyurea, infliximab, methotrexate, methoxsalen, mometasone, pramoxine, prednisone, prednisolone, prednicarbate, resorcinol, tazarotene, triamcinolone and ustekinumab.

[00105] In some embodiments, one or more selective active agents are selected from the group consisting of abatacept, acetaminophen, acetaminophen/hydrocodone, acetaminophen/tramadol, adalimumab, alemtuzumab, aluminum hydroxide/aspirin/calcium carbonate/magnesium hydroxide, anakinra, aspirin, auranofin, aurothioglucose, atorvastatin, azathioprine, celecoxib, certolizumab, chondroitin, cortisone, corticotropin, cyclophosphamide, cyclosporine, daclizumab, dexamethasone, diclofenac, diclofenac/misoprostol, diflunisal, doxycycline, esomeprazole, esomeprazole/naproxen, etanercept, etodolac, famotidine, famotidine/ibuprofen, fenoprofen, flurbiprofen, glucosamine, gold sodium thiomalate, golimumab, hydroxychloroquine, ibuprofen, indomethacin, infliximab, interferon, interferon gamma-1b, ketoprofen, lansoprazole, lansoprazole/naproxen, leflunomide, levamisole, meclofenamate, meloxicam, methotrexate, methylprednisone, methylprednisolone, methyl salicylate, minocycline, mycophenolate mofetil, nabumetone, naproxen, oxaprozin, penicillamine, phenytoin, piroxicam, prednisone, primrose oil, rituximab, rofecoxib, salsalate, sulindac, sulfasalazine, tetracycline, tocilizumab, tofacitinib, tolmetin, tramadol, triamcinolone, trolamine salicylate and valdecoxib.

[00106] In some embodiments, one or more selective active agents are selected from the group consisting of abatacept, acetaminophen, acetaminophen/hydrocodone, acetaminophen/tramadol, acitretin, adalimumab, alclometasone, alefacept, alemtuzumab, aloe vera, aluminum hydroxide/aspirin/calcium carbonate/magnesium hydroxide, amcinonide, ammonium lactate/urea, ammonium lactate/halobetasol, anakinra, anthralin, aspirin, auranofin, aurothioglucose, atorvastatin, azathioprine, benzocaine/pyrilamine/zinc oxide, betamethasone, betamethasone/calcipotriene, calcipotriene, celecoxib, certolizumab, chondroitin, clobetasol, clocortolone, coal tar, coal tar/salicylic acid, corticotropin, cortisone, cyclophosphamide, cyclosporine, daclizumab, desonide, desoximetasone, dexamethasone, diclofenac, diclofenac/misoprostol, diflorasone, diflunisal, doxycycline, esomeprazole, esomeprazole/naproxen, etanercept, etodolac, famotidine, famotidine/ibuprofen, fenoprofen, fluocinonide, flurandrenolide, flurbiprofen, fostamatinib, glucosamine, gold sodium thiomalate, golimumab, halcinonide, halobetasol, hydrocortisone, hydrocortisone/pramoxine, hydroxyurea, hydroxychloroquine, ibuprofen, indomethacin, infliximab, interferon, interferon gamma-1b, ibrutinib, ketoprofen, lansoprazole, lansoprazole/naproxen, leflunomide, lenalidomide, levamisole, meclofenamate, meloxicam, methotrexate, methoxsalen, methylprednisone, methylprednisolone, methyl salicylate, minocycline, mometasone, mycophenolate mofetil, nabumetone, naproxen, oxaprozin, penicillamine, phenytoin, piroxicam, pomalidomide, pramoxine, prednisone, prednisolone, prednicarbate, primrose oil, resorcinol, rituximab, rofecoxib, salsalate, sulindac, sulfasalazine, tazarotene, tetracycline, tocilizumab, tofacitinib, tolmetin, tramadol, triamcinolone, trolamine salicylate, ustekinumab, valdecoxib, 3-(5-amino-2-methyl-4-oxo-4H-quinazolin-3-yl)-piperidine-2,6-dione, and (S)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisindolin-2-yl)piperidine-2,6-dione.

[00107] In some embodiments, one or more selective active agents are selected from the group consisting of a Btk inhibitor, a cereblon targeting agent, a Tyk2 inhibitor, a Syk inhibitor, a JNK inhibitor, a MK2 inhibitor, a ERP5 inhibitor, a PD-1 inhibitor, a TIMP-3 inhibitor, a IKK-2 inhibitor, a LH2B inhibitor, a PKC-theta inhibitor, a IRAK4 inhibitor, a ROCK inhibitor, and a ROR-gamma-T inhibitor.

[00108] Administration of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminoisindoline-1,3-dione and a second active agent to a patient can occur simultaneously or sequentially by the same or different routes of administration. The suitability of a particular route of administration employed for a particular second active agent will depend on the second active agent itself (*e.g.*, whether it can be administered orally or topically without

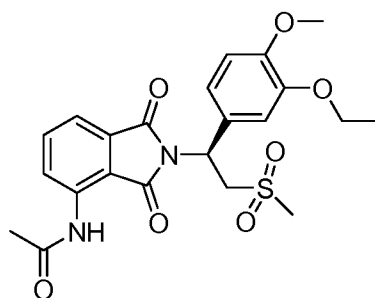
decomposition prior to entering the blood stream) and the subject being treated. Particular routes of administration for the second active agents or ingredients are known to those of ordinary skill in the art. See, e.g., *The Merck Manual*, 448 (17th ed., 1999).

[00109] The amount of a second active agent administered can be determined based on the specific agent used, the subject being treated, the severity and stage of disease and the amount(s) of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione and any optional additional second active agents concurrently administered to the patient. Those of ordinary skill in the art can determine the specific amounts according to conventional procedures known in the art. In the beginning, one can start from the amount of the second active agent that is conventionally used in the therapies and adjust the amount according to the factors described above. See, e.g., *Physician's Desk Reference* (59th Ed., 2005).

[00110] In certain embodiments, the second active agent is administered orally, topically, intravenously or subcutaneously and once to four times daily in an amount of from about 1 to about 1,000 mg, from about 5 to about 500 mg, from about 10 to about 350 mg or from about 50 to about 200 mg. The specific amount of the second active agent will depend on the specific agent used, the age of the subject being treated, the severity and stage of disease and the amount(s) of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione and any optional additional second active agents concurrently administered to the patient.

4.3 Apremilast

[00111] Without being limited by theory, apremilast is believed to be the (+) enantiomer of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-4-acetylaminisoindolin-1,3-dione having the following structure:



[00112] Apremilast may be prepared according to methods disclosed in U.S. Patent Nos. 6,962,940; 7,208,516; 7,427,638; or 7,893,101, the entirety of each which is incorporated herein by reference. In a specific method, apremilast may be prepared, for example, by the following process.

[00113] A stirred solution of 1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethylamine (1.0 g, 3.7 mmol) and 3-acetamidophthalic anhydride (751 mg, 3.66 mmol) in acetic acid (20 mL) was heated at reflux for 15 h. The solvent was removed *in vacuo* to yield an oil. Chromatography of the resulting oil yielded the product as a yellow solid (1.0 g, 59% yield): mp, 144 °C; ¹H NMR (CDCl₃) δ: 1.47 (t, J=7.0 Hz, 3H, CH₃), 2.26 (s, 3H, CH₃), 2.88 (s, 3H, CH₃), 3.75 (dd, J=4.4, 14.3 Hz, 1H, CH), 3.85 (s, 3H, CH₃), 4.11 (q, J=7 Hz, 2H, CH₂), 5.87 (dd, J=4.3, 10.5 Hz, 1H, NCH), 6.82-6.86 (m, 1H, Ar), 7.09-7.11 (m, 2H, Ar), 7.47 (d, J= 7 Hz, 1H, Ar), 7.64 (t, J= 8 Hz, 1H, Ar), 8.74 (d, J= 8 Hz, 1H, Ar), 9.49 (br s, 1H, NH); ¹³C NMR (CDCl₃) δ: 14.61, 24.85, 41.54, 48.44, 54.34, 55.85, 64.43, 111.37, 112.34, 115.04, 118.11, 120.21, 124.85, 129.17, 130.96, 136.01, 137.52, 148.54, 149.65, 167.38, 169.09, 169.40; Anal Calc'd. for C₂₂H₂₄NO₇S: C, 57.38; H, 5.25; N, 6.08. Found: C, 57.31; H, 5.34; N, 5.83.

[00114] Preparation of 3-aminophthalic acid: 10% Pd/C (2.5 g), 3-nitrophthalic acid (75.0 g, 355 mmol) and ethanol (1.5 L) were charged to a 2.5 L Parr hydrogenator under a nitrogen atmosphere. Hydrogen was charged to the reaction vessel for up to 55 psi. The mixture was shaken for 13 hours, maintaining hydrogen pressure between 50 and 55 psi. Hydrogen was released and the mixture was purged with nitrogen 3 times. The suspension was filtered through a celite bed and rinsed with methanol. The filtrate was concentrated *in vacuo*. The resulting solid was reslurried in ether and isolated by vacuum filtration. The solid was dried *in vacuo* to a constant weight, affording 54 g (84% yield) of 3-aminophthalic acid as a yellow product. ¹H-NMR (DMSO-d₆) δ: 3.17 (s, 2H), 6.67 (d, 1H), 6.82 (d, 1H), 7.17 (t, 1H), 8-10 (br, s, 2H); ¹³C-NMR (DMSO-d₆) δ: 112.00, 115.32, 118.20, 131.28, 135.86, 148.82, 169.15, 170.09.

[00115] Preparation of 3-aminophthalic anhydride: A 1 L 3-necked round bottom flask was equipped with a mechanical stirrer, thermometer, and condenser and charged with 3-aminophthalic acid (108 g, 596 mmol) and acetic anhydride (550 mL). The reaction mixture was heated to reflux for 3 hours and cooled to about 25 °C and further to 0-5 °C for another 1 hour. The crystalline solid was collected by vacuum filtration and washed with ether. The solid product was dried *in vacuo* at ambient temperature to a constant weight, giving 75 g (61% yield) of 3-acetamidophthalic anhydride as a white product. ¹H-NMR (CDCl₃) δ: 2.21 (s, 3H), 7.76 (d, 1H), 7.94 (t, 1H), 8.42 (d, 1H), 9.84 (s, 1H).

[00116] Resolution of 2-(3-ethoxy-4-methoxyphenyl)-1-(methylsulphonyl)-eth-2-ylamine: A 3 L 3-necked round bottom flask was equipped with a mechanical stirrer, thermometer, and condenser and charged with 2-(3-ethoxy-4-methoxyphenyl)-1-(methylsulphonyl)-eth-2-ylamine (137.0 g, 500 mmol),

N-acetyl-L-leucine (52 g, 300 mmol), and methanol (1.0 L). The stirred slurry was heated to reflux for 1 hour. The stirred mixture was allowed to cool to ambient temperature and stirring was continued for another 3 hours at ambient temperature. The slurry was filtered and washed with methanol (250 L). The solid was air-dried and then dried *in vacuo* at ambient temperature to a constant weight, giving 109.5 g (98% yield) of the crude product (85.8% ee). The crude solid (55.0 g) and methanol (440 mL) were brought to reflux for 1 hour, cooled to room temperature and stirred for an additional 3 hours at ambient temperature. The slurry was filtered and the filter cake was washed with methanol (200 mL). The solid was air-dried and then dried *in vacuo* at 30 °C to a constant weight, yielding 49.6 g (90% recovery) of (*S*)-2-(3-ethoxy-4-methoxyphenyl)-1-(methylsulphonyl)-eth-2-ylamine-N-acetyl-L-leucine salt (98.4% ee). Chiral HPLC (1/99 EtOH/20 mM KH₂PO₄ @ pH 7.0, Ultron Chiral ES-OVS from Agilent Technologies, 150 mm x 4.6 mm, 0.5 mL/min., @ 240 nm): 18.4 min (*S*-isomer, 99.2%), 25.5 min (*R*-isomer, 0.8%).

[00117] Final preparation of apremilast: A 500 mL 3-necked round bottom flask was equipped with a mechanical stirrer, thermometer, and condenser. The reaction vessel was charged with (*S*)-2-(3-ethoxy-4-methoxyphenyl)-1-(methylsulphonyl)-eth-2-yl amine N-acetyl-L-leucine salt (25 g, 56 mmol, 98% ee), 3-acetamidophthalic anhydride (12.1 g, 58.8 mmol), and glacial acetic acid (250 mL). The mixture was refluxed over night and then cooled to <50° C. The solvent was removed *in vacuo*, and the residue was dissolved in ethyl acetate. The resulting solution was washed with water (250 mL x 2), saturated aqueous NaHCO₃ (250 mL x 2), brine (250 mL x 2), and dried over sodium sulphate. The solvent was evaporated *in vacuo*, and the residue recrystallized from a binary solvent containing ethanol (150 mL) and acetone (75 mL). The solid was isolated by vacuum filtration and washed with ethanol (100 mL x 2). The product was dried *in vacuo* at 60 °C to a constant weight, affording 19.4 g (75% yield) of apremilast with 98% ee. Chiral HPLC (15/85 EtOH/20 mM KH₂PO₄ @ pH 5, Ultron Chiral ES-OVS from Agilent Technology, 150 mm x 4.6 mm, 0.4 mL/min., @ 240 nm): 25.4 min (*S*-isomer, 98.7%), 29.5 min (*R*-isomer, 1.2%). ¹H-NMR (CDCl₃) δ: 1.47 (t, 3H), 2.26 (s, 3H), 2.87 (s, 3H), 3.68-3.75 (dd, 1H), 3.85 (s, 3H), 4.07-4.15 (q, 2H), 4.51-4.61 (dd, 1H), 5.84-5.90 (dd, 1H), 6.82-8.77 (m, 6H), 9.46 (s, 1H); ¹³C-NMR (DMSO-d₆) δ: 14.66, 24.92, 41.61, 48.53, 54.46, 55.91, 64.51, 111.44, 112.40, 115.10, 118.20, 120.28, 124.94, 129.22, 131.02, 136.09, 137.60, 148.62, 149.74, 167.46, 169.14, 169.48.

4.4 Pharmaceutical Compositions and Dosage Forms

[00118] Pharmaceutical compositions can be used in the preparation of individual, single unit dosage forms. Pharmaceutical compositions and dosage forms can comprise apremilast or a

pharmaceutically acceptable salt or solvate thereof and a second active agent. Examples of the optional second active agents are disclosed herein (*see, e.g.*, section 4.2.1). Pharmaceutical compositions and dosage forms can further comprise one or more carriers, excipients or diluents.

[00119] The pharmaceutical compositions provided herein are suitable for oral administration can be presented as discrete dosage forms, such as, but not limited to, tablets (*e.g.*, chewable tablets), caplets, capsules and liquids (*e.g.*, flavored syrups). Such dosage forms contain predetermined amounts of active ingredients and can be prepared by methods of pharmacy well known to those skilled in the art. *See generally, Remington's Pharmaceutical Sciences*, 20th ed., Mack Publishing, Easton PA (2000).

[00120] Typical oral dosage forms are prepared by combining the active ingredients in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. Non-limiting examples of excipients suitable for use in oral liquid or aerosol dosage forms include water, glycols, oils, alcohols, flavoring agents, preservatives and coloring agents. Non-limiting examples of excipients suitable for use in solid oral dosage forms (*e.g.*, powders, tablets, capsules and caplets) include starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders and disintegrating agents.

[00121] Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid excipients are employed. If desired, tablets can be coated by standard aqueous or nonaqueous techniques. Such dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers or both and then shaping the product into the desired presentation if necessary.

[00122] For example, a tablet can be prepared by compression or molding. Compressed tablets can be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as powder or granules, optionally mixed with an excipient. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[00123] Non-limiting examples of excipients that can be used in oral dosage forms include binders, fillers, disintegrants and lubricants. Non-limiting examples of binders suitable for use in pharmaceutical compositions and dosage forms include corn starch, potato starch or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate,

carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (*e.g.*, Nos. 2208, 2906, 2910), microcrystalline cellulose and mixtures thereof.

[00124] Non-limiting examples of suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL® (microcrystalline cellulose) PH-101, AVICEL® (microcrystalline cellulose) PH-103, AVICEL RC-581® (crystalline cellulose and carboxymethylcellulose sodium), AVICEL® (microcrystalline cellulose) PH-105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, PA), and mixtures thereof. A specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC-581® (crystalline cellulose and carboxymethylcellulose sodium). Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103™ ® (microcrystalline cellulose) PH-103 and Starch 1500® LM (pregelatinized starch).

[00125] Non-limiting examples of fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include talc, calcium carbonate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch and mixtures thereof. The binder or filler in pharmaceutical compositions is typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

[00126] Disintegrants are used in the compositions to provide tablets that disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients should be used to form solid oral dosage forms. The amount of disintegrant used varies based upon the type of formulation and is readily discernible to those of ordinary skill in the art. Typical pharmaceutical compositions comprise from about 0.5 to about 15 weight percent of disintegrant, preferably from about 1 to about 5 weight percent of disintegrant.

[00127] Non-limiting examples of disintegrants that can be used in pharmaceutical compositions and dosage forms include agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrillin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other algin, other celluloses, gums and mixtures thereof.

[00128] Non-limiting examples of lubricants that can be used in pharmaceutical compositions and dosage forms include calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar and mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL200® (silica), manufactured by W.R. Grace Co. of Baltimore, MD), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, TX), CAB-O-SIL® (fumed silica) (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, MA) and mixtures thereof. If used at all, lubricants are typically used in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

[00129] Non-limiting examples of dosage forms include tablets; caplets; capsules, such as soft elastic gelatin capsules; sachets; troches; lozenges; dispersions; suppositories; powders; aerosols (*e.g.*, nasal sprays or inhalers); gels; liquid dosage forms suitable for oral or mucosal administration to a patient, including suspensions (*e.g.*, aqueous or non-aqueous liquid suspensions, oil-in-water emulsions or water-in-oil emulsions), solutions and elixirs.

[00130] The composition, shape and type of dosage forms will typically vary depending on their use. For example, a dosage form used in the acute treatment of a disease may contain larger amounts of one or more of the active ingredients it comprises than a dosage form used in the chronic treatment of the same disease. These and other ways in which specific dosage forms will vary from one another will be readily apparent to those skilled in the art. *See, e.g., Remington's Pharmaceutical Sciences*, 20th ed., Mack Publishing, Easton PA (2,000).

[00131] Typical pharmaceutical compositions and dosage forms comprise one or more excipients. Suitable excipients are well known to those skilled in the art of pharmacy and non-limiting examples of suitable excipients are provided herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a patient. The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form. For example, the decomposition of some active ingredients can be accelerated by some excipients such as lactose or when exposed to water. Active ingredients that comprise primary or secondary amines are particularly susceptible to such accelerated decomposition.

[00132] In certain embodiments, provided herein are anhydrous pharmaceutical compositions and dosage forms comprising active ingredients, since water can facilitate the degradation of some compounds. For example, the addition of water (*e.g.*, 5%) is widely accepted in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. *See, e.g.*, Jens T. Carstensen, *Drug Stability: Principles & Practice*, 2d. Ed., Marcel Dekker, NY, NY, 1995, pp. 379-80. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment and use of formulations.

[00133] Anhydrous pharmaceutical compositions and dosage forms can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms that comprise lactose and at least one active ingredient that comprises a primary or secondary amine are preferably anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging and/or storage is expected.

[00134] An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are preferably packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Non-limiting examples of suitable packaging include hermetically sealed foils, plastics, unit dose containers (*e.g.*, vials), blister packs and strip packs.

[00135] Also provided herein are pharmaceutical compositions and dosage forms that comprise one or more compounds that reduce the rate by which an active ingredient will decompose. Such compounds, which are referred to herein as “stabilizers,” include, but are not limited to, antioxidants such as ascorbic acid, pH buffers or salt buffers. Like the amounts and types of excipients, the amounts and specific types of active ingredients in a dosage form may differ depending on factors such as, but not limited to, the route by which it is to be administered to patients. However, typical oral dosage forms comprise apremilast in an amount of 10 mg, 20 mg, 30 mg, or 40 mg. In a particular embodiment, the oral dosage forms are 10 mg, 20 mg, 30 mg, or 40 mg tablets.

4.5 Delayed Release Dosage Forms

[00136] In certain embodiments, active ingredients can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Non-limiting examples of controlled release means or delivery devices include those described in U.S. Patent Nos.:

3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, 5,674,533, 5,059,595, 5,591,767,

5,120,548, 5,073,543, 5,639,476, 5,354,556 and 5,733,566, each of which is incorporated herein by reference. Such dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients. In certain embodiments, provided herein are single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps and caplets that are adapted for controlled-release.

[00137] All controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include extended activity of the drug, reduced dosage frequency and increased patient compliance. In addition, controlled-release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug and can thus affect the occurrence of side (*e.g.*, adverse) effects.

[00138] Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect and gradually and continually release of other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water or other physiological conditions or compounds.

5. EXAMPLES

[00139] Some embodiments are illustrated by the following non-limiting examples. The examples should not be construed as a limitation in the scope thereof.

5.1 Biological Activity of Apremilast in Preclinical Models

[00140] Arthritic conditions are considered to be a Th1 autoimmune disease because of the involvement of pro-inflammatory cytokines, interferon (INF) γ and tumor necrosis factor (TNF)- α .

Elevation of cyclic nucleotide adenosine 3',5'-cyclic monophosphate (cAMP) inhibits the release of inflammatory mediators, including TNF- α . A cellular mechanism for the inactivation of cAMP is its breakdown by cyclic nucleotide phosphodiesterases (PDEs). The inhibition of PDE4 is particularly effective in the inhibition of inflammatory mediator release. Thus, compounds that inhibit PDE4 specifically may inhibit inflammation with a minimum of unwanted side effects.

[00141] Inhibition of TNF- α : Apremilast inhibits TNF- α production in PBMCs (IC₅₀ of 77 nM), in human whole blood (IC₅₀ of 294), and in a mouse model (EC₅₀ of 0.05 mg/kg). The test methods were as described in WO 03/080049; Muller *et al.*, *J. Med. Chem.*, 1996, 39:3238; and Muller *et al.*, *Bioorg. Med. Chem. Lett.*, 1999, 9:1625-30.

[00142] Inhibition of PDE4: Phosphodiesterase 4 enzyme was purified from U937 human monocytic cells by gel filtration chromatography, and phosphodiesterase reactions were carried out as previously described. See Muller *et al.*, *Bioorg. Med. Chem. Lett.*, 1998, 8(19): 2669-2674. Briefly, reactions were carried out in 96-well deep-well plates in 50 mM Tris HCl pH 7.5, 5 mM MgCl₂, 1 μ M cyclic adenosine monophosphate (cAMP), plus 10 nM [3H]-cAMP for 45 min at 30°C. The reactions were terminated by boiling, treated with 1 mg/ml snake venom, and separated using AG-1X8 ion exchange resin (BioRad). Reactions consumed less than 15% of available substrate. Apremilast inhibited PDE4 with an IC₅₀ of 73.5 nM.

[00143] PDE4 selectivity: Apremilast selectively inhibits PDE4 over PDE1 (23% inhibition at 10 μ M), PDE2 (6% inhibition at 10 μ M), PDE3 (20% inhibition at 10 μ M), PDE5 (3% inhibition at 10 μ M), PDE6 (-6% inhibition at 10 μ M) and PDE7 (IC₅₀ of 20.5 μ M). PDE1, 2, 3 and 5 enzyme assays were prepared as described by Hidaka and Asano. *Biochem. Biophys. Acta.*, 1976, 429:485; see also Nichol森 *et al.*, *Trends Pharmacol. Sci.*, 1991, 12:19. The PDE6 enzyme assay was prepared according to Baehr *et al.*, *J. Biol. Chem.*, 1979, 254:11669 and Gillespie *et al.*, *Mol. Pharm.*, 1989, 36: 773. The PDE7 enzyme assay was prepared according to Bloom and Beavo. *Proc. Natl. Acad. Sci. USA*, 1996, 93:14188-92.

5.2 Clinical Data of Treating or Managing a Liver Disease or a Liver Function Abnormality using Apremilast (PALACE 1, 2, and 3)

[00144] Apremilast was studied in Phase 3 trials in both psoriatic arthritis and psoriasis patient populations and a Phase 2 trial in rheumatoid arthritis patients on background methotrexate. Patients in these studies showed improvement in liver functions as well as a reduction of liver function test (LFT) abnormalities. The improvement in mild baseline liver function test abnormalities has been observed with apremilast daily use without any prescribed changes in physical activity, social or

dietary habits. The majority of the patient populations in both the psoriatic arthritis and psoriasis studies were overweight with the mean BMI for subjects greater than or equal to 30, more than half were consuming alcoholic beverages regularly, approximately 60% were taking methotrexate at an average dose of 15 mg daily, and 70% were using non-steroidal anti-inflammatory drugs (NSAIDs). Despite the balanced distribution of risk factors (both obesity and alcohol consumption are risk factors for fatty liver disease, and the use of NSAIDs and methotrexate increase the risk for liver function test abnormalities), the pooled populations had a similar number of subjects with abnormal LFTs at baseline. During the course of the study, there was observed a higher proportion of subjects in the apremilast treatment groups (both 20 mg BID and 30 mg BID) with normal LFTs (*i.e.* normal levels of ALT and AST) at subsequent placebo-controlled study visits at week 4, week 16, and week 24 (*See* Tables 1 to 10 from PALACE 1, 2, and 3 studies).

[00145] Of the subjects tested for ALT at week 4, the 20 mg BID group showed a 8.7% increase in the number of patients with “normal” levels of ALT compared to the placebo group. At week 16, these patients showed a 12.4% increase in the number of patients with “normal” levels of ALT compared to the placebo group. At week 24, these patients showed a 14.9% increase in the number of patients with “normal” levels of ALT compared to the placebo group. *See* Table 1.

[00146] Of the subjects tested for ALT at week 4, the 30 mg BID group showed a 21.8% increase in the number of patients with “normal” levels of ALT compared to the placebo group. At week 16, these patients showed a 16.5% increase in the number of patients with “normal” levels of ALT compared to the placebo group. At week 24, these patients showed a 36.2% increase in the number of patients with “normal” levels of ALT compared to the placebo group. *See* Table 1.

Table 1: Summary of Percent Change of Alanine Aminotransferase During Apremilast Treatment (PALACE 1, 2, and 3)

ALT		Baseline High	Normal			High	
		n	n	%	% difference from Placebo	n	%
Week 4	Placebo	70	26	37.1%	0	44	62.9%
	20 mg BID	83	38	45.8%	8.7	45	54.2%
	30 mg BID	56	33	58.9%	21.8	23	41.1%
Week 16	Placebo	65	33	50.8%	0	32	49.2%
	20 mg BID	76	48	63.2%	12.4	28	36.8%
	30 mg BID	52	35	67.3%	16.5	17	32.7%
Week 24	Placebo	15	6	40.0%	0	9	60.0%

	20 mg BID	51	28	54.9%	14.9	23	45.1%
	30 mg BID	42	32	76.2%	36.2	10	23.8%

[00147] Of the subjects tested for AST at week 4, the 20 mg BID group showed a 9% increase in the number of patients with “normal” levels of AST compared to the placebo group. At week 16, these patients showed a 4.3% decrease in the number of patients with “normal” levels of AST compared to the placebo group. At week 24, these patients showed a 5.6% increase in the number of patients with “normal” levels of AST compared to the placebo group. See Table 2.

[00148] Of the subjects tested for AST at week 4, the 30 mg BID group showed a 5.4% increase in the number of patients with “normal” levels of AST compared to the placebo group. At week 16, these patients showed a 9.2% increase in the number of patients with “normal” levels of AST compared to the placebo group. At week 24, these patients showed a 25.8% increase in the number of patients with “normal” levels of AST compared to the placebo group. See Table 2.

Table 2: Summary of Percent Change of Aspartate Aminotransferase During Apremilast Treatment (PALACE 1, 2, and 3)

AST		Baseline High	Normal			High	
		n	n	%	% difference from Placebo	n	%
Week 4	Placebo	42	22	52.4%	0	20	47.6%
	20 mg BID	44	27	61.4%	9	17	38.6%
	30 mg BID	45	26	57.8%	5.4	19	42.2%
Week 16	Placebo	38	25	65.8%	0	13	34.2%
	20 mg BID	39	24	61.5%	-4.3	15	38.5%
	30 mg BID	40	30	75.0%	9.2	10	25.0%
Week 24	Placebo	14	7	50.0%	0	7	50.0%
	20 mg BID	27	15	55.6%	5.6	12	44.4%
	30 mg BID	33	25	75.8%	25.8	8	24.2%

Table 3: Levels of Alanine Aminotransferase at Week 24 of Apremilast Treatment in Placebo Group (PALACE 1, 2, and 3)

Placebo	Week 24							
ALT	Low		Normal		High		Total	
Baseline	n	%	n	%	n	%	N	%
Low	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Normal	0	0.0%	129	92.8%	10	7.2%	139	93.3%

High	0	0.0%	3	30.0%	7	70.0%	10	6.7%
Total	0	0.0%	132	88.6%	17	11.4%	149	100.0%

Table 4: Levels of Alanine Aminotransferase at Week 24 of Apremilast Treatment in 20 mg BID Group (PALACE 1, 2, and 3)

APR 20mg BID	Week 24							
ALT	Low		Normal		High		Total	
Baseline	n	%	n	%	n	%	N	%
Low	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Normal	0	0.0%	365	95.5%	17	4.5%	382	89.0%
High	0	0.0%	26	55.3%	21	44.7%	47	11.0%
Total	0	0.0%	391	91.1%	38	8.9%	429	100.0%

Table 5: Levels of Alanine Aminotransferase at Week 24 of Apremilast Treatment in 30 mg BID Group (PALACE 1, 2, and 3)

APR 30mg BID	Week 24							
ALT	Low		Normal		High		Total	
Baseline	n	%	n	%	n	%	N	%
Low	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Normal	0	0.0%	370	95.6%	17	4.4%	387	90.8%
High	0	0.0%	29	74.4%	10	25.6%	39	9.2%
Total	0	0.0%	399	93.7%	27	6.3%	426	100.0%

Table 6: Levels of Aspartate Aminotransferase at Week 24 of Apremilast Treatment in Placebo Group (PALACE 1, 2, and 3)

Placebo	Week 24							
AST	Low		Normal		High		Total	
Baseline	n	%	n	%	n	%	N	%
Low	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Normal	0	0.0%	123	89.8%	14	10.2%	137	93.2%
High	0	0.0%	6	60.0%	4	40.0%	10	6.8%
Total	0	0.0%	129	87.8%	18	12.2%	147	100.0%

Table 7: Levels of Aspartate Aminotransferase at Week 24 of Apremilast Treatment in 20 mg BID Group (PALACE 1, 2, and 3)

APR 20mg BID	Week 24							
AST	Low		Normal		High		Total	
Baseline	n	%	n	%	n	%	N	%
Low	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Normal	0	0.0%	383	95.0%	20	5.0%	403	94.6%
High	0	0.0%	14	60.9%	9	39.1%	23	5.4%
Total	0	0.0%	397	93.2%	29	6.8%	426	100.0%

Table 8: Levels of Aspartate Aminotransferase at Week 24 of Apremilast Treatment in 30 mg BID Group (PALACE 1, 2, and 3)

APR 30mg BID	Week 24							
AST	Low		Normal		High		Total	
Baseline	n	%	n	%	n	%	N	%
Low	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Normal	0	0.0%	379	96.2%	15	3.8%	394	92.9%
High	0	0.0%	22	73.3%	8	26.7%	30	7.1%
Total	0	0.0%	401	94.6%	23	5.4%	424	100.0%

Table 9: Percent of Patients With Changed Alanine Aminotransferase Levels at End of Apremilast Treatment, by Treatment Group (PALACE 1, 2, and 3)

ALT			
Treatment	High to Normal	Normal to High	Net Benefit
Placebo	30.0%	7.2%	15.0%
APR 20 BID	55.3%	4.5%	40.6%
APR 30 BID	74.4%	4.4%	51.8%
Difference between Placebo and APR 30 BID	44.4%	-2.8%	36.8%

Table 10: Percent of Patients With Changed Aspartate Aminotransferase Levels at End of Apremilast Treatment, by Treatment Group (PALACE 1, 2, and 3)

AST

Treatment	High to Normal	Normal to High	Net Benefit
Placebo	60.0%	10.2%	25.0%
APR 20 BID	60.9%	5.0%	32.6%
APR 30 BID	73.3%	3.8%	48.9%
Difference between Placebo and APR 30 BID	13.3%	-6.4%	23.9%

5.3 Clinical Data of Treating or Managing a Liver Disease or a Liver Function Abnormality using Apremilast (PSOR-008 and PSOR-009)

[00149] Apremilast was studied in Phase 3 trials in patients with moderate to severe plaque psoriasis. Patients in these studies showed improvement in liver functions as well as a reduction of liver function test (LFT) abnormalities. The improvement in mild baseline liver function test abnormalities has been observed with apremilast daily use without any prescribed changes in physical activity, social or dietary habits. During the course of the study, there was observed a higher proportion of subjects in the apremilast treatment group (30 mg BID) with normal LFTs (*i.e.* normal levels of ALT and AST) at subsequent placebo-controlled study visits at week 16. *See* Tables 11 to 16 from PSOR-008 and PSOR-009 studies.

[00150] Of the subjects tested for ALT at week 16, the 30 mg BID group showed a 3.1% increase in the number of patients who went from high to normal levels of ALT compared to the placebo group. *See* Table 15.

[00151] Of the subjects tested for AST at week 16, the 30 mg BID group showed a 17.9% increase in the number of patients who went from high to normal levels of AST compared to the placebo group. *See* Table 16.

Table 11: Levels of Alanine Aminotransferase at Week 16 of Apremilast Treatment in Placebo Group (PSOR-008 and PSOR-009)

Placebo	Week 16							
ALT	Low		Normal		High		Total	
Baseline	n	%	n	%	n	%	n	%
Low	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Normal	0	0.0%	305	94.1%	19	5.9%	324	89.8%
High	0	0.0%	20	54.1%	17	45.9%	37	10.2%
Total	0	0.0%	325	90.0%	36	10.0%	361	100.0%

Table 12: Levels of Alanine Aminotransferase at Week 16 of Apremilast Treatment in 30 mg BID Group (PSOR-008 and PSOR-009)

APR 30mg BID	Week 16							
ALT	Low		Normal		High		Total	
Baseline	n	%	n	%	n	%	n	%
Low	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Normal	0	0.0%	646	96.3%	25	3.7%	671	89.7%
High	0	0.0%	44	57.1%	33	42.9%	77	10.3%
Total	0	0.0%	690	92.2%	58	7.8%	748	100.0%

Table 13: Levels of Aspartate Aminotransferase at Week 16 of Apremilast Treatment in Placebo Group (PSOR-008 and PSOR-009)

Placebo	Week 16							
AST	Low		Normal		High		Total	
Baseline	n	%	n	%	n	%	n	%
Low	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Normal	0	0.0%	320	97.6%	8	2.4%	328	90.9%
High	0	0.0%	14	42.4%	19	57.6%	33	9.1%
Total	0	0.0%	334	92.5%	27	7.5%	361	100.0%

Table 14: Levels of Aspartate Aminotransferase at Week 16 of Apremilast Treatment in 30 mg BID Group (PSOR-008 and PSOR-009)

APR 30mg BID	Week 16							
AST	Low		Normal		High		Total	
Baseline	n	%	n	%	n	%	n	%
Low	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Normal	0	0.0%	666	97.2%	19	2.8%	685	91.6%
High	0	0.0%	38	60.3%	25	39.7%	63	8.4%
Total	0	0.0%	704	94.1%	44	5.9%	748	100.0%

Table 15: Percent of Patients With Changed Alanine Aminotransferase Levels at End of Apremilast Treatment, by Treatment Group (PSOR-008 and PSOR-009)

ALT			
Treatment	High to Normal	Normal to High	Net Benefit

Placebo	54.1%	5.9%	35.7%
APR 30 BID	57.1%	3.7%	53.7%
Difference	3.1%	-2.1%	17.9%

Table 16: Percent of Patients With Changed Aspartate Aminotransferase Levels at End of Apremilast Treatment, by Treatment Group (PSOR-008 and PSOR-009)

AST			
Treatment	High to Normal	Normal to High	Net Benefit
Placebo	42.4%	2.4%	34.1%
APR 30 BID	60.3%	2.8%	46.3%
Difference	17.9%	0.3%	12.2%

5.4 Clinical Data of Treating or Managing a Liver Disease or a Liver Function Abnormality using Apremilast (RA-002)

[00152] Apremilast was studied in a Phase 2 trial in patients with active rheumatoid arthritis who have had an inadequate response to methotrexate. Patients in these studies showed improvement in liver functions as well as a reduction of liver function test (LFT) abnormalities. The improvement in mild baseline liver function test abnormalities has been observed with apremilast daily use without any prescribed changes in physical activity, social or dietary habits. During the course of the study, there was observed a higher proportion of subjects in the 30 mg BID apremilast treatment group with normal LFTs at subsequent placebo-controlled study visits at week 16. *See* Tables 17 to 24 from RA-002 studies.

[00153] Of the subjects tested for ALT at week 16, the 30 mg BID group showed a 0% increase in the number of patients who went from high to normal levels of ALT compared to the placebo group. *See* Table 23.

[00154] Of the subjects tested for AST at week 16, the 30 mg BID group showed a 50% increase in the number of patients who went from high to normal levels of AST compared to the placebo group. *See* Table 24.

Table 17: Levels of Alanine Aminotransferase at Week 16 of Apremilast Treatment in Placebo Group (RA-002)

Placebo	Week 16			
	Low	Normal	High	Total
ALT				

Baseline	n	%	n	%	n	%	n	%
Low	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Normal	0	0.0%	65	100.0%	0	0.0%	65	91.5%
High	0	0.0%	4	66.7%	2	33.3%	6	8.5%
Total	0	0.0%	69	97.2%	2	2.8%	71	100.0%

Table 18: Levels of Alanine Aminotransferase at Week 16 of Apremilast Treatment in 20 mg BID Group (RA-002)

APR 20mg BID	Week 16							
ALT	Low		Normal		High		Total	
Baseline	n	%	n	%	n	%	n	%
Low	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Normal	0	0.0%	63	95.5%	3	4.5%	66	94.3%
High	0	0.0%	1	25.0%	3	75.0%	4	5.7%
Total	0	0.0%	64	91.4%	6	8.6%	70	100.0%

Table 19: Levels of Alanine Aminotransferase at Week 16 of Apremilast Treatment in 30 mg BID Group (RA-002)

APR 30mg BID	Week 16							
ALT	Low		Normal		High		Total	
Baseline	n	%	n	%	n	%	n	%
Low	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Normal	0	0.0%	62	96.9%	2	3.1%	64	95.5%
High	0	0.0%	2	66.7%	1	33.3%	3	4.5%
Total	0	0.0%	64	95.5%	3	4.5%	67	100.0%

Table 20: Levels of Aspartate Aminotransferase at Week 16 of Apremilast Treatment in Placebo Group (RA-002)

Placebo	Week 16							
AST	Low		Normal		High		Total	
Baseline	n	%	n	%	n	%	n	%
Low	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Normal	0	0.0%	65	97.0%	2	3.0%	67	94.4%
High	0	0.0%	2	50.0%	2	50.0%	4	5.6%
Total	0	0.0%	67	94.4%	4	5.6%	71	100.0%

Table 21: Levels of Aspartate Aminotransferase at Week 16 of Apremilast Treatment in 20 mg BID Group (RA-002)

APR 20mg BID	Week 16							
	Low		Normal		High		Total	
AST	n	%	n	%	n	%	n	%
Baseline								
Low	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Normal	0	0.0%	64	97.0%	2	3.0%	66	94.3%
High	0	0.0%	2	50.0%	2	50.0%	4	5.7%
Total	0	0.0%	66	94.3%	4	5.7%	70	100.0%

Table 22: Levels of Aspartate Aminotransferase at Week 16 of Apremilast Treatment in 30 mg BID Group (RA-002)

APR 30mg BID	Week 16							
	Low		Normal		High		Total	
AST	n	%	n	%	n	%	n	%
Baseline								
Low	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Normal	0	0.0%	61	95.3%	3	4.7%	64	95.5%
High	0	0.0%	3	100.0%	0	0.0%	3	4.5%
Total	0	0.0%	64	95.5%	3	4.5%	67	100.0%

Table 23: Percent of Patients With Changed Alanine Aminotransferase Levels at End of Apremilast Treatment, by Treatment Group (RA-002)

ALT			
Treatment	High to Normal	Normal to High	Net Benefit
Placebo	66.7%	0.0%	66.7%
APR 20 BID	25.0%	4.5%	14.3%
APR 30 BID	66.7%	3.1%	40.0%
Difference between Placebo and APR 30 BID	0.0%	3.1%	-26.7%

Table 24: Percent of Patients With Changed Aspartate Aminotransferase Levels at End of Apremilast Treatment, by Treatment Group (RA-002)

AST			
Treatment	High to Normal	Normal to High	Net Benefit
Placebo	50.0%	3.0%	33.3%
APR 20 BID	50.0%	3.0%	33.3%
APR 30 BID	100.0%	4.7%	50.0%
Difference between Placebo and APR 30 BID	50.0%	1.7%	16.7%

5.5 Clinical Data of Treating or Managing a Liver Disease or a Liver Function Abnormality using Apremilast (PSA-005)

[00155] Apremilast was studied in a Phase 3 trial in patients with active psoriatic arthritis who have not been previously treated with disease-modifying antirheumatic drugs. Patients in these studies showed improvement in liver functions as well as a reduction of liver function test (LFT) abnormalities. The improvement in mild baseline liver function test abnormalities has been observed with apremilast daily use without any prescribed changes in physical activity, social or dietary habits. During the course of the study, there was observed a higher proportion of subjects in both the 20 mg and 30 mg BID apremilast treatment groups with normal LFTs (*i.e.* normal levels of ALT and AST) at subsequent placebo-controlled study visits at week 24. *See* Tables 25 to 34 from PSA-005 studies.

[00156] Of the subjects tested for ALT at week 24, the 30 mg BID group showed a 22.7% increase in the number of patients who went from high to normal levels of ALT compared to the placebo group. *See* Table 33.

[00157] Of the subjects tested for AST at week 24, the 30 mg BID group showed a 25% increase in the number of patients who went from high to normal levels of AST compared to the placebo group. *See* Table 34.

Table 25: Percent of Patients With Changed Alanine Aminotransferase Levels at Various Weeks of Apremilast Treatment, by Treatment Group (PSA-005)

ALT		Baseline High	Normal		High	
		n	n	%	n	%
Week 4	Placebo	11	6	54.5%	5	45.5%
	20 mg BID	10	7	70.0%	3	30.0%
	30 mg BID	11	3	27.3%	8	72.7%
Week 16	Placebo	9	5	55.6%	4	44.4%
	20 mg BID	8	7	87.5%	1	12.5%
	30 mg BID	11	7	63.6%	4	36.4%
Week 24	Placebo	2	1	50.0%	1	50.0%
	20 mg BID	8	7	87.5%	1	12.5%
	30 mg BID	11	8	72.7%	3	27.3%

Table 26: Percent of Patients With Changed Aspartate Aminotransferase Levels at Various Weeks of Apremilast Treatment, by Treatment Group (PSA-005)

AST		Baseline High	Normal		High	
		n	n	%	n	%
Week 4	Placebo	12	7	58.3%	5	41.7%
	20 mg BID	7	2	28.6%	5	71.4%
	30 mg BID	12	6	50.0%	6	50.0%
Week 16	Placebo	10	6	60.0%	4	40.0%
	20 mg BID	5	4	80.0%	1	20.0%
	30 mg BID	12	7	58.3%	5	41.7%
Week 24	Placebo	2	1	50.0%	1	50.0%
	20 mg BID	5	3	60.0%	2	40.0%
	30 mg	12	9	75.0%	3	25.0%

	BID					
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Table 27: Levels of Alanine Aminotransferase at Week 24 of Apremilast Treatment in Placebo Group (PSA-005)

Placebo	Week 24							
ALT	Low		Normal		High		Total	
Baseline	n	%	n	%	n	%	n	%
Low	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Normal	0	0.0%	48	94.1%	3	5.9%	51	96.2%
High	0	0.0%	1	50.0%	1	50.0%	2	3.8%
Total	0	0.0%	49	92.5%	4	7.5%	53	100.0%

Table 28: Levels of Alanine Aminotransferase at Week 24 of Apremilast Treatment in 20 mg BID Group (PSA-005)

APR 20mg BID	Week 24							
ALT	Low		Normal		High		Total	
Baseline	n	%	n	%	n	%	n	%
Low	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Normal	0	0.0%	145	96.7%	5	3.3%	150	94.9%
High	0	0.0%	7	87.5%	1	12.5%	8	5.1%
Total	0	0.0%	152	96.2%	6	3.8%	158	100.0%

Table 29: Levels of Alanine Aminotransferase at Week 24 of Apremilast Treatment in 30 mg BID Group (PSA-005)

APR 30mg BID	Week 24							
ALT	Low		Normal		High		Total	
Baseline	n	%	n	%	n	%	n	%
Low	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Normal	0	0.0%	136	95.1%	7	4.9%	143	92.9%
High	0	0.0%	8	72.7%	3	27.3%	11	7.1%
Total	0	0.0%	144	93.5%	10	6.5%	154	100.0%

Table 30: Levels of Aspartate Aminotransferase at Week 24 of Apremilast Treatment in Placebo Group (PSA-005)

Placebo	Week 24							
AST	Low		Normal		High		Total	
Baseline	n	%	n	%	n	%	n	%
Low	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Normal	0	0.0%	49	96.1%	2	3.9%	51	96.2%
High	0	0.0%	1	50.0%	1	50.0%	2	3.8%
Total	0	0.0%	50	94.3%	3	5.7%	53	100.0%

Table 31: Levels of Aspartate Aminotransferase at Week 24 of Apremilast Treatment in 20 mg BID Group (PSA-005)

APR 20mg BID	Week 24							
AST	Low		Normal		High		Total	
Baseline	n	%	n	%	n	%	n	%
Low	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Normal	0	0.0%	149	98.0%	3	2.0%	152	96.8%
High	0	0.0%	3	60.0%	2	40.0%	5	3.2%
Total	0	0.0%	152	96.8%	5	3.2%	157	100.0%

Table 32: Levels of Aspartate Aminotransferase at Week 24 of Apremilast Treatment in 30 mg BID Group (PSA-005)

APR 30mg BID	Week 24							
AST	Low		Normal		High		Total	
Baseline	n	%	n	%	n	%	n	%
Low	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Normal	0	0.0%	138	97.9%	3	2.1%	141	92.2%
High	0	0.0%	9	75.0%	3	25.0%	12	7.8%
Total	0	0.0%	147	96.1%	6	3.9%	153	100.0%

Table 33: Percent of Patients With Changed Alanine Aminotransferase Levels at End of Apremilast Treatment, by Treatment Group (PSA-005)

ALT			
Treatment	High to Normal	Normal to High	Net Benefit
Placebo	50.0%	5.9%	20.0%
APR 20 BID	87.5%	3.3%	53.8%
APR 30 BID	72.7%	4.9%	44.4%
Difference between Placebo and APR 30 BID	22.7%	-1.0%	24.4%

Table 34: Percent of Patients With Changed Aspartate Aminotransferase Levels at End of Apremilast Treatment, by Treatment Group (PSA-005)

AST			
Treatment	High to Normal	Normal to High	Net Benefit
Placebo	50.0%	3.9%	25.0%
APR 20 BID	60.0%	2.0%	37.5%
APR 30 BID	75.0%	2.1%	60.0%
Difference between Placebo and APR 30 BID	25.0%	-1.8%	35.0%

5.6 Clinical Data of Treating or Managing Pruritus using Apremilast (ESTEEM 1 and 2)

[00158] Two randomized, double-blind, placebo controlled, multicenter clinical studies were performed in patients with moderate to severe plaque psoriasis who had a body surface area (BSA) involvement of $\geq 10\%$, static Physician Global Assessment (sPGA) of ≥ 3 (moderate or severe disease), Psoriasis Area and Severity Index (PASI) score ≥ 12 , and who were candidates for phototherapy or systemic therapy. Patients were randomized with Apremilast in an amount of 30 mg twice per day or placebo for the first 16 weeks, and from Weeks 16 to 32, all patients received Apremilast in an amount of 30 mg twice per day.

[00159] Results: Significant improvements (reductions) in pruritus, as measured by the mean change in area from Baseline, were detected in patients receiving Apremilast compared with placebo-treated patients at Week 16 (ESTEEM 1: Apremilast 30 mg BID: -31.5%; placebo: -7.5%; and ESTEEM 2: Apremilast 30 mg BID: -33.5%; placebo: -12.2%). *See Table 35.*

TABLE 35: Clinical response at Week 16 in Studies ESTEEM 1 AND 2

	ESTEEM 1		ESTEEM 2	
	Placebo	Apremilast 30 mg BID	Placebo	Apremilast 30 mg BID
Change in Pruritus Visual Analog Scale (mm \pm SD)	-7.3 (\pm 27.08)	-31.5 (\pm 32.43)	-12.2 (\pm 30.94)	-33.5 (\pm 35.46)

[00160] Apremilast appears to demonstrate a dose response with greater improvement of abnormal LFTs for the 30 mg BID compared to the apremilast 20 mg BID treatment groups, and a progressively higher proportion of subjects with abnormal LFTs having normal LFTs with longer periods of treatment. The proportion of subjects with normal LFTs increases with treatment in the apremilast treatment groups from baseline to week 4 to week 16 and further improvement by week 24. The above data indicate that apremilast treatment improves liver function.

[00161] All of the references cited herein are incorporated by reference in their entirety. While the methods provided herein have been described with respect to the particular embodiments, it will be apparent to those skilled in the art that various changes and modifications can be made without departing from the spirit and scope as recited by the appended claims.

[00162] The embodiments described above are intended to be merely exemplary and those skilled in the art will recognize or will be able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials and procedures. All such equivalents are considered to be within the scope and are encompassed by the appended claims.

What is claimed is:

1. A compound for use in a method of treating or managing a liver disease or a liver function abnormality, wherein the method comprises orally administering to a patient having a liver disease or a liver function abnormality an effective amount of the compound, wherein the compound is stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione, or a pharmaceutically acceptable prodrug, polymorph, salt or solvate thereof.
2. The compound for use of claim 1, wherein the stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione is administered once or twice daily.
3. The compound for use of claim 2, wherein the stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione is administered in an amount of about 10 mg, about 20 mg, about 30 mg, or about 40 mg, once daily.
4. The compound for use of claim 2, wherein the stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione is administered in an amount of about 10 mg, about 20 mg, about 30 mg, or about 40 mg, twice daily.
5. The compound for use of claim 1, wherein the stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione comprises greater than about 90% by weight of (+) isomer based on the total weight percent of the compound.
6. The compound for use of claim 1, wherein the stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione comprises greater than about 95% by weight of (+) isomer based on the total weight percent of the compound.
7. The compound for use of claim 1, wherein the stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminisoindoline-1,3-dione comprises greater than about 96% by weight of (+) isomer based on the total weight percent of the compound.

8. The compound for use of claim 1, wherein the stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione comprises greater than about 97% by weight of (+) isomer based on the total weight percent of the compound.

9. The compound for use of claim 1, wherein the stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione comprises greater than about 98% by weight of (+) isomer based on the total weight percent of the compound.

10. The compound for use of claim 1, wherein the stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione comprises greater than about 99% by weight of (+) isomer based on the total weight percent of the compound.

11. The compound for use of claim 1, wherein the stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione is administered in a tablet form.

12. The compound for use of claim 11, wherein the tablet comprises a 10 mg, 20 mg, 30 mg, or 40 mg dose of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione.

13. The compound for use of claim 12, wherein the tablet comprises a 10 mg dose of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione.

14. The compound for use of claim 12, wherein the tablet comprises a 20 mg dose of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione.

15. The compound for use of claim 12, wherein the tablet comprises a 30 mg dose of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione.

16. The compound for use of claim 12, wherein the tablet comprises a 40 mg dose of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisindoline-1,3-dione.

17. The compound for use of claim 12, wherein the tablet further comprises lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc.

18. The compound for use of claim 17, wherein the tablet further comprises iron oxide red.

19. The compound for use of claim 17, wherein the tablet further comprises iron oxide red and iron oxide yellow.

20. The compound for use of claim 17, wherein the tablet further comprises iron oxide red, iron oxide yellow, and iron oxide black.

21. The compound for use of claim 1, wherein the method further comprises administering to the patient a therapeutically effective amount of one or more second active agents.

22. The compound for use of claim 21, wherein the one or more second active agents are medications for treating a liver disease or liver function abnormality.

23. The compound for use of claim 1, wherein the liver disease is fatty liver disease.

24. The compound for use of claim 1, wherein the liver disease is hepatic fibrosis.

25. The compound for use of claim 1, wherein the liver disease is nonalcoholic steatohepatitis.

26. The compound for use of claim 1, wherein the liver disease is alcoholic steatohepatitis.

27. The compound for use of claim 1, wherein the liver disease is drug-induced hepatitis.

28. The compound for use of claim 1, wherein the liver disease is toxin exposure hepatitis.
29. The compound for use of claim 1, wherein the liver disease is hemochromatosis.
30. The compound for use of claim 1, wherein the liver disease is acute porphyria.
31. The compound for use of claim 1, wherein the liver disease is autoimmune hepatitis.
32. The compound for use of claim 1, wherein the liver disease is sclerosis cholangitis.
33. The compound for use of claim 1, wherein liver disease is acute cholestatic jaundice.
34. The compound for use of claim 1, wherein the liver disease is acute hepatitis.
35. The compound for use of claim 1, wherein the liver disease is primary biliary cirrhosis.
36. The compound for use of claim 1, wherein the liver disease is lupus hepatitis.
37. The compound for use of claim 1, wherein the liver disease is Wilson's disease.
38. The compound for use of claim 1, wherein the liver disease is viral hepatitis.
39. The compound for use of claim 1, wherein the liver disease is bacterial hepatitis.
40. The compound for use of claim 1, wherein the liver disease is hepatic steatosis.
41. The compound for use of claim 1, wherein the liver disease is associated with pruritus.
42. The compound for use of claim 1, wherein the liver disease is relapsed or refractory to a prior treatment.
43. The compound for use of claim 23, wherein the fatty liver disease is nonalcoholic fatty liver disease.

44. The compound for use of claim 23, wherein the fatty liver disease is alcoholic fatty liver disease.

45. The compound for use of claim 43, wherein the nonalcoholic fatty liver disease is pediatric nonalcoholic fatty liver disease.

46. The compound for use of claim 1, wherein the liver function abnormality comprises an elevated level of alanine aminotransferase or aspartate aminotransferase in the patient.

47. The compound for use of claim 1, wherein the method comprises administering stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, substantially free of any salt, solvate, or prodrug forms of (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione.

48. The compound for use of claim 1, wherein the method comprises administering a pharmaceutically acceptable salt of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione.

49. The compound for use of claim 1, wherein the method comprises administering a pharmaceutically acceptable solvate of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione.

50. The compound for use of claim 1, wherein the method decreases the level of alanine aminotransferase or aspartate aminotransferase in the patient.

51. The compound for use of claim 1, wherein the method further comprises administering to the patient an additional treatment.

52. The compound for use of claim 51, wherein the additional treatment is surgical correction.

53. The compound for use of claim 51, wherein the additional treatment is a liver transplant.

54. A compound for use in a method of treating or managing pruritus associated with a liver disease or a liver function abnormality, wherein the method comprises orally administering to a patient having a liver disease or a liver function abnormality an effective amount of the compound, wherein the compound is stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminoisindoline-1,3-dione, or a pharmaceutically acceptable prodrug, polymorph, salt or solvate thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/036898

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4035 A61K9/20 A61P1/16
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, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 2009/120167 A1 (CELGENE CORP [US]; MULLER GEORGE W [US]; SCHAFER PETER H [US]; MAN HON) 1 October 2009 (2009-10-01) the whole document paragraph [0013] paragraph [0017] paragraph [0026] paragraph [0028] paragraph [0030] paragraph [0066] paragraph [0071] paragraph [0092] paragraph [0110] paragraph [0163] - paragraph [0165] paragraph [0169] paragraph [0186] - paragraph [0193] paragraph [0204] - paragraph [0205] claims 1,27,28,30, ----- -/-</p>	1-22,41, 42,46-53



Further documents are listed in the continuation of Box C.



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

"E" earlier application or patent but published on or after the international filing date

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

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"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

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Date of the actual completion of the international search

23 September 2015

Date of mailing of the international search report

16/12/2015

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Economou, Dimitrios

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2015/036898

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2008/234359 A1 (MULLER GEORGE W [US] ET AL) 25 September 2008 (2008-09-25) the whole document paragraph [0014] - paragraph [0015] paragraph [0018] paragraph [0027] paragraph [0029] paragraph [0031] paragraph [0069] - paragraph [0073] paragraph [0079] paragraph [0082] paragraph [0090] - paragraph [0091] paragraph [0093] paragraph [0097] paragraph [0173] - paragraph [0175] paragraph [0179] paragraph [0186] paragraph [0188] - paragraph [0205] paragraph [0219] - paragraph [0221] claims 1,36,38,40,42 -----	1-22,41, 42,46-53
X	WO 2011/063102 A1 (CELGENE CORP [US]; ZELDIS JEROME B [US]) 26 May 2011 (2011-05-26) the whole document claims 1-13 -----	1,2, 4-22,42, 46-53

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/036898

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

23, 25, 26, 40, 43-45(completely); 1-22, 24, 41, 42, 46-53(partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 23, 25, 26, 40, 43-45(completely); 1-22, 24, 41, 42, 46-53(partially)

(+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione for use in the treatment of fatty liver disease, nonalcoholic steatohepatitis, alcoholic steatohepatitis, nonalcoholic fatty liver disease, alcoholic fatty liver disease, pediatric nonalcoholic fatty liver disease.

2. claims: 27, 28(completely); 1-22, 41, 42, 46-53(partially)

(+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione for use in the treatment of drug induced hepatitis, and toxin exposure hepatitis.

3. claims: 29(completely); 1-22, 24, 41, 42, 46-53(partially)

(+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione for use in the treatment of hemochromatosis

4. claims: 30(completely); 1-22, 24, 41, 42, 46-53(partially)

(+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione for use in the treatment of acute porphyria

5. claims: 31, 36(completely); 1-22, 41, 42, 46-53(partially)

(+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione for use in the treatment of autoimmune hepatitis

6. claims: 32(completely); 1-22, 41, 42, 46-53(partially)

(+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione for use in the treatment of sclerosing cholangitis

7. claims: 34, 38, 39(completely); 1-22, 24, 41, 42, 46-53(partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

(+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione for use in the treatment of acute hepatitis, viral hepatitis and bacterial hepatitis.

8. claims: 35(completely); 1-22, 24, 41, 42, 46-53(partially)

(+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione for use in the treatment of primary biliary cirrhosis.

9. claims: 37(completely); 1-22, 24, 41, 42, 46-53(partially)

(+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione for use in the treatment of Wilson's disease

10. claims: 54(completely); 1-22, 24, 41, 42, 46-53(partially)

(+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione for use in the treatment of pruritus associated with a liver disease

11. claim: 33

(+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione for use in the treatment of acute cholestatic jaundice

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2015/036898

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