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DESCRIPTION

Description

BACKGROUND OF THE INVENTION

[0001] Many current medicines suffer from poor absorption, distribution, metabolism and/or excretion (ADME) properties that prevent their wider use or limit their use in certain indications. Poor ADME properties are also a major reason for the failure of drug candidates in clinical trials. While formulation technologies and prodrug strategies can be employed in some cases to improve certain ADME properties, these approaches often fail to address the underlying ADME problems that exist for many drugs and drug candidates. One such problem is rapid metabolism that causes a number of drugs, which otherwise would be highly effective in treating a disease, to be cleared too rapidly from the body. A possible solution to rapid drug clearance is frequent or high dosing to attain a sufficiently high plasma level of drug. This, however, introduces a number of potential treatment problems such as poor patient compliance with the dosing regimen, side effects that become more acute with higher doses, and increased cost of treatment. A rapidly metabolized drug may also expose patients to undesirable toxic or reactive metabolites.

[0002] Another ADME limitation that affects many medicines is the formation of toxic or biologically reactive metabolites. As a result, some patients receiving the drug may experience toxicities, or the safe dosing of such drugs may be limited such that patients receive a suboptimal amount of the active agent. In certain cases, modifying dosing intervals or formulation approaches can help to reduce clinical adverse effects, but often the formation of such undesirable metabolites is intrinsic to the metabolism of the compound.

[0003] In some select cases, a metabolic inhibitor will be co-administered with a drug that is cleared too rapidly. Such is the case with the protease inhibitor class of drugs that are used to treat HIV infection. The FDA recommends that these drugs be co-dosed with ritonavir, an inhibitor of cytochrome P450 enzyme 3A4 (CYP3A4), the enzyme typically responsible for their metabolism (see Kempf, D.J. et al., Antimicrobial agents and chemotherapy, 1997, 41(3): 654-60). Ritonavir, however, causes adverse effects and adds to the pill burden for HIV patients who must already take a combination of different drugs. Similarly, the CYP2D6 inhibitor quinidine has been added to dextromethorphan for the purpose of reducing rapid CYP2D6 metabolism of dextromethorphan in a treatment of pseudobulbar affect. Quinidine, however, has unwanted side effects that greatly limit its use in potential combination therapy (see Wang, L et al., Clinical Pharmacology and Therapeutics, 1994, 56(6 Pt 1): 659-67; and FDA label for quinidine at www.accessdata.fda.gov).

[0004] In general, combining drugs with cytochrome P450 (CYP) inhibitors is not a satisfactory strategy for decreasing drug clearance. The inhibition of a CYP enzyme's activity can affect the metabolism and clearance of other drugs metabolized by that same enzyme. CYP inhibition can cause other drugs to accumulate in the body to toxic levels.

[0005] A potentially attractive strategy for improving a drug's metabolic properties is deuterium modification. In this approach, one attempts to slow the CYP-mediated metabolism of a drug or to reduce

the formation of undesirable metabolites by replacing one or more hydrogen atoms with deuterium atoms. Deuterium is a safe, stable, nonradioactive isotope of hydrogen. Compared to hydrogen, deuterium forms stronger bonds with carbon. In select cases, the increased bond strength imparted by deuterium can positively impact the ADME properties of a drug, creating the potential for improved drug efficacy, safety, and/or tolerability. At the same time, because the size and shape of deuterium are essentially identical to those of hydrogen, replacement of hydrogen by deuterium would not be expected to affect the biochemical potency and selectivity of the drug as compared to the original chemical entity that contains only hydrogen.

[0006] Over the past 35 years, the effects of deuterium substitution on the rate of metabolism have been reported for a very small percentage of approved drugs (see, e.g., Blake, MI et al, J Pharm Sci, 1975, 64:367-91; Foster, AB, Adv Drug Res, 1985, 14:1-40 ("Foster"); Kushner, DJ et al, Can J Physiol Pharmacol, 1999, 79-88; Fisher, MB et al, Curr Opin Drug Discov Devel, 2006, 9:101-09 ("Fisher")). The results have been variable and unpredictable. For some compounds deuteration caused decreased metabolic clearance *in vivo*. For others, there was no change in metabolism. Still others demonstrated increased metabolic clearance. The variability in deuterium effects has also led experts to question or dismiss deuterium modification as a viable drug design strategy for inhibiting adverse metabolism (see Foster at p. 35 and Fisher at p. 101).

[0007] The effects of deuterium modification on a drug's metabolic properties are not predictable even when deuterium atoms are incorporated at known sites of metabolism. Only by actually preparing and testing a deuterated drug can one determine if and how the rate of metabolism will differ from that of its non-deuterated counterpart. See, for example, Fukuto et al. (J. Med. Chem., 1991, 34, 2871-76). Many drugs have multiple sites where metabolism is possible. The site(s) where deuterium substitution is required and the extent of deuteration necessary to see an effect on metabolism, if any, will be different for each drug.

[0008] Ruxolitinib phosphate, is a heteroaryl-substituted pyrrolo[2,3-d]pyrimidines also known as 3(R)-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]propanenitrile phosphate and as (R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate, inhibits Janus Associated Kinases (JAKs) JAK1 and JAK2. These kinases mediate the signaling of a number of cytokines and growth factors important for hematopoiesis and immune function. JAK signaling involves recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors, activation and subsequent localization of STATs to the nucleus leading to modulation of gene expression.

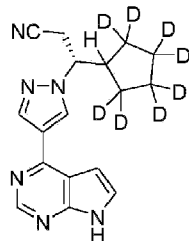
[0009] Ruxolitinib phosphate is currently approved for the treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis. Ruxolitinib phosphate is also currently in clinical trials for the treatment of additional conditions.

[0010] An article by Harris, J.E. et al. entitled "Rapid skin repigmentation on oral ruxolitinib in a patient with coexistent vitiligo and alopecia areata (AA)" was published in the Journal of the American Academy of Dermatology, vol. 74, no. 2 (11 December 2015), pages 370-371. US 2015/0239896 A1, entitled "Deuterated derivatives of ruxolitinib", was published on 27 August 2015.

[0011] Despite the beneficial activities of ruxolitinib, there is a continuing need for new compounds to treat the aforementioned diseases and conditions.

SUMMARY OF THE INVENTION AND OTHER DISCLOSURES

[0012] It has now been found that deuterated analogs of ruxolitinib (including Compound (I), also referred to as (R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-(cyclopentyl-2,2,3,3,4,4,5,5-ds)propanenitrile, or D8-ruxolitinib), are useful for the treatment of hair-loss disorders, including alopecia areata. Compound (I) is represented by the following structural formula:



Compound (I)

[0013] The present invention relates to Compound (I), or a pharmaceutically acceptable salt thereof, for use in a method of treating a hair loss disorder in a human subject, as defined in the attached claims. Compound (I) can be administered as a pharmaceutically acceptable salt, such as the phosphate salt.

[0014] Disclosed herein is Compound (I), or a pharmaceutically acceptable salt thereof, for use in a method of treating a hair loss disorder, the method comprising administering to a subject (e.g., a mammalian subject) an effective amount of Compound (I), or a pharmaceutically acceptable salt thereof (i.e., an equivalent amount of a pharmaceutically acceptable salt, such as the phosphate salt)), once or twice per day, wherein the amount of Compound (I), or a pharmaceutically acceptable salt thereof, is in the range of about 4 mg/day to about 50 mg/day, for example, about 5 mg/day, about 10 mg/day, about 20 mg/day, about 30 mg/day, about 40 mg/day, or about 50 mg/day. However, in the invention defined in the attached claims, the amount of Compound (I), or a pharmaceutically acceptable salt thereof, is about 16 mg/day or 24 mg/day. In certain embodiments, the amount of Compound (I), or a pharmaceutically acceptable salt thereof is 8mg or 12 mg twice per day. In certain embodiments, the hair loss disorder is alopecia areata. In the invention defined in the attached claims, the subject is a human. Compound (I), or a pharmaceutically acceptable salt thereof (such as the phosphate salt), can be administered orally at any of the foregoing dosages. Compound (I), or a pharmaceutically acceptable salt thereof, can be administered orally at any of the foregoing dosages in a pharmaceutical formulation which is a tablet.

[0015] Disclosed herein is Compound (I), or a pharmaceutically acceptable salt thereof, for use in a method for treating hair loss disorders, the method comprising topically administering to a subject (e.g., a mammalian subject) an effective amount of Compound (I), or a pharmaceutically acceptable salt thereof (i.e., an equivalent amount of a pharmaceutically acceptable salt, such as the phosphate salt). The compound can be administered in a pharmaceutical composition which is formulated for topical administration, such as a cream, ointment, lotion, foam or the like.

[0016] Disclosed herein is Compound (I), or a pharmaceutically acceptable salt thereof, for use in a method for inducing hair growth in a subject, the method comprising administering to a mammalian subject an effective amount of Compound (I), or a pharmaceutically acceptable salt thereof (i.e., an equivalent amount of a pharmaceutically acceptable salt, such as the phosphate salt), once or twice per day, wherein the amount of Compound (I), or a pharmaceutically acceptable salt thereof, is in the range of about 4 mg/day to about 50 mg/day, for example, about 5 mg/day, about 10 mg/day, about 20 mg/day, about 30 mg/day, about 40 mg/day, or about 50 mg/day. The amount of Compound (I), or a

pharmaceutically acceptable salt thereof, can be about 4 mg/day, 8 mg/day, 16 mg/day, 32 mg/day or 48 mg/day. The amount of Compound (I), or a pharmaceutically acceptable salt thereof, can be 8 mg/day, 16 mg/day, 24 mg/day, or 32 mg/day. The subject may suffer from a hair loss disorder, such as alopecia areata. The subject can be a human. The subject can be a human 6 years of age or older. Compound (I), or a pharmaceutically acceptable salt thereof (such as the phosphate salt), can be administered orally at any of the foregoing dosages. Compound (I), or a pharmaceutically acceptable salt thereof, can be administered orally at any of the foregoing dosages in a pharmaceutical formulation which is a tablet.

[0017] Disclosed herein is Compound (I), or a pharmaceutically acceptable salt thereof, for use in a method for treating autoimmune skin disorders, the method comprising administering to a subject (e.g., a mammalian subject) an effective amount of Compound (I), or a pharmaceutically acceptable salt thereof (i.e., an equivalent amount of a pharmaceutically acceptable salt, such as the phosphate salt), once or twice per day, wherein the amount of Compound (I), or a pharmaceutically acceptable salt thereof, is in the range of about 4 mg/day to about 50 mg/day, for example, about 5 mg/day, about 10 mg/day, about 20 mg/day, about 30 mg/day, about 40 mg/day, or about 50 mg/day. The amount of Compound (I), or a pharmaceutically acceptable salt thereof, can be about 4 mg/day, 8 mg/day, 16 mg/day, 32 mg/day or 48 mg/day. The amount of Compound (I), or a pharmaceutically acceptable salt thereof, can be 8 mg/day, 16 mg/day, 24 mg/day, or 32 mg/day. The amount of Compound (I), or a pharmaceutically acceptable salt thereof can be 4 mg, 8mg, 12 mg or 16 mg twice per day. The autoimmune skin disorder can be alopecia areata, vitiligo, atopic dermatitis (eczema), or psoriasis. The subject can be a human. Compound (I), or a pharmaceutically acceptable salt thereof (such as the phosphate salt), can be administered orally at any of the foregoing dosages. Compound (I), or a pharmaceutically acceptable salt thereof, can be administered orally at any of the foregoing dosages in a pharmaceutical formulation which is a tablet.

[0018] Another aspect of the invention is Compound (I), or a pharmaceutically acceptable salt thereof (i.e., an equivalent amount of a pharmaceutically acceptable salt, such as the phosphate salt), for use in treating hair loss disorders that can be treated by compounds that modulate the activity of Janus kinase 1 (JAK1) and/or Janus kinase 2 (JAK2). The compound may be administered at the dosing regimens disclosed herein. In certain embodiments, the hair loss disorder is alopecia areata.

[0019] Disclosed herein is a pharmaceutical composition comprising Compound (I), in the range of about 4 mg to about 50 mg (for example, about 5 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, or about 50 mg), or an equivalent amount of a pharmaceutically acceptable salt thereof (i.e., an equivalent amount of a pharmaceutically acceptable salt, such as the phosphate salt), together with a pharmaceutically acceptable carrier or diluent. The amount of Compound (I), or a pharmaceutically acceptable salt thereof, can be about 4 mg, 8 mg, 16 mg, 24 mg, 32 mg or 48 mg. The amount of Compound (I), or a pharmaceutically acceptable salt thereof, can be 4 mg, 8 mg, 12 mg, or 16 mg. The pharmaceutical composition can be a tablet.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020]

FIG. 1 shows the design and results from a single ascending dose (SAD) trial in healthy volunteers. FIG. 1A depicts the SAD study design; FIG. 1B is a graph showing plasma concentration of CTP-543 (Compound (I)) from 0 - 48 hours after dosing; FIG. 1C is a table showing mean PK parameters for CTP-543 (Compound (I)) in the SAD study.

FIG. 2 shows the design and results from a multiple ascending dose (MAD) trial in healthy volunteers. FIG. 2A depicts the MAD study design; FIG. 2B is a graph showing plasma concentration of CTP-543 (Compound (I)) from 0 - 24 hours on Day 1 and Day 7 of the MAD study; FIG. 2C is a table showing mean PK parameters for CTP-543 (Compound (I)) in the MAD study.

DETAILED DESCRIPTION OF THE INVENTION AND OTHER DISCLOSURES

Definitions

[0021] The term "treat" means decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease (e.g., a disease or disorder delineated herein), lessen the severity of the disease or improve the symptoms associated with the disease. For example, treatment of a hair loss disorder includes regrowth of hair, prevention of further hair loss, or diminishing the rate of hair loss.

[0022] "Hair loss disorder" means any condition or disorder that results in loss of hair on one or more areas of the body. Hair loss disorders include androgenetic alopecia, alopecia areata, telogen effluvium, alopecia areata, alopecia totalis, and alopecia universalis.

[0023] The term "mammal", as used herein, includes humans, as well as non-human mammals such as cats, dogs, sheep, cattle, pigs, goats and non-human primates (including monkeys and apes).

[0024] It will be recognized that some variation of natural isotopic abundance occurs in a synthesized compound depending upon the origin of chemical materials used in the synthesis. Thus, a preparation of ruxolitinib will inherently contain small amounts of deuterated isotopologues. The concentration of naturally abundant stable hydrogen and carbon isotopes, notwithstanding this variation, is small and immaterial as compared to the degree of stable isotopic substitution of compounds of this invention. See, for instance, Wada, E et al., Seikagaku, 1994, 66:15; Gannes, LZ et al., Comp Biochem Physiol Mol Integr Physiol, 1998, 119:725.

[0025] In Compound (I), any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. Also unless otherwise stated, when a position is designated specifically as "D" or "deuterium", the position is understood to have deuterium at an abundance that is at least 6000 times greater than the natural abundance of deuterium, which is 0.015% (i.e., at least 90% incorporation of deuterium).

[0026] The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope.

[0027] In other embodiments, Compound (I) has an isotopic enrichment factor for each designated deuterium atom of at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

[0028] The term "isotopologue" refers to a species in which the chemical structure differs from Compound (I) only in the isotopic composition thereof.

[0029] The term "compound," when referring to Compound (I), refers to a collection of molecules having an identical chemical structure, except that there may be isotopic variation among the constituent atoms of the molecules. Thus, it will be clear to those of skill in the art that a compound represented by a particular chemical structure containing indicated deuterium atoms, will also contain lesser amounts of isotopologues having hydrogen atoms at one or more of the designated deuterium positions in that structure. The relative amount of such isotopologues in Compound (I) will depend upon a number of factors including the isotopic purity of deuterated reagents used to make the compound and the efficiency of incorporation of deuterium in the various synthesis steps used to prepare the compound.

[0030] A salt of Compound (I) can be formed between an acid and a basic group of the compound. A pharmaceutically acceptable acid addition salt of Compound (I) can be a phosphate salt.

[0031] The term "pharmaceutically acceptable," as used herein, refers to a component that is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and other mammals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A "pharmaceutically acceptable salt" means any non-toxic salt that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention. A "pharmaceutically acceptable counterion" is an ionic portion of a salt that is not toxic when released from the salt upon administration to a recipient.

[0032] Acids commonly employed to form pharmaceutically acceptable salts include inorganic acids such as hydrogen bisulfide, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and phosphoric acid, as well as organic acids such as paratoluenesulfonic acid, salicylic acid, tartaric acid, bitartaric acid, ascorbic acid, maleic acid, besylic acid, fumaric acid, gluconic acid, glucuronic acid, formic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, lactic acid, oxalic acid, para-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid and acetic acid, as well as related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propionate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephthalate, sulfonate, xylene sulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β -hydroxybutyrate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and other salts. Pharmaceutically acceptable acid addition salts include those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and especially those formed with organic acids such as maleic acid.

[0033] The term "stable compounds," as used herein, refers to compounds which possess stability sufficient to allow for their manufacture and which maintain the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., formulation into therapeutic products, intermediates for use in production of therapeutic compounds, isolatable or storable intermediate compounds, treating a disease or condition responsive to therapeutic agents).

[0034] "D" and "d" both refer to deuterium. "Stereoisomer" refers to both enantiomers and diastereomers.

"Tert" and "t-" each refer to tertiary. "US" refers to the United States of America.

[0035] "Substituted with deuterium" refers to the replacement of one or more hydrogen atoms with a corresponding number of deuterium atoms.

[0036] Disclosed herein is Compound (I), or a pharmaceutically acceptable salt thereof, for use in a method of treating hair loss disorders, the method comprising administering to a mammalian subject an effective amount of Compound (I), or a pharmaceutically acceptable salt thereof (i.e., an equivalent amount of a pharmaceutically acceptable salt, such as the phosphate salt), once or twice per day, wherein the amount of Compound (I), or a pharmaceutically acceptable salt thereof, is in the range of about 4 mg/day to about 50 mg/day (such as 4 mg/day to 50 mg/day), for example, about 5 mg/day (such as 5 mg/day), about 10 mg/day (such as 10 mg/day), about 20 mg/day (such as 20 mg/day), about 30 mg/day (such as 30 mg/day), about 40 mg/day (such as 40 mg/day), or about 50 mg/day (such as 50 mg/day).

[0037] In the invention defined in the attached claims, the amount of Compound (I), or a pharmaceutically acceptable salt thereof administered in the method for treating hair loss disorders, is about 16 mg/day (such as 16 mg/day) or about 24 mg/day (such as 24 mg/day).

[0038] In certain embodiments, the amount of Compound (I), or a pharmaceutically acceptable salt thereof, is 21.1 mg/day of Compound (I) phosphate, e.g., administered as a 10.5 mg dose twice daily. In certain embodiments, the amount of Compound (I), or a pharmaceutically acceptable salt thereof, is 31.6 mg/day of Compound (I) phosphate, e.g., administered as a 15.8 mg dose twice daily.

[0039] In certain embodiments, the amount of Compound (I), or a pharmaceutically acceptable salt thereof administered in the method for treating hair loss disorders is about 8 mg (such as 8 mg) twice per day. In a specific embodiment, Compound (I) is administered as about 10.5 mg (such as 10.5 mg) of the phosphate salt of Compound (I) twice per day.

[0040] In certain embodiments, the amount of Compound (I), or a pharmaceutically acceptable salt thereof administered in the method for treating hair loss disorders is about 12 mg (such as 12 mg) twice per day. In a specific embodiment, Compound (I) is administered as about 15.8 mg (such as 15.8 mg) of the phosphate salt of Compound (I) twice per day. In certain embodiments, the hair loss disorder is alopecia areata. In the invention defined in the attached claims, the subject is a human. In one embodiment, the subject is a human 6 years of age or older. Compound (I), or a pharmaceutically acceptable salt thereof (such as the phosphate salt), can be administered orally at any of the dosages described herein. Compound (I), or a pharmaceutically acceptable salt thereof, can be administered orally at any of the dosages described herein in a pharmaceutical formulation which is a tablet.

[0041] Alopecia areata is an autoimmune disease that results in partial or complete loss of hair on the scalp and body that may affect up to 650,000 Americans at any given time. The scalp is the most commonly affected area, but any hair-bearing site can be affected alone or together with the scalp. Onset of the disease can occur throughout life and affects both women and men. Alopecia areata can be associated with serious psychological consequences, including anxiety and depression. There are currently no drugs approved by the U.S. Food and Drug Administration (FDA) for the treatment of alopecia areata.

[0042] In certain embodiments, the alopecia areata is moderate to severe alopecia areata (for example, hair loss over at least 30% of the scalp, hair loss over at least 40% of the scalp, or hair loss over at least

50% of the scalp).

[0043] Compound (I) can be administered orally once a day. Compound (I) can be administered orally twice per day.

[0044] Effective doses will also vary, as recognized by those skilled in the art, depending on the diseases treated, the severity of the disease, the route of administration, the sex, age and general health condition of the subject, excipient usage, the possibility of co-usage with other therapeutic treatments such as use of other agents and the judgment of the treating physician.

[0045] The administration of Compound (I), or a pharmaceutically acceptable salt thereof (such as the phosphate salt), can continue for as long as necessary to treat a hair loss disorder, e.g., for one week, two weeks, one month, two months, three months, four months, six months, one year, two years, five years, ten years, or longer.

[0046] The efficacy of treatment of hair loss disorders such as alopecia areata can be measured in a variety of ways, some of which are known in the art. For example, the "severity of alopecia tool", otherwise known as SALT, is a validated assessment scale - developed by the National Alopecia Areata Foundation working committee - to evaluate the degree of hair loss. See, e.g., Olsen EA, Hordinsky MK, Price VH, et al. Alopecia areata investigational assessment guidelines - Part II. J Am Acad Dermatol 2004; 51: 440-447. The SALT score is calculated for a patient by measuring the percentage of hair loss in each of the 4 areas of the scalp and adding the total to achieve a composite score. Hair regrowth is reflected by a decrease in the SALT score. For example, no hair on the scalp would have a SALT score of 100 while complete hair regrowth would be a SALT score of 0. Methods of treatment as described herein can provide a SALT score improvement of at least 10 points after treatment (for example, from a SALT score of 100 prior to treatment to a SALT score of 90 after treatment). Methods of treatment as described herein can provide a SALT score improvement of at least 20 points, 30 points, 40 points, 50 points, 60 points, 70 points, 80 points, 90 points, or 100 points. Methods of treatment as described herein can provide after treatment at least a 20% improvement from baseline in the patient's SALT score, or at least a 30% improvement from baseline in the patient's SALT score, or at least a 40% improvement from baseline in the patient's SALT score, or at least a 50% improvement from baseline in the patient's SALT score, or at least a 60% improvement from baseline in the patient's SALT score, or at least a 70% improvement from baseline in the patient's SALT score.

[0047] In certain embodiments, treatment is continued for a period of at least four weeks, or at least 8 weeks, or at least 12 weeks, or at least 16 weeks, or at least 20 weeks, or at least 24 weeks, or at least 28 weeks, or at least 32 weeks, or at least 36 weeks, or at least 40 weeks, or at least 44 weeks, or at least 48 weeks, or at least 52 weeks.

[0048] In certain embodiments, Compound (I), or a pharmaceutically acceptable salt thereof, is administered in combination with a second therapeutic agent. Preferably, the second therapeutic agent is an agent useful in the treatment of hair loss disorders or autoimmune conditions, such as inhibitors of JAK1, JAK2, or JAK3, and/or STAT1. Such inhibitors include ruxolitinib, tofacitinib, baricitinib, filgotinib, and the like. Other orally administered second therapeutic agents include agents used in the treatment of alopecia areata, including, for example, oral corticosteroids.

[0049] For pharmaceutical compositions that comprise a second therapeutic agent, an effective amount of the second therapeutic agent is between about 20% and 100% of the dosage normally utilized in a monotherapy regime using just that agent. Preferably, an effective amount is between about 70% and

100% of the normal monotherapeutic dose. The normal monotherapeutic dosages of these second therapeutic agents are well known in the art. See, e.g., Wells et al., eds., *Pharmacotherapy Handbook*, 2nd Edition, Appleton and Lange, Stamford, Conn. (2000); *PDR Pharmacopoeia*, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. (2000); the FDA-approved labeling information for ruxolitinib and tofacitinib; and clinical trial information for baricitinib and filgotinib.

[0050] It is expected that some of the second therapeutic agents referenced above will act synergistically with Compound (I). When this occurs, it will allow the effective dosage of the second therapeutic agent and/or Compound (I), or a pharmaceutically acceptable salt thereof, to be reduced from that required in a monotherapy. This has the advantage of minimizing toxic side effects of either the second therapeutic agent or Compound (I), or a pharmaceutically acceptable salt thereof, synergistic improvements in efficacy, improved ease of administration or use and/or reduced overall expense of compound preparation or formulation.

[0051] Any of the methods of treatment described above may comprise the further step of co-administering to the subject in need thereof one or more second therapeutic agents. The choice of second therapeutic agent may be made from any second therapeutic agent known to be useful for treatment of hair loss disorders such as alopecia areata. The choice of second therapeutic agent is also dependent upon the particular disease or condition to be treated. Examples of second therapeutic agents that may be employed are those set forth above for use in combination compositions comprising Compound (I), or a pharmaceutically acceptable salt thereof, and a second therapeutic agent. Additional therapeutic agents include agents used in the treatment of alopecia areata, including, for example, topical minoxidil, injected corticosteroids, and anthralin cream or ointment.

[0052] The term "co-administered" as used herein means that the second therapeutic agent may be administered together with Compound (I) or a pharmaceutically acceptable salt thereof, as part of a single dosage form (such as a composition comprising Compound (I) and a second therapeutic agent as described above) or as separate, multiple dosage forms. Alternatively, the additional agent may be administered prior to, consecutively with, or following the administration of Compound (I), or a pharmaceutically acceptable salt thereof. In such combination therapy treatment, both Compound (I), or a pharmaceutically acceptable salt thereof, and the second therapeutic agent(s) are administered by conventional methods. The administration of a composition comprising both Compound (I), or a pharmaceutically acceptable salt thereof, and a second therapeutic agent, to a subject does not preclude the separate administration of that same therapeutic agent, any other second therapeutic agent or Compound (I), or a pharmaceutically acceptable salt thereof, to said subject at another time during a course of treatment.

[0053] Effective amounts of these second therapeutic agents are well known to those skilled in the art and guidance for dosing may be found in patents and published patent applications referenced herein, as well as in Wells et al., eds., *Pharmacotherapy Handbook*, 2nd Edition, Appleton and Lange, Stamford, Conn. (2000); *PDR Pharmacopoeia*, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. (2000), and other medical texts. However, it is well within the skilled artisan's purview to determine the second therapeutic agent's optimal effective-amount range.

[0054] Where a second therapeutic agent is administered to a subject, the effective amount of Compound (I), or a pharmaceutically acceptable salt thereof, can be less than its effective amount would be where the second therapeutic agent is not administered. The effective amount of the second therapeutic agent can be less than its effective amount would be where Compound (I), or a pharmaceutically acceptable salt thereof, is not administered. In this way, undesired side effects associated with high doses of either

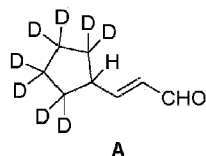
agent may be minimized. Other potential advantages (including improved dosing regimens and/or reduced drug cost) will be apparent to those of skill in the art.

[0055] Disclosed herein is a pharmaceutical composition comprising Compound (I), in the range of about 4 mg to about 50 mg (for example, about 5 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, or about 50 mg), or an equivalent amount of a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent. The amount of Compound (I), or a pharmaceutically acceptable salt thereof, can be about 4 mg, 8 mg, 16 mg, 24 mg, 32 mg or 48 mg. The amount of Compound (I), or a pharmaceutically acceptable salt thereof, can be 4 mg, 8 mg, 12 mg, or 16 mg. The amount of Compound (I), or a pharmaceutically acceptable salt thereof, can be 5.3 mg, 10.5 mg, 10.6 mg, 15.8 mg or 21.1 mg of Compound (I) phosphate. The pharmaceutical composition can be a tablet.

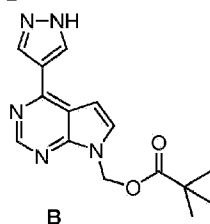
[0056] Disclosed herein is a unit dose form comprising Compound (I), in the range of about 4 mg to about 50 mg (for example, about 5 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, or about 50 mg), or an equivalent amount of a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent. The amount of Compound (I), or a pharmaceutically acceptable salt thereof, can be about 4 mg, 8 mg, 16 mg, 24 mg, 32 mg or 48 mg. The amount of Compound (I), or a pharmaceutically acceptable salt thereof, can be 4 mg, 8 mg, 12 mg, or 16 mg. The amount of Compound (I), or a pharmaceutically acceptable salt thereof, can be 5.3 mg, 10.5 mg, 10.6 mg, 15.8 mg or 21.1 mg of Compound (I) phosphate. The unit dose form can be a tablet.

[0057] In one embodiment, any atom not designated as deuterium is present at its natural isotopic abundance in Compound (I), or a pharmaceutically acceptable salt thereof.

[0058] The synthesis of Compound (I), or a pharmaceutically acceptable salt thereof (such as the phosphate salt) may be readily achieved by the methods described U.S. Patent No. 9,249,149 with appropriate modifications. For example, U.S. Patent No. 9,249,149 describes the use of a D9-intermediate 15 to produce a D9-ruxolitinib product; use of the intermediate A



in the methods described in U.S. Patent No. 9,249,149 furnishes Compound (I). Additionally, intermediate B

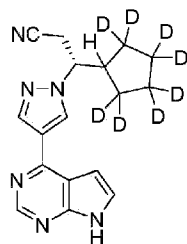


can be used instead of intermediate 14 of U.S. Patent No. 9,249,149 to prepare Compound (I); removal of the amino protecting group can be accomplished with basic cleavage (e.g., with sodium hydroxide). Phosphoric acid can be used to convert Compound (I) (Free base) to its phosphate salt. Additional methods of preparing ruxolitinib (i.e., non-deuterated Compound (I)) are disclosed in U.S. Patent No. 9,000,161, and can be used, with use of suitable deuterated reagents, to prepare Compound (I).

[0059] Such methods can be carried out utilizing corresponding deuterated and optionally, other isotope-containing reagents and/or intermediates to synthesize the compounds delineated herein, or invoking standard synthetic protocols known in the art for introducing isotopic atoms to a chemical structure.

[0060] Disclosed herein are pharmaceutical compositions comprising an effective amount of Compound (I), or a pharmaceutically acceptable salt thereof (i.e., an equivalent amount of a pharmaceutically acceptable salt, such as the phosphate salt); and a pharmaceutically acceptable carrier. The carrier(s) are "acceptable" in the sense of being compatible with the other ingredients of the formulation and, in the case of a pharmaceutically acceptable carrier, not deleterious to the recipient thereof in an amount used in the medicament. The pharmaceutical composition can be provided as a unit dose form.

[0061] Disclosed herein is a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and 4 to 50 mg of a compound represented by the following structural formula:



Compound (I)

or a pharmaceutically acceptable salt thereof (i.e., an equivalent amount of a pharmaceutically acceptable salt, such as the phosphate salt).

[0062] Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions disclosed herein include ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[0063] If required, the solubility and bioavailability of Compound (I) in pharmaceutical compositions may be enhanced by methods well-known in the art. One method includes the use of lipid excipients in the formulation. See "Oral Lipid-Based Formulations: Enhancing the Bioavailability of Poorly Water-Soluble Drugs (Drugs and the Pharmaceutical Sciences)," David J. Hauss, ed. Informa Healthcare, 2007; and "Role of Lipid Excipients in Modifying Oral and Parenteral Drug Delivery: Basic Principles and Biological Examples," Kishor M. Wasan, ed. Wiley-Interscience, 2006.

[0064] Another known method of enhancing bioavailability is the use of an amorphous form of a compound optionally formulated with a poloxamer, such as LUTROL™ and PLURONIC™ (BASF Corporation), or block copolymers of ethylene oxide and propylene oxide. See United States patent 7,014,866; and United States patent publications 20060094744 and 20060079502.

[0065] The pharmaceutical compositions disclosed herein include those suitable for oral administration. Other formulations may conveniently be presented in unit dosage form, e.g., tablets, sustained release capsules, granules, and in liposomes, and may be prepared by any methods well known in the art of pharmacy. See, for example, Remington: The Science and Practice of Pharmacy, Lippincott Williams & Wilkins, Baltimore, MD (20th ed. 2000).

[0066] Such preparative methods include the step of bringing into association with the molecule to be

administered ingredients such as the carrier that constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers, liposomes or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[0067] Compound (I) can be administered orally. Compositions suitable for oral administration may be presented as discrete units such as capsules, sachets, or tablets each containing a predetermined amount of the active ingredient; a powder or granules; a solution or a suspension in an aqueous liquid or a non-aqueous liquid; an oil-in-water liquid emulsion; a water-in-oil liquid emulsion; packed in liposomes; or as a bolus, etc. Soft gelatin capsules can be useful for containing such suspensions, which may beneficially increase the rate of compound absorption. Compound (I) can be administered orally as a tablet.

[0068] In the case of tablets for oral use, carriers that are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added. The composition can be in the form of a tablet. Exemplary formulations for the tablet are disclosed in US. Patent No. 8,754,224.

[0069] A tablet formulation can contain about 4 mg to about 50 mg of Compound (I), or an equivalent amount of a pharmaceutically acceptable salt thereof (such as the phosphate salt), and the following inactive ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, and povidone. Wet granulation followed by compression provides tablets comprising Compound (I), or a pharmaceutically acceptable salt thereof. For example, to prepare a 200 mg tablet comprising the equivalent of 16 mg of Compound (I), 10.6 wt% of Compound (I) phosphate and 64.44 wt% Avicel PH-101 microcrystalline cellulose are mixed in a higher shear granulator, and an 8.5% w/w aqueous Kollidon 30 solution (containing Kollidon 30, a polyvinylpyrrolidone (povidone); 5 wt% (based on the total formulation weight) is added during mixing to form granules. The granules are tray-dried in an oven at 60±10°C and milled using a Quadro Comil U5 mill. The granules retained on the comil screen are forced through a #20 mesh sieve using a stainless steel spatula. The resulting milled granules are mixed with Avicel PH-200 microcrystalline cellulose (18.5 wt%), Aerosil 200 colloidal silicon dioxide (0.5 wt%) and Hyqual magnesium stearate (1 wt%) in a Turbula mixer to form the final blend. The final blend is compressed into 200 mg tablets using a Riva Piccola rotary press tooled with 0.451" × 0.229" D-type modified capsule shape tooling. Each tablet contains 21.1 mg Compound (I) (equivalent to 16 mg of Compound (I) free base).

[0070] The tablet can contain about 10.5 mg or about 10.6 mg of the phosphate salt of Compound (I) (equivalent to 8 mg of Compound (I) free base).

[0071] The tablet can comprise the following ingredients:

| 4 mg Tablet | | | |
|----------------------------|----------------|------|----------------------|
| Component | Function | Wt % | Amount per unit (mg) |
| Compound (I) Phosphate | Active | 2.6 | 5.3* |
| Microcrystalline Cellulose | Diluent/Binder | 90.9 | 181.7 |
| Povidone | Binder | 5.0 | 10.0 |
| Colloidal Silicon Dioxide | Glidant | 0.5 | 1.0 |

| 4 mg Tablet | | | |
|--|-----------|---------------------------|----------------------|
| Component | Function | Wt % | Amount per unit (mg) |
| Magnesium Stearate | Lubricant | 1.0 | 2.0 |
| Purified Water | Solvent | Removed during processing | |
| Total | | 100.0 | 200.0 |
| *Equivalent to 4 mg Compound (I) free base | | | |

[0072] The tablet can comprise the following ingredients:

| 8 mg Tablet | | | |
|--|----------------|---------------------------|----------------------|
| Component | Function | Wt % | Amount per unit (mg) |
| Compound (I) Phosphate | Active | 5.2 | 10.5* |
| Microcrystalline Cellulose | Diluent/Binder | 90.8 | 181.5 |
| Povidone | Binder | 2.5 | 5.0 |
| Colloidal Silicon Dioxide | Glidant | 0.5 | 1.0 |
| Magnesium Stearate | Lubricant | 1.0 | 2.0 |
| Purified Water | Solvent | Removed during processing | |
| Total | | 100.0 | 200.0 |
| *Equivalent to 8 mg Compound (I) free base | | | |

[0073] The tablet can comprise the following ingredients:

| 8 mg Tablet | | | |
|--|----------------|---------------------------|----------------------|
| Component | Function | Wt % | Amount per unit (mg) |
| Compound (I) Phosphate | Active | 5.3 | 10.6* |
| Microcrystalline Cellulose | Diluent/Binder | 88.2 | 176.4 |
| Povidone | Binder | 5.0 | 10.0 |
| Colloidal Silicon Dioxide | Glidant | 0.5 | 1.0 |
| Magnesium Stearate | Lubricant | 1.0 | 2.0 |
| Purified Water | Solvent | Removed during processing | |
| Total | | 100.0 | 200.0 |
| *Equivalent to 8 mg Compound (I) free base | | | |

[0074] The tablet can comprise the following ingredients:

| 16 mg Tablet | | | |
|----------------------------|----------------|------|----------------------|
| Component | Function | Wt % | Amount per unit (mg) |
| Compound (I) Phosphate | Active | 10.6 | 21.1* |
| Microcrystalline Cellulose | Diluent/Binder | 82.9 | 165.9 |
| Povidone | Binder | 5.0 | 10.0 |
| Colloidal Silicon Dioxide | Glidant | 0.5 | 1.0 |

| 16 mg Tablet | | | |
|---|-----------|---------------------------|----------------------|
| Component | Function | Wt % | Amount per unit (mg) |
| Magnesium Stearate | Lubricant | 1.0 | 2.0 |
| Purified Water | Solvent | Removed during processing | |
| Total | | 100.0 | 200.0 |
| *Equivalent to 16 mg Compound (I) free base | | | |

[0075] A composition can further comprises a second therapeutic agent. The second therapeutic agent may be selected from any compound or therapeutic agent known to have or that demonstrates advantageous properties when administered with a compound having the same mechanism of action as ruxolitinib.

[0076] The second therapeutic agent can be an agent useful in the treatment of hair loss disorders or autoimmune conditions, including inhibitors of JAK1, JAK2, or JAK3, and/or STAT1. Such inhibitors include ruxolitinib, tofacitinib, baricitinib and filgotinib. Other second therapeutic agents include oral corticosteroids.

[0077] Disclosed herein are separate dosage forms of Compound (I), or a pharmaceutically acceptable salt thereof, and one or more of any of the above-described second therapeutic agents, wherein Compound (I), or a pharmaceutically acceptable salt thereof, and second therapeutic agent are associated with one another. The term "associated with one another" as used herein means that the separate dosage forms are packaged together or otherwise attached to one another such that it is readily apparent that the separate dosage forms are intended to be sold and administered together (within less than 24 hours of one another, consecutively or simultaneously).

[0078] In the pharmaceutical compositions disclosed herein, Compound (I), or a pharmaceutically acceptable salt thereof, can be present in an effective amount. As used herein, the term "effective amount" refers to an amount which, when administered in a proper dosing regimen, is sufficient to treat the target disorder.

[0079] The interrelationship of dosages for animals and humans (based on milligrams per meter squared of body surface) is described in Freireich et al., Cancer Chemother. Rep, 1966, 50: 219. Body surface area may be approximately determined from height and weight of the subject. See, e.g., Scientific Tables, Geigy Pharmaceuticals, Ardsley, N.Y., 1970, 537.

[0080] An effective amount of Compound (I) (either as the free base, or as an equivalent amount of a pharmaceutically acceptable salt, such as the phosphate salt) can range from about 4 mg to 50 mg per day (such as 4 mg to 50 mg per day), such as, about 5 mg/day (such as 5 mg/day), about 10 mg/day (such as 10 mg/day), about 20 mg/day (such as 20 mg/day), about 30 mg/day (such as 30 mg/day), about 40 mg/day (such as 40 mg/day), or about 50 mg/day (such as 50 mg/day). The amount can be about 4 mg/day (such as 4 mg/day), about 8 mg/day (such as 8 mg/day), about 16 mg/day (such as 16 mg/day), about 24 mg/day (such as 24 mg/day), about 32 mg/day (such as 32 mg/day) or about 48 mg/day (such as 48 mg/day). A dose of about 4 mg/day (such as 4 mg/day), about 8 mg/day (such as 8 mg/day), about 16 mg/day (such as 16 mg/day), about 24 mg/day (such as 24 mg/day), about 32 mg/day (such as 32 mg/day) or about 48 mg/day (such as 48 mg/day) can be administered once a day. A dose of 16 mg/day can be administered as two 8 mg tablets of Compound (I) (either as the free base, or as an equivalent amount of a pharmaceutically acceptable salt, such as the phosphate salt) administered

together (i.e., as a single dose). A dose of 16 mg/day can be administered as one 16 mg tablet of Compound (I) (either as the free base, or as an equivalent amount of a pharmaceutically acceptable salt, such as the phosphate salt). A dose of 4 mg/day, 8 mg/day, 16 mg/day, 24 mg/day, 32 mg/day or 48 mg/day can be administered in divided doses, twice a day (e.g., a 48 mg/day dose is administered as 24 mg twice daily). A dose of 8 mg/day, 16 mg/day, 24 mg/day, or 32 mg/day can be administered in divided doses, twice a day (e.g., a 32 mg/day dose is administered as 16 mg of Compound (I) (either as the free base, or as an equivalent amount of a pharmaceutically acceptable salt, such as the phosphate salt) twice daily, i.e., in separate doses. A dose of 16 mg/day can be administered as 8 mg of Compound (I) (either as the free base, or as an equivalent amount of a pharmaceutically acceptable salt, such as the phosphate salt) twice daily, i.e., in separate doses. It will be understood that reference to an amount of Compound (I), or a pharmaceutically acceptable salt thereof, includes an amount of a pharmaceutically acceptable salt of Compound (I) (such as the phosphate salt) which is equivalent to the stated amount of Compound (I) as the free base (e.g., 10.5 mg of Compound (I) phosphate salt is equivalent to 8 mg of Compound (I) free base).

[0081] An effective amount of Compound (I), or a pharmaceutically acceptable salt thereof can be about 8 mg (such as 8 mg) twice per day. Compound (I) can be administered as about 10.5 mg (such as 10.5 mg) of the phosphate salt of Compound (I) twice per day.

[0082] An effective amount of Compound (I), or a pharmaceutically acceptable salt thereof can be about 12 mg (such as 12 mg) twice per day. An effective amount of Compound (I) can be about 15.8 mg (such as 15.8 mg) of the phosphate salt of Compound (I) twice per day.

Examples

Example 1. Determination of Metabolic Stability of D-Ruxolitinib using CYP3A4 Supersomes

Materials and Methods:

[0083] *Materials:* CYP3A4 supersomes[™] were obtained from Corning Gentest. β -nicotinamide adenine dinucleotide phosphate, reduced form (NADPH), magnesium chloride (MgCl_2), and dimethyl sulfoxide (DMSO) were purchased from Sigma-Aldrich. Deuterated test compounds were supplied by Concert Pharmaceuticals.

[0084] *Determination of Metabolic Stability:* 10 mM stock solutions of test compounds were prepared in DMSO. The 7.5 mM stock solutions were diluted to 12.75 μM in acetonitrile (ACN). The CYP3A4 supersomes were diluted in 0.1 M potassium phosphate buffer, pH 7.4, containing 3 mM MgCl_2 . The diluted supersomes were added to wells of a 96-well deep-well polypropylene plate in triplicate. A 10 μL aliquot of the 12.75 μM test compound was added to the supersomes and the mixture was pre-warmed for 10 minutes. Reactions were initiated by addition of pre-warmed NADPH solution. The final reaction volume was 0.5 mL and contained 50 pmol/mL CYP3A4 supersomes, 0.25 μM test compound, and 2 mM NADPH in 0.1 M potassium phosphate buffer, pH 7.4, and 3 mM MgCl_2 . The reaction mixtures were incubated at 37°C and 50 μL aliquots were removed at 0, 5, 10, 20, and 30 minutes and added to shallow-well 96-well plates which contained 50 μL of ice-cold ACN with internal standard to stop the

reactions. The plates were stored at 4°C for 20 minutes after which 100 µL of water was added to the wells of the plate before centrifugation to pellet precipitated proteins. Supernatants were transferred to another 96-well plate and analyzed for amounts of parent remaining by LC-MS/MS using an Applied Biosystems mass spectrometer.

[0085] Data analysis: The *in vitro* $t_{1/2}$ s for test compounds were calculated from the slopes of the linear regression of % parent remaining (ln) vs incubation time relationship.
 $\text{in vitro } t_{1/2} = 0.693/k$

$k = -[\text{slope of linear regression of \% parent remaining}(\ln) \text{ vs incubation time}]$

[0086] Data analysis was performed using Microsoft Excel Software.

[0087] It was found that Compound (I) had a $t_{1/2}$, about 80% longer than the $t_{1/2}$ of non-deuterated ruxolitinib. These results show that Compound (I) is substantially more stable metabolically than ruxolitinib in the CYP3A4 supersome assay.

Example 2. Determination of Metabolic Stability of D-Ruxolitinib using Human Liver Microsomes

[0088] Materials: Human liver microsomes (20 mg/mL) were obtained from Xenotech, LLC (Lenexa, KS). β -nicotinamide adenine dinucleotide phosphate, reduced form (NADPH), magnesium chloride (MgCl₂), and dimethyl sulfoxide (DMSO) were purchased from Sigma-Aldrich. Deuterated test compounds were supplied by Concert Pharmaceuticals.

[0089] Determination of Metabolic Stability: 7.5 mM stock solutions of test compounds were prepared in DMSO. The 7.5 mM stock solutions were diluted to 12.5 µM in acetonitrile (ACN). The human liver microsomes were diluted in 0.1 M potassium phosphate buffer, pH 7.4, containing 3 mM MgCl₂. The diluted microsomes were added to wells of a 96-well deep-well polypropylene plate in triplicate. A 10 µL aliquot of the 12.5 µM test compound was added to the microsomes and the mixture was pre-warmed for 10 minutes. Reactions were initiated by addition of pre-warmed NADPH solution. The final reaction volume was 0.5 mL and contained 5 mg/mL human liver microsomes, 0.25 µM test compound, and 2 mM NADPH in 0.1 M potassium phosphate buffer, pH 7.4, and 3 mM MgCl₂. The reaction mixtures were incubated at 37°C, and 50 µL aliquots were removed at 0, 5, 10, 20, and 30 minutes and added to shallow-well 96-well plates which contained 50 µL of ice-cold ACN with internal standard to stop the reactions. The plates were stored at 4°C for 20 minutes after which 100 µL of water was added to the wells of the plate before centrifugation to pellet precipitated proteins. Supernatants were transferred to another 96-well plate and analyzed for amounts of parent remaining by LC-MS/MS using an Applied Biosystems mass spectrometer.

[0090] Data analysis: The *in vitro* $t_{1/2}$ s for test compounds were calculated from the slopes of the linear regression of % parent remaining (ln) vs incubation time relationship.
 $\text{in vitro } t_{1/2} = 0.693/k$

$k = -[\text{slope of linear regression of \% parent remaining}(\ln) \text{ vs incubation time}]$

[0091] Data analysis was performed using Microsoft Excel Software.

[0092] It was found that Compound (I) had a $t_{1/2}$ about 75% longer than the $t_{1/2}$ of non-deuterated ruxolitinib. These results show that Compound (I) is substantially more stable metabolically than ruxolitinib in the HLM assay.

Example 3 - Human Studies

[0093] Single Ascending Dose (SAD) Study: Healthy volunteers were administered doses of Compound (I) or placebo under fasted conditions. The objective of the study was to evaluate the pharmacokinetics of a single dose of 8 mg, 16 mg, 32 mg, or 48 mg of Compound (I) as the phosphate salt (e.g., 10.5 mg of Compound (I) phosphate salt is equivalent to 8 mg of Compound (I) free base). For each dose group, 6 subjects received Compound (I), and 2 subjects received placebo. The study design is shown in FIG. 1A. Metabolites of Compound (I) were analyzed. Doses of Compound (I) were administered as Compound (I) phosphate salt as a powder-in-capsule, administered with water. The preliminary results are shown in FIGS. 1B and 1C.

[0094] Multiple Ascending Dose Study: Healthy volunteers were administered doses of Compound (I) or placebo under fasted conditions. The objective of the study was to evaluate the pharmacokinetics of daily administration of 8 mg, 16 mg, 24 mg, or 32 mg of Compound (I) as the phosphate salt (e.g., 10.5 mg of Compound (I) phosphate salt is equivalent to 8 mg of Compound (I) free base). Compound (I) was administered once per day (QD) (8 mg, 24 mg, 32 mg doses) or twice per day (BID) (two 8 mg doses totaling 16 mg/day, or two 16 mg doses totaling 32 mg/day) for seven consecutive days. For each dose group, 8 subjects received Compound (I), and 2 subjects received placebo. The study design is shown in FIG. 1A. Metabolites of Compound (I) were analyzed. Doses of Compound (I) were administered as 8 mg tablets, with water. The preliminary results are shown in FIGS. 1B and 1C.

[0095] Final results are shown in the following table:

| | Median (range) | Arithmetic Mean (CV%) | | | | | | |
|---------------------------|--------------------------|-----------------------------|-----------------------|-------------------------------------|------------------------------------|------------------------------|------------------|-----------------|
| Treatment | T _{max} (hr) | C _{max} (ng/mL) | t _{1/2} (hr) | AUC _{0-24hr} (hr*ng/mL) | AUC _{0-inf} (hr*ng/mL) | C _{24hr} (ng/mL) | CL/F (L/hr) | Vz/F (L) |
| CTP-543 8 mg (n=6) | 1.25 (0.50 - 1.50) | 118 (28.4%) | 3.14 (28.4%) | 584 (31.3%) | 589 (31.6%) | 1.02 (94.9%) | 14.92 (34.9%) | 64.1 (27.8%) |
| CTP-543 16 mg (n=6) | 1.50 (0.50 - 3.20) | 260 (39.2%) | 3.32 (25.9%) | 1329 (34.7%) | 1347 (35.2%) | 2.77 (78.4%) | 13.87 (52.4%) | 61.0 (28.0%) |
| CTP-543 32mg (n=6) | 1.25 (0.50 - 2.00) | 535 (29.0%) | 3.52 (15.9%) | 2424 (25.2%) | 2462 (26.3%) | 5.60 (104.5%) | 13.88 (30.2%) | 68.4 (21.3%) |
| CTP-543 48mg (n=5) | 1.50 (0.50 - 2.00) | 853 (25.7%) | 3.61 (21.4%) | 4095 (34.2%) | 4159 (35.1%) | 9.26 (80.1%) | 12.75 (34.1%) | 63.2 (25.6%) |

[0096] Preliminary results from the SAD study are shown in FIGS. 1B and 1C. Preliminary results from the MAD study are shown in FIGS. 2B and 2C. Final results from the MAD study are shown in the following tables. In FIGS. 1 and 2, CTP-543 is Compound (I), administered as the phosphate salt.

| | | Median (range) | Arithmetic Mean (CV%) | | | |
|--------------------------|--------------|--------------------------|-----------------------------|--|------------------------------|-----------------------|
| Dose Level of CTP-543 | Study Day | T _{max} (hr) | C _{max} (ng/mL) | AUC _{tau} / AUC _{0-24hr} (hr*ng/mL) | C _{24hr} (ng/mL) | t _{1/2} (hr) |
| 8 mg QD (n=7) | Day 1 | 1.00 (0.50 - 2.00) | 156 (31.2%) | 704 (26.4%) | 0.86 (45.3%) | 3.23 (9.6%) |
| | Day 7 | 1.00 (0.25 - 1.50) | 151 (34.1%) | 668 (27.8%) | 1.01 (75.0%) | 3.51 (20.9%) |
| 24 mg QD (n=8) | Day 1 | 0.50 (0.25 - 2.00) | 384 (22.2%) | 1672 (25.7%) | 2.48 (134%) | 3.14 (28.8%) |
| | Day 7 | 1.00 (0.50 - 2.00) | 310 (22.9%) | 1534 (25.2%) | 3.39 (160%) | 3.50 (25.2%) |
| 32 mg QD (n=8) | Day 1 | 0.75 (0.50 - 2.00) | 509 (32.8%) | 2219 (36.2%) | 2.95 (141%) | 2.86 (32.1%) |
| | Day 7 | 0.75 (0.50 - 2.00) | 492 (18.0%) | 2104 (27.8%) | 5.12 (153%) | 3.45 (37.1%) |
| | | Median (range) | Arithmetic Mean (CV%) | | | |
| Dose Level of CTP-543 | Study Day | T _{max} (hr) | C _{max} (ng/mL) | AUC _{tau} / AUC _{0-12hr} (hr*ng/mL) | C _{12hr} (ng/mL) | t _{1/2} (hr) |
| 8 mg BID (n=4) | Day 1 | 1.00 (0.50 - 1.50) | 160 (17.5%) | 703 (24.5%) | 13.7 (55.9%) | 3.77 (23.4%) |
| | Day 7 | 1.50 (0.25 - 2.00) | 183 (25.7%) | 844 (39.8%) | 13.2 (59.6%) | 4.20 (32.3%) |
| 16 mg BID (n=8) | Day 1 | 1.00 (0.50 - 2.00) | 290 (19.7%) | 1062 (22.5%) | 15.3 (53.9%) | 2.89 (31.4%) |
| | Day 7 | 0.75 (0.50 - 2.00) | 288 (36.3%) | 1127 (26.6%) | 16.5 (71.6%) | 3.53 (19.3%) |

[0097] In the combined SAD and MAD studies, a total of 77 subjects were dosed (60 received CTP-543; 17 received placebo). CTP-543 was rapidly absorbed and did not accumulate with repeated dosing. No serious adverse events were reported; the most common adverse event reported was headache. No withdrawal or dose modification related to CTP-543 occurred. Cases of mild neutropenia resolved or trended toward recovery after dosing completion. Severe neutropenia (Grade 3 or 4) was not observed.

[0098] In the Phase 1 study, Compound (I) was generally well tolerated. Based on these studies, doses of 8 mg BID (twice daily), 12 mg BID, 16 mg BID and 32 mg BID were selected.

[0099] Additional findings from the Phase 1 study show that the average systemic exposure of 16 mg BID of Compound (I), the highest dose being evaluated in the Phase 2a trial described below, appears comparable to published findings for average reported exposure of the 20 mg BID ruxolitinib dose shown to be effective at inducing hair regrowth in patients with moderate to severe alopecia. (See, e.g., JCI Insight. 2016;1(15):e89790. doi:10.1172/jci.insight.89790.)

[0100] Pharmacodynamic analyses were also performed during the MAD study of the Phase 1 trial to assess the inhibition of IL-6- and IFN- γ -mediated JAK/STAT signaling. Consistent with the established pharmacological activity of CTP-543 (Compound (I)), a dose-related reduction in IL-6-stimulated phosphorylated STATS (pSTAT3) was observed. In general, pSTAT3 inhibition in all treatment groups returned to approximate baseline values at 24 hours post-dose. Also, IFN- γ -mediated STAT1 signaling, which is believed to play a key role in the pathogenesis of alopecia areata, was significantly inhibited in disease-relevant immune cell types at all doses evaluated.

[0101] A Phase 2a trial has been designed to evaluate the safety and efficacy of Compound (I) after 12 months of dosing with the primary efficacy analysis at week 24. The Phase 2a trial is a double-blind, randomized, placebo-controlled, parallel dose trial to evaluate the safety and efficacy of Compound (I) in adult patients with moderate-to-severe alopecia areata. Approximately 100 patients will be randomized to receive one of four doses of Compound I as the phosphate salt (e.g., 10.5 mg of Compound (I) phosphate salt is equivalent to 8 mg of Compound (I) free base). The four doses of Compound (I) are 4, 8 (i.e., about 10.5 mg of Compound (I) phosphate salt), 12 and 16 mg twice daily, and there is also a patient group receiving placebo. The primary outcome measure will utilize the severity of alopecia tool (SALT) after 24 weeks of dosing. The trial will include an additional 28 weeks of dosing where all patients enrolled in the study will receive Compound (I).

REFERENCES CITED IN THE DESCRIPTION

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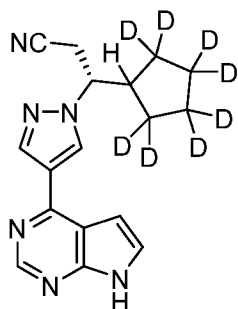
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PATENTKRAV

Det, der hævdes, er:

- 5 1. En forbindelse repræsenteret ved følgende strukturelle formel:



Forbindelse (I)

, eller et farmaceutisk acceptabelt salt deraf, til anvendelse i en

fremgangsmåde til behandling af en hårtabslidelse hos et menneske, hvilken

fremgangsmåde omfatter indgivelse af ca. 16 mg/dag, eller ca. 24 mg/dag til individet, af

nævnte stof (I) eller farmaceutisk acceptabelt salt deraf,

- 10 hvor, når en position er specifikt udpeget som "D" (deuterium), har denne position mindst 90 % inkorporering af deuterium.

2. Forbindelse til anvendelse ifølge krav 1, hvor når en position er specifikt udpeget som "D" (deuterium), har denne position mindst 95% inkorporering af deuterium.

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3. Forbindelse til anvendelse ifølge krav 1 eller krav 2, hvor når en position er specifikt udpeget som "D" (deuterium), har denne position mindst 97 % inkorporering af deuterium.

4. Forbindelse til anvendelse ifølge et hvilket som helst af kravene 1-3, hvor fremgangsmåden
- 20 til behandling af en hårtabslidelse hos et menneske omfatter indgivelse af ca. 16 mg/dag til individet af nævnte forbindelse (I) eller farmaceutisk acceptabelt salt deraf.

5. Forbindelse til anvendelse ifølge et hvilket som helst af kravene 1-3, hvor fremgangsmåden
- 25 til behandling af en hårtabslidelse hos et menneske omfatter indgivelse af ca. 24 mg/dag til individet af nævnte forbindelse (I) eller farmaceutisk acceptabelt salt deraf.

6. Forbindelse til anvendelse ifølge et hvilket som helst af kravene 1-5, hvor hårtabslidelsen er alopecia areata.
- 5 7. Forbindelse til anvendelse ifølge et hvilket som helst af kravene 1-4 og 6, hvor fremgangsmåden til behandling af en hårtabslidelse hos et menneske omfatter indgivelse to gange om dagen af ca. 8 mg til individet af forbindelse (I), eller et farmaceutisk acceptabelt salt deraf.
- 10 8. Forbindelse til anvendelse ifølge et hvilket som helst af kravene 1-3, 5 og 6, hvor fremgangsmåden til behandling af en hårtabslidelse hos et menneske omfatter indgivelse to gange om dagen af ca. 12 mg til individet af forbindelse (I), eller et farmaceutisk acceptabelt salt deraf.
- 15 9. Forbindelse til anvendelse ifølge et hvilket som helst af kravene 1-6, hvor forbindelsen indgives en gang om dagen.
10. Forbindelse til anvendelse ifølge et hvilket som helst af kravene 1-6, hvor forbindelsen indgives to gange om dagen.
- 20 11. Forbindelse til anvendelse ifølge et hvilket som helst af kravene 1-10, hvor i forbindelse (I), ethvert atom, der ikke er betegnet som deuterium, er til stede i dets naturlige isotopiske overflod.
- 25 12. Forbindelse til anvendelse ifølge krav 7, hvor forbindelse (I) indgives som ca. 10,5 mg fosfatsalt to gange dagligt.
13. Forbindelse til anvendelse ifølge krav 8, hvor forbindelse (I) indgives som ca. 15,8 mg fosfatsalt to gange dagligt.
- 30 14. Forbindelse til anvendelse ifølge et hvilket som helst af kravene 1-13, hvor forbindelsen indgives oralt.
15. Forbindelse til anvendelse ifølge et hvilket som helst af kravene 1-14, hvor forbindelsen indgives i en farmaceutisk formulering, som er en tablet.

16. Forbindelse til anvendelse ifølge krav 15, hvor tabletten omfatter:

- 5 (a) (i) ca. 5,2 vægt% fosfatsalt af forbindelse (I),
(ii) ca. 90,8 vægt% mikrokrySTALLinsk cellulose,
(iii) ca. 2,5 vægt% povidon,
(iv) ca. 0,5 vægt% kolloid siliciumdioxid og
(v) ca. 1,0 vægt% magnesiumstearat; eller
- 10 (b) (i) ca. 5,3 vægt% fosfatsalt af forbindelse (I),
(ii) ca. 88,2 vægt% mikrokrySTALLinsk cellulose,
(iii) ca. 5,0 vægt% povidon,
(iv) ca. 0,5 vægt% kolloid siliciumdioxid, og
(v) ca. 1,0 vægt% magnesiumstearat; eller
- 15 (c) (i) ca. 10,6 vægt% fosfatsalt af forbindelse (I),
(ii) ca. 82,9 vægt% mikrokrySTALLinsk cellulose,
(iii) ca. 5,0 vægt% povidon,
(iv) ca. 0,5 vægt% kolloid siliciumdioxid og
(v) ca. 1,0 vægt% magnesiumstearat.

17. Forbindelse til anvendelse ifølge krav 16, hvor sammensætningen er en 200 mg tablet
20 omfattende

- (a) ca. 10,6 mg,
(b) ca. 21,1 mg eller
(c) ca. 10,5 mg
fosfatsalt af forbindelse (I).

DRAWINGS

Drawing

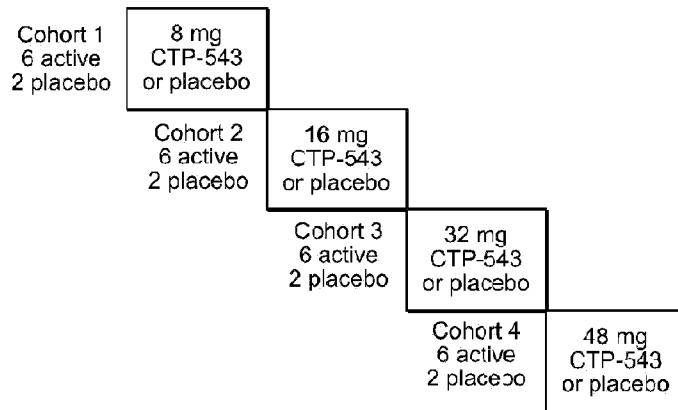


FIG. 1A

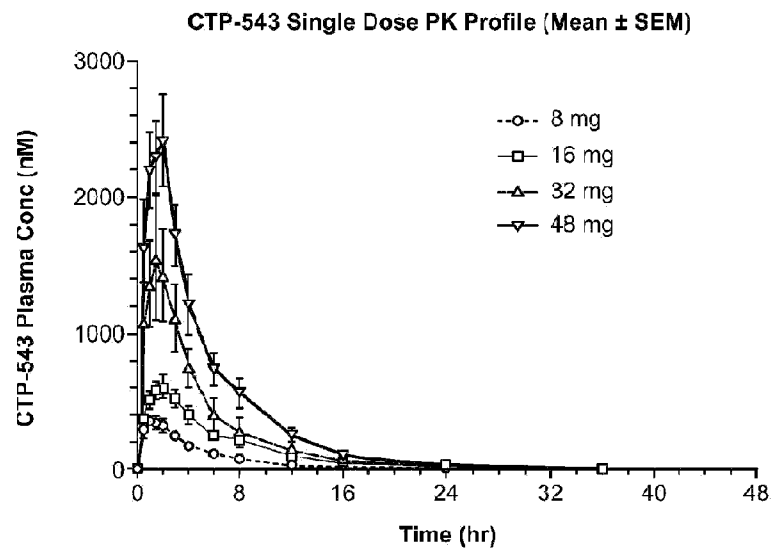


FIG. 1B

Mean (CV%) Single Ascending Dose PK Parameters

| CTP-543 Dose | C _{max} (nM) | T _{max} ^a (hr) | T _{1/2} (hr) | AUC _{0-inf} (nM*hr) | CL/F (L/hr) |
|--------------|-----------------------|------------------------------------|-----------------------|------------------------------|-------------|
| 8 mg | 376 (28%) | 1.25 (0.5-1.5) | 3.1 (29%) | 1875 (32%) | 14.9 (35%) |
| 16 mg | 687 (24%) | 1.75 (0.5-3.0) | 3.3 (26%) | 3959 (30%) | 14.5 (47%) |
| 32 mg | 1702 (29%) | 1.25 (0.5-2.0) | 3.5 (16%) | 7831 (26%) | 13.9 (30%) |
| 48 mg | 2714 (26%) | 1.50 (0.5-2.0) | 3.6 (21%) | 13237 (35%) | 12.7 (34%) |

Data presented are preliminary results; ^a Median values (range)

FIG. 1C

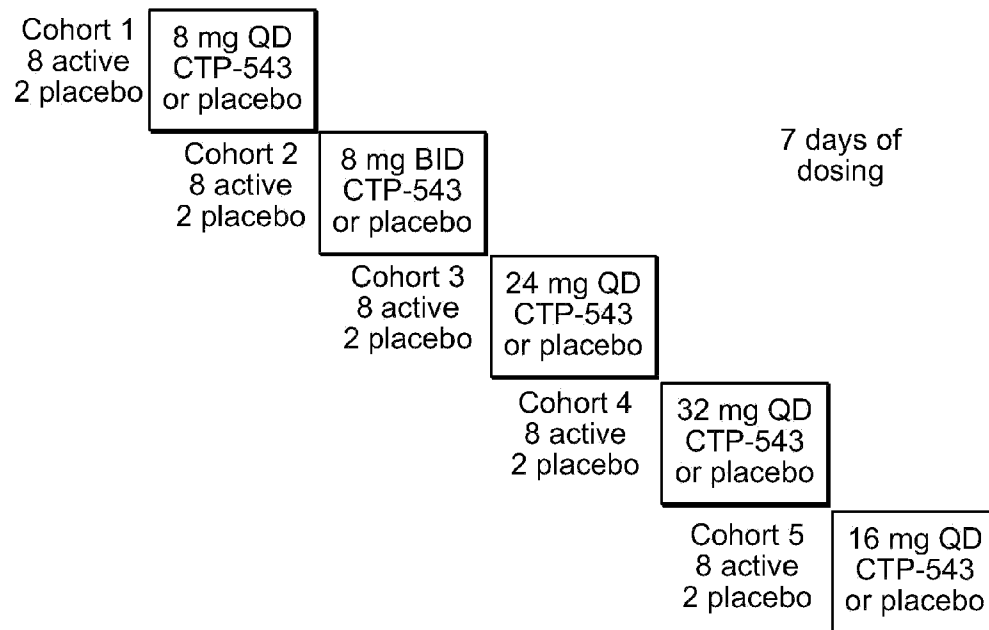


FIG. 2A

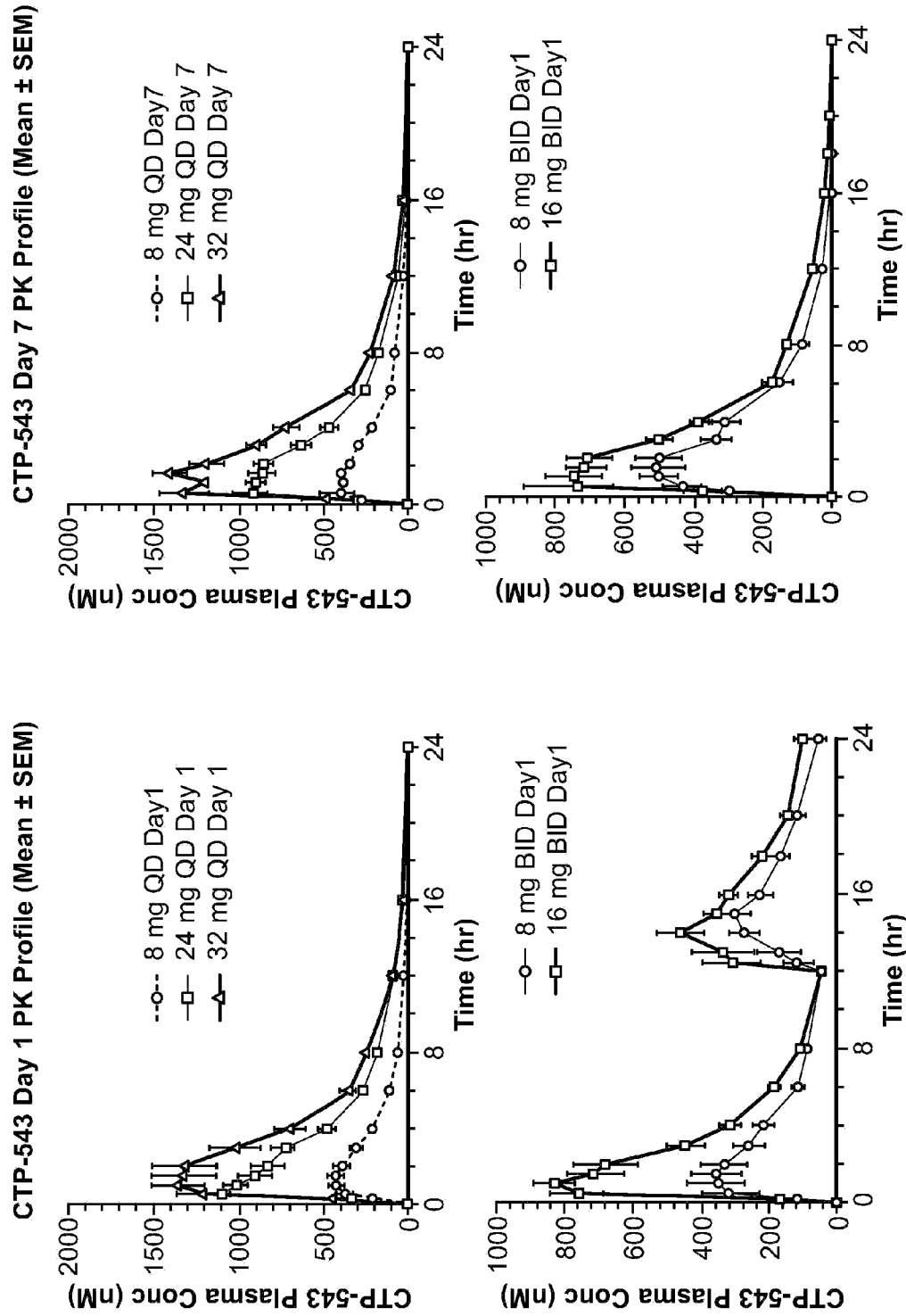


FIG. 2B

Mean (CV%) Multiple Ascending Dose Steady-State PK Parameters

| CTP-543 Dose | C _{max} (nM) | T _{max} ^a (hr) | T _{1/2} (hr) | AUC ₀₋₂₄ (nM*hr) | CL _{ss} /F(L/hr) |
|--------------|-----------------------|------------------------------------|-----------------------|-----------------------------|---------------------------|
| 8 mg QD | 480 (34%) | 1.0 (0.25-1.5) | 3.5 (21%) | 2131 (28%) | 12.7 (25%) |
| 24 mg QD | 986 (23%) | 1.0 (0.5-2.0) | 3.5 (25%) | 4868 (25%) | 16.5 (22%) |
| 32 mg QD | 1564 (18%) | 0.75 (0.5-2.0) | 3.5(37%) | 6684 (28%) | 16.5(33%) |
| | | | | | |
| CTP-543 Dose | C _{max} (nM) | T _{max} ^a (hr) | T _{1/2} (hr) | AUC ₀₋₁₂ (nM*hr) | CL _{ss} /F(L/hr) |
| 8 mg BID | 564 (24%) | 1.5 (0.25-2.0) | 3.9 (34%) | 2615 (36%) | 10.7 (34%) |
| 16 mg BID | 917 (36%) | 0.75 (0.5-2.0) | 3.5 (19%) | 3577 (26%) | 15.0 (24%) |

Data presented are preliminary results; ^a Median values (range)

FIG. 2C