COMBINATION FORMULATION OF TWO ANTIVIRAL COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit under 35 U.S.C. § 119(e) to U.S. Provisional Application Number 61/870,712, filed on August 27, 2013, U.S. Provisional Application Number 61/898,690, filed on November 1, 2013, and U.S. Provisional Application Number 61/907,308, filed on November 21, 2013, the entirety of which are incorporated herein by reference.

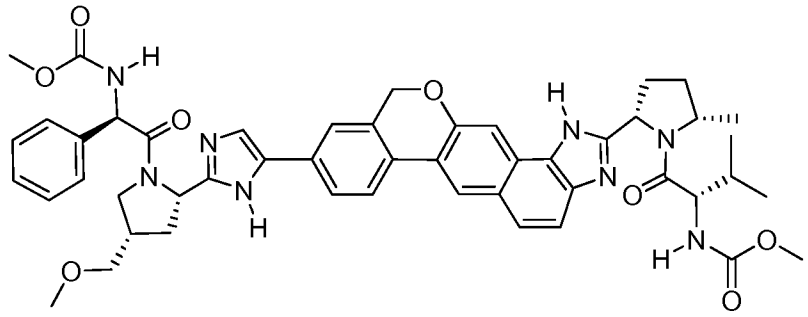
BACKGROUND

[0002] Hepatitis C is recognized as a chronic viral disease of the liver which is characterized by liver disease. Although drugs targeting the liver are in wide use and have shown effectiveness, toxicity and other side effects have limited their usefulness. Inhibitors of hepatitis C virus (HCV) are useful to limit the establishment and progression of infection by HCV as well as in diagnostic assays for HCV.

[0003] The compounds methyl {(2S)-1-[(2S,5S)-2-(9-{2-[(2S,4S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate, designated herein as Compound I and (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino) propanoate, designated herein as sofosbuvir, are known to be an effective anti-HCV agents, as described for example in U.S. Patent Nos. 7,964,580 and 8,575,135. However, the therapeutic benefits of the administration of Compound I and crystalline sofosbuvir were not heretofore known.

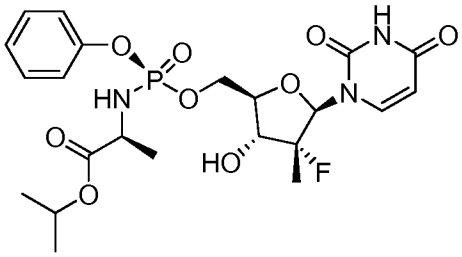
SUMMARY

[0004] Compound I (see, for example, WO 2013/075029 and U.S. Patent No. 8,575,135) has the following chemical structure:



I.

[0005] Sofosbuvir is a selective inhibitor of non-structural protein 5B (NS5B) (see, for example, WO 2010/132601 and U.S. Patent No. 7,964,580). The chemical name of sofosbuvir is (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate:



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[0006] Aspects of the disclosure relate to pharmaceutical composition comprising: a) an effective amount of Compound I, wherein the Compound I is substantially amorphous; and b) an effective amount of sofosbuvir, wherein the sofosbuvir is substantially crystalline.

[0007] Further aspects of the disclosure relate to pharmaceutical dosage forms and tablets. The disclosure also provides methods for using the combination in the treatment of hepatitis C.

[0008] It is contemplated that the solid dispersions disclosed herein would demonstrate one or more of increased bioavailability, elimination of or reduced food-effect, reduced negative drug-drug interaction with acid suppressive therapies, reduced variability across patient populations, and/or improved dose linearity at higher doses when compared with administration of Compound I and/or sofosbuvir alone.

DETAILED DESCRIPTION

1. Definitions

[0009] As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

[0010] As used herein, the term "about" used in the context of quantitative measurements means the indicated amount ± 10%. For example, "about 2:8" would mean 1.8-2.2:7.2-8.8.

[0011] The term "amorphous" refers to a state in which the material lacks long range order at the molecular level and, depending upon temperature, may exhibit the physical properties of a solid or a liquid. Typically such materials do not give distinctive X-ray diffraction patterns and, while exhibiting the properties of a solid, are more formally described as a liquid. Upon heating, a change from solid to liquid properties occurs which is characterized by a change of state, typically second order (glass transition).

[0012] The term "crystalline" refers to a solid phase in which the material has a regular ordered internal structure at the molecular level and gives a distinctive X-ray diffraction pattern with defined peaks. Such materials when heated sufficiently will also exhibit the properties of a liquid, but the change from solid to liquid is characterized by a phase change, typically first order (melting point).

[0013] The term "substantially amorphous" as used herein is intended to mean that greater than 50%; or greater than 55%; or greater than 60%; or greater than 65%; or greater than 70%; or greater than 75%; or greater than 80%; or greater than 85%; or greater than 90%; or greater than 95%, or greater than 99% of the compound present in a composition is in amorphous form. "Substantially amorphous" can also refer to material which has no more than about 20% crystallinity, or no more than about 10% crystallinity, or no more than about 5% crystallinity, or no more than about 2% crystallinity.

[0014] The term "substantially crystalline" as used herein is intended to mean that greater than 50%; or greater than 55%; or greater than 60%; or greater than 65%; or greater than 70%; or greater than 75%; or greater than 80%; or greater than 85%; or greater than 90%; or greater than 95%, or greater than 99% of the compound present in a composition is in crystalline form. "Substantially crystalline" can also refer to material which has no more than about 20%, or no more than about 10%, or no more than about 5%, or no more than about 2% in the amorphous form.

[0015] The term "polymer matrix" as used herein is defined to mean compositions comprising one or more polymers in which the active agent is dispersed or included within the matrix.

[0016] The term "solid dispersion" refers to the dispersion of one or more active agents in a polymer matrix at solid state prepared by a variety of methods, including spray drying, the melting (fusion), solvent, or the melting-solvent method.

[0017] The term "amorphous solid dispersion" as used herein, refers to stable solid dispersions comprising an amorphous active agent and a polymer. By "amorphous active agent," it is meant that the amorphous solid dispersion contains active agent in a substantially amorphous solid state form.

[0018] The term "pharmaceutically acceptable" indicates that the material does not have properties that would cause a reasonably prudent medical practitioner to avoid administration of the material to a patient, taking into consideration the disease or conditions to be treated and the respective route of administration. For example, it is commonly required that such a material be essentially sterile, e.g., for injectibles.

[0019] The term "carrier" refers to a glidant, diluent, adjuvant, excipient, or vehicle with which the compound is administered. Examples of carriers are described herein and also in "Remington's Pharmaceutical Sciences" by E.W. Martin.

[0020] The term "polymer" refers to a chemical compound or mixture of compounds consisting of repeating structural units created through a process of polymerization. Suitable polymers useful in this invention are described throughout.

[0021] The term "pharmaceutically acceptable polymer" refers to a polymer that does not have properties that would cause a reasonably prudent medical practitioner to avoid administration of the material to a patient, taking into consideration the disease or conditions to be treated and the respective route of administration.

[0022] The term "diluent" refers to chemical compounds that are used to dilute the compound of interest prior to delivery. Diluents can also serve to stabilize compounds. Non-limiting examples of diluents include starch, saccharides, disaccharides, sucrose, lactose, polysaccharides, cellulose, cellulose ethers, hydroxypropyl cellulose, sugar alcohols, xylitol, sorbitol, maltitol, microcrystalline cellulose, calcium or sodium carbonate, lactose, lactose

monohydrate, dicalcium phosphate, cellulose, compressible sugars, dibasic calcium phosphate dehydrate, mannitol, microcrystalline cellulose, and tribasic calcium phosphate.

[0023] The term "binder" when used herein relates to any pharmaceutically acceptable film which can be used to bind together the active and inert components of the carrier together to maintain cohesive and discrete portions. Non-limiting examples of binders include hydroxypropylcellulose, hydroxypropylmethylcellulose, povidone, copovidone, and ethyl cellulose.

[0024] The term "disintegrant" refers to a substance which, upon addition to a solid preparation, facilitates its break-up or disintegration after administration and permits the release of an active ingredient as efficiently as possible to allow for its rapid dissolution. Non-limiting examples of disintegrants include maize starch, sodium starch glycolate, croscarmellose sodium, crospovidone, microcrystalline cellulose, modified corn starch, sodium carboxymethyl starch, povidone, pregelatinized starch, and alginic acid.

[0025] The term "lubricant" refers to an excipient which is added to a powder blend to prevent the compacted powder mass from sticking to the equipment during the tabletting or encapsulation process. It aids the ejection of the tablet form the dies, and can improve powder flow. Non-limiting examples of lubricants include magnesium stearate, stearic acid, silica, fats, calcium stearate, polyethylene glycol, sodium stearyl fumarate, or talc; and solubilizers such as fatty acids including lauric acid, oleic acid, and C_8/C_{10} fatty acid.

[0026] The term "film coating" refers to a thin, uniform, film on the surface of a substrate (e.g. tablet). Film coatings are particularly useful for protecting the active ingredient from photolytic degradation. Non-limiting examples of film coatings include polyvinylalcohol based, hydroxyethylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000 and cellulose acetate phthalate film coatings.

[0027] The term "glidant" as used herein is intended to mean agents used in tablet and capsule formulations to improve flow-properties during tablet compression and to produce an anti-caking effect. Non-limiting examples of glidants include colloidal silicon dioxide, talc, fumed silica, starch, starch derivatives, and bentonite.

[0028] The term "effective amount" refers to an amount that is sufficient to effect treatment, as defined below, when administered to a mammal in need of such treatment. The

therapeutically effective amount will vary depending upon the patient being treated, the weight and age of the patient, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art.

[0029] The term "treatment" or "treating," to the extent it relates to a disease or condition includes preventing the disease or condition from occurring, inhibiting the disease or condition, eliminating the disease or condition, and/or relieving one or more symptoms of the disease or condition.

[0030] The term "sustained virologic response" refers to the absence of detectable RNA (or wherein the RNA is below the limit of detection) of a virus (i.e. HCV) in a patient sample (i.e. blood sample) for a specifc period of time after discontinuation of a treatment. For example, a SVR at 4 weeks indicates that RNA was not detected or was below the limit of dectection in the patient at 4 weeks after discontinuing HCV therapy.

[0031] The term "% w/w" as used herein refers to the weight of a component based on the total weight of a composition comprising the component. For example, if component A is present in an amount of 50% w/w in a 100 mg composition, component A is present in an amount of 50 mg.

2. Pharmaceutical Compositions

[0032] The pharmaceutical compositions of the disclosure provide for a combination of an effective amount of Compound I and an effective amount of sofosbuvir wherein the sofosbuvir is substantially crystalline.

A. Compound I

[0033] Compound I has previously been described (see, for example, WO 2013/075029) and can be prepared by methods described therein. In one embodiment, the pharmaceutical composition comprises Compound I formulated as a solid dispersion dispersed within a polymer matrix formed by a pharmaceutically acceptable polymer. The starting material of the solid dispersion can be a variety of forms of Compound I including crystalline forms, amorphous form, salts thereof, solvates and free base. In one embodiment, the Compound I is substantially amorphous. In certain embodiments, the Compound I is the free base.

[0034] Various techniques are well known in the art for preparing solid dispersions including, but not limited to melt-extrusion, spray-drying, lyophilization, and solution-evaporation.

[0035] Melt-extrusion is the process of embedding a compound in a thermoplastic carrier. The mixture is processed at elevated temperatures and pressures, which disperses the compound in the matrix at a molecular level to form a solid solution. Extruded material can be further processed into a variety of dosage forms, including capsules, tablets and transmucosal systems.

[0036] For the solution-evaporation method, the solid dispersion can be prepared by dissolving the compound in a suitable liquid solvent and then incorporating the solution directly into the melt of a polymer, which is then evaporated until a clear, solvent free film is left. The film is further dried to constant weight.

[0037] For the lyophilization technique, the compound and carrier can be co-dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion.

[0038] For spray dried solid dispersions, the solid dispersion can be made by a) mixing the compound and polymer in a solvent to provide a feed solution; and b) spray drying the feed solution to provide the solid dispersion.

[0039] Spray dried solid dispersions of Compound I provide improved *in vivo* and *in vitro* performance and manufacturability/scalability relative to the other formulation approaches, such as wet and dry granulation formulations. In one embodiment, the Compound I is substantially amorphous. In certain embodiments, the Compound I is the free base. In other embodiments, the Compound I is the amorphous free base.

[0040] The selection of the polymer for the solid dispersion is based on the stability and physical characteristics of Compound I in the solution. Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol (Soluplus®) and copovidone solid dispersions both showed adequate stability and physical characteristics. In one embodiment, the polymer used in the solid dispersion is polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol (Soluplus®) or copovidone. Accordingly, in a certain embodiment, the polymer used in the solid dispersion is polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol (Soluplus®). In another embodiment, the polymer used in the solid dispersion is copovidone.

[0041] In one embodiment, the polymer used in the solid dispersion of Compound I is hydrophilic. Non-limiting examples of hydrophilic polymers include polysaccharides, polypeptides, cellulose derivatives such as methyl cellulose, sodium carboxymethylcellulose, hydroxyethylcellulose, ethylcellulose, hydroxypropyl methylcellulose acetate-succinate, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, and hydroxypropylcellulose, povidone, copovidone, hypromellose, pyroxylin, polyethylene oxide, polyvinyl alcohol, and methacrylic acid copolymers.

[0042] In a further embodiment, the polymer is non-ionic. Non-ionic polymers showed benefits in screening solubility experiments. Non-limiting examples of non-ionic polymers include hypromellose, copovidone, povidone, methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, ethylcellulose, pyroxylin, polyethylene oxide, polyvinyl alcohol, polyethylene glycol, and polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol (Soluplus®).

[0043] In another embodiment, the polymer is ionic. Examples of ionic polymers include hydroxypropyl methylcellulose acetate-succinate, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, and methacrylic acid copolymers.

[0044] In a further embodiment, the polymer is selected from the group consisting of hypromellose, hydroxypropyl cellulose, Soluplus®, copovidone, and povidone. In a specific embodiment, the polymer is copovidone. In another specific embodiment, the polymer is polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol (Soluplus®).

[0045] In certain embodiments, the weight ratio of Compound I to polymer is from about 5:1 to about 1:5. In further embodiments, the weight ratio of Compound I to polymer is about 5:1 to about 1:4, or from about 5:1 to about 1:3, or from about 5:1 to about 1:2, or from about 2:1 to about 1:2, or from about 2:1 to about 1:1. In a specific embodiment, the weight ratio of Compound I to polymer is about 1:1. In another embodiment, the weight ratio of Compound I to polymer is about 1:2. In further embodiments, the weight ratio of Compound I to polymer is about 5:1, 4:1, 3:1, 2:1, 1:1, 1:5, 1:4, 1:3, or 1:2.

[0046] The solid dispersion of Compound I may be present in the pharmaceutical composition in a therapeutically effective amount. In some embodiments, the pharmaceutical composition comprises from about 1% to about 40% w/w of the solid dispersion of Compound I. In further embodiments, the composition comprises from about 1% to about

35% w/w, or from about 1% to about 30% w/w, or from about 1% to about 25% w/w, or from about 1% to about 20% w/w of the solid dispersion of Compound I. In a specific embodiment, the pharmaceutical composition comprises about 8.3% w/w of the solid dispersion of Compound I. In a further specific embodiment, the pharmaceutical composition comprises about 20% of the solid dispersion of Compound I. In further embodiments, the pharmaceutical composition comprises about 1% w/w, about 5% w/w, about 8% w/w, about 10% w/w, about 20% w/w, about 25% w/w, about 30% w/w, about 35% w/w, about 40% w/w, or about 45% w/w of the solid dispersion of Compound I.

[0047] Compound I may be present in the pharmaceutical composition in a therapeutically effective amount. In some embodiments, the pharmaceutical composition comprises from about 0.1% to about 50% w/w of Compound I. In further embodiments, the composition comprises from about 0.1% to about 40% w/w, or from about 0.1% to about 35% w/w, or from about 0.5% to about 25% w/w, or from about 0.5% to about 20% w/w, or from about 0.5% to about 15% w/w, or from about 0.5% to about 10% w/w of Compound I. In further embodiments, the pharmaceutical composition comprises about 0.1% w/w, 0.5% w/w, 1% w/w, 2% w/w, 4% w/w, 5% w/w, about 7% w/w, about 10% w/w, about 12% w/w, about 15% w/w, about 17% w/w, about 20% w/w, about 25% w/w, about 30% w/w, about 35% w/w, about 40% w/w, or about 45% w/w of Compound I. In a specific embodiment, the pharmaceutical composition comprises about 4.2% w/w of Compound I. In another specific embodiment, the pharmaceutical composition comprises about 10% w/w of Compound I.

[0048] As noted above, after the Compound I is mixed with the polymer, the mixture can then be solubilized in a solvent. It is within the skill of those in the art to select an appropriate solvent based on the drug and/or polymer properties such as solubility, glass transition temperature, viscosity, and molecular weight. Acceptable solvents include but are not limited to, water, acetone, methyl acetate, ethyl acetate, chlorinated solvents, ethanol, dichloromethane, and methanol. In one embodiment, the solvent is selected from the group consisting of ethanol, dichloromethane, and methanol. In a further embodiment, the solvent is ethanol or methanol. In a specific embodiment, the solvent is ethanol.

[0049] Upon solubilization of the compound and polymer mixture with the solvent, the mixture may then be spray dried. Spray drying is a well known process wherein a liquid feedstock is dispersed into droplets into a drying chamber along with a heated process gas stream to aid in solvent removal and to produce a powder product. Suitable spray drying

parameters are known in the art, and it is within the knowledge of a skilled artisan in the field to select appropriate parameters for spray drying. The target feed concentration is generally about 10 to about 50% with a target of about 20% and a viscosity of about 1 to about 300 cP, or about 1 to about 80 cP, or about 4 to 60 cP. The inlet temperature of the spray dry apparatus is typically about 50-190° C, while the outlet temperature is about 30-90° C. The two fluid nozzle and hydrolic pressure nozzle can be used to spray dry Compound I. The two fluid nozzle gas flow can be about 1-100 kg/hr, the hydrolic pressure nozzle flow can be about 15-300 kg/hr, and the chamber gas flow may be about 25-2500 kg/hr. The spray-dried material typically has particle size (D_{90}) less than about 200 μm, or less than about 120 μm, or about 70 to about 80 μm, or in some instances, less than about 25 μm. In some instances, a milling step may be used, if desired to further reduce the particle size. Further descriptions of spray drying methods and other techniques for forming amorphous dispersions are provided in U.S. Pat. No. 6,763,607 and U.S. Pat. Pub. No. 2006-0189633, the entirety of each of which is incorporated herein by reference.

[0050] Spray drying out of ethanol resulted in high yields across a wide range of spray-drying outlet temperatures with no material accumulation on the spray dry chamber. Furthermore, Compound I demonstrated good chemical stability in the ethanolic feed solution.

B. Sofosbuvir

[0051] Sofosbuvir has previously been described in U.S. Pat. No.: 7,964,580 and U.S. Pat. Pub. Nos: 2010/0016251, 2010/0298257, 2011/0251152 and 2012/0107278. The sofosbuvir is provided as substantially crystalline in the pharmaceutical compositions described herein. Examples of preparing crystalline forms of sofosbuvir are disclosed in U.S. Pat. Pub. Nos: 2010/0298257 and 2011/0251152, both of which are incorporated by reference. Crystalline forms, Forms 1-6, of sofosbuvir are described in U.S. Pat. Pub. Nos.: 2010/0298257 and 2011/0251152, both of which are incorporated by reference. Forms 1-6 of sofosbuvir have the following characteristic X-ray powder diffraction (XRPD) pattern 2θ-values measured according to the XRPD methods disclosed therein:

(1) 2θ-reflections at about: 7.5, 9.6, and 18.3 °2θ ± 0.2 (Form 1);

(2) 2θ-reflections at about: 5.0, 7.3, and 18.1°2θ ± 0.2 (Form 1);

(3) 2θ-reflections at about: 6.9, 24.7, and 25.1 °2θ ± 0.2 (Form 2);

(4) 2θ-reflections at about: 19.7, 20.6, and 24.6 °2θ ± 0.2 (Form 3);

(5) 2θ-reflections at about: 5.0, 6.8, and 24.9 °2θ ± 0.2 (Form 4);

(6) 2θ-reflections at about: 5.2, 6.6, and 19.1 °2θ ± 0.2 (Form 5); and

(7) 2θ-reflections at about: 6.1, 20.1, and 20.8 °2θ ± 0.2 (Form 6).

[0052] Form 6, as described in the patent publications above, may be referred to as Form 2, such as for example, by the Food and Drug Administration. Forms 1 and 6 are alternatively characterized by the following characteristic XRPD pattern 2θ-values as measured according to the methods disclosed in U.S. Pat. Pub. Nos.: 2010/0298257 and 2011/0251152:

(1) 2θ-reflections at about: 5.0 and 7.3 °2θ ± 0.2 (Form 1); and

(2) 2θ-reflections at about: 6.1 and 12.7 °2θ ± 0.2 (Form 6).

[0053] In one embodiment, the crystalline sofosbuvir has XRPD 2θ-reflections (°2θ ± 0.2) at about:

(1) 7.5, 9.6, and 18.3 °2θ ± 0.2; (Form 1A)

(2) 5.0, 7.3, and 18.1 °2θ ± 0.2; (Form 1B)

(3) 6.9, 24.7, and 25.1 °2θ ± 0.2; (Form 2)

(4) 19.7, 20.6, and 24.6 °2θ ± 0.2; (Form 3)

(5) 5.0, 6.8, and 24.9 °2θ ± 0.2; (Form 4)

(6) 5.2, 6.6, and 19.1 °2θ ± 0.2; (Form 5) or

(7) 6.1, 20.1, and 20.8 °2θ ± 0.2; (Form 6).

[0054] In certain embodiments, the crystalline sofosbuvir has XRPD 2θ-reflections at about:

(1) 5.2, 7.5, 9.6, 16.7, 18.3, and 22.2 °2θ ± 0.2 (Form 1);

(2) 5.0, 7.3, 9.4, and 18.1°2θ ± 0.2 (Form 1);

(3) 4.9, 6.9, 9.8, 19.8, 20.6, 24.7, 25.1, and 26.1 °2θ ± 0.2 (Form 2);

(4) 6.9, 9.8, 19.7, 20.6, and 24.6 °2θ ± 0.2 (Form 3);

(5) 5.0, 6.8, 19.9, 20.6, 20.9, and 24.9 °2θ ± 0.2 (Form 4);

(6) 5.2, 6.6, 7.1, 15.7, 19.1, and 25.0 °2θ ± 0.2 (Form 5); or

(7) 6.1, 8.2, 10.4, 12.7, 17.2, 17.7, 18.0, 18.8, 19.4, 19.8, 20.1, 20.8, 21.8, and 23.3 °2θ ± 0.2 (Form 6).

[0055] In a further embodiment, crystalline sofosbuvir has XRPD 2θ-reflections at about: 6.1, 8.2, 10.4, 12.7, 17.2, 17.7, 18.0, 18.8, 19.4, 19.8, 20.1, 20.8, 21.8, and 23.3°2θ ± 0.2. In yet a further embodiment, crystalline sofosbuvir has XRPD 2θ-reflections at about: 6.1 and 12.7 °2θ ± 0.2.

[0056] Sofosbuvir may be present in the pharmaceutical composition in a therapeutically effective amount. In some embodiments, the pharmaceutical compositions comprises from about 10% to about 70% w/w of sofosbuvir. In further embodiments, the composition comprises from about 15% to about 65% w/w, or from about 20% to about 60% w/w, or from about 25% to about 55% w/w, or from about 30% to about 50% w/w, or from about 35% to about 45% w/w of sofosbuvir. In further embodiments, the pharmaceutical composition comprises about 10% w/w, about 15% w/w, about 20% w/w, about 25% w/w, about 30% w/w, about 35% w/w, about 40%, about 45% w/w, about 50% w/w, about 55% w/w, about 60% w/w, about 65% w/w, or about 70% w/w, or about 75% w/w. In a specific embodiment, the pharmaceutical composition comprises about 40% w/w of sofosbuvir. In another specific embodiment, the pharmaceutical composition comprises about 67% w/w of sofosbuvir.

C. Excipients

[0057] The pharmaceutical compositions provided in accordance with the present disclosure are usually administered orally. This disclosure therefore provides pharmaceutical compositions that comprise a solid dispersion comprising Compound I and sofosbuvir as described herein and one or more pharmaceutically acceptable excipients or carriers including but not limited to, inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers, disintegrants, lubricants, binders, glidants, adjuvants, and combinations thereof. Such compositions are prepared in a manner well known in the pharmaceutical art (see, e.g., Remington's Pharmaceutical Sciences, Mace Publishing Co., Philadelphia, PA 17th Ed. (1985); and Modern Pharmaceutics, Marcel Dekker, Inc. 3rd Ed. (G.S. Banker & C.T. Rhodes, Eds.).

[0058] The pharmaceutical compositions may be administered in either single or multiple doses by oral administration. Administration may be via capsule, tablet, or the like. In one embodiment, the Compound I is in the form of a tablet. In a further embodiment, the tablet is a compressed tablet. In making the pharmaceutical compositions that include the solid

described herein, the active ingredient is usually diluted by an excipient and/or enclosed within such a carrier that can be in the form of a capsule, tablet, sachet, paper or other container. When the excipient serves as a diluent, it can be in the form of a solid, semi-solid or liquid material (as above), which acts as a vehicle, carrier or medium for the active ingredient.

[0059] The pharmaceutical composition may be formulated for immediate release or sustained release. A "sustained release formulation" is a formulation which is designed to slowly release a therapeutic agent in the body over an extended period of time, whereas an "immediate release formulation" is a formulation which is designed to quickly release a therapeutic agent in the body over a shortened period of time. In some cases the immediate release formulation may be coated such that the therapeutic agent is only released once it reached the desired target in the body (e.g. the stomach). In a specific embodiment, the pharmaceutical composition is formulated for immediate release.

[0060] The pharmaceutical composition may further comprise pharmaceutical excipients such as diluents, binders, fillers, glidants, disintegrants, lubricants, solubilizers, and combinations thereof. Some examples of suitable excipients are described herein. When the pharmaceutical composition is formulated into a tablet, the tablet may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

[0061] In one embodiment, the pharmaceutical composition comprises a diluent selected from the group consisting of dicalcium phosphate, cellulose, compressible sugars, dibasic calcium phosphate dehydrate, lactose, lactose monohydrate, mannitol, microcrystalline cellulose, starch, tribasic calcium phosphate, and combinations thereof.

[0062] In further embodiments, the pharmaceutical composition comprises lactose monohydrate in an amount from about 0 to about 60% w/w, or from about 0 to about 45% w/w, or from about 5 to about 40% w/w, or from about 5 to about 35% w/w, or from about 5 to about 25% w/w, or from about 10 to about 20% w/w. In specific embodiments, the lactose monohydrate is present at about 0% w/w, about 5% w/w, at about 10% w/w, at about 15% w/w, at about 20% w/w, at about 25% w/w, at about 30% w/w, at about 35% w/w, at about 40% w/w, at about 45% w/w, or at about 50% w/w.

[0063] In yet further embodiments, the pharmaceutical composition comprises microcrystalline cellulose in an amount from about 1 to about 40% w/w, or from about 1 to about 35% w/w, or from about 5% to about 35% w/w, or from about 15 to about 35% w/w, or from about 20 to about 35% w/w. In specific embodiments, the microcrystalline cellulose is present in an amount of about 5%, or about 10%, or about 15%, or about 20%, or about 25%, or about 30%, or about 35%, or about 40%w/w.

[0064] In other embodiments, the pharmaceutical composition comprises a disintegrant selected from the group consisting of croscarmellose sodium, crospovidone, microcrystalline cellulose, modified corn starch, povidone, pregelatinized starch, sodium starch glycolate, and combinations thereof.

[0065] In certain embodiments, the pharmaceutical composition comprises croscarmellose sodium in an amount from about 1 to about 20% w/w, or from about 1 to about 15% w/w, or from about 1 to about 10% w/w, or from about 1 to about 8% w/w, or from about 2 to about 8% w/w. In specific embodiments, the croscarmellose sodium is present in an amount of about 1%, or about 3%, or about 6%, or about 8%, or about 10%, or about 13%, or about 15% w/w. In a further specific embodiment, the croscarmellose sodium is in an amount of about 5% w/w. In another specific embodiment, the croscarmellose sodium is in an amount of about 3% w/w.

[0066] In other embodiments, the pharmaceutical composition comprises a glidant selected from the group consisting of colloidal silicon dioxide, talc, starch, starch derivatives, and combinations thereof.

[0067] In further embodiments, the pharmaceutical composition comprises colloidal silicon dioxide in an amount from about 0 to about 5% w/w, or from about 0 to about 4.5% w/w, or from about 0 to about 4% w/w, or from about 0.5 to about 5.0% w/w, or from about 0.5 to about 3% w/w, or from about 0.5 to about 2% w/w, or from about 0.5 to about 1.5% w/w. In specific embodiments, the colloidal silicon dioxide is present in an amount of about 0% w/w, 0.1% w/w, 0.5% w/w, 0.75% w/w, 1.25% w/w, 1.5% w/w, or 2% w/w. In a further specific embodiment, the colloidal silicon dioxide is present in an amount of about 1% w/w. In another specific embodiment, the colloidal silicon dioxide is present in an amount of about 0% w/w.

[0068] In other embodiments, the pharmaceutical composition comprises a lubricant selected from the group consisting of calcium stearate, magnesium stearate, polyethylene glycol, sodium stearyl fumarate, stearic acid, talc, and combinations thereof.

[0069] In further embodiments, the pharmaceutical composition comprises magnesium stearate in an amount from about 0.1 to about 3% w/w, or from about 0.1 to about 2.5% w/w, or from about 0.5 to about 3% w/w, or from about 0.5 to about 2.5% w/w, or from about 0.5 to about 2% w/w, or from about 1 to about 3% w/w, or from about 1 to about 2% w/w. In specific embodiments, the magnesium stearate is present in an amount of about 0.1%, or about 0.5, or about 1%, or about 1.5%, or about 2%, or about 2.5%, or about 3% w/w. In a further specific embodiment, the magnesium stearate is in an amount of about 1.5% w/w.

[0070] In one embodiment, the pharmaceutical composition comprises a) about 30 to about 50% w/w of sofosbuvir and b) about 1 to about 45 %w/w of the solid dispersion comprising Compound I. In a related embodiment, the composition comprises a) about 40% w/w of sofosbuvir and b) about 20% w/w of the solid dispersion comprising Compound I. In yet a further related embodiment, the composition further comprises a) about 5 to about 40% w/w microcrystalline cellulose, b) about 1 to about 10% w/w croscarmellose sodium, and c) about 0.1 to about 3% w/w magnesium stearate. In a another embodiment, the composition comprises a) about 67% w/w of sofosbuvir and b) about 8% w/w of the solid dispersion comprising Compound I. In yet another embodiment, the composition further comprises a) about 5 to about 25% w/w microcrystalline cellulose, b) about 1 to about 10% w/w croscarmellose sodium, and c) about 0.1 to about 3% w/w magnesium stearate.

3. Pharmaceutical Dosage Forms

[0071] The disclosure provides for tablets, pills, and the like, comprising the pharmaceutical compositions or dosage forms described herein. The tablets or pills of the present disclosure may be coated to provide a dosage form affording the advantage of prolonged action or to protect from the acid conditions of the stomach. The tablets may also be formulated for immediate release as previously described. In certain embodiments, the tablet comprises a film coating. A film coating is useful for limiting photolytic degradation. Suitable film coatings are selected by routine screening of commercially available preparations. In one embodiment, the film coating is a polyvinylalcohol-based coating.

[0072] The tablets may be formulated into a monolayer or bilayer tablet. Typically, monolayer tablet comprise the active ingredients (i.e., Compound I and sofosbuvir) co-mixed in a single uniform layer. For making monolayer tablets, exemplary methods include, but are not limited to coblend (or bi-granulation) and codry granulation. Coblend granulation is a multi-step process consisting of separate dry granulations for each active ingredient with excipients followed by the blending of the two granulations together. Codry granulation comprises dry granulating both active ingredients and excipients together.

[0073] Bilayer tablets comprise the active ingredients (i.e., Compound I and sofosbuvir) in separate layers and can be made by making a blend comprising excipients and one active ingredient (i.e., Compound I), and making a separate blend comprising the second active ingredient (i.e., sofosbuvir) and excipients. One blend may then be precompressed, and the second blend may then be added on top of the first precompressed blends. The resulting tablet comprises two separate layers, each layer comprising a different active ingredient.

[0074] In one embodiment, the tablet comprises a) about 30 to about 70% w/w of sofosbuvir and b) about 1 to about 45 %w/w of the solid dispersion comprising Compound I. In a related embodiment, the tablet comprises a) about 40% w/w of sofosbuvir and b) about 20% w/w of the solid dispersion comprising Compound I. In a related embodiment, the tablet comprises a) about 67% w/w of sofosbuvir and b) about 8% w/w of the solid dispersion comprising Compound I. In a further embodiment, the tablet comprises a) about 300 to about 500 mg of sofosbuvir and b) about 5 to about 150 mg of Compound I. In a yet further embodiment, the tablet comprises a) about 400 mg of sofosbuvir and b) about 100 mg of Compound I. In a yet further embodiment, the tablet comprises a) about 400 mg of sofosbuvir and b) about 25 mg of Compound I. In related embodiment, the tablet further comprises a) about 5 to about 40% w/w microcrystalline cellulose, b) about 1 to about 10% w/w croscarmellose sodium, and c) about 0.1 to about 3% w/w magnesium stearate. In another related embodiment, the tablet further comprises a) about 15 to about 40% w/w microcrystalline cellulose, b) about 1 to about 10% w/w croscarmellose sodium, and c) about 0.1 to about 3% w/w magnesium stearate.

[0075] In some embodiments, the pharmaceutical compositions as described herein are formulated in a unit dosage or pharmaceutical dosage form. The term "unit dosage forms" or "pharmaceutical dosage forms" refers to physically discrete units suitable as unitary dosages for human patients and other mammals, each unit containing a predetermined quantity of

active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient (e.g., a tablet or capsule). The compounds are generally administered in a pharmaceutically effective amount. In some embodiments, each dosage unit contains from 1 mg to 2 g of Compound I. In other embodiments, the pharmaceutical dosage form comprises from about 1 to about 450 mg, or about 5 to about 300 mg, or about 5 to about 150 mg, or about 5 to about 100 mg, or about 5 to about 50 mg, or about 5 to about 25 mg, or about 50 to about 150 mg, or about 5 to about 10 mg, or about 70 to about 120 mg, or about 90 to about 110 mg. In specific embodiments, the pharmaceutical dosage form comprises about 5, or about 10, or about 15, or about 25, or about 50, or about 100, or about 150, or about 200, or about 250, or about 300, or about 450, or about 600 mg of Compound I. In a further specific embodiment, the pharmaceutical dosage form comprises about 25 mg of Compound I. In yet a further specific embodiment, the pharmaceutical dosage form comprises about 100 mg of Compound I.

[0076] In other embodiments, the pharmaceutical dosage form comprises from about 1 mg to about 3g of sofosbuvir. In other embodiments, the pharmaceutical dosage form comprises from about 1 to about 800 mg, or about 100 to about 700 mg, or about 200 to about 600 mg, or about 300 to about 500 mg, or about 350 to about 450 mg, of sofosbuvir. In specific embodiments, the pharmaceutical dosage form comprises about 50, or about 100, or about 150, or about 200, or about 250, or about 300, or about 350, or about 450, or about 500, or about 550, or about 600, or about 650, or about 700, or about 750, or about 800 mg of sofosbuvir. In a further specific embodiment, the pharmaceutical dosage form comprises about 400 mg of sofosbuvir. It will be understood, however, that the amount of Compound I and/or sofosbuvir actually administered usually will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered and its relative activity, the age, weight and response of the individual patient, the severity of the patient's symptoms, and the like.

[0077] In a specific embodiment, the pharmaceutical dosage form comprises about 400 mg of sofosbuvir and about 100 mg of Compound I. In another specific embodiment, the pharmaceutical dosage form comprises about 400 mg of sofosbuvir and about 25 mg of Compound I.

[0078] In one embodiment, the pharmaceutical composition, or alternatively, the pharmaceutical dosage form or tablet comprises about 100 mg of Compound I formulated in

a solid dispersion comprising a polymer:Compound I ratio of 1:1, about 400 mg crystalline sofosbuvir, microcrystalline cellulose in an amount from about 5 to about 40% w/w, croscarmellose sodium in an amount from about 1 to about 10% w/w, and magnesium stearate in an amount from about 0.1 to about 3% w/w. In one embodiment, the polymer is copovidone.

[0079] In another embodiment, the pharmaceutical composition, or alternatively, the pharmaceutical dosage form or tablet comprises about 25 mg of Compound I formulated in a solid dispersion comprising a polymer:Compound I ratio of 1:1, about 400 mg crystalline sofosbuvir, microcrystalline cellulose in an amount from about 5 to about 25% w/w, croscarmellose sodium in an amount from about 1 to about 10% w/w, and magnesium stearate in an amount from about 0.1 to about 3% w/w. In one embodiment, the polymer is copovidone.

[0080] In further embodiments, the pharmaceutical composition, pharmaceutical dosage form, or tablet as described herein is free of negative drug-drug interactions.

4. Methods of Use

[0081] The solid dispersions, pharmaceutical compositions, pharmaceutical dosage forms, and tablets of Compound I and sofosbuvir as described herein are administered to a patient suffering from hepatitis C virus (HCV) in a daily dose by oral administration. In one embodiment, the patient is human.

[0082] In one embodiment, the solid dispersions, pharmaceutical compositions, pharmaceutical dosage forms, and tablets of Compound I and sofosbuvir as described herein are effective in treating one or more of genotype 1 HCV infected patients, genotype 2 HCV infected patients, genotype 3 HCV infected patients, genotype 4 HCV infected patients, genotype 5 HCV infected patients, and/or genotype 6 HCV infected patients. In one embodiment, the solid dispersions, pharmaceutical compositions, pharmaceutical dosage forms, and tablets of Compound I and sofosbuvir as described herein are effective in treating genotype 1 HCV infected patients, including genotype 1a and/or genotype 1b. In another embodiment, the solid dispersions, pharmaceutical compositions, pharmaceutical dosage forms, and tablets of Compound I and sofosbuvir as described herein are effective in treating genotype 2 HCV infected patients, including genotype 2a, genotype 2b, genotype 2c and/or genotype 2d. In another embodiment, the solid dispersions, pharmaceutical compositions, pharmaceutical dosage forms, and tablets of Compound I and sofosbuvir as described herein

are effective in treating genotype 3 HCV infected patients, including genotype 3a, genotype 3b, genotype 3c, genotype 3d, genotype 3e and/or genotype 3f. In another embodiment, the solid dispersions, pharmaceutical compositions, pharmaceutical dosage forms, and tablets of Compound I and sofosbuvir as described herein are effective in treating genotype 4 HCV infected patients, including genotype 4a, genotype 4b, genotype 4c, genotype 4d, genotype 4e, genotype 4f, genotype 4g, genotype 4h, genotype 4i and/or genotype 4j. In another embodiment, the solid dispersions, pharmaceutical compositions, pharmaceutical dosage forms, and tablets of Compound I and sofosbuvir as described herein are effective in treating genotype 5 HCV infected patients, including genotype 5a. In another embodiment, the solid dispersions, pharmaceutical compositions, pharmaceutical dosage forms, and tablets of Compound I and sofosbuvir as described herein are effective in treating genotype 6 HCV infected patients, including genotype 6a. In one embodiment, the solid dispersions, pharmaceutical compositions, pharmaceutical dosage forms, and tablets of Compound I and sofosbuvir as described herein are pangenotypic, meaning they are useful across all genotypes and drug resistant mutants thereof.

[0083] In some embodiments, the pharmaceutical composition, pharmaceutical dosage form, or tablet of Compound I and sofosbuvir as described herein is administered, either alone or in combination with one or more therapeutic agent(s) for treating HCV (such as a HCV NS3 protease inhibitor or an inhibitor of HCV NS5B polymerase), for about 24 weeks, for about 16 weeks, or for about 12 weeks or less. In further embodiments, the pharmaceutical composition, pharmaceutical dosage form, or tablet of Compound I and sofosbuvir is administered , either alone or in combination with one or more therapeutic agent(s) for treating HCV (such as a HCV NS3 protease inhibitor or an inhibitor of HCV NS5B polymerase), for about 24 weeks or less, about 22 weeks or less, about 20 weeks or less, about 18 weeks or less, about 16 weeks or less, about 12 weeks or less, about 10 weeks or less, about 8 weeks or less, about 6 weeks or less, or about 4 weeks or less. The pharmaceutical composition, pharmaceutical dosage form, or tablet may be administered once daily, twice daily, once every other day, two times a week, three times a week, four times a week, or five times a week.

[0084] In further embodiments, a sustained virologic response is achieved at about 24 weeks, at about 20 weeks, at about 16 weeks, at about 12 weeks, at about 10 weeks, at about

8 weeks, at about 6 weeks, or at about 4 weeks, or at about 4 months, or at about 5 months, or at about 6 months, or at about 1 year, or at about 2 years.

[0085] In one embodiment, the daily dose is 25 mg of Compound I and 400 mg of sofosbuvir administered in the form of a tablet. In a further embodiment, the daily dose is a tablet comprising a) about 50 to about 70% w/w of sofosbuvir, b) about 1 to about 45% w/w of the solid dispersion comprising Compound I, c) about 5 to about 25% w/w microcrystalline cellulose, d) about 1 to about 10% w/w croscarmellose sodium, and e) about 0.1 to about 3% w/w magnesium stearate.

[0086] In one embodiment, the daily dose is 100 mg of Compound I and 400 mg of sofosbuvir administered in the form of a tablet. In a further embodiment, the daily dose is a tablet comprising a) about 30 to about 50% w/w of sofosbuvir, b) about 1 to about 45% w/w of the solid dispersion comprising Compound I, c) about 5 to about 40% w/w microcrystalline cellulose, d) about 1 to about 10% w/w croscarmellose sodium, and e) about 0.1 to about 3% w/w magnesium stearate.

[0087] In further embodiments, the patient is also suffering from cirrhosis. In yet a further embodiment, the patient is not suffereing from cirrhosis.

5. Combination Therapy

[0088] In the methods described herein, the method can further comprise the administration of another therapeutic agent for treating HCV and other conditions such as HIV infections. In one embodiment, non-limiting examples of suitable additional therapeutic agents include one or more interferons, ribavirin or its analogs, HCV NS3 protease inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, nucleoside or nucleotide inhibitors of HCV NS5B polymerase, non-nucleoside inhibitors of HCV NS5B polymerase, HCV NS5A inhibitors, TLR-7 agonists, cyclophillin inhibitors, HCV IRES inhibitors, pharmacokinetic enhancers, and other drugs or therapeutic agents for treating HCV.

[0089] More specifically, the additional therapeutic agent may be selected from the group consisting of:

1) interferons, *e.g.*, pegylated rIFN-alpha 2b (PEG-Intron), pegylated rIFN-alpha 2a (Pegasys), rIFN-alpha 2b (Intron A), rIFN-alpha 2a (Roferon-A), interferon alpha (MOR-22, OPC-18, Alfaferone, Alfanative, Multiferon, subalin), interferon alfacon-1 (Infergen), interferon alpha-n1 (Wellferon), interferon alpha-n3 (Alferon), interferon-beta (Avonex, DL-

8234), interferon-omega (omega DUROS, Biomed 510), albinterferon alpha-2b (Albuferon), IFN alpha-2b XL, BLX-883 (Locteron), DA-3021, glycosylated interferon alpha-2b (AVI-005), PEG-Infergen, PEGylated interferon lambda-1 (PEGylated IL-29), and belerofon;

2) ribavirin and its analogs, *e.g.*, ribavirin (Rebetol, Copegus), and taribavirin (Viramidine);

3) HCV NS3 protease inhibitors, *e.g.*, boceprevir (SCH-503034, SCH-7), telaprevir (VX-950), TMC435350, BI-1335, BI-1230, MK-7009, VBY-376, VX-500, GS-9256, GS-9451, BMS-605339, PHX-1766, AS-101, YH-5258, YH5530, YH5531, ABT-450, ACH-1625, ITMN-191, MK5172, MK6325, and MK2748;

4) alpha-glucosidase 1 inhibitors, *e.g.*, celgosivir (MX-3253), Miglitol, and UT-231B;

5) hepatoprotectants, *e.g.*, emericasan (IDN-6556), ME-3738, GS-9450 (LB-84451), silibilin, and MitoQ;

6) nucleoside or nucleotide inhibitors of HCV NS5B polymerase, *e.g.*, R1626, R7128 (R4048), IDX184, IDX-102, BCX-4678, valopicitabine (NM-283), MK-0608, and INX-189 (now BMS986094);

7) non-nucleoside inhibitors of HCV NS5B polymerase, *e.g.,* PF-868554, VCH-759, VCH-916, JTK-652, MK-3281, GS-9190, VBY-708, VCH-222, A848837, ANA-598, GL60667, GL59728, A-63890, A-48773, A-48547, BC-2329, VCH-796 (nesbuvir), GSK625433, BILN-1941, XTL-2125, ABT-072, ABT-333, GS-9669, PSI-7792, and GS-9190;

8) HCV NS5A inhibitors, *e.g.*, GS-5885, AZD-2836 (A-831), BMS-790052, ACH-3102, ACH-2928, MK8325, MK4882, MK8742, PSI-461, IDX719, ABT-267 and A-689;

9) TLR-7 agonists, *e.g.*, imiquimod, 852A, GS-9524, ANA-773, ANA-975, AZD-8848 (DSP-3025), and SM-360320;

10) cyclophillin inhibitors, *e.g.*, DEBIO-025, SCY-635, and NIM811;

11) HCV IRES inhibitors, *e.g.*, MCI-067;

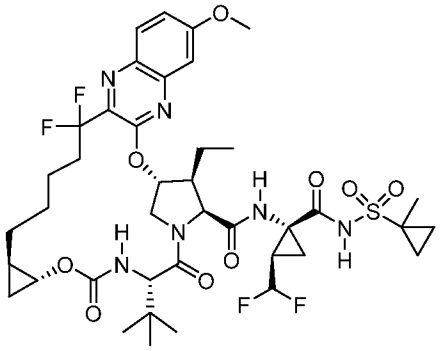
12) pharmacokinetic enhancers, *e.g.*, BAS-100, SPI-452, PF-4194477, TMC-41629, GS-9350, GS-9585, and roxythromycin; and

13) other drugs for treating HCV, *e.g.*, thymosin alpha 1 (Zadaxin), nitazoxanide (Alinea, NTZ), BIVN-401 (virostat), PYN-17 (altirex), KPE02003002, actilon (CPG-10101), GS-9525, KRN-7000, civacir, GI-5005, XTL-6865, BIT225, PTX-111, ITX2865, TT-033i, ANA 971, NOV-205, tarvacin, EHC-18, VGX-410C, EMZ-702, AVI 4065, BMS-650032, BMS-791325, Bavituximab, MDX-1106 (ONO-4538), Oglufanide, and VX-497 (merimepodib).

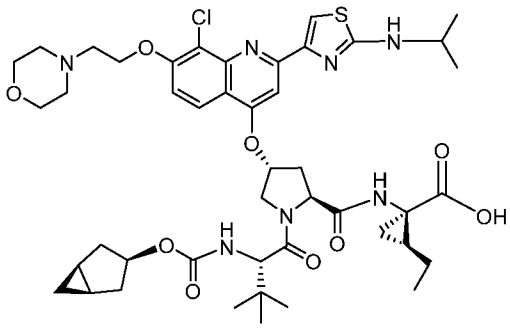
[0090] In another embodiment, the additional therapeutic agent used in combination with the pharmaceutical compositions as described herein can be any agent having a therapeutic effect when used in combination with the pharmaceutical compositions as described herein. For example, the therapeutic agent used in combination with the pharmaceutical compositions as described herein can be interferons, ribavirin analogs, NS3 protease inhibitors, NS5B polymerase inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

[0091] In certain embodiments, the additional therapeutic agent is selected from the group consisting of non-nucleoside inhibitors of HCV NS5B polymerase (ABT-072 and ABT-333), HCV NS5A inhibitors (ABT-267, ACH-3102 and ACH-2928) and HCV NS3 protease inhibitors (ABT-450 and ACH-1625).

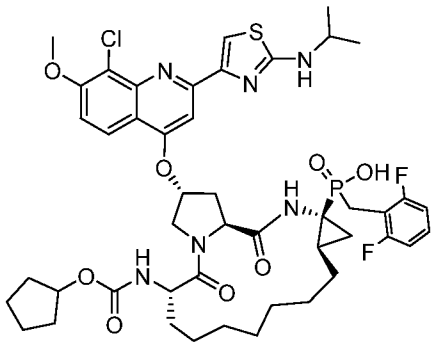
[0092] In one embodiment, the additional therapeutic agent used in combination with the pharmaceutical compositions as described herein is a HCV NS3 protease inhibitor. Non-limiting examples include one or more compounds selected from the group consisiting of:



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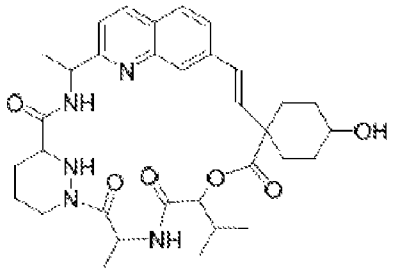


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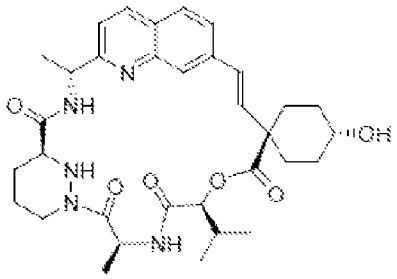


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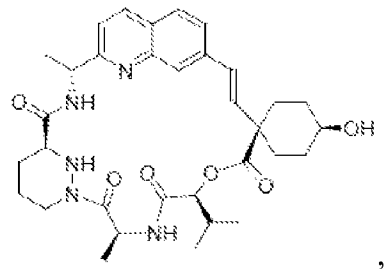
[0093] In another embodiment, the additional therapeutic agent used in combination with the pharmaceutical compositions as described herein is a cyclophillin inhibitor, including for example, a cyclophilin inhibitor disclosed in WO 2013/185093. Non-limiting examples include one or more compounds selected from the group consisiting of:



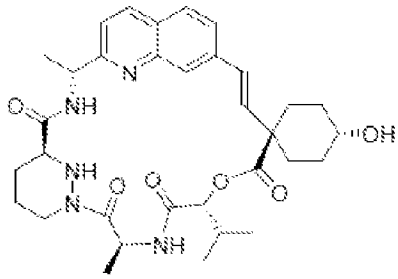
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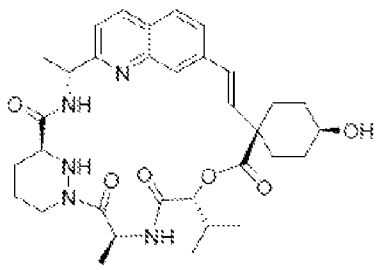
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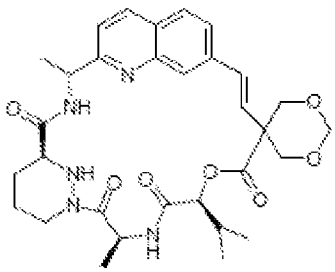
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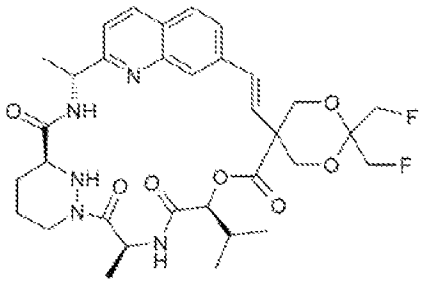
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, and stereoisomers and mixtures of stereoisomers thereof.

[0094] In another embodiment, the additional therapeutic agent used in combination with the pharmaceutical compositions as described herein is a non-nucleoside inhibitor of HCV NS5B polymerase. A non-limiting example includes GS-9669.

[0095] Examples of additional anti-HCV agents which can be combined with the compositions provided herein include, without limitation, the following:

A. interferons, for example, pegylated rIFN-alpha 2b (PEG-Intron), pegylated rIFN-alpha 2a (Pegasys), rIFN-alpha 2b (Intron A), rIFN-alpha 2a (Roferon-A), interferon alpha (MOR-22, OPC-18, Alfaferone, Alfanative, Multiferon, subalin), interferon alfacon-1 (Infergen), interferon alpha-n1 (Wellferon), interferon alpha-n3 (Alferon), interferon-beta (Avonex, DL-8234), interferon-omega (omega DUROS, Biomed 510), albinterferon alpha-2b (Albuferon), IFN alpha XL, BLX-883 (Locteron), DA-3021, glycosylated interferon alpha-2b (AVI-005), PEG-Infergen, PEGylated interferon lambda (PEGylated IL-29), or belerofon, IFN alpha-2b XL, rIFN-alpha 2a, consensus IFN alpha, infergen, rebif, pegylated IFN-beta, oral interferon alpha, feron, reaferon, intermax alpha, r-IFN-beta, and infergen + actimmuneribavirin and ribavirin analogs, e.g., rebetol, copegus, VX-497, and viramidine (taribavirin);

B. NS5A inhibitors, for example, Compound X-1 (described below), Compound X-2 (described below), ABT-267, Compound X-3 (described below), JNJ-47910382, daclatasvir (BMS-790052), ABT-267, MK-8742, EDP-239, IDX-719, PPI-668, GSK-2336805, ACH-3102, A-831, A-689, AZD-2836 (A-831), AZD-7295 (A-689), and BMS-790052;

C. NS5B polymerase inhibitors, for example, Compound X-4 (described below), Compound X-5 (described below), ABT-333, Compound X-6 (described below), ABT-072, Compound X-7 (described below), tegobuvir (GS-9190), GS-9669, TMC647055, setrobuvir

(ANA-598), filibuvir (PF-868554), VX-222, IDX-375, IDX-184, IDX-102, BI-207127, valopicitabine (NM-283), PSI-6130 (R1656), PSI-7851, BCX-4678, nesbuvir (HCV-796), BILB 1941, MK-0608, NM-107, R7128, VCH-759, GSK625433, XTL-2125, VCH-916, JTK-652, MK-3281, VBY-708, A848837, GL59728, A-63890, A-48773, A-48547, BC-2329, BMS-791325, and BILB-1941;

D. NS3 protease inhibitors, for example, Compound X-8, Compound X-9, Compound X-10, ABT-450, Compound X-11 (described below), simeprevir (TMC-435), boceprevir (SCH-503034), narlaprevir (SCH-900518), vaniprevir (MK-7009), MK-5172, danoprevir (ITMN-191), sovaprevir (ACH-1625), neceprevir (ACH-2684), Telaprevir (VX-950), VX-813, VX-500, faldaprevir (BI-201335), asunaprevir (BMS-650032), BMS-605339, VBY-376, PHX-1766, YH5531, BILN-2065, and BILN-2061;

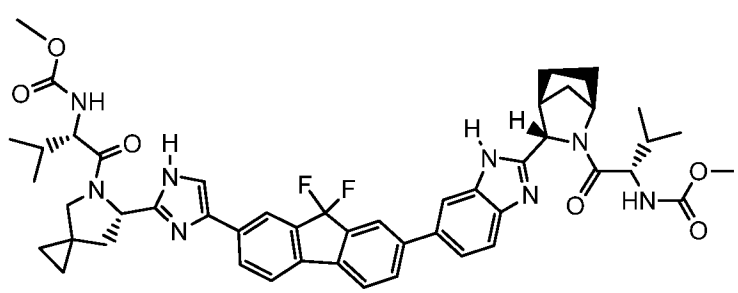
E. alpha-glucosidase 1 inhibitors, for example, celgosivir (MX-3253), Miglitol, and UT-231B;

F. hepatoprotectants, e.g., IDN-6556, ME 3738, MitoQ, and LB-84451;

G. non-nucleoside inhibitors of HCV, e.g., benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, and phenylalanine derivatives; and

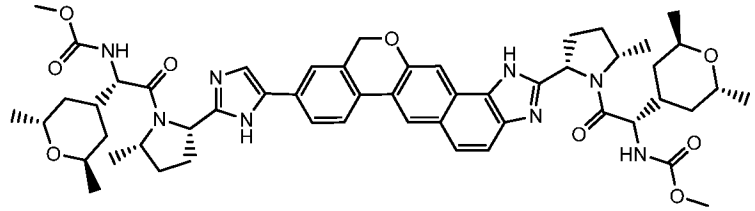
H. other anti-HCV agents, e.g., zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), DEBIO-025, VGX-410C, EMZ-702, AVI 4065, bavituximab, oglufanide, PYN-17, KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975, XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, and NIM811.

[0096] Compound X-1 is an inhibitor of the HCV NS5A protein and is represented by the following chemical structure:

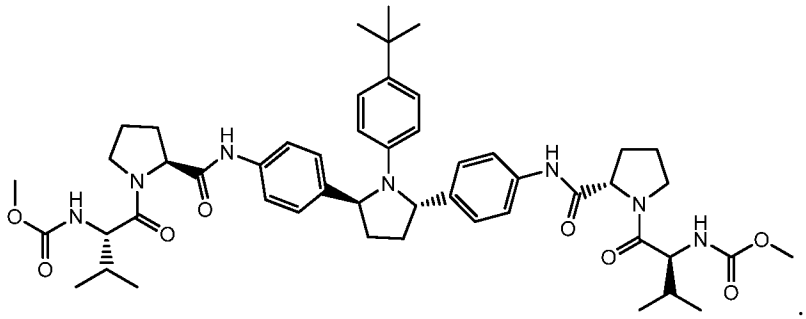


[0097] (*see, e.g.*, . U.S. Patent Application Pub. No. 2010/0310512 A1.).

[0098] Compound X-2 is an NS5A inhibitor and is represented by the following chemical structure:

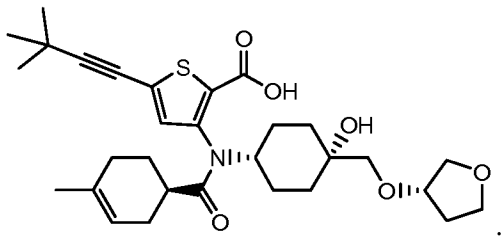


[0099] Compound X-3 is an NS5A inhibitor and is represented by the following chemical structure:

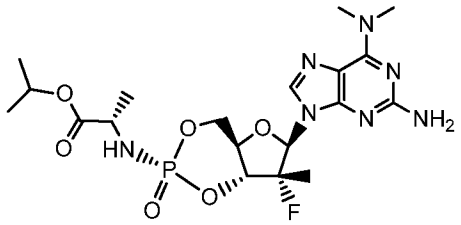


[0100] See U.S. Publication No. 2013/0102525 and references therein.

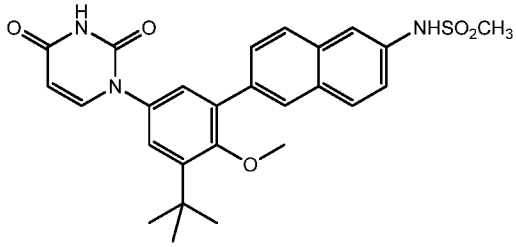
[0101] Compound X-4 is an NS5B Thumb II polymerase inhibitor and is represented by the following chemical structure:



[0102] Compound X-5 is a nucleotide inhibitor prodrug designed to inhibit replication of viral RNA by the HCV NS5B polymerase, and is represented by the following chemical structure:

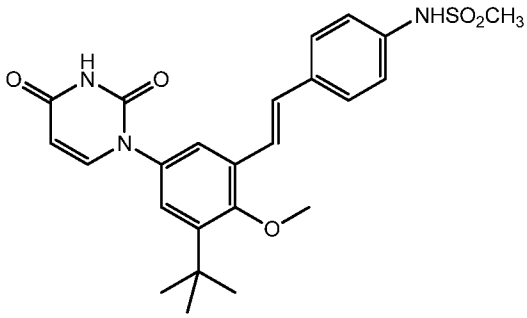


[0103] Compound X-6 is an HCV polymerase inhibitor and is represented by the following structure:



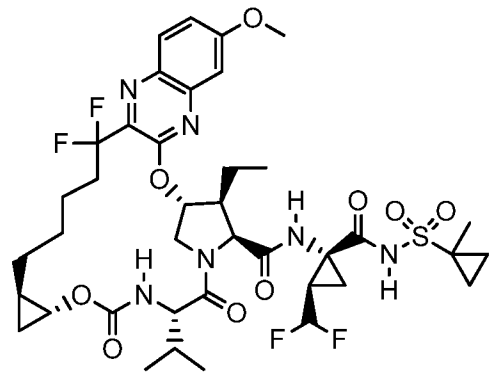
[0104] See U.S. Publication No. 2013/0102525 and references therein.

[0105] Compound X-7 is an HCV polymerase inhibitor and is represented by the following structure:



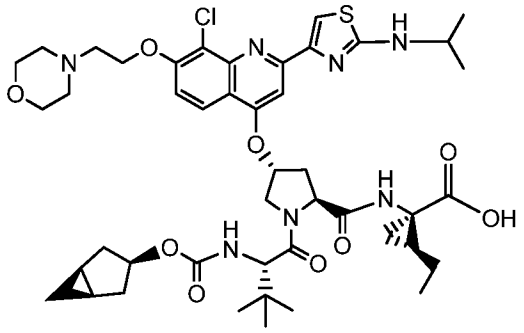
[0106] See U.S. Publication No. 2013/0102525 and references therein.

[0107] Compound X-8 is an HCV protease inhibitor and is represented by the following chemical structure:



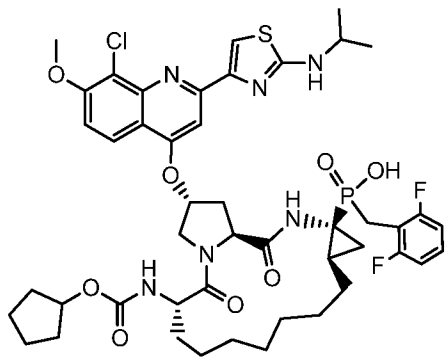
[0108] See U.S. Publication No. 2014/0017198 and references therein..

[0109] Compound X-9 is an HCV protease inhibitor and is represented by the following chemical structure:

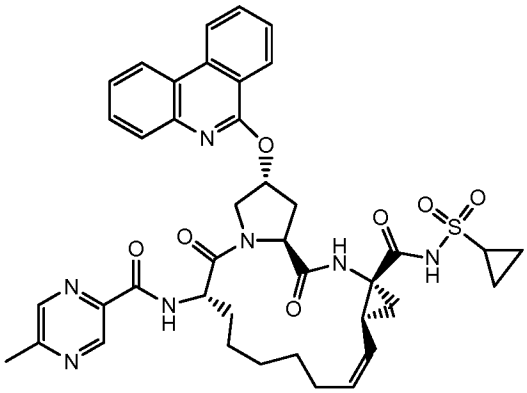


[0110] See U.S. Patent No. 8,178,491 and references therein.

[0111] Compound X-10 is an HCV protease inhibitor and is represented by the following chemical structure:



[0112] Compound X-11 is an HCV protease inhibitor and is represented by the following chemical structure:



[0113] See U.S. Publication No. 2013/0102525 and references therein.

[0114] In another embodiment, the present application provides for a method of treating hepatitis C in a human patient in need thereof comprising administering to the patient a therapeutically effective amount of a pharmaceutical composition as described herein and an additional therapeutic selected from the group consisting of pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, IFN alpha-2b XL, rIFN-alpha 2a, consensus IFN alpha, infergen, rebif, locteron, AVI-005, PEG-infergen, pegylated IFN-beta, oral interferon alpha, feron, reaferon, intermax alpha, r-IFN-beta, infergen + actimmune, IFN-omega with DUROS, albuferon, rebetol, copegus, levovirin, VX-497, viramidine (taribavirin), A-831, A-689, NM-283, valopicitabine, R1626, PSI-6130 (R1656), HCV-796, BILB 1941, MK-0608, NM-107, R7128, VCH-759, PF-868554, GSK625433, XTL-2125, SCH-503034 (SCH-7), VX-950 (Telaprevir), ITMN-191, and BILN-2065, MX-3253 (celgosivir), UT-231B, IDN-6556, ME 3738, MitoQ, and LB-84451, benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, and phenylalanine derivatives, zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), DEBIO-025, VGX-410C, EMZ-702, AVI 4065, bavituximab, oglufanide, PYN-17, KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975 (isatoribine), XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, and NIM811 and a pharmaceutically acceptable carrier or excipient.

[0115] In yet another embodiment, the present application provides a combination pharmaceutical agent comprising:

a) a first pharmaceutical composition comprising an effective amount of Compound I; and an effective amount of sofosbuvir wherein the sofosbuvir is substantially crystalline as described herein and

b) a second pharmaceutical composition comprising at least one additional therapeutic agent selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, interferons, ribavirin analogs, NS3 protease inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV, and combinations thereof.

[0116] The additional therapeutic agent may be one that treats other conditions such as HIV infections. Accordingly, the additional therapeutic agent may be a compound useful in treating HIV, for example HIV protease inhibiting compounds, non-nucleoside inhibitors of HIV reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, interferons, ribavirin analogs, NS3 protease inhibitors, NS5b polymerase inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

[0117] More specifically, the additional therapeutic agent may be selected from the group consisting of

1) HIV protease inhibitors, *e.g.*, amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, lopinavir + ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), AG1859, DG35, L-756423, RO0334649, KNI-272, DPC-681, DPC-684, and GW640385X, DG17, PPL-100,

2) a HIV non-nucleoside inhibitor of reverse transcriptase, *e.g.,* capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, and TMC-120, TMC-278 (rilpivirine), efavirenz, BILR 355 BS, VRX 840773, UK-453,061, RDEA806,

3) a HIV nucleoside inhibitor of reverse transcriptase, *e.g.,* zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, racivir (±-FTC), D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, fosalvudine tidoxil, apricitibine (AVX754), amdoxovir, KP-1461, abacavir + lamivudine, abacavir + lamivudine + zidovudine, zidovudine + lamivudine,

4) a HIV nucleotide inhibitor of reverse transcriptase, *e.g.,* tenofovir, tenofovir disoproxil fumarate + emtricitabine, tenofovir disoproxil fumarate + emtricitabine + efavirenz, and adefovir,

5) a HIV integrase inhibitor, *e.g.*, curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, S-1360, zintevir (AR-177), L-870812, and L-870810, MK-0518 (raltegravir), BMS-707035, MK-2048, BA-011, BMS-538158, GSK364735C,

6) a gp41 inhibitor, *e.g.*, enfuvirtide, sifuvirtide, FB006M, TRI-1144, SPC3, DES6, Locus gp41, CovX, and REP 9,

7) a CXCR4 inhibitor, *e.g.*, AMD-070,

8) an entry inhibitor, *e.g.*, SP01A, TNX-355,

9) a gp120 inhibitor, *e.g.*, BMS-488043 and BlockAide/CR,

10) a G6PD and NADH-oxidase inhibitor, *e.g.*, immunitin,

11) a CCR5 inhibitor, *e.g.,* aplaviroc, vicriviroc, INCB9471, PRO-140, INCB15050, PF-232798, CCR5mAb004, and maraviroc,

12) an interferon, *e.g.*, pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, IFN alpha-2b XL, rIFN-alpha 2a, consensus IFN alpha, infergen, rebif, locteron, AVI-005, PEG-infergen, pegylated IFN-beta, oral interferon alpha, feron, reaferon, intermax alpha, r-IFN-beta, infergen + actimmune, IFN-omega with DUROS, and albuferon,

13) ribavirin analogs, e.g., rebetol, copegus, levovirin, VX-497, and viramidine (taribavirin)

14) NS5a inhibitors, e.g., A-831, A-689, and BMS-790052,

15) NS5b polymerase inhibitors, e.g., NM-283, valopicitabine, R1626, PSI-6130 (R1656), HCV-796, BILB 1941, MK-0608, NM-107, R7128, VCH-759, PF-868554, GSK625433, and XTL-2125,

16) NS3 protease inhibitors, e.g., SCH-503034 (SCH-7), VX-950 (Telaprevir), ITMN-191, and BILN-2065,

17) alpha-glucosidase 1 inhibitors, e.g., MX-3253 (celgosivir) and UT-231B,

18) hepatoprotectants, e.g., IDN-6556, ME 3738, MitoQ, and LB-84451,

19) non-nucleoside inhibitors of HCV, e.g., benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, and phenylalanine derivatives,

20) other drugs for treating Hepatitis C, *e.g.*, zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), DEBIO-025, VGX-410C, EMZ-702, AVI 4065, bavituximab, oglufanide, PYN-17, KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975 (isatoribine), XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, and NIM811,

21) pharmacokinetic enhancers, e.g., BAS-100 and SPI452, 20) RNAse H inhibitors, e.g., ODN-93 and ODN-112, and

22) other anti-HIV agents, e.g., VGV-1, PA-457 (bevirimat), ampligen, HRG214, cytolin, polymun, VGX-410, KD247, AMZ 0026, CYT 99007, A-221 HIV, BAY 50-4798, MDX010 (iplimumab), PBS119, ALG889, and PA-1050040.

[0118] In one embodiment, the additional therapeutic agent is ribavirin. Accordingly, methods described herein include a method of treating hepatitis C in a human patient in need thereof comprising administering to the patient a therapeutically effective amount of ribavirin and a therapeutically effective amount of a pharmaceutical composition, pharmaceutical dosage form, or tablet as described herein. In a further embodiment, the ribavirin and pharmaceutical composition, pharmaceutical dosage form, or tablet comprising sofosbuvir and Compound I is administered for about 12 weeks or less. In further embodiments, the ribavirin and pharmaceutical composition, pharmaceutical dosage form, or tablet comprising sofosbuvir and Compound I is administered for about 8 weeks or less, or for about 6 weeks or less, or for about 4 weeks or less.

[0119] It is contemplated that the additional therapeutic agent will be administered in a manner that is known in the art and the dosage may be selected by someone of skill in the art. For example, the additional agent may be administered in a dose from about 0.01 milligrams to about 2 grams per day.

EXAMPLES

[0120] In the following examples and throughout this disclosure, abbreviations as used herein have respective meanings as follows:

%CV	Percent coefficient of variation
AUC	Area Under the Curve
AUC_{inf}	Area under the plasma concentration-time curve from time zero extrapolated to the infinite time
AUC_{tau}	Area under the plasma concentration-time curve for a dosing interva
CL	Drug clearance
C_{last}	Last observed plasma concentration
C_{max}	Maximum Concentration
cP	Centipoise
EC_{50}	Concentration of a compound inhibiting birus replication by 50%
E_{max}	Maximal effect range
F	Bioavailability
FDC	Fixed dose combination
GLSM	Geometric least-squares means
GT	Genotype
h or hr	Hour
HCV	Hepatitis C virus
HFM	High-fat/high-calorie meal
ICH	International Conference on Harmonisation; Impurities guidelines
kg	Kilogram
LLOQ	Lower limit of quantitation
m	Meter
MFM	Moderate-fat/moderate-calorie meal
mg	Milligram
mL	Milliliter
ng	Nanogram
°C	Degrees Celsius
PD	Pharmacodynamics
PK	Pharmacokinetics
Q1, Q3	first quartile, third quartile
RNA	Ribonucleic Acid

s	Second
SAE	Serious adverse event
SOF	Sofosbuvir (GS-7977; formerly PSI-7977)
SVR	Sustained Virologic Response
$t_{1/2}$	Half-life (h)
t_{last}	Time of last observed plasma concentration(h)
t_{max}	Time to reach C_{max} (h)
w	Weight
XRPD	Xray Powder Diffraction
μm	Micrometer

Example 1: Tablet Preparation and Formulation

A. Dose Selection of Tablets

i. Sofosbuvir

[0121] The sofosbuvir dose selected for the tablet formulation is 400 mg once daily. Support for the 400 mg sofosbuvir dose can be derived from E_{max} PK/PD modeling with early virological and human exposure data which also supports the selection of a 400 mg sofosbuvir dose over others tested.

[0122] The mean sofosbuvir major metabolite AUC_{tau} for the 400 mg sofosbuvir dose is associated with approximately 77% of the maximal HCV RNA change from baseline achievable as determined by this model, a value which is on the cusp of the plateau of the exposure-response sigmoidal curve. In a sigmoidal E_{max} model, there is a relatively linear exposure-response relationship in the 20 to 80% maximal effect range. Therefore, given that sofosbuvir exposure with 200 mg tablets appears dose-proportional with single doses up to 1200 mg, doses below 400 mg are expected to yield considerable reductions in the magnitude of HCV RNA change from baseline. Similarly, in order to improve upon an efficacy prediction of 77% in the plateau of the exposure-response curve, substantial increases in exposure (and hence dose) would be needed for an appreciable increase in antiviral effect.

[0123] The sofosbuvir dose of 400 mg once daily was associated with higher SVR rates in genotype 1 HCV infected patients as compared to the 200 mg once daily dose when given in conjunction with additional HCV therapeutics for 24 weeks. Safety and tolerability appeared

similar across both dose levels. In addition, when sofosbuvir 400 mg once daily plus other HCV therapeutics were given to genotype 2 or 3 HCV infected patients, 100% SVR24 was observed.

ii. Compound I

[0124] Following single and multiple oral doses of Compound I, maximum plasma concentrations occurred between 1.50 and 3.25 hours (median T_{max}). Compound I exhibited nonlinear PK across the dose range of 5 to 450 mg. Increases in exposure, as assessed by AUC and C_{max}, were greater than dose-proportional from 5 to 50 mg and were less than dose-proportional from 50 to 450 mg. Consistent with the half-life of Compound I, modest accumulation was observed with time. After multiple once-daily doses of Compound I greater than 5 mg, the mean plasma concentrations of Compound I at 24 hours postdose were above the protein-adjusted concentration of a compound inhibiting virus replication by 50% (EC_{50}) for genotype 1 to 6 HCV replicons (**Table 1**)

Table 1

PK Parameter	5 mg (N = 12)	50 mg (N = 12)	100 mg (N = 24)	150 mg (N = 12)	450 mg (N = 12)
Single Dose (Cohorts 1–6[a])					
AUC_{last} (ng•h/mL)	134.2 (69.6)	2970.7 (40.1)	4985.6 (44.8)	4925.9 (48.0)	9503.8 (34.5)
AUC_{inf} (ng•h/mL)	158.9 (64.0)	3017.2 (40.1)	5055.0 (45.3)	4978.3 (47.8)	9578.1 (34.3)
C_{max} (ng/mL)	22.4 (55.4)	371.3 (32.7)	574.9 (37.2)	608.4 (46.7)	1121.6 (31.7)
C_{last} (ng/mL)	1.40 (26.9)	2.34 (61.4)	2.85 (80.3)	2.23 (40.1)	3.28 (50.5)
T_{max} (h)	1.50	2.50	2.50	2.75	3.25
	(1.50, 2.00)	(2.00, 3.00)	(2.50, 3.00)	(2.50, 3.50)	(2.50, 3.75)
T_{last} (h)	24.00	72.00	95.00	96.00	96.00
	(14.00, 36.00)	(48.00, 96.00)	(71.50, 96.00)	(84.02, 96.00)	(96.00, 96.00)
$t_{1/2}$ (h)	11.20	13.62	15.73	16.16	14.97
	(5.40, 16.89)	(10.62, 16.47)	(12.63, 17.11)	(14.55, 17.55)	(12.91, 16.73)
CL/F (mL/h)	58,398.0	19,188.4	24,617.9	72,185.5	53,676.4
	(124.4)	(39.2)	(50.8)	(196.4)[b]	(42.5)

Multiple Dose (Cohorts 1–4[a])				
PK Parameter	**5 mg (N = 12)**	**50 mg (N = 12)**	**150 mg (N = 12)**	**450 mg (N = 12)**
AUCtau (ng•h/mL)	172.3 (51.7)	3032.6 (40.4)	4890.8 (45.4)	9511.2 (40.9)
C_{max} (ng/mL)	28.3 (49.3)	411.4 (40.7)	669.4 (48.1)	1195.7 (38.0)
C_{tau} (ng/mL)	2.2 (76.0)	37.9 (59.5)	63.4 (42.8)	127.7 (44.3)
T_{max} (h)	2.00 (1.25, 2.50)	2.50 (2.25, 3.00)	2.50 (2.50, 3.50)	3.00 (2.50, 4.25)
T_{last} (h)	24.00 (24.00, 24.00)	24.00 (24.00, 24.00)	24.00 (24.00, 24.00)	24.00 (24.00, 24.00)
$t_{1/2}$ (h)	13.73 (13.19, 15.88)	13.02 (11.43, 16.23)	15.15 (12.03, 15.63)	11.74 (10.64, 13.12)
CL_{SS}/F (mL/h)	36,095.7 (46.4)	19,593.0 (50.5)	45,082.3 (88.3)	58,804.6 (57.3)

Note: All PK parameters are reported as mean (%CV), except for T_{max}, T_{last}, and $t_{1/2}$, which are reported as median (Q1, Q3).

[a] Compound I dosing by cohort: Cohort 1 = 50 mg, Cohort 2 = 150 mg, Cohort 3 = 5 mg, Cohort 4 = 450 mg, Cohorts 5 and 6 (pooled in the fasted state) = 100 mg.

[b] Mean (%CV) CL/F for the Compound I 150 mg group (excluding one patient) was 31,403.8 (40.5) mL/h.

B. Solid Dispersion Comprising Compound I

[0125] To make the tablets comprising the combination of sofosbuvir and Compound I as described herein, a solid dispersion comprising Compound I was co-formulated with crystalline sofosbuvir. The starting material of the solid dispersion can be a variety of forms of Compound I including crystalline forms, amorphous form, salts thereof, solvates and/or free base. In certain embodiments, Compound I is the amorphous free base.

[0126] The spray dry feed solution was prepared by solubilizing Compound I and polymer in the feed solvent. In certain cases, aggressive mixing or homogenization can be used to avoid clumping of the composition.

[0127] The feed solution was initially evaluated for appropriate solvent with regard to solubility, stability, and viscosity. Ethanol, methanol, acetone, and dichloromethane all

demonstrated excellent solubility. Ethanol and methanol-based feed stocks were assessed for preparation ease and spray dried at a range of inlet and outlet temperatures to assess the robustness of the spray dry process. Both solvents gave rapid dissolution of Compound I and copovidone.

[0128] Spray drying out of ethanol resulted in high yields across a wide range of spray-drying outlet temperatures with no material accumulation on the spray dry chamber. Overall, the Compound I solid dispersion in a Compound I to copovidone ratio of 1:1 demonstrated good chemical stability in the ethanolic feed solution.

[0129] An ethanolic solution of 10% Compound I and 10% copovidone was prepared using homogenization. Viscosity of ethanolic solutions of Compound I:copovidone were low.

[0130] Spray drying was conducted using a commercially available spray dryer (e.g., Anhydro, Buchi, or Niro spray dryer).

[0131] Organic volatile impurities, including the spray dry solvent ethanol may be rapidly removed during secondary drying in a tray oven 60 °C, purged with room air or via a double cone dryer. Loss on drying can be attributable to water, which can be confirmed by Karl Fischer titration. Residual ethanol was reduced below ICH guidelines of 0.5% w/w by 6 hours of drying.

C. Tablet Preparation

i. Monolayer Tablet

[0132] The solid dispersion comprising Compound I was blended with sofosbuvir and excipients and milled to facilitate mixing and blend uniformity. Either a coblend or codry granulation process can be used. Coblend granulation is a multi-step process consisting of separate dry granulations for each active ingredient with excipients followed by the blending of the two granulations together. Codry granulation consisted of dry granulating both active ingredients and excipients together.

[0133] An in-process milling step may be used to deagglomerate relatively small but hard agglomerates present in the drug substance. To limit any loss of drug substance, Compound I may be blended with all intragranular excipients prior to milling through a conical screen mill, e.g., with a 125R screen and a tip speed of 6 m/s. A milling step was tested, but found to be unnecessary. A secondary blend may be conducted prior to lubrication with magnesium

stearate, followed by roller compaction and milling through an in-line oscillating mill. This process results in powder blends with satisfactory flow characteristics and compression properties.

[0134] The granules were then mixed with a lubricant prior to tablet compression. The total resulting core tablet weight was about 1000 mg for the 100 mg Compound I/ 400 mg Sofosbuvir tablet. The total resulting core tablet weight was about 600 mg for the 25 mg Compound I/ 400 mg Sofosbuvir tablet.

[0135] Film-coating of the tablets is provided to reduce photolytic degradation. Tablets were coated to a target 3% weight gain. The film-coating material was a polyvinylalcohol-based coating. Exemplary tablet formulations are provided in **Tables 2** and **3**.

Table 2

Ingredient	**% w/w**	**Component Weight (mg/tablet)**
Sofosbuvir	66.7	400
Compound I Solid Dispersion (Compound I:copovidone 1:1)	8.3	50
Microcrystalline Cellulose	20.5	123
Croscarmellose Sodium	3	18
Magnesium Stearate	1.5	9
Total Tablet Core Weight	**100**	**600**
Film coating	3	18
Purified Water	--	--
Total Coated Tablet Weight		**618**

Table 3

Ingredient	% w/w	Component Weight (mg/tablet)
Sofosbuvir	40	400
Compound I Solid Dispersion (Compound I:copovidone 1:1)	20	200
Microcrystalline Cellulose	35.5	355
Croscarmellose Sodium	3	30
Magnesium Stearate	1.5	15
Total Tablet Core Weight	**100**	**1000**
Film coating	3	30
Purified Water	--	--
Total Coated Tablet Weight		**1030**

ii. Bilayer Tablet

[0136] Tablets comprising the co-formulation of a solid dispersion comprising Compound I and crystalline sofosbuvir can also be made as a bilayer tablet wherein each active ingredient is in a separate layer. To make the bilayer tablet, a Compound I:copovidone solid dispersion is made by dissolving Compound I and copovidone into ethanol, and then spray drying the mixture. The spray dried Compound I:copovidone (1:1) solid dispersion is further dried in a secondary dryer. Next, the spray dried Compound I:copovidone solid dispersion is then blended with excipients. The mixture is milled and then blended with lubricant prior to dry granulation. The Compound I granules are blended with extragranular lubricant. Separately, the sofosbuvir drug substance is blended with excipients, and then the mixture is milled and then blended with lubricant prior to dry granulation. The sofosbuvir granules are then blended with extragranular lubricant. Finally, the sofosbuvir powder blend and Compound I powder blend are compressed into bilayer tablet cores. The bilayer tablet cores are then film-coated prior to packaging. Representative example compositions of a bilayer tablets comprising the solid dispersion of Compound I and sofosbuvir are shown in **Tables 4** and **5.**

Table 4

Ingredient	% w/w	Component Weight (mg/tablet)
Layer 1		
Sofosbuvir	57	400
Microcrystalline Cellulose	13	90
Croscarmellose Sodium	3.5	24
Magnesium Stearate	1	8
Layer 2		
Compound I Solid Dispersion (Compound I:copovidone 1:1)	7	50
Microcrystalline Cellulose	14.5	100
Croscarmellose Sodium	3.5	25
Magnesium Stearate	0.5	3
Total Tablet Core	**100.00**	**700**

Table 5

Ingredient	% w/w	Component Weight (mg/tablet)
Layer 1		
Sofosbuvir	40	400
Microcrystalline Cellulose	14	140
Croscarmellose Sodium	2.4	24
Magnesium Stearate	0.8	8

Layer 2		
Compound I Solid Dispersion (Compound I:copovidone 1:1)	20	200
Microcrystalline Cellulose	19	190
Croscarmellose Sodium	3	30
Magnesium Stearate	0.8	8
Total Tablet Core	**100**	**1000**

Example 2: Drug-drug interaction between SOF and Compound I

[0137] A PK drug-drug interaction between SOF and Compound I was evaluated. Compound I plasma exposures (AUC_{tau}, C_{max}, and C_{tau}) were not affected by the coadministration of SOF, and thus no dose adjustment is required for Compound I. Sofosbuvir plasma exposures increased approximately 1.8-fold (C_{max}) and 2.4-fold (AUC) when coadministered with Compound I. SOF metabolite I C_{max} and AUC increased approximately 1.6- and 1.8-fold, respectively, when SOF was coadministered with Compound I (solid dispersion, Compound I:copovidone 1:1). approximately 1.8-fold (C_{max}) and 2.4-fold (AUC) when coadministered with Compound I. SOF metabolite II (the predominant circulating nucleoside metabolite of SOF) Cmax decreased approximately 36%, but AUC was unaffected by coadministration of SOF and Compound I. See **Table 6**.

Table 6

Compound I			
Compound I PK Parameter	**Compound I 150 mg (N = 18)**	**SOF 400 mg + Compound I 150 mg (N = 18)**	**% GLSM Ratio (SOF+ Compound I / Compound I) (90% CI)**
AUC_{tau}(ng•h/mL)	7284.95	8138.22	111.71 (107.54, 116.04)
C_{max} (ng/mL)	932.27	987.69	105.94 (101.86, 110.20)
C_{tau} (ng/mL)	101.09	118.90	117.61 (111.94, 123.57)

SOF			
SOF PK Parameter	**SOF 400 mg (N = 18)**	**SOF 400 mg + Compound I 150 mg (N = 18)**	**% GLSM Ratio (SOF+ Compound I /SOF) (90% CI)**
AUC_{last}(ng•h/mL)	1154.59	2749.10	238.10 (214.62, 264.16)
AUC_{inf} (ng•h/mL)	1159.50	2756.96	237.77 (214.27, 263.85)
C_{max} (ng/mL)	880.28	1593.80	181.06 (149.43, 219.38)
SOF metabolite I			
SOF metabolite I PK Parameter	**SOF 400 mg (N = 18)**	**SOF 400 mg + Compound I 150 mg (N = 18)**	**% GLSM Ratio (SOF+ Compound I /SOF) (90% CI)**
AUC_{last}(ng•h/mL)	1861.41	3394.32	182.35 (167.52, 198.50)
AUC_{inf} (ng•h/mL)	1926.09	3455.70	179.42 (165.03, 195.06)
C_{max} (ng/mL)	455.77	736.88	161.68 (145.27, 179.94)
SOF metabolite II			
SOF metabolite II PK Parameter	**SOF 400 mg (N = 18)**	**SOF 400 mg + Compound I 150 mg (N = 18)**	**% GLSM Ratio (SOF+ Compound I /SOF) (90% CI)**
AUC_{last}(ng•h/mL)	11,173.87	12,610.86	112.86 (107.90, 118.05)
AUC_{inf} (ng•h/mL)	11,842.52	13,774.96	116.32 (110.99, 121.90)
C_{max} (ng/mL)	1080.97	693.62	64.17 (58.45, 70.44)

Note: Data are reported as GLSM. Cohort 7 = SOF 400 mg single dose (Day 1); Compound I 150 mg multiple doses (Days 5–13); Compound I 150 mg + SOF 400 mg single dose (Day 14).

[0138] The effect of Compound I on SOF (and SOF metabolite I) exposure is likely due to Compound I inhibition of the intestinal efflux drug transporters p-glycoprotein (Pgp) and possibly breast cancer resistance protein (BCRP), as SOF is known to be a substrate of these transporters. The increase in the systemic exposure of SOF (and SOF metabolite I) by Compound I was similar to that seen previously with Pgp and/or BCRP inhibitors and does not warrant any SOF dose modification.

Example 3: Food Effect

[0139] The exposure of Compound I solid dispersion (Compound I:copovidone 1:1) administered with a high-fat/high-calorie meal (HFM) as a single agent was modestly reduced (14% decrease in AUC and 25% decrease in Cmax) compared to fasted administration (**Table 7**). The exposure of Compound I (solid dispersion) when administered with a HFM as part of the sofosbuvir/Compound I (solid dispersion) FDC was comparatively improved, resulting in a modest increase in exposure compared to fasted administration (~20% increase in AUC and ~5% increase in Cmax, **Table 8**). This increase in exposure suggests that the bioavailability of Compound I administered as part of the sofosbuvir/Compound I FDC is improved relative to Compound I as a single agent tablet. **Table 8**, below shows exposures and GMRs of Compound I from the fixed dose combination under the different fed states.

Table 7

Compound I PK Parameter	GLSM		% GLSM Ratio (Fed/Fasted)	90% CI
	Compound I 100 mg Fed (N = 12)	Compound I 100 mg Fasted (N = 12)		
Light Breakfast				
AUClast(ng•h/mL)	6728.66	5389.63	124.84	(110.02, 141.67)
AUC_{inf} (ng•h/mL)	6820.80	5469.11	124.72	(109.94, 141.48)
C_{max} (ng/mL)	784.70	581.72	134.89	(116.84, 155.74)
HFM				
AUClast(ng•h/mL)	3222.57	3746.30	86.02	(73.17, 101.12)
AUC_{inf} (ng•h/mL)	3267.75	3786.61	86.30	(73.43, 101.42)
C_{max} (ng/mL)	364.39	485.72	75.02	(62.56, 89.97)

Table 8

Mean (%CV)	SOF/ Compound I FDC			MFM/ Fasted GMR (90% CI)	HFM/ Fasted GMR (90% CI)
	(Fasted, N = 30)	(MFM, N = 30)	(HFM, N = 30)		
AUC_{inf} (ng·hr/mL)	4520 (47.6)	5930 (44.3)	5060 (43.4)	1.33 (1.10, 1.63)	1.21 (0.99, 1.48)
AUC_{last} (ng·hr/mL)	4440 (47.7)	5850 (44.1)	4990 (43.2)	1.34 (1.09, 1.64)	1.22 (0.99, 1.49)
C_{max} (ng/mL)	562 (44.6)	710 (39.4)	544 (35.9)	1.29 (1.07, 1.56)	1.05 (0.87, 1.26)

Example 4: Safety and Efficacy of Treatment with Interferon-free, Ribavirin-free, Combination of Compound I and Sofosbuvir for 12 Weeks in Treatment Naïve Patients with Genotype 1-6 HCV Infection

[0140] Compound I is a HCV NS5A inhibitor that has demonstrated potent activity against genotype 1-6 HCV in a 3-day monotherapy study. This example shows the results of the study of the combination of sofosbuvir (SOF) and Compound I solid dispersion (Compound I:copovidone 1:1) in patients with genotype 1-6 HCV infection.

[0141] Methods: Treatment naïve genotype 1-6 HCV-infected patients without cirrhosis were randomized 1:1 to receive 400 mg of SOF and 25 mg of Compound I once daily or 400 mg of SOF and 100 mg of Compound I once daily for 12 weeks.

[0142] Results: 154 patients (36% GT1, 14% GT2, 35% GT3, 9% GT4, < 1% GT5, and 6% GT6) were randomized and treated; 64% were male, 85% white, and 48% had IL28B CC genotype. All patients had HCV RNA < LLOQ by week 4 of treatment except one genotype 3 HCV-infected patient treated with 400 mg of SOF and 25 mg of Compound I (this patient stopped treatment for non-response at Week 8). Results through post-treatment week 4 (SVR4) are presented below. Two patients relapsed, one with genotype 1 HCV infection and one with genotype 3 HCV infection, both received 400 mg of SOF and 25 mg of Compound I. The most frequently reported adverse events (> 10%) were fatigue, headache and nausea. There were no discontinuations due to adverse events. Four patients reported 5 SAEs; none were considered related to study drug. There was no evidence of drug related changes in hematologic, chemistry or urinalysis parameters.

[0143] The treatment of SOF and Compound I for 12 weeks was well tolerated and resulted

in high SVR4 rates in patients with genotype 1-6 HCV infection (**Table 9**).

Table 9: SVR4 in Patients Treated with SOF + Compound I for 12 Weeks

HCV genotype	SOF (400mg) + Compound I (25mg)	SOF (400mg) + Compound I (100mg)
GT1	96% (26/27)	100% (28/28)
GT2	91% (10/11)[a]	100% (10/10)
GT3	89% (24/27)[a]	100% (27/27)
GT4	100% (7/7)	86% (6/7)[a]
GT5	100% (1/1)	-
GT6	100% (4/4)	100% (5/5)

a. One patient per group was lost to follow-up prior to posttreatment week 4.

[0144] It should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification, improvement and variation of the inventions embodied therein herein disclosed may be resorted to by those skilled in the art, and that such modifications, improvements and variations are considered to be within the scope of this invention. The materials, methods, and examples provided here are representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the invention.

[0145] The invention has been described broadly and generically herein. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the invention. This includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

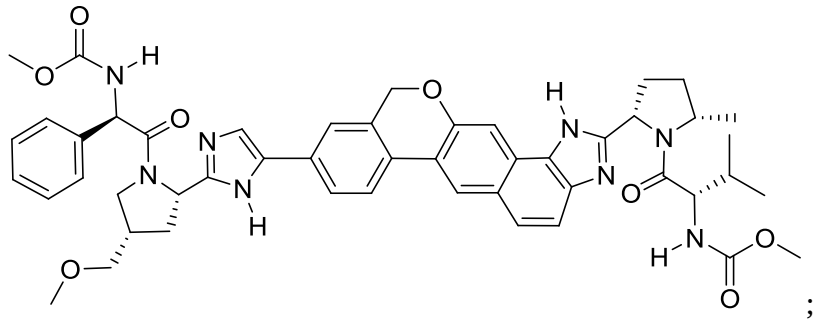
[0146] In addition, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group.

[0147] All publications, patent applications, patents, and other references mentioned herein are expressly incorporated by reference in their entirety, to the same extent as if each were incorporated by reference individually. In case of conflict, the present specification, including definitions, will control.

WE CLAIM:

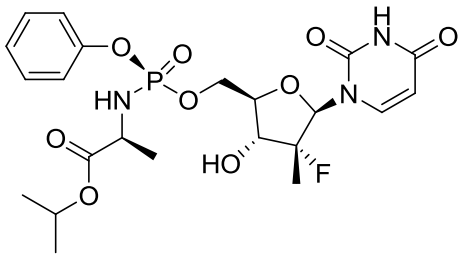
1. A pharmaceutical composition in the form of a fixed dose combination tablet comprising:

a) from about 1% to about 25% w/w of a solid dispersion comprising Compound I dispersed within a polymer matrix formed by copovidone, wherein the weight ratio of Compound I to copovidone in the solid dispersion is about 1:1 and wherein Compound I is substantially amorphous having the formula:



;

b) from about 35% to about 45% w/w of substantially crystalline sofosbuvir having the formula:



c) from about 30% to about 40% w/w of microcrystalline cellulose;

d) from about 1% to about 5% w/w of croscarmellose sodium; and

e) from about 0.5% to about 2.5% w/w of magnesium stearate.

2. The pharmaceutical composition of claim 1 wherein the crystalline sofosbuvir has XRPD 2θ-reflections (° ± 0.2θ) at about: 6.1 and 12.7.

3. The pharmaceutical composition of claim 1 wherein the crystalline sofosbuvir has XRPD 2θ-reflections (° ± 0.2θ) at about: 6.1, 20.1 and 20.8.

4. The pharmaceutical composition of any one of claims 1 to 3, comprising about 40% w/w of sofosbuvir.

5. The pharmaceutical composition of one of claims 1 to 4, comprising about 20% w/w of the solid dispersion.

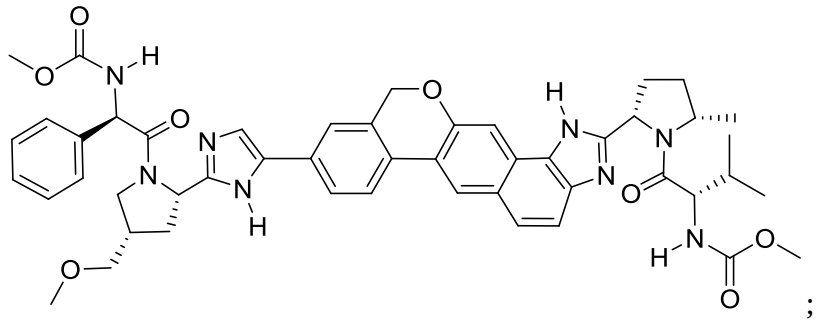
6. The pharmaceutical composition of any one of claims 1 to 5, comprising about 35.5% w/w of microcrystalline cellulose.

7. The pharmaceutical composition of any one of claims 1 to 6, comprising about 3% w/w of croscarmellose sodium.

8. The pharmaceutical composition of any one of claims 1 to 7, comprising about 1.5% w/w of magnesium stearate.

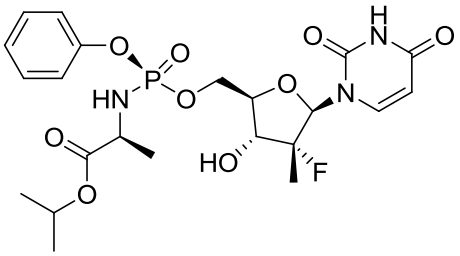
9. A pharmaceutical composition in the form of a fixed dose combination tablet comprising:

a) about 20% w/w of a solid dispersion comprising Compound I dispersed within a polymer matrix formed by copovidone, wherein the weight ratio of Compound I to copovidone in the solid dispersion is about 1:1 and wherein Compound I is substantially amorphous having the formula:



;

b) about 40% w/w of substantially crystalline sofosbuvir having the formula:



;

c) about 35.5% w/w of microcrystalline cellulose;

d) about 3% w/w of croscarmellose sodium; and

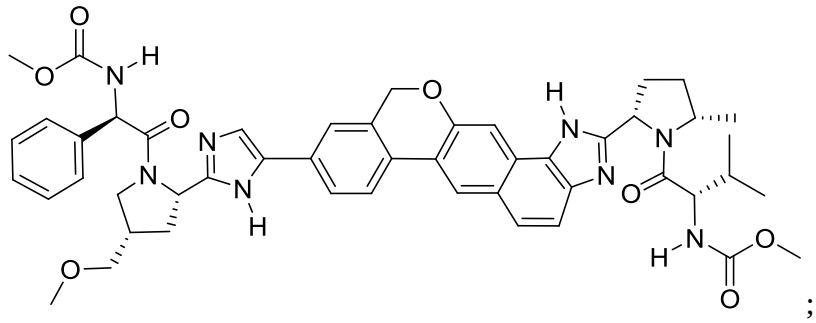
e) about 1.5% w/w of magnesium stearate.

10. The pharmaceutical composition of claim 9 wherein the crystalline sofosbuvir has XRPD 2θ-reflections (° ± 0.2θ) at about: 6.1 and 12.7.

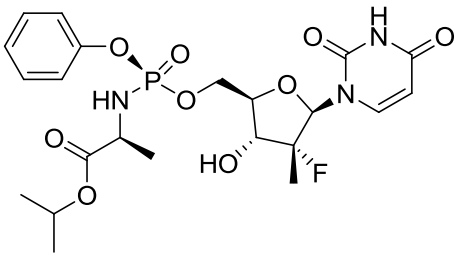
11. The pharmaceutical composition of claim 9 wherein the crystalline sofosbuvir has XRPD 2θ-reflections (° ± 0.2θ) at about: 6.1, 20.1 and 20.8.

12. A pharmaceutical composition in the form of a fixed dose combination tablet comprising:

a) about 200 mg of a solid dispersion comprising Compound I dispersed within a polymer matrix formed by copovidone, wherein the weight ratio of Compound I to copovidone in the solid dispersion is about 1:1 and wherein Compound I is substantially amorphous having the formula:


;

b) about 400 mg of substantially crystalline sofosbuvir having the formula:


;

c) about 355 mg of microcrystalline cellulose;

d) about 30 mg of croscarmellose sodium; and

e) about 15 mg of magnesium stearate.

13. The pharmaceutical composition of claim 12 wherein the crystalline sofosbuvir has XRPD 2θ-reflections (° ± 0.2θ) at about: 6.1 and 12.7.

14. The pharmaceutical composition of claim 12 wherein the crystalline sofosbuvir has XRPD 2θ-reflections (° ± 0.2θ) at about: 6.1, 20.1 and 20.8.

15. The pharmaceutical composition of any one of claims 1 to 14, wherein the tablet comprises a film coating.

16. The pharmaceutical composition of claim 15, wherein the film coating is a polyvinylalcohol-based coating.