



(43) International Publication Date
12 September 2014 (12.09.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/138374 A1

(51) International Patent Classification:

A61K 38/06 (2006.01) A61K 31/7056 (2006.01)
A61K 31/4709 (2006.01) A61P 31/14 (2006.01)
A61K 31/506 (2006.01) A61P 1/16 (2006.01)

(21) International Application Number:

PCT/US2014/021150

(22) International Filing Date:

6 March 2014 (06.03.2014)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/774,827 8 March 2013 (08.03.2013) US

(71) Applicant (for all designated States except US):

BOEHRINGER INGELHEIM INTERNATIONAL GMBH [DE/DE]; Binger Strasse 173, 55216 Ingelheim am Rhein (DE).

(72) Inventor; and

(71) Applicant (for US only): **MENSA, Frederico** [AR/US];

c/o VP, IP Legal, Boehringer Ingelheim USA Corp., 900 Ridgebury Rd., P.O. Box 368, Ridgefield, Connecticut 06877-0368 (US).

(74) Agents: **MORRIS, Michael P.** et al.; Boehringer Ingel-

heim Pharmaceuticals, Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877-0368 (US).

(81) Designated States (unless otherwise indicated, for every

kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every

kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(54) Title: ORAL COMBINATION THERAPY FOR TREATING HCV INFECTION IN SPECIFIC PATIENT SUB-POPULATION

(57) Abstract: The present invention relates to therapeutic combinations comprising (a) Compound (1), or a pharmaceutically acceptable salt thereof, as herein described, (b) Compound (2), or a pharmaceutically acceptable salt thereof, as herein described, and optionally (c) ribavirin, and methods of using such therapeutic combinations for treating HCV infection or alleviating one or more symptoms thereof in a patient having decompensated liver disease and/or hepatic impairment.



WO 2014/138374 A1

ORAL COMBINATION THERAPY FOR TREATING HCV INFECTION IN SPECIFIC PATIENT SUB-POPULATION

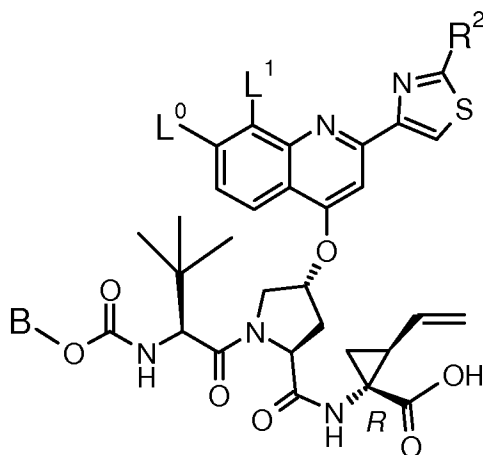
5 TECHNICAL FIELD OF THE INVENTION

The present invention relates to therapeutic combinations comprising Compounds (1) and (2) as herein described, or a pharmaceutically acceptable salt thereof, and optionally ribavirin. The present invention also relates to methods of using such therapeutic combinations for treating HCV infection (preferably (chronic) HCV genotype 1 infection, for example subgenotype 1b) or alleviating one or more symptoms thereof in a patient having decompensated liver disease (for example decompensated liver cirrhosis) and/or having hepatic impairment, for example having moderate hepatic impairment (such as e.g. defined by Child-Pugh B classification).

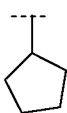
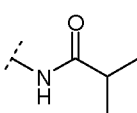
15 BACKGROUND OF THE INVENTION

The following Compound (1) (faldaprevir):

20



(1)

wherein **B** is ; **L**⁰ is MeO-; **L**¹ is Br; and **R**² is 

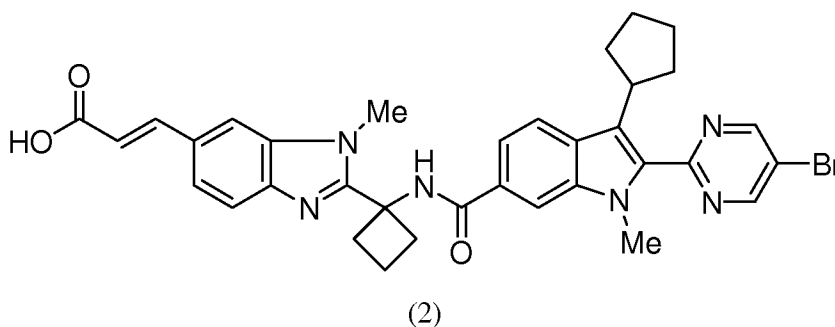
having the chemical name: 1-{[4-[8-Bromo-2-(2-isopropylcarbamoyl-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-1-(R)-(2-cyclopentyloxycarbonyl amino-3,3-(S)-dimethyl-buteryl)-pyrrolidine-(S)-2-carbonyl]-amino}-2-(S)-vinyl-cyclopropane-(R)-carboxylic acid, is known as a selective and potent inhibitor of the HCV NS3 serine protease and useful in the treatment of HCV infection. Compound (1) falls within the scope of the acyclic peptide series of HCV inhibitors disclosed in U.S. Patents RE 40,525, 7,514,557 and 7,585,845. Compound (1) is disclosed specifically as Compound # 1055 in U.S. Patent 7,585,845, and as Compound # 1008 in U.S. Patent 7,514,557. Compound (1), and pharmaceutical formulations thereof, can be prepared according to the general procedures found in the above-cited references, all of which are herein incorporated by reference in their entirety. Preferred forms of Compound (1) include the crystalline forms, in particular the crystalline sodium salt form as described in U.S. Patent 8,232,293, also incorporated herein by reference.

Data demonstrating the activity of Compound (1) as an inhibitor of the HCV NS3 serine protease and its corresponding demonstrated utility in the treatment of HCV infection in patients, can be found in U.S. Patent 7,585,845, as well as in numerous publications presenting the preclinical characterization or clinical trial results with Compound (1). See, e.g., Sulkowski MS, et al, Hepatol (2009), Vol. 50, pg. 2A, Abstract LB3; Sulkowski MS, et al., J Hepatol (2010) Vol. 52, Supp. 1, pgs. S462-S463, Abstract 1190; Berg et al., Hepatol (2010), Vol. 52, Supp. S1, Abstract 804; and White PW, et al., Antimicrob Agents Chemother (2010) 54(11):4611-4618.

A combination therapy regimen including administering Compound (1) with an interferon-alpha and ribavirin is described in U.S. Patent Application Publication No. 2010/0068182. However, in view of the potential side-effects and overall inconvenience of treatment with an interferon (administered by injection), there is a continuing need in the field for

alternative therapies for the treatment and prevention of HCV infection which do not involve the use of an interferon.

The following Compound (2):



having the chemical name: (E)-3-[2-(1-{[2-(5-Bromo-pyrimidin-2-yl)-3-cyclopentyl-1-methyl-1H-indole-6-carbonyl]-amino}-cyclobutyl)-3-methyl-3H-benzimidazol-5-yl]-acrylic acid, is known as a selective and potent inhibitor of the HCV NS5B RNA-dependent RNA polymerase and useful in the treatment of HCV infection. Compound (2) falls within the scope of HCV inhibitors disclosed in U.S. Patents 7,141,574 and 7,582,770, and 7,893,084. Compound (2) is disclosed specifically as Compound # 3085 in U.S. Patent 7,582,770. Compound (2), and pharmaceutical formulations thereof, can be prepared according to the general procedures found in the above-cited references, all of which are herein incorporated by reference in their entirety. Preferred forms of Compound (2) include the crystalline forms, in particular the crystalline sodium salt form which can be prepared as described in US Application Publication US 2012/0122887. Additionally, US Patent Application Publication US 2012/0135949 discloses the use of a combination of Compound (1), Compound (2) and, optionally, ribavirin, for the interferon-free treatment of HCV infection.

It is known in the art that particular HCV subtypes and patient subgenotypes may respond differently to HCV therapy. HCV Genotype 1a is traditionally more difficult to treat and are less responsive to antiviral therapy than Genotype 1b. See, e.g., Ghany, Marc et al. “An Update on Treatment of Genotype 1 Chronic Hepatitis C Virus Infection; 2011

Practice Guideline by the American Association for the Study of Liver Diseases“, *Hepatology*, 54(4): 1433-44 (2011)). In addition, and for example with interferon-based therapy, specific single nucleotide polymorphisms (SNPs) located on the long arm of chromosome 19 within the gene cluster of IL-28B (Interleukin (IL) 28B, (also called
5 lambda interferon), of the patient undergoing therapy can directly effect the responsiveness of that patient to the antiviral therapy. In particular, patients having a non-CC genotype of SNP rs12979860 or a non-TT genotype of rs8099917 are traditionally more difficult to treat and are less responsive in terms of a sustained virological response (SVR) than patients having the CC or TT genotype.. The SNP that was most strongly associated with
10 SVR in the genome-wide analysis was rs12979860 followed by rs 099917. See, e.g., Ge et al., *Nature*, 461:399-401 (2009) and Balagopal, *Gastroenterology*, 139:1865-1876 (2010). See G. Cairns, “Gene variant that helps hepatitis C treatment may hinder HIV treatment”, 2011, at: <http://www.bhiva.org/News.aspx?NewsID=a7503829-94b9-4d2f-bd91-1d2fbaad6e8d>.

15

Currently, two direct acting antiviral agents (DAAs), HCV protease inhibitors, telaprevir and boceprevir, have been approved for HCV treatment in selected countries.

Combination therapies of telaprevir with pegylated alfa interferon (PegIFN) and ribavirin (RBV) or of boceprevir with PegIFN/RBV represent available standard therapies for HCV
20 patients with chronic HCV genotype 1 infection with compensated liver disease (mild hepatic impairment or Child-Pugh A classification). However, both these compounds are given three times daily (t.i.d.), are associated with substantial side effects, and are not approved regimens for patients with moderate hepatic impairment (Child-Pugh B classification).

25

Thus, there is a need in the art for therapies that are effective against more difficult-to-treat patient subpopulations, for example those exhibiting decompensated liver disease (cirrhosis), a patient population with a high unmet medical need and no available antiviral treatment options, as pegylated interferon is contraindicated since, for example, it is poorly
30 tolerated and associated with serious adverse events, high discontinuation rates and a faster liver chirrosis progression in this population.

Applicants have discovered that excellent antiviral results can be achieved by combining the HCV protease inhibitor Compound (1) with an HCV polymerase inhibitor Compound (2), as hereinafter described, and optionally ribavirin, as a combination therapy without the use of an interferon, including in hard-to-treat patient populations (such as e.g. including patients with HCV genotype 1 infection and liver cirrhosis).

Further, a 2-fold increase in exposure of both Compound (1) and Compound (2) in compensated cirrhotic patients compared to non-cirrhotic patients has been observed. As such, it is expected that Compound (1) and Compound (2) exposure in patients with decompensated liver disease and/or hepatic impairment (for example, moderate hepatic impairment as defined by Child-Pugh B classification) will be at least 2-fold higher than that of non-cirrhotic patients. Thus, the combination according to the present invention is expected to be for example useful for the purpose of the present invention.

15

BRIEF SUMMARY OF THE INVENTION

The present invention provides the combination of Compounds (1) and (2) as herein described, or the pharmaceutically acceptable salts thereof, and optionally ribavirin, as an interferon-free regimen, for use in treating traditionally difficult-to-treat HCV patient subpopulations, for example those exhibiting decompensated liver disease and/or having hepatic impairment, for example having moderate hepatic impairment (such as e.g. defined by Child-Pugh B classification).

The present invention provides a method of treating HCV infection or alleviating one or more symptoms thereof in a patient comprising the step of administering to the patient an effective amount of a therapeutic combination comprising Compounds (1) and (2) as herein described, or a pharmaceutically acceptable salt thereof, and optionally ribavirin and wherein the patient has decompensated liver disease and/or hepatic impairment, for example moderate hepatic impairment (such as e.g. defined by Child-Pugh B

30

classification). The two or three actives of the combination can be administered simultaneously or separately, as part of a regimen.

5 The present invention further provides for a packaged pharmaceutical composition comprising a Compound (1), which is accompanied by written instructions indicating administering Compound (1) with Compound (2) and optionally ribavirin for the treatment of HCV infection wherein the patient has decompensated liver disease and/or hepatic impairment, for example moderate hepatic impairment (such as e.g. defined by Child-Pugh B classification).

10

The present invention further provides for a packaged pharmaceutical composition comprising a Compound (2), which is accompanied by written instructions indicating administering Compound (1) with Compound (2) and optionally ribavirin for the treatment of HCV infection wherein the patient has decompensated liver disease and/or hepatic
15 impairment, for example moderate hepatic impairment (such as e.g. defined by Child-Pugh B classification).

DETAILED DESCRIPTION OF THE INVENTION

20 Definitions

The term “moderate hepatic impairment” means patients scoring a Grade B on the Child-Pugh classification scoring system (sometimes called the Child-Turcotte-Pugh scoring system). The Child-Pugh scoring system is used to classify and assess the prognosis of
25 chronic liver disease, mainly cirrhosis. The score employs five clinical measures of liver disease in the setting of liver cirrhosis: bilirubin, albumin, blood coagulation (as determined by prothrombin time [PT] or by INR), evidence of ascites, and evidence of encephalopathy. Each measure is scored 1-3, with 3 indicating most severe derangement:

30

Measure	1 point	2 points	3 points
Total bilirubin, $\mu\text{mol/l}$ (mg/dl)	<34 (≤ 2)	34-50 (2-3)	>50 (> 3)
Serum albumin, g/l	>35	28-35	<28
Blood coagulation: PT: seconds prolonged INR	1-3 <1.7	4-6 1.71-2.30	> 6 > 2.30
Ascites	None	Slight, or controlled medically	Moderate or severe
Encephalopathy	None	Grade 1-2	Grade 3-4

Chronic liver disease is classified into Child-Pugh class A to C, employing the added score from above, with Class B comprising patients having moderate hepatic impairment:

Points	Class
5-6	A
7-9	B
10-15	C

- 5 Therefore patients exhibiting such clinical conditions according to Child-Pugh B classification are considered as having moderate hepatic impairment.

Accordingly, Child-Pugh class A comprises patients having mild hepatic impairment, Child-Pugh class B comprises patients having moderate hepatic impairment, and Child-
 10 Pugh class C comprises patients having severe hepatic impairment. The term “hepatic impairment” as used herein includes patients having mild, moderate or severe hepatic impairment.

Decompensated liver disease is characterized by failure of the liver to maintain adequate
 15 function. It represents a progressed or advanced stage of liver disease (particularly liver

cirrhosis) with extensive liver damage and impaired liver function, usually due to severe scarring, leading to fibrosis and/or cirrhosis caused by chronic liver inflammation. Patients exhibiting clinical conditions according to Child-Pugh B or Child-Pugh C classifications are usually patients having decompensated liver disease.

5

Liver cirrhosis may be defined as at least one of the following:

- a) Metavir Grade =4 or Ishak Grade $\geq$ 5 on liver biopsy
- b) liver stiffness of $\geq$ 13 kPa on fibroscan

10 “Compound (1)” and “Compound (2)” are as defined above.

“HCV infection” as used herein means infection by any subtype of the Hepatitis C Virus, including subtypes 1-6 (preferably subtype 1, for example subgenotype 1b), and includes both acute and chronic HCV infection.

15

“Ribavirin” refers to 1- β -D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide, available from ICN Pharmaceuticals, Inc., Costa Mesa, Calif. and is described in the Merck Index, compound No. 8199, Eleventh Edition. Its manufacture and formulation is described in U.S. Pat. No. 4,211,771. Preferred marketed ribavirin products include REBETOL® and

20 COPEGUS®. The term further includes derivatives or analogs thereof, such as those described in U.S. Pat. Nos. 6,063,772, 6,403,564 and 6,277,830. For example, derivatives or analogs include modified ribavirins such as 5'-amino esters, ICN Pharmaceutical's L-enantiomer of ribavirin (ICN 17261), 2'-deoxy derivatives of ribavirin and 3-carboxamidine derivatives of ribavirin, viramidine (previously known as ribamidine) and

25 the like.

The term “pharmaceutically acceptable salt” means a salt of a Compound of formula (1) which is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response,

30 and the like, commensurate with a reasonable benefit/risk ratio, generally water or oil-soluble or dispersible, and effective for their intended use.

The term includes pharmaceutically-acceptable acid addition salts and pharmaceutically-acceptable base addition salts. Lists of suitable salts are found in, e.g., S. M. Birge et al., *J. Pharm. Sci.*, 1977, 66, pp. 1-19.

5

The term "pharmaceutically-acceptable acid addition salt" means those salts which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acid, nitric acid, phosphoric acid, and the like, and organic acids such as acetic acid, trifluoroacetic acid, adipic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, butyric acid, camphoric acid, camphorsulfonic acid, cinnamic acid, citric acid, digluconic acid, ethanesulfonic acid, glutamic acid, glycolic acid, glycerophosphoric acid, hemisulfic acid, hexanoic acid, formic acid, fumaric acid, 2-hydroxyethane-sulfonic acid (isethionic acid), lactic acid, hydroxymaleic acid, malic acid, malonic acid, mandelic acid, mesitylenesulfonic acid, methanesulfonic acid, naphthalenesulfonic acid, nicotinic acid, 2-naphthalenesulfonic acid, oxalic acid, pamoic acid, pectinic acid, phenylacetic acid, 3-phenylpropionic acid, pivalic acid, propionic acid, pyruvic acid, salicylic acid, stearic acid, succinic acid, sulfanilic acid, tartaric acid, p-toluenesulfonic acid, undecanoic acid, and the like.

20

The term "pharmaceutically-acceptable base addition salt" means those salts which retain the biological effectiveness and properties of the free acids and which are not biologically or otherwise undesirable, formed with inorganic bases such as ammonia or hydroxide, carbonate, or bicarbonate of ammonium or a metal cation such as sodium, potassium, lithium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like. For example preferred are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically acceptable organic nontoxic bases include salts of primary, secondary, and tertiary amines, quaternary amine compounds, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion-exchange resins, such as methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine, triethylamine, isopropylamine, tripropylamine, tributylamine, ethanolamine,

30

diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, tetramethylammonium compounds, tetraethylammonium compounds, 5 pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine, dibenzylamine, N,N-dibenzylphenethylamine, 1-phenamine, N,N'-dibenzylethylenediamine, polyamine resins, and the like. For example preferred organic nontoxic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline, and caffeine.

10 The term "therapeutic combination" as used herein means a combination of one or more active drug substances, i.e., compounds having a therapeutic utility. Typically, each such compound in the therapeutic combinations of the present invention will be present in a pharmaceutical composition comprising that compound and a pharmaceutically acceptable 15 carrier. The compounds in a therapeutic combination of the present invention may be administered simultaneously or separately, as part of a regimen.

Embodiments of the Invention

20 According to a general embodiment, the present invention provides for a method of treating HCV infection or alleviating one or more symptoms thereof in a patient comprising the step of administering to the patient an effective amount of a therapeutic combination of a Compound (1) as defined herein, or a pharmaceutically acceptable salt thereof, a Compound (2) as defined herein, or a pharmaceutically acceptable salt thereof, 25 and optionally ribavirin, and wherein the patient has decompensated liver disease (for example decompensated cirrhosis) and/or having hepatic impairment, for example having moderate hepatic impairment. An additional embodiment is directed to the use of Compound (1), or a pharmaceutically acceptable salt thereof, and Compound (2) or a pharmaceutically acceptable salt thereof, for the manufacture of pharmaceutical 30 compositions of each compound, for use together or in combination, optionally also with ribavirin, in the treatment of HCV infection in a patient that has decompensated liver

disease (for example decompensated cirrhosis) and/or having hepatic impairment, for example having moderate hepatic impairment.

Additional general embodiments include a packaged pharmaceutical composition
5 comprising a packaging containing one or more doses of Compound (1) or a
pharmaceutically acceptable salt thereof, or containing one or more doses of Compound
(2) or a pharmaceutically acceptable salt thereof, together with written instructions
directing the co-administration of Compound (1), Compound (2) and optionally ribavirin
for the treatment of HCV infection wherein the patient has decompensated liver disease
10 (for example decompensated cirrhosis) and/or having hepatic impairment, for example
having moderate hepatic impairment. Another embodiment is directed to a kit for the
treatment of HCV infection in a patient comprising: (a) one or more doses of Compound
(1) or a pharmaceutically acceptable salt thereof, and (b) one or more doses of Compound
(2) or a pharmaceutically acceptable salt thereof, and (c) optionally ribavirin, together with
15 written instructions directing the co-administration of Compound (1), Compound (2) and
optionally ribavirin for the treatment of HCV infection wherein the patient has
decompensated liver disease (for example decompensated cirrhosis) and/or having hepatic
impairment, for example having moderate hepatic impairment.

20 In administering the therapeutic combinations of the present invention, each active agent
can be administered together at the same time or separately at different times in separate
dosage administrations. The present invention contemplates and includes all such dosage
regimens when administering the double or triple therapeutic combinations as defined
herein.

25

Accordingly, within this invention it is to be understood that a combination according to
this invention may envisage the simultaneous, concurrent, sequential, successive, alternate
or separate administration of the active components.

Further, in this context, “combination” or “combined” within the meaning of this invention
30 may include, without being limited, fixed and non-fixed (e.g. free) forms (including kits)

and uses, such as e.g. the simultaneous, concurrent, sequential, successive, alternate or separate use of the components.

Preferably, the Compound (1) as defined herein, or a pharmaceutically acceptable salt thereof, the Compound (2) as defined herein, or a pharmaceutically acceptable salt thereof, and the optional ribavirin, are each administered orally.

Although this combination therapy is expected to be effective against all HCV genotypes, it is for example useful in treating patients having HCV genotype 1 infection, including subtypes 1a and/or, for example, 1b. A preferred embodiment within the present invention is directed to the treatment of patients having the HCV subtype 1b.

The combination therapy of the instant invention is also useful in treating patients having decompensated liver disease, for example, patients having fibrosis or cirrhosis of the liver and/or having hepatic impairment, for example having moderate hepatic impairment (such as e.g. defined by Child-Pugh B classification).

In a specific preferred sub-embodiment, the patient has first been identified as having decompensated liver disease and/or hepatic impairment, for example moderate hepatic impairment (such as e.g. defined by Child-Pugh B classification), prior to the step of administering the therapeutic combination of the present invention.

The patient population to be treated with the combination therapy of the present invention can be further classified into “treatment-naïve” patients, i.e., those patient who have not received any prior treatment for HCV infection and “treatment experienced” patients, i.e., those patients who have undergone prior treatment for HCV, such as treatment experienced with prior relapse (e.g. defined as viral load rebound with HCV RNA level > 25 IU/mL during the post-treatment period in patients who had plasma HCV RNA level undetected at end of all previous treatment) or treatment experienced with interferon intolerance (e.g. defined as patients who had to stop a previous PegIFN/RBV regimen before week 12 of treatment due to safety or tolerability issues).

According to an alternative embodiment, the present invention provides a method of reducing HCV-RNA levels in a patient in need thereof, comprising the step of administering to said patient a therapeutic combination according to the present invention.

5 Preferably, the method of the present invention reduces the HCV-RNA levels in a patient to a level below the lower limit of quantification (or “BLQ”). A BLQ level of HCV RNA as used in the present invention means a level below 25 International Units (IU) per ml of serum or plasma of a patient as measured by quantitative, multi-cycle reverse transcriptase PCR methodology according to the WHO international standard (Saladhanha J, Lelie N and
10 Heath A, Establishment of the first international standard for nucleic acid amplification technology (NAT) assays for HCV RNA. WHO Collaborative Study Group. Vox Sang 76:149-158, 1999). Such methods are well known in the art. In a preferred embodiment, the method of the present invention reduces the HCV-RNA levels in a patient to less than 25 IU per ml of serum or plasma. In another embodiment the method of the present
15 invention reduces the HCV-RNA levels in a patient to less than a detectible level. In a preferred embodiment, the method of the present invention reduces the HCV-RNA levels in a patient to less than 25 IU per ml of plasma, such as at 4 weeks, 12 weeks or 24 weeks after end of treatment, preferably at 12 weeks after end of treatment.

20 In another embodiment the method of the present invention reduces the HCV-RNA levels in a patient to less than a detectible level (below the limit of detection, BLD). Treatment decisions for duration of HCV therapy can be made based on BLD, and combinations of BLQ and BLD HCV RNA at subsequent timepoints during initial treatment. Typical time points include HCV RNA measurements at 4, 8, and 12 weeks after initiation of therapy,
25 and results are utilized to guide further treatment duration “response-guided therapy”. Cure from HCV infection is typically inferred if HCV RNA remained BLD 12-24 weeks after end of HCV treatment. Thus, in additional embodiments, the method of the present invention results in an HCV-RNA level in the patient that is less than a detectible level at 12 weeks after the end of all treatment.

30

The first component of the therapeutic combination, namely, Compound (1) or a pharmaceutically acceptable salt thereof is comprised in a composition. Such a composition comprises Compound (1), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable adjuvant or carrier. Typical pharmaceutical compositions that
5 may be used for Compound (1), or a pharmaceutically acceptable salt thereof, are as described in U.S. Patent 7,585,845. Further specific examples of compositions are as set forth in the examples section below.

The appropriate dosage amounts, administration forms and/or regimens for a particular
10 patient can be determined by methods analogous to those known in the art and by reference to the disclosures referred to herein, such as e.g. by reference to the disclosures in U.S. RE40,525 and 7,585,845 for Compound (1), U.S. Patents 7,141,574; 7,582,770 and 7,893,084 for Compound (2).

15 In general, the Compound (1) or a pharmaceutically acceptable salt thereof may be administered at a maintenance dosage of at least 40 mg/day (in single or divided doses). Additional embodiments for dosage amounts and ranges may include (in single or divided doses):

- (a) at least 100 mg/day
- 20 (b) at least 120 mg/day
- (c) at least 200 mg/day
- (d) at least 240 mg/day
- (e) at least 360 mg/day
- (f) at least 480 mg/day
- 25 (g) from about 40 mg/day to about 480 mg/day
- (h) from about 120 mg/day to about 240 mg/day
- (i) from about 240 mg/day to about 480 mg/day
- (j) about 120 mg/day
- (k) about 240 mg/day
- 30 (l) about 360 mg/day
- (m) about 480 mg/day

Although Compound (1) or a pharmaceutically acceptable salt thereof may be administered in single or divided daily doses, once a day administration (QD) of the daily dose is preferred. As the skilled artisan will appreciate, however, lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combinations (co-medications), the severity and course of the infection, the patient's disposition to the infection and the judgment of the treating physician. Specific factors affecting dosing may include, for example, individual patient factors which modify the adsorption, distribution, metabolism and excretion of Compound (1); the specific HCV Genotype; the specific IL28B genotype of the patient; the patient's innate/adaptive immune response to HCV; acute vs. chronic HCV infection; and the disposition of ribavirin based on host factors. In general, the compound is most desirably administered at a concentration level that will generally afford antivirally effective results without causing any harmful or deleterious side effects.

In another embodiment according to the invention, a loading dose amount of Compound (1) is administered for the first administration dose of the treatment. The loading dose amount is higher than the dose amount administered for subsequent administrations in the treatment, which are referred to as maintenance doses. Preferably, the loading dose amount is about double in quantity, by weight, of the amount in subsequent administrations in the treatment. For example, in one embodiment, the first dose of Compound (1) administered at a loading dosage of about 240 mg and subsequent maintenance doses of Compound (1) are administered at a dosage of about 120 mg. In another embodiment, the first dose of Compound (1) administered at a loading dosage of about 480 mg and subsequent maintenance doses of Compound (1) are administered at a dosage of about 240 mg. In another embodiment, the first dose of Compound (1) administered is at a dosage of about 960 mg and subsequent doses of Compound (1) are administered at a dosage of about 480 mg.

By using this loading dose concept, a clear advantage is that it is thereby possible to achieve steady state levels of active drug in the patient's system earlier than would otherwise be achieved. A higher blood level is achieved early by using a loading dose preferably double the maintenance dose at first intake. Reaching the targeted steady state
5 level of active drug earlier in therapy also means that there is less possibility of insufficient drug exposure at the beginning of therapy so that resistant viral strains have a smaller chance of emerging.

The second component of the therapeutic combination, namely, Compound (2) or a
10 pharmaceutically acceptable salt thereof is comprised in a composition. Such a composition comprises Compound (2), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable adjuvant or carrier. Typical pharmaceutical compositions that may be used for Compound (1), or a pharmaceutically acceptable salt thereof, are as described in U.S. Patent 7,582,770.

15

In general, the Compound (2) or a pharmaceutically acceptable salt thereof may be administered at dosage amounts and in dose ranges that may include (in single or divided doses):

- (a) at least 600 mg/day
- 20 (b) at least 800 mg/day
- (c) at least 1200 mg/day
- (d) at least 1800 mg/day
- (e) at least 2400 mg/day
- (f) from about 800 mg/day to about 2400 mg/day
- 25 (g) from about 1200 mg/day to about 1800 mg/day
- (h) from about 1800 mg/day to about 2400 mg/day
- (i) from about 1200 mg/day to about 2400 mg/day
- (j) about 1200 mg/day
- (k) about 1800 mg/day
- 30 (l) about 2400 mg/day

Although Compound (2) or a pharmaceutically acceptable salt thereof may be administered in single or divided daily doses, twice a day (BID) or thrice a day administration (TID) of the divided daily dose is preferred. As the skilled artisan will appreciate, however, lower or higher doses than those recited above may be required. Specific dosage and treatment
5 regimens for any particular patient will depend upon a variety of factors, including the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the infection, the patient's disposition to the infection and the judgment of the treating physician. In general, the compound is most desirably administered at a concentration level that will generally afford antivirally
10 effective results without causing any harmful or deleterious side effects.

In another embodiment according to the invention, an induction dose amount of Compound (2) is administered for the first administration dose of the treatment. The induction dose amount is higher than the dose amount administered for subsequent
15 administrations in the treatment. Preferably, the induction dose amount is about double to triple in quantity, by weight, of the amount in subsequent administrations in the treatment. For example, in one embodiment, the first dose of Compound (2) administered at dosage of about 1200 mg and subsequent doses of Compound (2) are administered at a dosage of about 600 mg. In another embodiment, the first dose of Compound (2) administered at a
20 dosage of about 1200 mg and subsequent doses of Compound (2) are administered at a dosage of about 400 mg.

By using this induction dose concept, a clear advantage is that it is thereby possible to achieve a greater drop in initial viral load. Maximizing initial viral response with the first
25 dose and then sustaining the drop with a subsequent lower dose also restricts the selection of potential resistant variants.

The optional third component of the therapeutic combination, namely ribavirin, is comprised in a pharmaceutical composition. Typically, such compositions comprise
30 ribavirin and a pharmaceutically acceptable adjuvant or carrier and are well known in the

art, including in a number of marketed ribavirin formulations. Formulations comprising ribavirin are also disclosed, e.g., in US Patent 4,211,771.

The types of ribavirin that may be used in the combination are as outlined hereinabove in the definitions section. In one preferred embodiment, the ribavirin is either REBETOL® or COPEGUS® and they may be administered at their labeled dosage levels indicated for interferon plus ribavirin combination therapy for the treatment of HCV infection. Of course, with the triple combination therapy of the present invention it may be possible to use a lower dosage of ribavirin, e.g., lower than is used the current standard interferon plus ribavirin therapy, while delivering the same or better efficacy than the current standard therapy with less side-effects usually associated with such therapy.

According to various embodiments, the ribavirin may be administered at dosages of (in single or divided doses):

- (a) between 200 mg/day to about 1800 mg/day;
- (b) between about 800 mg/day to about 1200 mg/day;
- (c) between about 1000 mg/day to about 1200 mg/day;
- (d) about 1000 mg/day
- (e) about 1200 mg/day
- (f) between about 300 mg/day to about 800 mg/day
- (g) between about 300 mg/day to about 700 mg/day
- (h) between 500 mg/day to about 700 mg/day
- (i) between 400 mg/day to about 600 mg/day
- (j) about 400 mg/day
- (k) about 600 mg/day
- (l) about 800 mg/day

According to one embodiment, the ribavirin composition comprises ribavirin in a formulation suitable for dosing once a day or twice daily. For example, if a therapeutic combination comprises about 1000 mg/day dosage of ribavirin, and a dosing of two times a day is desired, then the therapeutic combination will comprise ribavirin in a formulation,

e.g., a tablet, containing, e.g., about 200 mg of ribavirin, with the first dose of 600 mg (or 400 mg), followed by a second dose of 400 mg (or 600 mg) at least 6 hours apart.

For example, in one embodiment the present invention contemplates a method of treating
5 hepatitis C viral (HCV) infection (preferably (chronic) HCV genotype 1 infection, for
example subgenotype 1b) or alleviating one or more symptoms thereof in a patient that has
decompensated liver disease (for example decompensated liver cirrhosis) and/or hepatic
impairment, for example having moderate hepatic impairment (such as e.g. defined by
Child-Pugh B classification), comprising the step of administering to the patient an
10 effective amount of:

- (a) Compound (1) or a pharmaceutically acceptable salt thereof, such as at a
dosage of from about 40 mg per day to about 480 mg per day;
- (b) Compound (2) or a pharmaceutically acceptable salt thereof, such as at a
15 dosage of from about 800 mg/day to about 2400 mg/day; and
- (c) optionally ribavirin, such as at a dosage of from about 200 mg/day to about
1800 mg/day.

In another embodiment the present invention contemplates a method of treating hepatitis C
20 viral (HCV) infection (preferably (chronic) HCV genotype 1 infection, for example
subgenotype 1b) or alleviating one or more symptoms thereof in a patient that has
decompensated liver disease (for example decompensated liver cirrhosis) and/or hepatic
impairment, for example having moderate hepatic impairment (such as e.g. defined by
Child-Pugh B classification), comprising the step of administering to the patient a
25 therapeutic combination comprising:

- (a) Compound (1) or a pharmaceutically acceptable salt thereof at an oral dosage
from about 120 mg/day to about 240 mg/day;
- (b) Compound (2) or a pharmaceutically acceptable salt thereof at an oral dosage
30 from about 800 mg/day to about 1200 mg/day; and
- (c) optionally ribavirin at an oral dosage from about 1000 mg/day to about 1200
mg/day.

In another embodiment the present invention contemplates a method of treating hepatitis C viral (HCV) infection (preferably (chronic) HCV genotype 1 infection, for example subgenotype 1b) or alleviating one or more symptoms thereof in a patient that has been identified as having decompensated liver disease (for example decompensated liver cirrhosis) and/or hepatic impairment, for example having moderate hepatic impairment (such as e.g. defined by Child-Pugh B classification), comprising the step of administering to the patient a therapeutic combination comprising:

- 10 (a) Compound (1) or a pharmaceutically acceptable salt thereof at an oral dosage of about 120 mg/day or about 240 mg/day;
- (b) Compound (2) or a pharmaceutically acceptable salt thereof at an oral dosage of about 800 mg/day; and
- (c) optionally ribavirin at an oral dosage from about 1000 mg/day to about 1200
- 15 mg/day.

In another embodiment the present invention contemplates a method of treating hepatitis C viral (HCV) infection (preferably (chronic) HCV genotype 1 infection, for example subgenotype 1b) or alleviating one or more symptoms thereof in a patient that has been identified as having decompensated liver disease (for example decompensated liver cirrhosis) and/or hepatic impairment, for example having moderate hepatic impairment (such as e.g. defined by Child-Pugh B classification), comprising the step of administering to the patient a therapeutic combination comprising:

- 25 (a) Compound (1) or a pharmaceutically acceptable salt thereof at an oral dosage of about 120 mg/day or about 240 mg/day;
- (b) Compound (2) or a pharmaceutically acceptable salt thereof at an oral dosage of about 1200 mg/day; and
- (c) optionally ribavirin at an oral dosage from about 1000 mg/day to about 1200
- 30 mg/day.

In another embodiment the present invention contemplates a method of treating hepatitis C viral (HCV) infection (preferably (chronic) HCV genotype 1 infection, for example subgenotype 1b) or alleviating one or more symptoms thereof in a patient that has been identified as having decompensated liver disease (for example decompensated liver
5 cirrhosis) and/or hepatic impairment, for example having moderate hepatic impairment (such as e.g. defined by Child-Pugh B classification), comprising the step of administering to the patient:

- 10 (a) Compound (1) or a pharmaceutically acceptable salt thereof at an oral dosage of about 120 mg once daily (preferably additionally 120 mg loading dose for a total of 240 mg once daily on Day 1);
- (b) Compound (2) or a pharmaceutically acceptable salt thereof at an oral dosage of about 400 mg twice daily; and
- (c) optionally ribavirin at an oral dosage of about 1000 mg/day or about 1200
15 mg/day (preferably weight-based twice daily dosing).

In another embodiment the present invention contemplates a method of treating hepatitis C viral (HCV) infection (preferably (chronic) HCV genotype 1 infection, for example subgenotype 1b) or alleviating one or more symptoms thereof in a patient that has been
20 identified as having decompensated liver disease (for example decompensated liver cirrhosis) and/or hepatic impairment, for example having moderate hepatic impairment (such as e.g. defined by Child-Pugh B classification), comprising the step of administering to the patient:

- 25 (a) Compound (1) or a pharmaceutically acceptable salt thereof at an oral dosage of about 120 mg once daily (preferably additionally 120 mg loading dose for a total of 240 mg once daily on Day 1);
- (b) Compound (2) or a pharmaceutically acceptable salt thereof at an oral dosage of about 600 mg twice daily; and
- 30 (c) optionally ribavirin at an oral dosage of about 1000 mg/day or about 1200 mg/day (preferably weight-based twice daily dosing).

Further embodiments include any of the above-mentioned embodiments, and where:

- (a) the therapy is a triple combination therapy including administration of Compound (1) or a pharmaceutically acceptable salt thereof, Compound (2) or a pharmaceutically acceptable salt thereof and ribavirin; or
- 5 (b) the therapy is a double combination therapy including administration of Compound (1) or a pharmaceutically acceptable salt thereof and Compound (2) or a pharmaceutically acceptable salt thereof, i.e., without any additional anti-HCV agents.

10 Further embodiments include any of the above-mentioned embodiments, and where:

- (a) the HCV infection is genotype 1, preferably genotype 1b, and the patient is a treatment-naïve patient; or
- (b) the HCV infection is genotype 1, preferably genotype 1b, and the patient is a treatment-experienced patient with prior relapse;
- 15 (c) the HCV infection is genotype 1, preferably genotype 1b, and the patient is a treatment-experienced patient with intolerance to interferon (for example to pegylated alfa interferon).

Further embodiments include any of the above-mentioned embodiments, and where the
20 patient has compensated cirrhosis of the liver.

Further embodiments include any of the above-mentioned embodiments, and where the Compound (1) or a pharmaceutically acceptable salt thereof is administered once a day, the Compound (2) or a pharmaceutically acceptable salt thereof is administered twice a day,
25 and the ribavirin, if included in the therapy, is administered twice a day.

Further embodiments include any of the above-mentioned embodiments and where the loading dose concept is used for Compound (1), e.g., the first dose of Compound (1) administered is double in quantity to the subsequent doses.

30

Further embodiments include any of the above-mentioned embodiments, and where the therapeutic regimen of the present invention is administered to the patient for at least about 4 weeks, more preferably at least about 12 weeks, at least about 16 weeks, at least about 24 weeks, at least about 28 weeks or at least about 48 weeks; such as e.g. at least about 24
5 weeks (e.g. for cirrhotic patients).

With respect to the double or triple combination therapies of the present invention, the present invention contemplates and includes all combinations of the various preferred embodiments and sub-embodiments as set forth herein.

10

An additional embodiment is directed to a packaged pharmaceutical composition comprising a packaging containing one or more doses of Compound (1) or a pharmaceutically acceptable salt thereof, or containing one or more doses of Compound (2) or a pharmaceutically acceptable salt thereof, each together with written instructions
15 directing the co-administration of Compound (1), Compound (2) and optionally ribavirin for the treatment of HCV infection in a patient that has decompensated liver disease (for example decompensated liver cirrhosis) and/or hepatic impairment, for example moderate hepatic impairment (such as e.g. defined by Child-Pugh B classification). In another embodiment, one or more doses of Compound (1), or a pharmaceutically acceptable salt thereof, and one or more doses of Compound (2), or a pharmaceutically acceptable salt thereof, and optionally ribavirin, are placed together in a single packaging forming a so-called "kit", which includes written instructions directing the co-administration of
20 Compound (1), Compound (2) and optionally ribavirin for the treatment of HCV infection in a patient that has decompensated liver disease (for example decompensated liver cirrhosis) and/or hepatic impairment, for example moderate hepatic impairment (such as e.g. defined by Child-Pugh B classification). In either case, the individual doses of Compound (1) or a pharmaceutically acceptable salt thereof, or Compound (2) or a pharmaceutically acceptable salt thereof, can be in the form of any of the standard pharmaceutical dosage forms, e.g. tablets, capsules, and packaged within any of the
25 standard types of pharmaceutical packaging materials, e.g. bottles, blister-packs, etc., that
30 may themselves be contained within an outer packaging material such as a paper/cardboard

box. The written instructions will typically be provided either on the packaging material(s) itself or on a separate paper (a so-called “package insert”) that is provided together with the dosage forms within the outer packaging material. All such packaging embodiments and variations thereof are embraced by the present invention.

5

Methods for determining diagnosis of decompensated liver disease and/or hepatic impairment

- 10 A diagnosis of decompensated liver disease, e.g. decompensated liver fibrosis or cirrhosis, and/or hepatic impairment can be confirmed clinically by skilled person, such as e.g. by measuring the individual patient’s clinical parameters necessary for the Child-Pugh classification scoring system. Moderate hepatic impairment is confirmed by obtaining a Class B grading using such system, as described hereinabove.

15

Methods for determining HCV subtype and subgenotypes

- Specific methods that have been used for HCV RNA quantification, HCV subtyping and IL28B genotyping are as detailed below. To the extent that other methods may be known and available in the art, and all are considered embraced within the present invention and can be used in connection therewith.

20

HCV RNA Quantification

- A plasma sample of about 6 ml is obtained from the patients and processed by using the Roche COBAS® TaqMan HCV/HPS assay (Version 2). The assay has a linear range from 25 to 3.91×10^8 IU/ml with a limit of detection between 10 and 20 IU/ml.

25

HCV Subtyping

- The HCV subtype was determined by using the TRUGENE® HCV Genotyping Assay. The assay directly amplifies and sequences the virus allowing direct examination of the viral RNA by producing bi-directional sequences using two fluorescently-labeled DNA

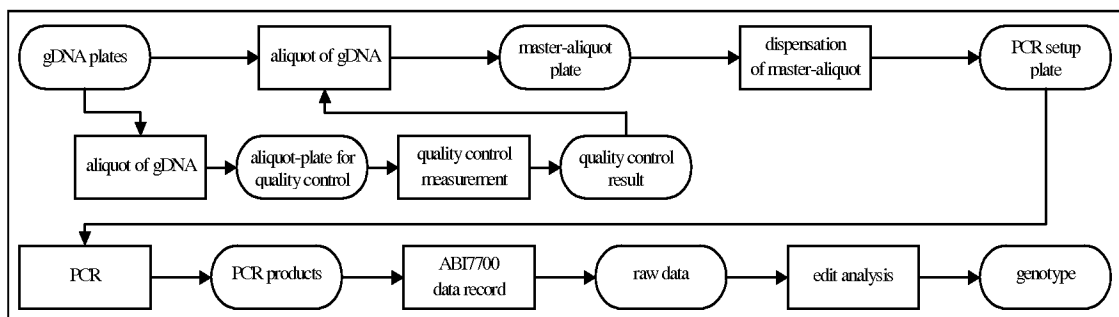
30

primers. The library includes viral isolates to allow determination of the 6 major hepatitis C genotypes and 41 sub-types.

Genotyping of IL28B

5 Genotype analysis was performed on DNA extracted from blood samples of the patients by using TaqMan PCR based test assays established by Beckman Coulter Genomics (Bernried, Germany) for the analysis of genetic variants.. The process flow of the genotype analysis consisted of the extraction of genomic DNA from blood samples, the application of established molecular genetic techniques to amplify the specific genetic target sites and
10 the detection and analysis of emission data of the fluorescent TaqMan probes employed in the amplification processes. Three kinds of controls were used for each product: a) one water control included prior to DNA isolation, b) one water control included after DNA isolation and c) one heterozygous and/or one homozygous (wild-type or variant) genotyping control.

15 The process flow for TaqMan based products for allelic discrimination applied in this



study is given in the figure above. The final genotype results for all samples and all products of each processing batch were combined using the Beckman Coulter Genomics software SNPsuite. The results include information regarding the genotype of each subject.

20 In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustrating embodiments of this invention, and are not to be construed as limiting the scope of the invention in any way. The reactants used in the examples below may be obtained either as described herein, or if not described herein, are themselves either commercially available or may be prepared from commercially

available materials by methods known in the art. Certain starting materials, for example, may be obtained by methods described in the International Patent Applications WO 2012/044520, WO 2010/033444, WO 2010/059667, WO 2011/005646, WO 2005/080388 WO 00/09543, WO 00/09558, WO 00/59929, U.S. Patents 6,323,180, 6,608,027,
5 7,514,557, 7,141,574; 7,582,770, 7,893,084 and 7,585,845.

Unless otherwise specified, solvents, temperatures, pressures, and other reaction conditions may be readily selected by one of ordinary skill in the art. Typically, reaction progress may be monitored by High Pressure Liquid Chromatography (HPLC), if desired, and
10 intermediates and products may be purified by chromatography on silica gel and/or by recrystallization.

Examples

I. Methods for Preparing Compound (1)

Methods for preparing amorphous Compound (1) and a general description of pharmaceutically acceptable salt forms can be found in US Patents RE 40,525, 7,514,557 and 7,585,845. Methods for preparing additional forms of Compound (1), in particular the
20 crystalline sodium salt form, can be found in U.S. Patent 8,232,293.

II. Formulations of Compound (1)

One example of a pharmaceutical formulation of Compound (1) include an oral solution formulation as disclosed in WO 2010/059667. Additional examples include capsules
25 containing a lipid-based liquid formulation, as disclosed in WO 2011/005646.

III. Methods for Preparing Compound (2) and Formulations of Compound (2)

Methods for preparing amorphous Compound (2) can be found in U.S. Patents 7,141,574, 7,582,770, and 7,893,084.

30

Methods for preparing additional forms of Compound (2), in particular the crystalline and amorphous sodium salt forms, can be found in U.S. Patent Application Publication US 2012/0122887.

- 5 Examples of pharmaceutical formulations containing Compound (2), in particular the crystalline and amorphous sodium salt forms, include the tablet formulations as disclosed in U.S. Patent Application Publication US 2012/0122887.

IV. Clinical Study:

10

For the clinical trial described below, the Compound (1) drug product is administered as a softgel capsule lipid-based formulation containing Compound (1) sodium salt. Compound (2) drug product is administered as a tablet formulation containing Compound (2) sodium salt.

15

A (randomised, double-blind, placebo-controlled) study is to be performed in treatment naïve and treatment experienced patients with chronic HCV infection of GT1, sub-GT1b virus only, having decompensated liver disease (for example decompensated liver cirrhosis) and/or hepatic impairment, for example moderate hepatic impairment (for
20 example as defined by Child-Pugh B classification as described herein), for example wherein:

1. Chronic HCV infection is diagnosed by positive anti-HCV antibodies and detected HCV RNA at screening in addition to at least one of the following:
 - a) positive anti-HCV antibodies or detected HCV RNA at least 6 months prior
25 to screening
 - b) liver biopsy consistent with chronic HCV infection
 - c) history of elevated ALT levels at least 6 months prior to screening
2. HCV infection, confirmed by genotypic testing at screening, of GT1, sub-GT1b virus.

3. HCV viral load $\geq$ 1,000 IU/ml at screening

4. Previous treatment status must be one of the following:

a) Treatment naïve: defined as patients who have never been previously treated with any interferon, with an investigational/approved DAA or any other HCV treatment regimen.

b) Treatment experienced with prior relapse: defined as HCV RNA level $>$ 25 IU/mL during the post-treatment period in patients who had plasma HCV RNA level undetected at end of all treatment

c) Treatment experienced interferon intolerant: defined as patients who had to stop a previous PegIFN/RBV regimen before week 12 of treatment due to safety or tolerability issues.

5. Liver cirrhosis is defined as at least one of the following:

a) Metavir Grade $\geq$ 4 or Ishak Grade $\geq$ 5 on liver biopsy

b) liver stiffness of $\geq$ 13 kPa on fibroscan

These patients are treated for 24 weeks with a combination according to the present invention:

(a) Compound (1) or a pharmaceutically acceptable salt thereof at an oral dosage of about 120 mg once daily (preferably additionally 120 mg loading dose for a total of 240 mg once daily on Day 1),

(b) Compound (2) or a pharmaceutically acceptable salt thereof either at an oral dosage of about 400 mg twice daily or at an oral dosage of about 600 mg twice daily, and

(c) optionally ribavirin at an oral dosage of about 1000 mg/day or about 1200 mg/day (preferably weight-based twice daily dosing);

and compared with patients who are treated with placebo.

Evidence of the therapeutic success/efficacy compared with patients who have been treated with placebo can be found in the greater proportion of patients achieving plasma HCV RNA level less than 25 IU/ml at 12 weeks after end of treatment.

Further therapeutic success in efficacy can be found in greater proportion of patients achieving plasma HCV RNA level less than 25 IU/ml at 4 weeks after end of treatment.

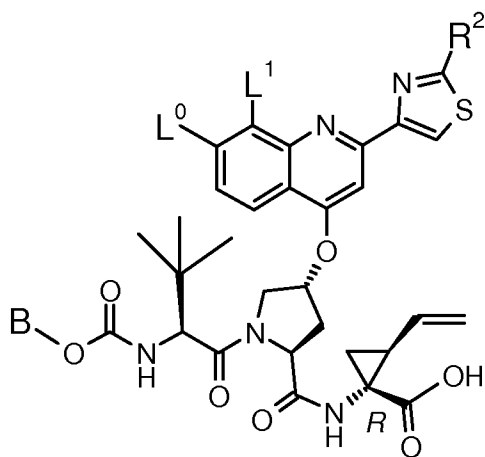
5

Further therapeutic success in efficacy can be found in greater proportion of patients achieving plasma HCV RNA level less than 25 IU/ml at 24 weeks after end of treatment.

CLAIMS

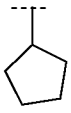
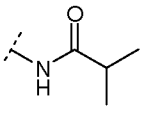
1. A method of treating hepatitis C viral (HCV) infection or alleviating one or more symptoms thereof in a patient comprising the step of administering to the patient a
5 therapeutic combination comprising:

(a) a compound of the following formula (1) or a pharmaceutically acceptable salt thereof:

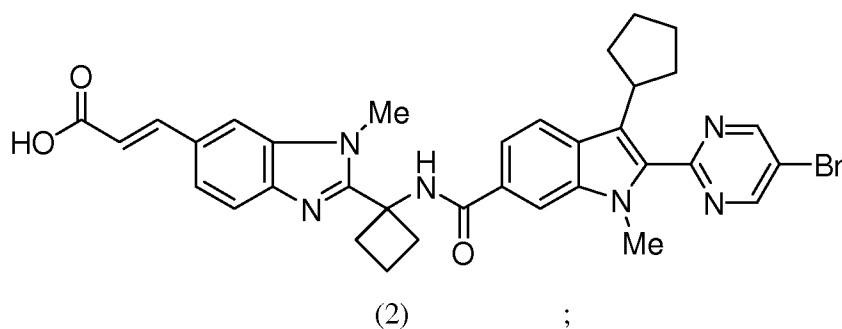


10

(1)

wherein **B** is ; **L**⁰ is MeO-; **L**¹ is Br; and **R**² is ;

(b) a compound of the following formula (2) or a pharmaceutically acceptable salt thereof:



15

(2)

and optionally (c) ribavirin;

and wherein the patient has decompensated liver disease and/or hepatic impairment.

- 5 2. The method according to claim 1, wherein the patient has HCV subtype 1.
3. The method according to claim 1, wherein the patient has HCV subtype 1b.
4. The method according to any of the preceding claims, wherein the patient has
10 decompensated liver cirrhosis.
5. The method according to any of the preceding claims, wherein the patient has moderate hepatic impairment.
- 15 6. The method according to any of the preceding claims, wherein the patient has moderate hepatic impairment as defined by Child-Pugh B classification.
7. The method according to any of the preceding claims, wherein said patient is a treatment-naive patient.
20
8. The method according to any of claims 1-6, wherein said patient is a treatment experienced patient.
9. The method according to any of the preceding claims, wherein the HCV-RNA
25 levels of said patient are reduced to less than 25 IU per ml of plasma, or to below the lower limit of quantification or to a less than detectable level as a result of the treatment.
10. The method according to any of the preceding claims wherein said therapeutic combination is administered for at least 24 weeks.
30
11. The method according to any of the preceding claims, wherein compound (1) or a

pharmaceutically acceptable salt thereof is orally administered at a dosage from about 40 mg per day to about 480 mg per day.

12. The method according to any of the preceding claims, wherein compound (1) or a
5 pharmaceutically acceptable salt thereof is orally administered at a dosage from about 120 mg per day to about 240 mg per day.

13. The method according to any of the preceding claims, wherein compound (1) is orally administered in the form of its sodium salt.

10

14. The method according to any of the preceding claims, wherein compound (2) or a pharmaceutically acceptable salt thereof is orally administered at a dosage from about 800 mg per day to about 2400 mg per day.

15. The method according to any of the preceding claims, wherein compound (2) or a pharmaceutically acceptable salt thereof is orally administered at a dosage from about 800 mg per day to about 1200 mg per day.

16. The method according to any of the preceding claims, wherein compound (2) is
20 orally administered in the form of its sodium salt.

17. The method according to any of the preceding claims, wherein said ribavirin is orally administered at a dosage from about 200 mg/day to about 1800 mg/day.

18. The method according to any of the preceding claims, wherein said ribavirin is
25 orally administered at a dosage from about 1000 mg/day to about 1200 mg/day.

19. The method according to any of the preceding claims, wherein the therapeutic combination administered is a triple combination therapy including administration of
30 Compound (1) or a pharmaceutically acceptable salt thereof, Compound (2) or a pharmaceutically acceptable salt thereof and ribavirin.

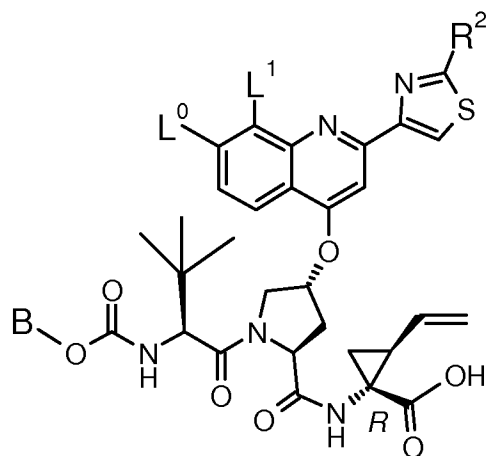
20. The method according to any of the preceding claims, wherein the therapeutic combination administered is a double combination therapy including administration of Compound (1) or a pharmaceutically acceptable salt thereof and Compound (2) or a pharmaceutically acceptable salt thereof without the administration of ribavirin.

21. The method according to any of the preceding claims, wherein the therapeutic combination comprises:

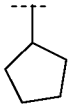
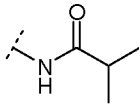
- 10 (a) Compound (1) or a pharmaceutically acceptable salt thereof at a dosage for oral administration from about 120 mg/day to about 240 mg/day, preferably 120 mg for once daily oral administration;
- (b) Compound (2) or a pharmaceutically acceptable salt thereof at a dosage for oral administration from about 800 mg/day to about 1200 mg/day, such as e.g. 400
15 mg or 600 mg each for twice daily oral administration; and
- (c) optionally ribavirin at a dosage for oral administration from about 1000 mg/day to about 1200 mg/day, preferably for twice daily oral administration.

22. The method according to any of the preceding claims, wherein the patient has first
20 been identified as having decompensated liver disease (for example decompensated liver cirrhosis) and/or hepatic impairment, for example moderate hepatic impairment (such as e.g. defined by Child-Pugh B classification) prior to the step of administering the therapeutic combination of the present invention.

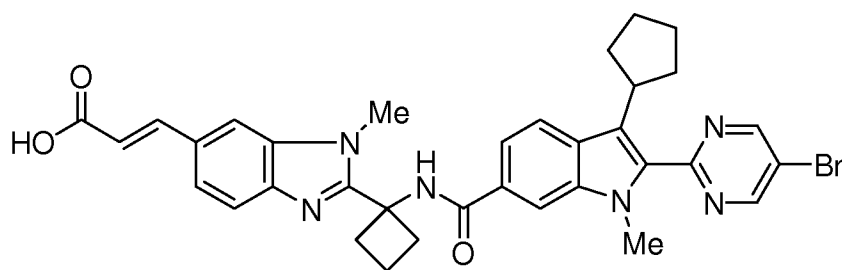
23. A packaged pharmaceutical composition comprising a packaging containing:
25 (a) one or more doses of the following Compound (1) or a pharmaceutically acceptable salt thereof:



(1)

wherein **B** is ; **L**⁰ is MeO-; **L**¹ is Br; and **R**² is ;

- 5 or (b) one or more doses of the following Compound (2) or a pharmaceutically acceptable salt thereof:



(2) ;

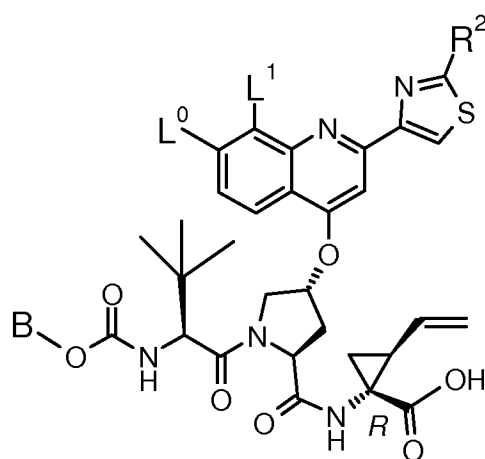
10

and written instructions directing the co-administration of Compound (1), or a pharmaceutically acceptable salt thereof, and Compound (2), or a pharmaceutically acceptable salt thereof, and optionally ribavirin, for the treatment of HCV infection (preferably (chronic) HCV genotype 1, for example subgenotype 1b, infection) in a patient

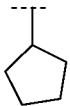
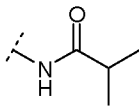
15 that has decompensated liver disease (for example decompensated liver cirrhosis) and/or

hepatic impairment, for example moderate hepatic impairment (such as e.g. defined by Child-Pugh B classification).

24. A kit for the treatment of HCV infection (preferably (chronic) HCV genotype 1,
 5 for example subgenotype 1b, infection) comprising:
 (a) one or more doses of the following Compound (1) or a pharmaceutically acceptable salt thereof:

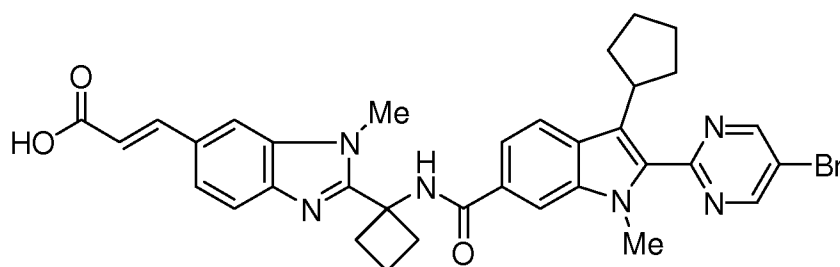


(1)

wherein **B** is ; **L**⁰ is MeO-; **L**¹ is Br; and **R**² is ;

and

- (b) one or more doses of the following Compound (2) or a pharmaceutically acceptable salt thereof:

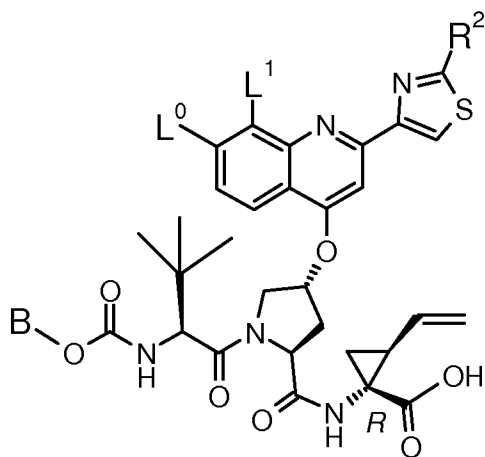


(2) ;

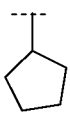
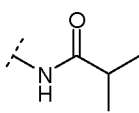
- 5 and written instructions directing the co-administration of Compound (1), or a pharmaceutically acceptable salt thereof, and Compound (2), or a pharmaceutically acceptable salt thereof, and optionally ribavirin for the treatment of HCV infection (preferably (chronic) HCV genotype 1, for example subgenotype 1b, infection) in a patient that has decompensated liver disease (for example decompensated liver cirrhosis) and/or
- 10 hepatic impairment, for example moderate hepatic impairment (such as e.g. defined by Child-Pugh B classification).

25. A compound of the following formula (1) or a pharmaceutically acceptable salt thereof:

15

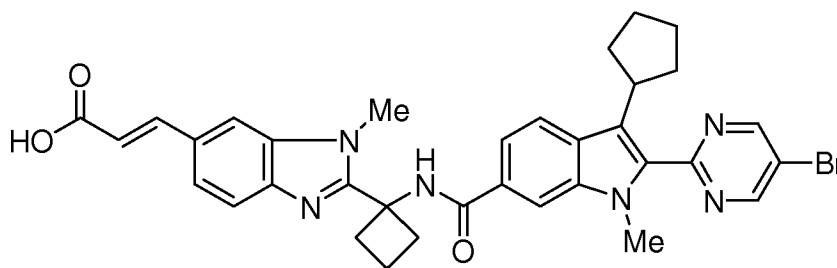


(1)

wherein **B** is ; **L**⁰ is MeO-; **L**¹ is Br; and **R**² is ,

for use in combination with a compound of the following formula (2) or a pharmaceutically acceptable salt thereof:

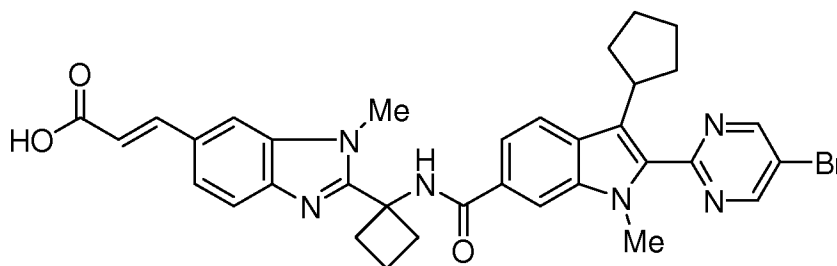
5



(2),

and optionally ribavirin, in a method for the treatment of HCV infection (preferably (chronic) HCV genotype 1, for example subgenotype 1b, infection) in a patient that has decompensated liver disease (for example decompensated liver cirrhosis) and/or hepatic impairment, for example moderate hepatic impairment (such as e.g. defined by Child-Pugh B classification).

26. A compound of the following formula (2) or a pharmaceutically acceptable salt thereof:



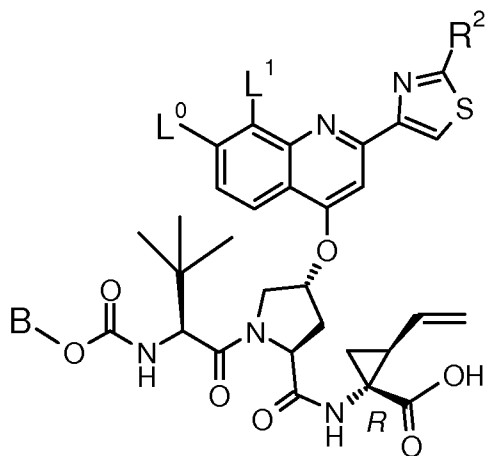
20

(2),

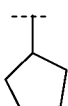
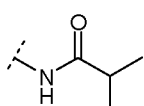
for use in combination with a compound of the following formula (1) or a pharmaceutically acceptable salt thereof:

5

10



(1)

wherein **B** is ; **L**⁰ is MeO-; **L**¹ is Br; and **R**² is ,

15 and optionally ribavirin, in a method for the treatment of HCV infection (preferably (chronic) HCV genotype 1, for example subgenotype 1b, infection) in a patient that has decompensated liver disease (for example decompensated liver cirrhosis) and/or hepatic impairment, for example moderate hepatic impairment (such as e.g. defined by Child-Pugh B classification).

20

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/021150

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K38/06 A61K31/4709 A61K31/506 A61K31/7056 A61P31/14
A61P1/16

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2013/147750 A1 (BOEHRINGER INGELHEIM INT [DE]; MENSA FEDERICO [US]) 3 October 2013 (2013-10-03) abstract; claims 1-25 ----- -/--	1,2,7-26



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

17 July 2014

Date of mailing of the international search report

28/07/2014

Name and mailing address of the ISA/

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

Authorized officer

Bazzanini, Rita

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2014/021150

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	S ZEUZEM ET AL: "SVR4 AND SVR12 WITH AN INTERFERON-FREE REGIMEN OF BI201335 AND BI207127 , +/- RIBAVIRIN , IN TREATMENT-NAIVE PATIENTS WITH CHRONIC GENOTYPE-1 HCV INFECTION: INTERIM RESULTS OF SOUND-C2.", JOURNAL OF HEPATOLOGY, vol. 56, no. Suppl. 2, 1 April 2012 (2012-04-01), - 22 April 2012 (2012-04-22), page S45, XP55127987, AMSTERDAM, NL ISSN: 0168-8278, DOI: 10.1016/S0168-8278(12)60115-9 abstract -----	1-3,7-26
X	V SORIANO ET AL: "THE EFFICACY AND SAFETY OF THE INTERFERON-FREE COMBINATION OF BI201335 AND BI207127 IN GENOTYPE 1 HCV PATIENTS WITH CIRRHOSIS - INTERIM ANALYSIS FROM SOUND-C2.", JOURNAL OF HEPATOLOGY, vol. 56, no. Suppl. 2, 1 April 2012 (2012-04-01), - 22 April 2012 (2012-04-22), page S559, XP55128460, AMSTERDAM, NL ISSN: 0168-8278, DOI: 10.1016/S0168-8278(12)61431-7 abstract -----	1-26
T	EVERSON G T ET AL: "The spectrum of hepatic functional impairment in compensated chronic hepatitis C: results from the Hepatitis C Anti-viral Long-term Treatment against Cirrhosis Trial", ALIMENTARY PHARMACOLOGY & THERAPEUTICS, BLACKWELL SCIENTIFIC PUBLICATIONS LTD., CAMBRIDGE, GB , vol. 27, no. 9 1 May 2008 (2008-05-01), pages 798-809, XP002681851, ISSN: 0269-2813, DOI: 10.1111/J.1365-2036.2008.03639.X Retrieved from the Internet: URL:http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2036.2008.03639.x/abstract [retrieved on 2008-02-08] page 798, paragraphs 4,5 page 799, left-hand column, paragraphs 1,3 page 806, left-hand column, paragraph 2 - right-hand column, paragraph 1 page 807, right-hand column, paragraph 2 -----	1-26

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2014/021150

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013147750	A1	03-10-2013	NONE
