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International application number: PCT/US2012/061085
International filing date: 19 October 2012 (19.10.2012)
Document type: Certified copy of priority document
Document details: Country/Office: US
Number: 61/550,360
Filing date: 21 October 2011 (21.10.2011)
Date of receipt at the International Bureau: 29 October 2012 (29.10.2012)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a), (b) or (b-bis)
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APPLICATION NUMBER: 61/550,360
FILING DATE: October 21, 2011
RELATED PCT APPLICATION NUMBER: PCT/US12/61085

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# Provisional Application for Patent Cover Sheet

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c)

## Inventor(s)

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All Inventors Must Be Listed – Additional Inventor Information blocks may be generated within this form by selecting the **Add** button.

## Title of Invention

METHODS FOR TREATING HCV

## Attorney Docket Number (if applicable)

24704US01

## Correspondence Address

Direct all correspondence to (select one):

- [ ] The address corresponding to Customer Number
- [ ] Firm or Individual Name

**Customer Number**

23446
The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

- No.
- Yes, the name of the U.S. Government agency and the Government contract number are:
Entity Status
Applicant claims small entity status under 37 CFR 1.27

- Yes, applicant qualifies for small entity status under 37 CFR 1.27
- No

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METHODS FOR TREATING HCV

FIELD OF THE INVENTION

[0001] The present invention relates to interferon-free and ribavirin-free treatment for HCV.

BACKGROUND OF THE INVENTION

[0002] The hepatitis C virus (HCV) is an RNA virus belonging to the Hepaciviruses genus in the Flaviviridae family. The enveloped HCV virion contains a positive stranded RNA genome encoding all known virus-specific proteins in a single, uninterrupted, open reading frame. The open reading frame comprises approximately 9500 nucleotides and encodes a single large polyprotein of about 3000 amino acids. The polyprotein comprises a core protein, envelope proteins E1 and E2, a membrane bound protein p7, and the non-structural proteins NS2, NS3, NS4A, NS4B, NS5A and NS5B.

[0003] HCV infection is associated with progressive liver pathology, including cirrhosis and hepatocellular carcinoma. Chronic hepatitis C may be treated with peginterferon-alpha in combination with ribavirin. Substantial limitations to efficacy and tolerability remain as many users suffer from side effects, and viral elimination from the body is often inadequate. Therefore, there is a need for new therapies to treat HCV infection.

BRIEF SUMMARY OF THE INVENTION

[0004] As one aspect of the present invention, methods for treating Hepatitis C Virus (HCV) infection in a subject are provided. The methods comprise administering at least two direct acting antiviral agents (DAAs) for a duration of twelve weeks or less, or for another duration as set forth herein. Preferably, the duration of administration is for eight weeks or less. Two or more direct acting antiviral agents (DAAs) are administered in amounts effective to provide a sustained virological response (SVR) another desired measure of effectiveness in a subject. The subject is not administered ribavirin during the duration of administering the at least two DAAs. Put another way, the methods exclude the administration of ribavirin to the subject. Preferably the subject is not administered interferon during the duration of administering the at least two DAAs. Put another way, the methods preferably exclude the
administration of interferon to the subject. In some embodiments, the methods further comprise administering an inhibitor of cytochrome P-450 (such as ritonavir) to the subject.

[0005] As another aspect, methods for treating Hepatitis C Virus (HCV) infection in a subject are provided. The methods comprise administering (a) therapeutic agent 1, (b) at least one polymerase inhibitor selected from the group consisting of therapeutic agent 2, therapeutic agent 3, and combinations thereof, (c) an inhibitor of cytochrome P-450 for a duration of twelve weeks or less, or for another duration as set forth herein. Therapeutic agent 1, the polymerase inhibitor(s), and the inhibitor of cytochrome P-450 are each administered in amounts effective to provide sustained virological response (SVR) or another measure of effectiveness in the subject.

[0006] As still another aspect, methods for treating a population of subjects having Hepatitis C Virus (HCV) infection are provided. The methods comprise administering at least two direct acting antiviral agents (DAAs) to the subjects for a duration of 12 weeks or less, wherein the at least two direct acting antiviral agents (DAAs) are administered to the subjects in amounts effective to result in sustained virological response (SVR) or another measure of effectiveness in at least about 70% of the population.

[0007] In the foregoing methods, the DAAs can be selected from the group consisting of protease inhibitors, nucleotide polymerase inhibitors, non-nucleotide polymerase inhibitors, NS3B inhibitors, NS4A inhibitors, NS5A inhibitors, NS5B inhibitors, cyclophilin inhibitors, and combinations of any of the foregoing. For example, in some embodiments, the DAAs used in the present methods comprise or consist of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor. The HCV polymerase inhibitor can be a nucleotide polymerase inhibitor or a non-nucleotide polymerase inhibitor.

[0008] In some embodiments, the HCV protease inhibitor is therapeutic agent 1 (described below) and the HCV polymerase inhibitor is therapeutic agent 2 and/or therapeutic agent 3 (also described below). By way of example, therapeutic agent 1 is administered a total daily dose of about 25 mg to about 250 mg or administered at least once daily at a dose of about 150 mg to about 250 mg, and therapeutic agent 2 is administered in a total daily dose of from about 300 mg to about 1800 mg or administered at least twice daily at doses of about 200 mg to about 400 mg. For some embodiments, the HCV protease inhibitor is therapeutic agent 1
and the non-nucleoside HCV polymerase inhibitor is therapeutic agent 3. By way of example, therapeutic agent 1 can be administered in a total daily dose of from about 25 mg to about 250 mg and therapeutic agent 3 can be administered in a daily dose of about 50 mg to about 1000 mg. Preferably, therapeutic agent 1 is administered at a total daily dose of about 250 mg and therapeutic agent 3 is administered at a total daily dose of 50 mg, alternatively 100 mg, alternatively 200 mg, alternatively 400 mg.

[0009] In some embodiments, the at least two DAAs comprise at least one HCV protease inhibitor and at least one NS5A inhibitor. Preferably, the HCV protease inhibitor is therapeutic agent 1 and the NS5A inhibitor is therapeutic agent 4. By way of example, therapeutic agent 1 can be administered at a total daily dosage of about 25 mg to about 250 mg, and therapeutic agent 4 can be administered in a total daily dose of about 25 mg to about 200 mg.

[0010] In the foregoing methods, the DAAs can be administered in any effective regimen, for example, they can each be administered daily. Each DAA can be administered either separately or in combination, and each DAA can be administered at least one a day, at least twice a day, or at least three times a day. In some preferred embodiments, therapeutic agent 3 is administered once daily or twice daily, and therapeutic agent 1 is administered once daily.

DETAILED DESCRIPTION OF THE INVENTION

[0011] The present methods can include administering therapeutic agent 1 to a subject. Therapeutic agent 1 is compound 1 or a pharmaceutically acceptable salt thereof. Compound 1 is also known as (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocycloprop[a]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14-a-carboxamide. Compound 1 is a potent HCV protease inhibitor. The synthesis and formulation of Compound 1 are described in U.S. Patent Application Publication No. 2010/0144608, U.S. Provisional Application Serial No. 61/339,964 filed on March 10, 2010, and U.S. Patent Application Serial No. 13/042,805 filed on March 8, 2011. All of these applications are incorporated herein by reference in their entireties. Therapeutic agent 1 includes various salts of compound 1. Therapeutic agent 1
may be administered in any suitable amount such as, for example, in doses of from about 0.01 to about 50 mg/kg body weight, alternatively from about 0.1 to about 25 mg/kg body weight. As non-limiting examples, therapeutic agent 1 may be administered in a total daily dose amount of from about 50-250 mg, preferably 100 mg-250 mg, and includes 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg and suitable amounts there between.

[0012] In preferred embodiments, ritonavir or another inhibitor of cytochrome P-450 is co-administered with therapeutic agent 1 to improve the pharmacokinetics of Compound 1.

[0013] The present methods can include administering therapeutic agent 2 to a subject. Therapeutic agent 2 is compound 2 or a salt thereof.

![Compound 2](image)

[0014] Compound 2 is also known N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl) methanesulfonamide as described in, for example, International Publication No. WO2009/039127, therapeutic agent 2 includes various salts of compound 2, such as sodium salts, potassium salts, and choline salts. Therapeutic agent 2 also includes crystalline forms of compound 2 and its salts such as solvate, hydrate, and solvent-free crystalline forms of compound 2 and its salts. Compositions comprising therapeutic agent 2 can be prepared as described in, for example, International Publication No. WO2009/039127 which is incorporated by reference herein.

[0015] Therapeutic agent 2 may be administered as a free acid, salt or particular crystalline form of compound 2. In embodiments, therapeutic agent 2 is administered as a sodium salt. Therapeutic agent 2 may be administered in any suitable amount such as, for example, in doses of from about 5 mg/kg to about 30 mg/kg. As non-limiting examples, therapeutic
agent 2 may be administered in a total daily dose amount of from about 300 mg to about 1800 mg, or from about 400 mg to about 1600 mg, or from about 600 mg to about 1800 mg, or from about 800 mg to about 1600 mg or any amounts there between. In embodiments, the total daily dosage amount for therapeutic agent 2 is about 300 mg. In embodiments, the total daily dosage amount for compound 2 is about 400 mg. In embodiments, the total daily dosage amount for therapeutic agent 2 is about 600 mg. In embodiments, the total daily dosage amount for therapeutic agent 2 is about 800 mg. In embodiments, the total daily dosage amount for therapeutic agent 2 is about 1200 mg. In embodiments, the total daily dosage amount for therapeutic agent 2 is about 1600 mg.

[0016] The present methods can include administering therapeutic agent 3 or a salt thereof to a subject. Therapeutic agent 3 is compound 3 or a salt thereof.

\[ \text{Compound 3} \]

[0017] Compound 3 is also known as (E)-N-(4-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxystyryl)phenyl)methanesulfonamide. As described in, for example, International Publication No. WO2009/039127, therapeutic agent 3 includes various salts of compound 3, such as sodium salts, potassium salts, and choline salts. Therapeutic agent 3 also includes crystalline forms of compound 3 and its salts such as solvate, hydrate, and solvent-free crystalline forms of compound 3 and its salts. Compositions comprising therapeutic agent 3 can be prepared as described in, for example, International Publication No. WO2009/039127 which is incorporated by reference herein.

[0018] Therapeutic agent 3 may be administered as a free acid, salt or particular crystalline form of compound 3. In embodiments, compound 3 is administered as a potassium salt.
Therapeutic agent 3 may be administered in any suitable amount such as, for example, in doses of from about 0.5 mg/kg to about 15 mg/kg or from about 1 mg/kg to about 10 mg/kg. As non-limiting examples, therapeutic agent 3 may be administered in a total daily dose amount of from about 50 mg to about 1000 mg or from about 100 mg to about 600 mg or from about 80 mg to about 320 mg or any amounts there between. In embodiments, the total daily dosage amount for therapeutic agent 3 is about 80 mg. In embodiments, the total daily dosage amount for therapeutic agent 3 is about 100 mg. In embodiments, the total daily dosage amount for therapeutic agent 3 is about 160 mg. In embodiments, the total daily dosage amount for therapeutic agent 3 is about 300 mg. In embodiments, the total daily dosage amount for therapeutic agent 3 is about 320 mg. In embodiments, the total daily dosage amount for therapeutic agent 3 is about 600 mg.

[0019] The present methods can include administering therapeutic agent 4 or a salt thereof to a subject. Therapeutic agent 4 is compound 4 or a salt thereof.

![Compound 4](image)

[0020] Compound 4 is also known as dimethyl (2S,2’S)-1,1’-(2S,2’S)-2,2’-(4,4’-(2S,5S)-1-(4-tert-butylphenyl)pyrrolidine-2,5,diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl)bis(3-methyl-1-oxobutane-2,1-diyl)dicarboximate. Compound 4 can be prepared as described in, for example, U.S. Publication No. 2010/0317568, which is incorporated herein by reference.

[0021] Therapeutic agent 4 may be administered as a free acid, or a salt form. Therapeutic agent 4 may be administered in any suitable amount such as, for example, in doses of from about 0.1 mg/kg to about 200 mg/kg body weight, or from about 0.25 mg/kg to about 100 mg/kg, or from about 0.3 mg/kg to about 30 mg/kg. As non-limiting examples, therapeutic agent 4 may be administered in a total daily dose amount of from about 5 mg to about 300
mg, or from about 25 mg to about 200 mg, or from about 25 mg to about 50 mg or any amounts there between. In embodiments, the total daily dosage amount for therapeutic agent 4 is about 25 mg. In embodiments, the total daily dosage amount for therapeutic agent 4 is about 50 mg.

[0022] The current standard of care (SOC) for the treatment of hepatitis C virus (HCV) includes a course of treatment of interferon, e.g. pegylated interferon (e.g., pegylated interferon-alpha-2a or pegylated interferon-alpha-2b, such as PEGASYS by Roche, or Peg-Interon by Schering-Plough) and the antiviral drug ribavirin (e.g., COPEGUS by Roche, Rebetol by Schering-Plough, or RIBASPHERE by Three Rivers Pharmaceuticals). The treatment often lasts for 24-48 weeks, depending on hepatitis C virus genotype. Other interferons include, but are not limited to, interferon-alpha-2a (e.g., Roferon-A by Roche), interferon-alpha-2b (e.g., Intron-A by Schering-Plough), and interferon alfacon-1 (consensus interferon) (e.g., Infergen by Valeant). Less than 50% of patients with chronic hepatitis C infection respond to this therapy. Further, interferon therapy has many side effects that hinder patient compliance and results in premature discontinuation of the treatment.

[0023] The interferon/ribavirin-based treatment may be physically demanding, and can lead to temporary disability in some cases. A substantial proportion of patients will experience a panoply of side effects ranging from a “flu-like” syndrome (the most common, experienced for a few days after the weekly injection of interferon) to severe adverse events including anemia, cardiovascular events and psychiatric problems such as suicide or suicidal ideation. The latter are exacerbated by the general physiological stress experienced by the patients.

[0024] The present methods provide effective treatment of Hepatitis C Virus infection without the use of interferon or ribavirin and for a shorter period of time, specifically a treatment duration of twelve weeks or less, alternatively eleven weeks or less, alternatively ten weeks or less, alternatively nine weeks or less, alternatively eight weeks or less, alternatively seven weeks or less, alternatively six weeks or less, alternatively five weeks or less, alternatively four weeks or less, or alternatively, three weeks or less.

[0025] In some embodiments, the present technology provides methods for treating Hepatitis C Virus (HCV) infection in a subject comprising administering at least two direct acting antiviral agents (DAAs) in the absence of interferon and ribavirin for a duration of twelve
weeks or less, alternatively eight weeks or less. Put another way, the present methods exclude interferon and ribavirin, or the subject does not receive interferon or ribavirin for the duration of the treatment. The at least two DAAs can be co-administered or can be administered independently and can be administered at least once a day, alternatively twice a day, alternatively three times a day.

[0026] In some embodiments, the methods of treatment comprise daily administration of two or more direct acting antiviral agents (DAAs), wherein a first DAA may be administered at least once a day, twice a day, or three times a day, and a second DAA may be administered once a day, twice a day, or three times a day. In some embodiments, a third DAA may be administered at least once a day, at least twice a day, or three times a day. The DAAs may be co-administered or administered at different times. Preferably, in the methods, at least two DAAs are administered in effective amounts to provide a desired measure of effectiveness in the subject. Preferably, the treatment has reduced side effects as compared with interferon treatments.

[0027] Various measures may be used to express the effectiveness of the present methods of HCV treatment. One such measure is rapid virological response (RVR), meaning that HCV is undetectable in the subject after 4 weeks of treatment, for example, after 4 weeks of administration of two or more of DAAs. Another measure is early virological response (EVR), meaning that the subject has >2log reduction in viral load after 12 weeks of treatment. Another measure is complete EVR (cEVR), meaning the HCV is undetectable in the serum of the subject after 12 weeks of treatment. Another measure is extended RVR (eRVR), meaning achievement of RVR and cEVR, that is, HCV is undetectable at week 4 and 12. Another measure is the presence or absence of detectable virus at the end of therapy (EOT). Another measure is sustained virological response (SVR), meaning that the virus is undetectable at the end of therapy and for 24 weeks after the end of therapy.

[0028] In some embodiments, the amounts of the two or more DAAs, and/or the duration of administration of the two or more DAAs, are effective to provide a rapid virological response (RVR) in a subject, or an early virological response (EVR) in a subject, or a complete EVR (cEVR) in a subject, or an extended RVR (eRVR) in a subject, or an absence of detectable virus at the end of therapy (EOT) in a subject. In some embodiments, the present methods
comprise treating a population of subjects having Hepatitis C Virus (HCV) infection, and the methods comprise administering at least two direct acting antiviral agents (DAAs) to the subjects for a duration of 12 weeks or less, or for another duration disclosed herein, wherein the at least two direct acting antiviral agents (DAAs) are administered to the subjects in amounts effective to provide a sustained virological response (SVR) in at least about 70% of the population, alternatively at least about 75% of the population, alternatively at least about 80% of the population, alternatively at least about 85% of the population, alternatively at least about 90% of the population, alternatively at least about 95% of the population, alternatively about 100% of the population. In other embodiments, the amount of direct acting antiviral agents (DAAs) and the duration of administration are effective to provide one or more of an SVR, an RVR, an EVR, a cEVR, an eRVR, or an absence of detectable virus at EOT, in at least about 70% of the population, alternatively at least about 75% of the population, alternatively at least about 80% of the population, alternatively at least about 85% of the population, alternatively at least about 90% of the population, alternatively at least about 95% of the population, alternatively about 100% of the population. For example, the present methods comprise administering at least two DAAs in amounts and for durations effective to provide a sustained virological response (SVR) in a subject. The present technology provides for a sustained virological response (SVR) of at least about 70% or higher SVR, preferably about 75% or higher SVR in patients treated by such methods herein described, more preferably at least 80% or higher SVR, and highly preferably at least 90% SVR. In some embodiments, the effective treatment of the present technology provides a rapid virological response (RVR) or undetectable level of HCV RNA in the bloodstream four (4) weeks of treatment in addition to a SVR.

[0029] A direct acting antiviral agent (DAA) of the present technology includes, but is not limited to, a protease inhibitor, a HCV polymerase inhibitor, an HCV NS5A inhibitor, an HCV NS5B inhibitor, an HCV NS4A inhibitor, an HCV NS5B inhibitor, an HCV entry inhibitor, a cyclophilin inhibitor, a CD81 inhibitor, or an internal ribosome entry site inhibitor. The HCV polymerase inhibitors may be a nucleoside polymerase inhibitor or a non-nucleoside polymerase inhibitor.

[0030] In yet another example of this aspect of the technology, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of
two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telaprevir and VX-222.

[0031] In another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs. The treatment lasts 7 weeks and does not include administration of any interferon or any ribavirin. The DAAs can be administered at the same or different dosing frequency. The patient being treated can be a naïve patient, or a non-interferon responder. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside polymerase inhibitor and at least one non-nucleoside inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and
Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 3 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telprevir and VX-222.

[0032] In yet another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs. The treatment lasts 6 weeks and does not include administration of any interferon or any ribavirin. The DAAs can be administered at the same or different dosing frequency. The patient being treated can be a naïve patient, or a non-interferon responder. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside polymerase inhibitor and at least one non-nucleoside inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt
thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 3 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telpruvir and VX-222.

[0033] In yet another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs. The treatment lasts 5 weeks and does not include administration of any interferon or any ribavirin. The DAAs can be administered at the same or different dosing frequency. The patient being treated can be a naïve patient, or a non-interferon responder. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor, or at least one nucleoside polymerase inhibitor and at least one non-nucleoside inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one
HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 3 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telaprevir and VX-222.

[0034] In yet another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs. The treatment lasts 4 weeks and does not include administration of any interferon or any ribavirin. The DAAs can be administered at the same or different dosing frequency. The patient being treated can be a naïve patient, or a non-interferon responder. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and
at least one nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside polymerase inhibitor and at least one non-nucleoside inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telprevir and VX-222.

[0035] In yet another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs. The treatment lasts 3 weeks (or even less, depending on the patient’s condition) and does not include administration of any interferon or any ribavirin. The DAAs can be administered at the same or different dosing frequency. The patient being treated can
be a naïve patient, or a non-interferon responder. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside polymerase inhibitor, and at least one non-nucleoside inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-
207127. In yet another example, the combination of two or more DAAs comprises telprevir and VX-222.

[0036] In yet another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs. The treatment lasts 12 weeks and does not include administration of any interferon or any ribavirin. The DAAs can be administered at the same or different dosing frequency. The patient being treated can be a naïve patient, or a non-interferon responder. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside polymerase inhibitor and at least one non-nucleoside inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 3 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another
example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telprevir and VX-222.

[0037] In yet another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs. The treatment lasts 11 weeks and does not include administration of any interferon or any ribavirin. The DAAs can be administered at the same or different dosing frequency. The patient being treated can be a naïve patient, or a non-interferon responder. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside polymerase inhibitor and at least one non-nucleoside inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a
combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 3 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telprevir and VX-222.

[0038] In yet another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs. The treatment lasts 10 weeks and does not include administration of any interferon or any ribavirin. The DAAs can be administered at the same or different dosing frequency. The patient being treated can be a naïve patient, or a non-interferon responder. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside polymerase inhibitor and at least one non-nucleoside inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or
more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 3 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises teliprevir and VX-222.

[0039] In yet another aspect, the present technology features a method of treating HCV, comprising administering to a patient in need thereof an effective amount of a combination of two or more DAAs. The treatment lasts 9 weeks and does not include administration of any interferon or any ribavirin. The DAAs can be administered at the same or different dosing frequency. The patient being treated can be a naïve patient, or a non-interferon responder. Each DAA can be selected from HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. For instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor (e.g., a combination of at least one HCV protease inhibitor and at least one non-nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor and at least one nucleoside polymerase inhibitor, or a combination of at least one HCV protease inhibitor, at least one nucleoside polymerase inhibitor and at least one non-nucleoside inhibitor). For another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor and at least one HCV NS5A inhibitor. For still
another instance, the combination of two or more DAAs can be a combination of at least one HCV protease inhibitor, at least one HCV polymerase inhibitor, and at least one HCV NS5A inhibitor. In one example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 3 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In still another example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In a further example, the combination of two or more DAAs is a combination of Compound 1 (or a salt thereof), Compound 2 (or a salt thereof) and Compound 4 (or a salt thereof). Compound 1 (or a salt thereof) can be co-formulated with ritonavir. In yet another example, the combination of two or more DAAs comprises PSI-7977 and PSI-938. In yet another example, the combination of two or more DAAs comprises PSI-7977 and TMC-435. In yet another example, the combination of two or more DAAs comprises BMS-790052 and BMS-650032. In yet another example, the combination of two or more DAAs comprises GS-5885, GS-9190, and GS-9451. In yet another example, the combination of two or more DAAs comprises BI-201335 and BI-207127. In yet another example, the combination of two or more DAAs comprises telprevir and VX-222.

[0040] In some embodiments, the present technology provides a method of treating Hepatitis C virus infection in a subject comprising administering daily a HCV protease inhibitor and a HCV polymerase inhibitor to the subject in the absence of interferon for a duration of twelve weeks or less, preferably eight weeks or less. In some embodiments, ritonavir (or an equivalent thereof) is co-administered with one or more protease inhibitors to improve the pharmacokinetics of the protease inhibitor(s). The treatment excludes administering ribavirin to the patient. In some embodiments, the HCV polymerase inhibitor is at least one nucleoside polymerase inhibitor or at least one non-nucleoside polymerase inhibitor. In
some embodiments, both a nucleoside polymerase inhibitors and a non-nucleoside polymerase inhibitor may be administered.

[0041] In some embodiments, a cytochrome P-450 inhibitor, e.g. ritonavir, is administered either in the same or separate pharmaceutical composition with the protease inhibitor (e.g. Compound 1 (or a pharmaceutically acceptable salt thereof)) to improve the pharmacokinetics. A cytochrome P450 inhibitor reduces the metabolism of protease inhibitors, such as Compound 1, thereby improving the pharmacokinetic and bioavailability of the protease inhibitor, for example Compound 1. More preferably, Compound 1 (or a pharmaceutically acceptable salt thereof) is co-formulated with ritonavir in the same dosage form. Other cytochrome P450 inhibitors, such as cobicistat, may also be administered in lieu of ritonavir, to enhance the pharmacokinetics of Compound 1 (or a pharmaceutically acceptable salt thereof).

[0042] Inhibitors of cytochrome P450, such as ritonavir, may be co-administered with the DAAs, either sequentially or simultaneously, in the same or different compositions. In embodiments, the cytochrome P450 inhibitors are administered in order to improve the pharmacokinetics of at least one of the DAAs. In embodiments, ritonavir is co-administered with therapeutic agent 1. In embodiments, ritonavir is co-administered with therapeutic agent 1 in the same compositions.

[0043] In some embodiments, the present technology provides a method of treating HCV infection comprising administering at least one protease inhibitor and at least one HCV polymerase inhibitor in a course of treatment of less than eight weeks in the absence of interferon. In some embodiments, the HCV polymerase inhibitor is Compound 1 ((or a pharmaceutically acceptable salt thereof).

[0044] Compound 1 is (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-((5-methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide. The synthesis and formulation of Compound 1 are described in U.S. Patent Application Publication No. 20100144608, U.S. Provisional Application Serial No. 61/339,964 filed on March 10, 2010, and U.S. Patent
Application Serial No. 13/042,805 filed on March 8, 2011. All of these applications are incorporated herein by reference in their entireties.

[0045] In some embodiments, the present technology provides a method of treating HCV infection comprising administering at least two DAAs, wherein the at least two DAAs include at least one protease and at least one HCV polymerase. In some embodiments, the at least two DAAs includes Compound I with at least one HCV polymerase inhibitor. In some embodiments, the HCV polymerase inhibitor is at least one non-nucleoside polymerase inhibitor. In some embodiments, the non-nucleoside polymerase inhibitor is therapeutic agent 2 or therapeutic agent 3 or a combination thereof.

[0046] In some embodiments, the present technology provides a method of treating HCV infection comprising administering a protease inhibitor, preferably therapeutic agent 1, with at least one NS5A inhibitor. In some embodiments, NS5A inhibitor is therapeutic agent 4.

[0047] In some embodiments of the present technology, a method of treating HCV infection comprises administering at least three DAAs to a subject for 8 weeks or less without administering interferon. The at least three DAAs can be at least one protease inhibitor, at least one HCV polymerase inhibitor, and at least one NS5A inhibitors. In a preferred embodiment, the at least one protease inhibitor is therapeutic agent 1, the at least one polymerase inhibitor is therapeutic agent 2 or therapeutic agent 3, and the at least one NS5A inhibitor is therapeutic agent 4.

[0048] Preferred HCV protease inhibitors include, but are not limited to, therapeutic agent 1, telaprevir (Vertex), boceprevir (Merk), BI-201335 (Boehringer Ingelheim), GS-9451 (Gilead), and BMS-650032 (BMS). Other suitable protease inhibitors include, but are not limited to, ACH-1095 (Achillion), ACH-1625 (Achillion), ACH-2684 (Achillion), AVL-181 (Avila), AVL-192 (Avila), BMS-650032 (BMS), danoprevir, GS-9132 (Gilead), GS-9256 (Gilead), IDX-136 (Idenix), IDX-316 (Idenix), IDX-320 (Idenix), MK-5172 (Merck), narlaprevir, PHX-1766 (Phenomix), telaprevir, TMC-435 (Tibotec), vaniprevir, VBY708 (Virobay), VX-500 (Vertex), VX-813 (Vertex), VX-985 (Vertex), or a combination thereof.

[0049] Preferred non-nucleoside HCV polymerase inhibitors for use in the present technology include, but are not limited to, therapeutic agent 2, therapeutic agent 3, GS-9190 (Gilead), BI-207127 (Boehringer Ingelheim), and VX-222 (VCH-222) (Vertex &
ViraChem). Preferred nucleoside HCV polymerase inhibitors include, but are not limited to, PSI-7977 (Pharmasset), and PSI-938 (Pharmasset). Other suitable and non-limiting examples of suitable HCV polymerase inhibitors include ANA-598 (Anadys), BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-791325 (BMS), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-9669 (Gilead), IDX-375 (Idenix), MK-3281 (Merck), tegobuvir, TMC-647055 (Tibotec), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-759 (Vertex), GS-6620 (Gilead), IDX-102 (Idenix), IDX-184 (Idenix), INX-189 (Inhibitex), MK-0608 (Merck), RG7128 (Roche), TMC64912 (Medivir), GSK625433 (GlaxoSmithKline), BCX-4678 (BioCryst), ALS-2200 (Alios BioPharma/Vertex), ALS-2158 (Alios BioPharma/Vertex), or a combination thereof. A polymerase inhibitor may be a nucleotide polymerase inhibitor, such as GS-6620 (Gilead), IDX-102 (Idenix), IDX-184 (Idenix), INX-189 (Inhibitex), MK-0608 (Merck), PSI-7977 (Pharmasset), PSI-938 (Pharmasset), RG7128 (Roche), TMC64912 (Medivir), ALS-2200 (Alios BioPharma/Vertex), ALS-2158 (Alios BioPharma/Vertex), or a combination therefore. A polymerase inhibitor may also be a non-nucleoside polymerase inhibitor, such as PF-00868554 (Pfizer), ANA-598 (Anadys), BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-791325 (BMS), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-9669 (Gilead), IDX-375 (Idenix), MK-3281 (Merck), tegobuvir, TMC-647055 (Tibotec), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-222 (VCH-222) (Vertex & ViraChem), VX-759 (Vertex), or a combination thereof.

[0050] Preferred NS5A inhibitors include, but are not limited to, therapeutic agent 4, BMS-790052 (BMS) and GS-5885 (Gilead). Non-limiting examples of suitable NS5A inhibitors include GSK62336805 (GlaxoSmithKline), ACH-2928 (Achillion), AZD2836 (AstraZeneca), AZD7295 (AstraZeneca), BMS-790052 (BMS), BMS-824393 (BMS), GS-5885 (Gilead), PPI-1301 (Presidio), PPI-461 (Presidio) A-831 (Arrow Therapeutics), A-689 (Arrow Therapeutics) or a combination thereof.

[0051] Non-limiting examples of suitable cyclophilin inhibitors include alisporovir (Novartis & Debiopharm), NM-811 (Novartis), SCY-635 (Scynexis), or a combination thereof.

[0052] Non-limiting examples of suitable HCV entry inhibitors include ITX-4520 (iTherx), ITX-5061 (iTherx), or a combination thereof.
The chemical structures of some of these HCV inhibitors are provided below:

Telaprevir

BI-201335
TMC-435 (TMC-435350)

Vaniprevir, MK-7009

BMS-650032 (Asunaprevir)
Tegobuvir

GS-333126 (GS-9190 or tegobuvir)

GS-0451

GS-9451

Mericitabine (R-4048)
BMS-790052 (daclatasvir)

Daclatasvir dihydrochloride

BIT-225
[0054] The following table lists non-limiting examples of the treatment regimens of the present technology. In each treatment regimen, the at least two DAA with or without ritonavir, are administered daily to an HCV patient under such treatment. Each treatment is interferon-free and ribavirin-free. Each treatment regimen may also optionally comprise administering one or more other additional DAAs to the patient. The duration of each treatment regimen may last, for example and without limitation, 12 weeks or less, at least 11 weeks or less, at least 10 weeks or less, at least 9 weeks or less, at least 8 weeks or less, alternatively 7 weeks or less, alternatively 6 weeks or less, alternatively 5 weeks or less, alternatively 4 weeks or less and may depend on the patient’s response. In any given regimen described below, the drugs can be, for example and without limitation, co-formulated in a single solid dosage form.

[0055] For instance, all drugs used in a regimen can be co-formulated in amorphous forms or molecularly dispersed in a matrix comprising a water-soluble polymer and optionally a surfactant; for another instance, therapeutic agent 1 and ritonavir (RTV) are formulated in an amorphous form or molecularly dispersed in a matrix comprising a water-soluble polymer and optionally a surfactant, and the other drug(s) are in crystalline form(s) and combined with amorphous Compound 1 and RTV in a single solid dosage form. For yet another instance, Compound 1 and RTV are formulated in a different dosage form than the other drug(s).
Non-Limiting Examples of Interferon-free and Ribavirin-free Treatment Regimens with two or more DAAs (with or without ritonavir)

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<th>Drugs Used in Treatment</th>
<th>Suitable total daily dosages</th>
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<tr>
<td>1</td>
<td>Therapeutic Agent 1 +</td>
<td>150-250 mg (pref. 250 mg)</td>
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<tr>
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<td>Therapeutic Agent 2</td>
<td>5-300 mg (pref. 25 mg)</td>
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<tr>
<td></td>
<td>Therapeutic Agent 4 +</td>
<td>150-250 mg (pref. 250 mg)</td>
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<td>5-300 mg (pref. 200 mg)</td>
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<td>2</td>
<td>Therapeutic Agent 1 +</td>
<td>150-250 mg (pref. 250 mg)</td>
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<tr>
<td></td>
<td>Therapeutic Agent 2 +</td>
<td>5-300 mg (pref. 25-200 mg)</td>
</tr>
<tr>
<td></td>
<td>Therapeutic Agent 2</td>
<td>300-1800 mg (pref. 400 mg)</td>
</tr>
<tr>
<td>3</td>
<td>Therapeutic Agent 1 +</td>
<td>150-250 mg (pref. 250 mg)</td>
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<tr>
<td></td>
<td>Therapeutic Agent 3 +</td>
<td>50-1000 mg (pref. 400 mg)</td>
</tr>
<tr>
<td></td>
<td>Therapeutic Agent 4</td>
<td>5-300 mg (pref. 25-200, more pref. 25 mg)</td>
</tr>
<tr>
<td>4</td>
<td>Therapeutic Agent 1 +</td>
<td>150-250 mg (pref. 250 mg or 200 mg)</td>
</tr>
<tr>
<td></td>
<td>Therapeutic Agent 2</td>
<td>300-1800 mg (pref. 800 mg)</td>
</tr>
<tr>
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<td>Therapeutic Agent 1 +</td>
<td>150-250 mg (pref. 250 mg or 200 mg)</td>
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<tr>
<td></td>
<td>Therapeutic Agent 2</td>
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<td>50-250 mg (pref. 200 mg)</td>
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<td>Therapeutic Agent 3</td>
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<td>7</td>
<td>Therapeutic Agent 1 +</td>
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<td>Therapeutic Agent 3</td>
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<td></td>
<td></td>
<td>300-1500 mg (pref. 1200 mg)</td>
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<td>11</td>
<td>GS-5885+ GS-9190+ GS-9451</td>
<td>3-200 mg (pref. 30-90 mg)</td>
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<td></td>
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<td>30-90 mg (pref. 60 mg)</td>
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<td>100-500 mg (pref. 200 mg)</td>
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<td>3-200 mg (pref. 30-90 mg)</td>
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<tr>
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<td>BI-201335 + BI-207127</td>
<td>100-400 mg (pref. 120 or 240 mg)</td>
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<td>300-3600 mg (pref. 1200-2100 mg)</td>
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<td>25-200 mg (pref. 75-150 mg)</td>
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<tr>
<td>15</td>
<td>telaprevir + VX-222</td>
<td>1000-2500 mg (pref. 2250 mg)</td>
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<tr>
<td></td>
<td></td>
<td>200-800 mg</td>
</tr>
</tbody>
</table>

* ritonavir or a suitable equivalent can be added to any one of these treatments as described may be added to any of these treatments at a daily total dosage as described in the present technology.

[0056] The treatments of the present technology may be effective in treating HCV infection against HCV genotypes 1, 2, 3, 4, 5, 6, including subgenotypes, such as 1a, 1b, 2a, and 3a.

[0057] In general, the total daily dose of the DAAs of the present technology may be administered (either as a single or divided dose) in amounts from about 0.001 mg/kg to about 200 mg/kg, or from about 0.001 mg/kg to about 30 mg/kg, or from about 0.001 mg/kg to
about 30 mg/kg, or from about 0.01 mg/kg, to about 10 mg/kg (i.e. mg of the compound or salt per kg body weight), and include any amounts or ranges there between, including, but not limited to increments of 0.001 mg/kg, 0.005 mg/kg, 0.01 mg/kg, 0.05 mg/kg, and multiple factors thereof (e.g. 0.25x, 0.5x, 1x, 2x, 3x, 5x, 10x, 100x, etc). Suitable dosages of the DAAs of the present technology include, but are not limited to, about 25 mg to about 2000 mg, about 25 mg to about 1500 mg, about 25 mg to about 1600 mg, about 25 mg to about 1000 mg, about 25 mg to about 800 mg, about 25 mg to about 500 mg, about 25 mg to about 250 mg, 50 mg to about 2000 mg, about 50 mg to about 1500 mg, about 50 mg to about 1600 mg, about 50 mg to about 1000 mg, about 50 mg to about 800 mg, about 50 mg to about 500 mg, about 50 mg to about 250 mg, and include about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 80 mg, about 90 mg, about 95 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 165 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 250 mg, and includes any increments there between, including increments of about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 10 mg, about 15 mg, about 20 mg, about 25, and multiples thereof (e.g. 0.25x, 0.5x, 1x, 2x, 3x, 5x, 10x, 100x, etc).

[0058] The cytochrome P-450 inhibitor may be administered in any suitable amount such as, for example, in doses of from about 0.3 mg/kg to about 2 mg/kg or from about 0.6 mg/kg to about 1.5 mg/kg. As non-limiting examples, the cytochrome P-450 inhibitor may be administered in a total daily dose amount of from about 25 mg to about 300 mg, or from about 50 mg to about 250 mg, or from about 100 mg to about 200 mg. In embodiments, the cytochrome P-450 inhibitor is administered in a total daily dose amount of about 25 mg. In embodiments, the cytochrome P-450 inhibitor is administered in a total daily dose amount of about 50 mg. In embodiments, the cytochrome P-450 inhibitor is administered in a total daily dose amount of about 75 mg. In embodiments, the cytochrome P-450 inhibitor is administered in a total daily dose amount of about 100 mg. In embodiments, the cytochrome P-450 inhibitor is administered in a total daily dose amount of about 125 mg.

[0059] The one or more DAAs can be administered, for example and without limitation, concurrently or sequentially. For instance, For example, a first DAA can be administered
immediately before or after the administration of the other DAA. A short delay or time gap may exist between the administration of the at least one DAA and ritonavir and that of the another DAA. The frequency of administration may also be different. For example, a first DAA may be administered once a day and a second DAA may be administered twice or three times a day. For example, a first DAA with or without ritonavir may be administered once daily, and a second DAA may be administered twice daily.

[0060] The DAAs of the present technology be co-formulated in a single dosage form. Non-limiting examples of suitable dosage forms include liquid or solid dosage forms. For example, a dosage form of compound 1 as a solid dosage form is described in U.S. Patent Application Serial No. 13/042,805, filed March 8, 2011 and entitled "Solid Compositions", the entire content of which is incorporated herein by reference. More preferably, the dosage form is a solid dosage form in which at least one of the DAAs is in an amorphous form, or highly preferably molecularly dispersed, in a matrix which comprises a pharmaceutically acceptable water-soluble polymer and a pharmaceutically acceptable surfactant. The other DAAs can also be in an amorphous form or molecularly dispersed in the matrix, or formulated in different form(s) (e.g., in a crystalline form).

[0061] The DAAs of the present technology can be formulated in different dosage forms. It will be understood that the total daily usage of the compounds and compositions to be administered will be decided by the attending physician within the scope of sound medical judgment.

[0062] Specific examples of other DAA agents that are suitable for the present methods include, but are not limited to, AP-H005, A-831 (Arrow Therapeutics) (NS5A inhibitor), A-689 (Arrow Therapeutics) (NS5A inhibitor), INX08189 (Inhibitex) (polymerase inhibitor), ITMN-191 (Intermune/Roche) (NS3/4A Protease inhibitor), VBY-376 (Protease Inhibitor) (Virobay), ACH-1625 (Achillion, Protease inhibitor), IDX136 (Idenex, Protease Inhibitor), IDX316, VX-813 (Vertex), SCH 900518 (Schering-Plough), TMC-435 (Tibotec), ITMN-191 (Intermune, Roche), MK-7009 (Merck), IDX-PI (Novartis), R7128 (Roche), PF-868554 (Pfizer) (non-nucleoside polymerase inhibitor), PF-4878691 (Pfizer), IDX-184 (Novartis), IDX-375 (Pharmaasset), PPI-461 (Presidio), BILB-1941 (Boehringer Ingelheim), GS-9190 (Gilead), BMS-790052 (BMS), CTS-1027 (Conatus), GS-9620 (Gilead), PF-4878691
(Pfizer), RO5303253 (Roche), ALS-2200 (Alios BioPharma/Vertex), ALS-2158 (Alios BioPharma/Vertex), GSK62336805 (GlaxoSmithKline), or any combinations thereof.

[0063] In one embodiment, a method for treating a naïve subject comprises administering Therapeutic agent 1 at a dose of 150 mg, Therapeutic agent 2 at a dose of 400 mg, and ritonavir at a dose of 100 mg, once a day for 12 weeks. At the end of treatment, the subject has no detectable virus.

[0064] In one embodiment, a method for treating a naïve subject comprises administering Therapeutic agent 1 at a dose of 250 mg, Therapeutic agent 3 at a dose of 400 mg, and ritonavir at a dose of 100 mg, once a day for 12 weeks. At the end of treatment, the subject has no detectable virus.

[0065] In another embodiment, a method for treating a naïve subject comprises administering Therapeutic agent 1 at a dose of 150 mg, Therapeutic agent 3 at a dose of 400 mg, and ritonavir at a dose of 100 mg, once a day for 12 weeks. At the end of treatment, the subject has no detectable virus.

[0066] In yet another embodiment, a method for treating a peginterferon + ribavirin (P/RBV) non-responder comprises administering Therapeutic agent 1 at a dose of 150 mg, Therapeutic agent 3 at a dose of 400 mg, and ritonavir at a dose of 100 mg, once a day for 12 weeks.

[0067] It should be understood that the above-described embodiments and examples are given by way of illustration, not limitation. Various changes and modifications within the scope of the present invention will become apparent to those skilled in the art from the present description.
CLAIMS

1. A method for treating Hepatitis C Virus (HCV) infection in a subject comprising administering at least two direct acting antiviral agents (DAAs) for a duration of twelve weeks or less,

   wherein the at least two direct acting antiviral agents (DAAs) are administered in an amount effective to result in sustained virological response (SVR).

2. The method of claim 1, wherein the subject is not administered interferon during the duration of administering the at least two DAAs.

3. The method of claim 1, wherein the method further comprises administering an inhibitor of cytochrome P450 to the subject.

4. The method of claim 1, wherein the at least two DAAs are administered daily.

5. The method of claim 1, wherein each DAA is administered either separately or in combination, and wherein each DAA is administered at least once a day, at least twice a day, or at least three times a day.

6. The method of claim 1, wherein the subject is not administered ribavirin during the duration of administering the at least two DAAs.

7. The method of claim 1, wherein the duration is eight weeks or less.

8. The method of claim 1, wherein the at least two DAAs is selected from the group consisting of protease inhibitors, nucleotide polymerase inhibitors, non-nucleotide polymerase inhibitors, NS3B inhibitors, NS4A inhibitors, NS5A inhibitors, NS5B inhibitors, and cyclophillin inhibitors.
9. The method of claim 1, wherein the at least two DAAs comprise at least one HCV protease inhibitor and at least one HCV polymerase inhibitor.

10. The method of claim 9, wherein the at least one HCV protease inhibitor is selected from the group consisting of therapeutic agent 1, telaprevir, boceprevir, BI-201335, GS-9451, BMS-650032, and combinations thereof.

11. The method of claim 9, wherein the at least one HCV polymerase inhibitor is at least one nucleotide polymerase inhibitor or at least one non-nucleotide polymerase inhibitor.

12. The method of claim 11, wherein the at least one nucleotide polymerase inhibitor is selected from the group consisting of PSI-7977, PSO-938, PSI-7977 and combinations thereof.

13. The method of claim 11, wherein the at least one non-nucleotide polymerase inhibitor is selected from the group consisting of therapeutic agent 2, therapeutic agent 3, GS-9190, BI-207127, VX-222 and combinations thereof.

14. The method of claim 10, wherein the HCV polymerase inhibitor is therapeutic agent 1 and the at least one HCV polymerase inhibitor is therapeutic agent 2.

15. The method of claim 14, wherein therapeutic agent 1 is administered a total daily dose of about 25 mg to about 250 mg and wherein therapeutic agent 2 is administered a total daily dose from about 300 mg to about 1800 mg.

16. The method of claim 15, wherein therapeutic agent 1 is administered at least once daily at about 150 mg to about 250 mg and therapeutic agent 2 is administered at least twice daily at about 200 mg to about 400 mg.
17. The method of any of claims 14-16, wherein ritonavir is administered at least once a day at about 50 mg-100 mg.

18. The method of claim 11, wherein the HCV protease inhibitor is therapeutic agent 1 and the non-nucleoside HCV polymerase inhibitor is therapeutic agent 3.

19. The method of claim 18, wherein therapeutic agent 1 is administered in a total daily dose of from about 25 mg to about 250 mg and wherein therapeutic agent 3 is administered in a daily dose of about 50 mg to about 1000 mg.

20. The method of claim 19, wherein therapeutic agent 1 is administered at a total daily dose of about 250 mg and therapeutic agent 3 is administered at a total daily dose of about 400 mg.

21. The method of claim 19, wherein therapeutic agent 3 is administered in a daily dose of 50 mg.

22. The method of claim 21, wherein therapeutic agent 3 is administered once daily or twice daily.

23. The method of any of claims 19-22, wherein therapeutic agent 1 is administered at a daily dose of about 250 mg.

24. The method of claim 23, wherein therapeutic agent 1 is administered once daily.

25. The method of claim 1, wherein the at least two DAAs comprise at least one HCV protease inhibitor and at least one NS5A inhibitor.

26. The method of claim 25, wherein the at least one HCV protease inhibitor is therapeutic agent 1 and the at least one NS5A inhibitor is therapeutic agent 4.
27. The method of claim 26, wherein therapeutic agent 1 is administered at a total daily dosage of about 25 mg to about 250 mg.

28. The method of claim 26, wherein therapeutic agent 4 is administered in a total daily dose of about 25 mg to about 200 mg.

29. A method for treating Hepatitis C Virus (HCV) infection in a subject comprising administering
   (a) therapeutic agent 1,
   (b) at least one polymerase inhibitor selected from the group consisting of therapeutic agent 2, therapeutic agent 3 and combinations thereof, and
   (c) an inhibitor of cytochrome P450 for a duration of twelve weeks or less,
   wherein the therapeutic agent 1, the at least one polymerase inhibitor, and the inhibitor of cytochrome P450 are administered in amounts effective to result in sustained virological response (SVR) in the subject.

30. A method for treating a population of subjects having Hepatitis C Virus (HCV) infection, the method comprising administering at least two direct acting antiviral agents (DAAs) to the subjects for a duration of 12 weeks or less, wherein the at least two direct acting antiviral agents (DAAs) are administered to the subjects in amounts and for a duration effective to provide a sustained virological response (SVR) in at least about 70% of the population.
ABSTRACT OF THE DISCLOSURE

[0068] The present invention features therapies for the treatment of HCV over a shorter duration of treatment, such as 12 weeks or less, which result in undetectable virus at the end of treatment and afterward. The therapies comprise administering at least direct acting antiviral agents to a subject. For example, the therapies comprise administering to a subject effective amounts of therapeutic agent 1, a protease inhibitor such as therapeutic agent 2 or therapeutic agent 3, an inhibitor of cytochrome P450. The therapies are ribavirin-free and preferably interferon-free.
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**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

**New International Application Filed with the USPTO as a Receiving Office**

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.