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(71) Applicant (for all designated States except US): **NO-VARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(72) Inventors; and

(71) Applicants (for US only): **BRASS, Clifford** [US/US]; c/o Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, New Jersey 07936 (US). **NAOUMOV, Nikolai** [GB/CH]; c/o Novartis Pharma AG, Postfach, CH-4002 Basel (CH).(74) Agent: **KURLANDSKY, David**; Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, New Jersey 07936 (US).

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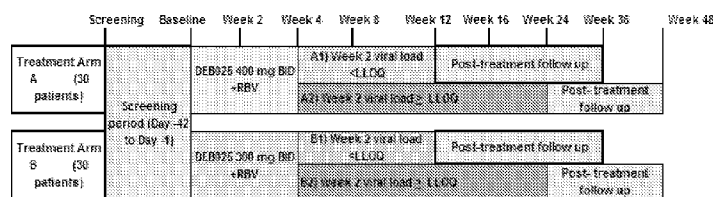
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(54) Title: NEW TREATMENTS OF HEPATITIS C VIRUS INFECTION

Figure 1 Study Design



(57) Abstract: The invention concerns the use of cyclophilin inhibitors in the treatment of Hepatitis C virus genotype 2 or 3 in a patient who has previously failed interferon therapy or is intolerant or unable to take interferon.

New treatments of Hepatitis C virus infection

Background of the Disclosure

The present disclosure relates to non-immunosuppressive cyclosporin derivatives and non-cyclosporin derived cyclophilin inhibitors which bind to cyclophilin, which are cyclophilin inhibitors, in particular to their pharmaceutical use of in the treatment of Hepatitis C virus infection.

The cyclosporins comprise a class of structurally distinctive, cyclic, poly-N-methylated undecapeptides, commonly possessing pharmacological, in particular, immunosuppressive, or anti-inflammatory activity. The first of the cyclosporins to be isolated was the naturally occurring fungal metabolite Cyclosporin or Cyclosporine, also known as cyclosporin A (CsA).

Non-immunosuppressive cyclophilin inhibitors have been generated by purposely designed chemical modification (amino acid substitution) of cyclosporine A, to increase the binding to cellular cyclophilins and to abolish the immunosuppressive activity. PCT/EP 2004/009804, WO 2005/021028, or WO 2006/071619 (which are incorporated by reference herein in their entirety) disclose non-immunosuppressive cyclosporins which bind to cyclophilin and have also been found to have an inhibitory effect on Hepatitis C virus (HCV). WO 2006/038088, incorporated herein by reference in its entirety, describes methods and compositions for the use of alisporivir in the treatment of HCV. Alisporivir (Debio-025 or DEB025 or DEB) is a cyclophilin (Cyp) inhibitor and its mode of action as an anti-HCV agent is via inhibition of host proteins, in particular of cyclophilin A, that are directly involved in HCV replication.

Chronic infection with hepatitis C virus (HCV) is a major and growing public health problem. It is a leading cause of cirrhosis, liver cancer and other liver-related morbidities. The World Health Organization (WHO) estimates that approximately 170 million people, 3% of the world's population are infected with hepatitis C; and that 3-4 million new infections occur each year. Among the six major HCV genotypes (G), HCV G3 is the second most prevalent worldwide after G1. The prevalence rates of G3 are between 5-10% of all cases with chronic hepatitis C infection in the USA, 50% in some European

countries, and reaching values above 50% in countries such as India (Amarapurkar D et al. (2001) Prevalence of hepatitis C genotypes in Indian patients and their clinical significance. *J Assoc Physicians India*. 49:983-5, Chandra M, et al. (2003) Prevalence, risk factors and genotype distribution of HCV and HBV infection in the tribal population: a community based study in south India. *Trop Gastroenterol*. 24(4):193-5). G2 (15%) is more common than G3 in USA (Alter MJ, Kruszon-Moran D, Nainan OV, et al (1999). The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *N Engl J Med*; 341: 556–62, Manos. MM, Shvachko VA et al (2012) Distribution of Hepatitis C Virus Genotypes in a Diverse US Integrated Health Care Population, *Journal of Medical Virology* 84:1744–1750 (2012)), however, G3 dominates the previous non-response population due to lower response rate to the INF based therapies in G3 patients with high viral load (Zeuzem S, Hultcrantz R, Bourliere M, et al (2004) Peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C in previously untreated patients infected with HCV genotypes 2 or 3. *J Hepatol*; 40: 993-9).

15 The primary goal of antiviral treatment is sustained virologic response (SVR), defined as the achievement of undetectable HCV ribonucleic acid (RNA) measured from serum by a sensitive Polymerase Chain Reaction (PCR) at 12 (SVR 12) and/or at 24 weeks (SVR 24) after the end of treatment (ETR). SVR 24 is universally accepted as equivalent of cure (Ghany MG, Strader DB, Thomas DL, et al. (2009) Diagnosis, Management, and Treatment of Hepatitis C: An Update. *Hepatology*; 49:1335-1374). Based on a recent analysis performed on over 10,000 patients in fifteen phase II and III trials, SVR 12 was shown to be as accurate as SVR 24 in evaluating SVR (with 98% positive predictive value and 99% negative predictive value) (Florian J, Chen PR, Jadhav J, et al (2011). Consideration of New Endpoints for Regulatory Approval and Dose Selection of Hepatitis C Therapies. AASLD 2011 Annual Meeting. Poster Presentation Nov 7, 2011).

25 The SVR with pegIFN α plus RBV in G2 treatment naïve patients is about 85% and in G3 treatment naïve patients is approximately 70% (Shiffman M et al, (2007). Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. ACCELERATE Investigators,. *N Engl J Med*. 12;357(2):124-34, Zeuzem S, Hultcrantz R, Bourliere M, et al (2004) Peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C in previously untreated patients infected with HCV genotypes 2 or 3. *J Hepatol*; 40: 993-9).

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Although SVR rates are higher than in patients infected with other genotypes, i.e. G1, treatment outcome, especially in G3 patients with high initial viral load and/or other aggravating conditions, is suboptimal. These patients have a relapse rate of 23% compared to that of 9% in G2 patients with similar baseline viral load (Zeuzem S, Hultcrantz R, Bourliere M, et al (2004) Peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C in previously untreated patients infected with HCV genotypes 2 or 3. *J Hepatol*; 40: 993-9).

Current available treatment for patients infected with G2 or 3 who failed previous therapy with interferon (IFN) and/or ribavirin (RBV) is peginterferon alpha (pegIFN α) once weekly plus daily RBV for 48 weeks. In a large study conducted by Dr. Poynard in this population, SVR 24 was achieved in 57% of relapsers and 36% of non-responders (52% cumulatively) (Poynard T, Colombo M, Bruix J et al (2009) Peginterferon alfa-2b and Ribavirin: Effective in Patients With Hepatitis C Who Failed Interferon-alfa/Ribavirin Therapy. *Gastroenterology* 2009; 136:1618-1628). Other than retreatment with longer durations of pegIFN plus RBV which is suboptimal, there are no other approved therapies available for G2 or 3 patients who have failed previous IFN/RBV treatment. Thus, patients with previous IFN/RBV treatment failures or intolerant or unable to take interferon remain a population with relative high unmet medical need.

Alisporivir (also known as DEB025, and previously known as Debio 025) is an orally available host targeting agent. DEB025 binds host proteins (cyclophilins) that the virus requires to replicate. It has shown potent anti-HCV activity in preclinical models (Coelmont L, Kaptein S, Paeshuyse J, et al. (2009) Debio 025, a cyclophilin binding molecule, is highly efficient in clearing HCV replicon containing cells, alone or when combined with Specifically Targeted Antiviral Therapy for HCV (STAT-C) inhibitors. *Antimicrob Agents Chemother*; 53:967-976, Paeshuyse J, Kaul A, De Clercq E, et al (2006) The non-immunosuppressive cyclosporin DEBIO-025 is a potent inhibitor of hepatitis C virus replication in vitro. *Hepatology*; 43:761-770, Inoue K, Umehara T, Ruegg UT, et al. (2007) Evaluation of a cyclophilin inhibitor in hepatitis C virus-infected chimeric mice in vivo. *Hepatology*; 45:921-928, Chatterji U, Bobardt M, Selvarajah S, et al (2009) The isomerase active site of cyclophilin A is critical for hepatitis C virus replication. *J Biol Chem*; 284: 16998-17005). Alisporivir currently has a unique position

in the current landscape of anti-HCV development as the only oral host acting agent in advanced development. Its key attributes demonstrated in vitro include: 1) pan-genotypic, 2) high barrier to resistance, 3) synergism with protease inhibitors, nucleoside polymerase inhibitors and NS5a inhibitors in particular, and 4) ability to treat the most common resistance associated variants from the various DAA classes (Tiongyip C et al. (2011) Host targeting cyclophilin inhibitor alisporivir presents a high barrier to resistance with no cross-resistance to direct acting antivirals. 6th International Workshop on Hepatitis C, Resistance and New Compounds. Cambridge, MA, June 24th, 2011).

The efficacy and safety of an IFN-free regimen with DEB025 in combination with RBV was explored in a recently completed multicenter, randomized, open-label, parallel-group phase IIb study with treatment-naïve chronic hepatitis C G2/3 patients (VITAL-1) (Pawlotsky J, Flisiak R, Rasenack J, et al (2012) Alisporivir plus Ribavirin achieves high rates of sustained HCV clearance (SVR 24) as interferon (IFN)-free or IFN-add-on regimen in treatment-naïve patients with HCV GT2 or GT3: Final results from VITAL-1 study. Presented at the American Association for the Study of Liver Diseases (AASLD) Boston, Nov. 13, 2012). Among patients who received IFN-free DEB025 therapy, up to half of the patients achieved undetectable HCV RNA by week 6 (49% in DEB025 600 mg QD+ RBV, 46% in DEB025 800 mg QD +RBV and 32% in DEB025 1000 mg QD). The majority of patients with detectable HCV RNA at week 6 experienced a reduction of 3 logs in HCV RNA from baseline. Both G2 and G3 patients had similar response rates to DEB025 IFN-free regimens. Among rapid virologic response (RVR) patients receiving full IFN-free DEB025 + RBV treatment, 96% achieved end of treatment responses and 84% SVR 12. 4% had viral breakthrough (3 patients) and 6% post-treatment relapse. The findings from this study demonstrate that the regimen of IFN-free DEB025 + RBV is an effective treatment option for patients with HCV G2/3 resulting in high rates of SVR 12, low viral breakthrough or post treatment relapse. IFN-free DEB025 treatment resulted in substantially lower rates of adverse events than IFN-containing treatment. These positive results suggest that DEB025 may have the potential to become an IFN-free oral treatment for a substantial proportion of treatment-naïve G2/3 patients.

Data from the study CDEB025A2210 (a Phase 2b study in G1 peg-IFN α 2a /RBV relapsers and non-responders) showed that 62% of patients in the alisporivir 400 mg BID

plus pegIFN/RBV achieved SVR 12 compared with 15% in the pegIFN/RBV control arm. In the most challenging sub-group of G1 patients, previous (null) non-responders with cirrhotics, up to 40% of patients achieved SVR 12 in alisporivir 400 mg BID plus pegIFN/RBV, compared to 0% in the pegIFN/RBV control group. These data suggest that alisporivir may be a particularly valuable treatment for the most difficult to treat population.

The present disclosure relates to the antiviral activity, pharmacokinetics and safety profiles of two different DEB025 doses (each administered as a twice a day (BID) regimen) in combination with RBV in the treatment of chronic hepatitis C G2/3 patients who have previously failed interferon therapy or are intolerant or unable to take interferon.

Thus, despite existing therapies, there remains a significant need for methods and compositions for the interferon free treatment of HCV which is safer, more tolerable, more efficacious with DEB025 doses (each administered as a BID regimen) with RBV only in the treatment of chronic hepatitis C G2/3 patients who have previously failed interferon therapy or are intolerant or unable to take interferon.

Summary of the Disclosure

Surprisingly it has been determined that cyclophilin inhibitors, in particular alisporivir, can provide an effective alternative to the standard of care in treatment of HCV. In particular, we have found that efficacious treatment of Hepatitis C virus genotype 2 and 3 infection in patients who previously failed interferon therapy or who are intolerant or unable to take interferon can be achieved when using alisporivir in the absence of or without interferon, thereby avoiding the side effects of the current standard of care treatment and thus improving patient compliance. Furthermore, alisporivir can provide an efficacious treatment of Hepatitis C virus genotype 2 and 3 infection in patients who previously failed interferon therapy or who are intolerant or unable to take interferon with treatment duration of half the duration of the standard of care treatment.

Accordingly, the present disclosure provides new anti-HCV treatments using alisporivir, in particular methods of treating hepatitis C virus genotype 2 and 3 infection in patients

who previously failed interferon therapy or who are intolerant or unable to take interferon comprising administering to the patient alisporivir in an amount of about 200 mg to 400 mg twice a day, preferably of about 400 mg twice per day.

5 The disclosure further provides alisporivir for use in the treatment or prevention of Hepatitis C virus genotype 2 and 3 infections or HCV induced disorders in patients who previously failed interferon therapy or who are intolerant or unable to take interferon.

Further, the following is described:

1.1 A method for treating Hepatitis C virus genotype 2 and 3 infections or HCV induced disorders in a patient, preferably in patients who previously failed interferon therapy or who are intolerant or unable to take interferon, comprising administering to the patient alisporivir in an amount of about 200 mg to about 400 mg twice a day in the absence of interferon.

1.2 A method for preventing or delaying the recurrence of HCV genotype 2 and 3 infection in a transplant recipient, comprising administering to the recipient alisporivir in an amount of about 200 mg to about 400 mg twice a day, preferably of about 400 mg twice per day in the absence of interferon.

1.3 A method for treating Hepatitis C virus genotype 2 and 3 infections or for treating HCV induced disorders in patients who previously failed interferon therapy or who are intolerant or unable to take interferon, comprising administering to the patient alisporivir in an amount of about 200 mg to about 400 mg twice a day, preferably of about 400 mg twice per day with a ribavirin for a treatment duration of at least 12 weeks in the absence of interferon.

1.4 A method for treating Hepatitis C virus genotype 2 and 3 infections or for treating HCV induced disorders patients who previously failed interferon therapy or who are intolerant or unable to take interferon, comprising administering to the patient alisporivir in an amount of about 200 mg to about 400 mg twice a day, preferably of about 400 mg twice per day with a ribavirin for a treatment duration of 12 to 24 weeks in the absence of interferon.

1.5 A method for treating Hepatitis C virus genotype 2 and 3 infections or for treating HCV induced disorders in patients who previously failed interferon therapy or

who are intolerant or unable to take interferon, comprising administering to the patient alisporivir in an amount of about 200 mg to about 400 mg twice a day, preferably of about 400 mg twice per day for a treatment duration of at least 12 weeks in the absence of interferon.

5 1.6 A method for treating Hepatitis C virus genotype 2 and 3 infections or for treating HCV induced disorders in patients who previously failed interferon therapy or who are intolerant or unable to take interferon, comprising administering to the patient alisporivir in an amount of about 200 mg to about 400 mg twice a day, preferably of about 400 mg twice per day for a treatment duration of 12 to 24 weeks in the absence of
10 interferon.

2. Use of alisporivir in the preparation of a pharmaceutical composition for use in any method as defined above.

3. Use of alisporivir in the preparation of a medicament for use in any method as defined above.

15 4. A pharmaceutical composition for use in any method as defined above, comprising alisporivir, together with one or more pharmaceutically acceptable diluents or carriers therefor.

5. A therapeutic regimen comprising administering alisporivir in an amount of about 200 mg to about 400 mg twice per day, preferably of about 400 mg twice per day in
20 combination with a ribavirin in the absence of interferon in patients who previously failed interferon therapy or who are intolerant or unable to take interferon.

6. A package comprising the pharmaceutical composition comprising alisporivir as defined above, in combination with instructions to administer the pharmaceutical composition in an amount of about 200 mg to about 400 mg twice a day,
25 preferably of about 400 mg twice per day.

7. A kit for the treatment of chronic hepatitis C virus genotype 2 and 3 infection.

Also contemplated herein are methods of reducing the HCV genotype 2 and 3 RNA in patients who previously failed interferon therapy or who are intolerant or unable to take

interferon comprising administering to the patient: alisporivir in an amount of about 200 mg to about 400 mg twice a day, preferably of about 400 twice per day in the absence of interferon.

5 Additional embodiments of the present disclosure relate to methods of treating hepatitis C genotype 2 and 3 infections in patients who previously failed interferon therapy or who are intolerant or unable to take interferon comprising administering to the patient: alisporivir in an amount of about 200 mg to about 400 mg twice a day, preferably of about 400 mg twice per day in the absence of interferon.

10 Additional embodiments of the present disclosure relate to methods of treating hepatitis C genotype 2 and 3 infections in patients who previously failed interferon therapy or who are intolerant or unable to take interferon comprising administering to the patient: alisporivir in combination with ribavirin, wherein alisporivir is administered in an amount of about 200 mg to about 400 mg twice a day in the absence of interferon.

Brief Description of the Figure

15 Figure 1 shows the DEB025A2233 trial design.
Figure 2 is a graph illustrating HCV RNA decline during the first 12 weeks of treatment (triple therapy with DEB025+ peg-IFN α 2a +RBV) in treatment-experienced GT1 patients.

20 Detailed Description of the Disclosure

List of abbreviations

	AE	adverse event
	ALT	alanine-aminotransferase
	AUC	area under the concentration vs time curve
25	BID	twice a day
	cEVR	complete early virologic response
	CHC	chronic hepatitis C
	C _{max}	maximum concentration
	C _{min}	minimum concentration
30	Cyp	cyclophilin

	DAA	direct acting antiviral
	ETR	end of treatment response
	EVR	early virologic response
	pEVR	partial early virologic response
5	FU	follow-up (after stopping treatment)
	GT	genotype
	Hb	haemoglobin
	HbsAg	hepatitis B surface antigen
	HBV	hepatitis B virus
10	HCV	hepatitis C virus
	HTAs	host targeting antiviral agents
	IB	Investigator Brochure
	IRT	interactive response technology
	IU	international units
15	LOD	limit of detection
	LOQ	limit of quantification
	MPA	Molecular Profiling Analysis (MPA)
	PCR	polymerase chain reaction
	PD	pharmacodynamics
20	PEG	polyethylene glycol
	peg-IFN α	pegylated interferon alfa
	PK	pharmacokinetics
	PT	preferred term
	QD	once a day
25	qPCR	quantitative polymerase chain reaction
	RBV	ribavirin
	RNA	ribonucleic acid
	mRNA	messenger RNA
	miRNA	micro RNA
30	RVR	rapid virologic response
	SAE	serious adverse event
	SOC	standard of care

	SVR	sustained virologic response
	UGT1A1 A1)	UGT1A1 gene (coding f. glucuronosyltransferase 1 family, polypeptide A1)
	WHO	World Health Organization
5	μl	microliter

Glossary of terms

Assessment	A procedure used to generate data required by the study
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	The planned stage of the subjects' participation in the study. Each epoch serves a purpose in the study as a whole. Typical epochs are: determination of subject eligibility, wash-out of previous treatments, exposure of subject to treatment or to follow-up on subjects after treatment has ended.
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product."
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This <i>includes</i> any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally <i>does not include</i> other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all investigational/study treatment administration and all assessments (including follow-up)

Definition of Virologic Response Parameters

Non-responder	Failure to achieve undetectable serum HCV RNA during treatment
i) Null non-responder	Failure to achieve a decrease in serum HCV RNA concentration $\geq 2 \log_{10}$ from baseline to treatment week 12
ii) Partial non-responder	HCV RNA decrease $\geq 2 \log_{10}$ from baseline to treatment week 12 but never undetectable during treatment
eRVR	"Extended Rapid Virologic Response by LOQ": serum HCV RNA < LOQ after 2 weeks of treatment
RVR	"Rapid Virologic Response by LOQ": serum HCV RNA < LOQ after 4 weeks of treatment
EVR	"Early Virologic Response": HCV RNA decrease $\geq 2 \log_{10}$ or HCV RNA < LOQ after 12 weeks of treatment
pEVR	"Partial Early Virologic Response": HCV RNA decrease $\geq 2 \log_{10}$ and still detectable after 12 weeks of treatment
cEVR	"Complete Early Viral Response": serum HCV RNA < LOQ after 12 weeks of treatment
ETR	"End of Treatment Response": HCV RNA undetectable (by < LOQ) at treatment end (completed or prematurely discontinued)
LOD	Lower limit of detection.
LOQ	Lower limit of quantification. < LOQ is used whenever "undetectable" is mentioned in the protocol unless it is specified elsewhere.
SVR4	"Sustained Virologic Response at week 4 FU": HCV RNA undetectable (by < LOQ) 4 weeks after end of treatment
SVR12 (=SVR)	"Sustained Virologic Response at week 12 FU": HCV RNA undetectable (by < LOQ) 12 weeks after end of treatment
SVR24	"Sustained Virologic Response at week 24 FU": HCV RNA undetectable (by < LOQ) 24 weeks after end of treatment
Viral breakthrough	Increase of HCV RNA by $\geq 1 \log_{10}$ above nadir (nadir = lowest HCV RNA level during treatment) while still on treatment or HCV RNA ≥ 100 IU / mL ($2 \log_{10}$) after previously being undetectable while still on treatment Viral breakthrough should be confirmed by a separate blood draw as soon as possible.
Relapse	Detectable HCV RNA > LOQ during post-treatment Follow Up after End of Treatment Response

- 5 The term "comprising" encompasses "including" as well as "consisting," e.g. a composition "comprising" X may consist exclusively of X or may include something additional, e.g., X + Y.

The term “about” in relation to a numerical value x means +/-10% unless the context dictates otherwise.

Additional embodiments of the present disclosure relate to method for treating hepatitis C genotype 2 and 3 infections in a patient comprising administering alisporivir to such a level that the level of viral RNA in the patient decreases to an undetectable level and that a sustained viral response is achieved at the end of the treatment period.

In the above embodiments and throughout this specification, the standard of care treatment is a treatment that is used to treat Hepatitis C infections. The currently used standard of care treatment involves administration of an interferon, in particular pegylated interferon in combination with a ribavirin.

In the above embodiments and throughout this specification, the initial phase is a period of about 3, about 4, about 5, about 6, or about 7 days. Preferably the initial phase is a period of at least about 3 days, e.g., 3 days, more preferably about 7 days, e.g., 7 days.

In the above embodiments and throughout this specification, the second phase is a period of about 11, about 23, about 47 or about 71 weeks. Preferably the second phase is a period of about 23 weeks, e.g., 23 weeks.

In the above embodiments and throughout this specification, the treatment duration is the duration of the initial and second phases, provided that no other duration is specified.

As used herein, "microgram/kilogram" means microgram drug per kilogram body weight of the mammal - including man - to be treated.

As used herein, the term “treatment” or “treat” refer to both prophylactic or preventative treatment as well as curative or disease modifying treatment, including treatment of patient at risk of contracting the disease or suspected to have contracted the disease as well as patients who are ill or have been diagnosed as suffering from a disease or medical condition, and includes suppression of clinical relapse. The treatment may be administered to a subject having a medical disorder or who ultimately may acquire the disorder, in order to prevent, cure, delay the onset of, reduce the severity of, or ameliorate one or more symptoms of a disorder or recurring disorder, or in order to prolong the survival of a subject beyond that expected in the absence of such treatment.

By “therapeutic regimen” is meant the pattern of treatment of an illness, e.g., the pattern of dosing used during HCV therapy. A therapeutic regimen may include an induction regimen and a maintenance regimen.

5 As used herein, the terms "subject" and “patient” include any human or nonhuman animal. The term "nonhuman animal" includes all vertebrates, e.g., mammals and non-mammals, such as nonhuman primates, sheep, dogs, cats, horses, cows, chickens, amphibians, reptiles, etc.

The term “pharmaceutically acceptable” means a nontoxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s).

10 The term “administering” in relation to a compound, e.g., alisporivir, is used to refer to delivery of that compound to a patient by any route.

As used herein, a “therapeutically effective amount” refers to an amount of alisporivir that is effective, upon single or multiple dose administration to a patient (such as a human) for treating, preventing, preventing the onset of, curing, delaying, reducing the severity of, ameliorating at least one symptom of a disorder or recurring disorder, or
15 prolonging the survival of the patient beyond that expected in the absence of such treatment. When applied to an individual active ingredient (e.g., alisporivir) administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect,
20 whether administered in combination, serially or simultaneously.

The term “treatment” or “treat” refer to both prophylactic or preventative treatment as well as curative or disease modifying treatment, including treatment of a patient at risk of contracting the disease or suspected to have contracted the disease as well as patients who are ill or have been diagnosed as suffering from a disease or medical condition, and
25 includes suppression of clinical relapse. The treatment may be administered to a patient having a medical disorder or who ultimately may acquire the disorder, in order to prevent, cure, delay the onset of, reduce the severity of, or ameliorate one or more symptoms of a disorder or recurring disorder, or in order to prolong the survival of a patient beyond that expected in the absence of such treatment.

The phrase “therapeutic regimen” means the dosing pattern of treatment of an illness, e.g., the dosing protocol used during the treatment of HCV. A therapeutic regimen may include an induction regimen and a maintenance regimen.

5 In some embodiments, ribavirin is administered at between about 800 to about 1200 mg per day, e.g., 1000 mg to 1200 mg per day. In some embodiments, ribavirin is administered based on the weight of the patient RBV 1000 - 1200 mg/day (1000 mg for patients < 75kg, 1200 mg/day for patients $\geq$ 75 kg of body weight at screening). In other embodiments, ribavirin is administered based on the HCV genotype of the patient.

10 In another embodiment, alisporivir may be administered with additional agents of the standard of care that promote the antiviral efficacy of the therapy treatment. The standard of care may include additional agents that promote the antiviral efficacy of the therapy treatment, such as substrate-based protease inhibitors of HCV NS3-4A serine protease, non-substrate-based NS3 protease inhibitors; NS5A and NS5B inhibitors, phenanthrenequinones, thiazolidines and benzanilides, nucleosides analogs, antisense
15 molecules directed against HCV genome or any cellular component that is required for viral replication, vaccine or antibody-based approaches to HCV treatment.

In treatment described above effective dosages of the drugs are administered in compositions, i.e. they may be administered together (i.e., simultaneously), but may also be administered separately or sequentially. In general, combination therapy is typically
20 administered together, the rationale being that such simultaneous administration induces multiple simultaneous stresses on the virus. The specific dosages given will depend on absorption, inactivation and excretion rate of the drugs as well as other factors. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated.

The terms "co-administration" or "combined administration" or “administered in
25 combination with” or the like as utilized herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time. Fixed combinations are also within the scope of the present disclosure. The administration of a pharmaceutical combination of the disclosure
30 results in a beneficial effect, e.g. a synergistic or additive therapeutic effect, compared to

a monotherapy applying only one of its pharmaceutically active ingredients or as compared to the current standard of care therapy. The treatment used in the methods described herein may be administered by any conventional route. One or more components may be administered parentally, e.g., in the form of injectable solutions or suspensions, or in the form of injectable deposit formulations. Preferably, alisporivir will be administered orally in the form of solutions or suspensions for drinking, tablets or capsules. Pharmaceutical compositions for oral administration comprising alisporivir typically further comprise one or more pharmaceutically acceptable carrier substances. Typically, these compositions are concentrated and need to be combined with an appropriate diluent, e.g., water, prior to administration. Pharmaceutical compositions for parenteral administration typically also include one or more excipients. Optional excipients include an isotonic agent, a buffer or other pH- controlling agent, and a preservative. These excipients may be added for maintenance of the composition and for the attainment of preferred ranges of pH (about 6.5-7.5) and osmolarity (about 300 mosm/L).

As used herein "twice per day" or BID means twice in any period of about 24 hour period.

The administration of alisporivir as described herein is in a single dose form or in more than one dosage form; one or more oral dosage forms may be administered at each time per day.

The alisporivir is preferably in a pharmaceutical composition, in unit dosage form such as a gelatin capsule, including 1) alisporivir in an amount of about 15% to about 20% by weight of the composition, 2) a lipophilic component, 3) a surfactant, 4) a polyethylene glycol, and 5) water in an amount of about 2% to about 15% by weight of the composition as disclosed in WO 2012/080176 and incorporated herein by reference. Other alisporivir formulations and dosage forms can also be utilized.

Direct acting antiviral agents, is used herein to mean agents that interfere with specific steps in the hepatitis C virus (HCV) replication cycle. Such agents may be, e.g., ribavirin derivatives, protease inhibitors, and polymerase inhibitors (e.g., nucleoside/nucleotide and non-nucleoside/nucleotide inhibitors). Exemplary direct acting antiviral agents include:

- boceprevir, telaprevir, ABT-072, ABT-450, ABT-333 by Abbott, ACH1625 by Achillion, ANA598 by Anadys Pharmaceuticals, AZD-7295 by AstraZeneca, BI201335, BI207127 by Boehringer Ingelheim Pharma, BMS650032, BMS790052, BMS791325, BMS824383 by Bristol Myers Squibb, Clemizole by Eiger BioPharmaceutucials, EDP239 by Enanta, 5 Filibuvir by Pfizer, GS9190 (Tegobuvir), GS9256 by Gilead, IDX375 by Idenix, GS-7977 (Sofosbuvir) by Gilead, RG7128 (mericitabine) by Pharmasset/Genentec, PPI-461 by Presidio RG7227 (Danoprevir) by InterMune/Genentech, SCH900518 (Narlaprevir), Vaniprevir by Merck, TMC435 by Medivir/Tibotec, VX-222, VX-759, VX-500, VX-916 by Vertex.
- 10 As used herein “up to 12 or 24 weeks” refers to the treatment duration and is intended to mean for about 12 weeks or about 24 weeks, respectively. It will be understood that therapy need not end at exactly the 12 or 24 week time period. For example, therapy may end a day or a few days before the 24 week period, and still be an equivalent within the scope and spirit of the current disclosure.
- 15 In one embodiment, the present disclosure further provides a method for treating Hepatitis C virus genotype 2 and 3 infections or HCV induced disorders in a patient, preferably a patient naive to treatment, comprising administering to the patient alisporivir in an amount of about 200 mg to about 400 mg twice a day in the absence of interferon.
- 20 In another embodiment, the present disclosure further provides a method for delaying the recurrence of HCV genotype 2 and 3 infection in a transplant recipient, comprising administering to the recipient alisporivir in an amount of about 200 mg to about 400 mg twice a day, preferably of about 400 mg twice per day in the absence of interferon.
- 25 In another embodiment, the present disclosure further provides a method for treating Hepatitis C virus genotype 2 and 3 infections or for treating HCV induced disorders in a patients who previously failed interferon therapy or who are intolerant or unable to take interferon, comprising administering to the patient alisporivir in an amount of about 200 mg to about 400 mg twice a day, preferably of about 400 mg twice per day with a ribavirin for a treatment duration of at least 12 weeks in the absence of interferon.

In another embodiment, the present disclosure further provides a method treating Hepatitis C virus genotype 2 and 3 infections or for treating HCV induced disorders in patients who previously failed interferon therapy or who are intolerant or unable to take interferon, comprising administering to the patient alisporivir in an amount of about 200 mg to about 400 mg twice a day in the absence of interferon, preferably of about 400 mg twice per day with a ribavirin for a treatment duration of 12 to 24 weeks in the absence of interferon.

In another embodiment, the present disclosure further provides a method for treating Hepatitis C virus genotype 2 and 3 infections or for treating HCV induced disorders in patients who previously failed interferon therapy or who are intolerant or unable to take interferon, comprising administering to the patient alisporivir in an amount of about 200 mg to about 400 mg twice a day in the absence of interferon, preferably of about 400 mg twice per day for a treatment duration of at least 12 weeks in the absence of interferon.

In another embodiment, the present disclosure further provides a method for treating Hepatitis C virus genotype 2 and 3 infections or for treating HCV induced disorders in patients who previously failed interferon therapy or who are intolerant or unable to take interferon, comprising administering to the patient alisporivir in an amount of about 200 mg to about 400 mg twice a day in the absence of interferon, preferably of about 400 mg twice per day for a treatment duration of 12 to 24 weeks in the absence of interferon.

In another embodiment, the present disclosure further provides for the use of alisporivir in the preparation of a pharmaceutical composition for use in any method as defined above.

In another embodiment, the present disclosure further provides for the use of alisporivir in the preparation of a medicament for use in any method as defined above.

In another embodiment, the present disclosure further provides a pharmaceutical composition for use in any method as defined above, comprising alisporivir, together with one or more pharmaceutically acceptable diluents or carriers therefor.

In another embodiment, the present disclosure further provides a therapeutic regimen comprising administering alisporivir in an amount of about 200 mg to about 400 mg twice

per day in the absence of interferon, preferably of about 400 mg twice per day in combination with a ribavirin in the absence of interferon.

In another embodiment, the present disclosure further provides a package comprising the pharmaceutical composition comprising alisporivir as defined above, in combination with
5 instructions to administer the composition in an amount of about 200 mg to about 400 mg twice a day in the absence of interferon, preferably of about 400 mg twice per day in the absence of interferon.

In another embodiment, the present disclosure further provides a kit for the treatment of chronic hepatitis C virus genotype 2 and 3 infection in a patient who previously failed
10 interferon therapy or who is intolerant or unable to take interferon.

Also contemplated herein are methods of reducing the HCV genotype 2 and 3 RNA in patients who previously failed interferon therapy or who are intolerant or unable to take interferon comprising administering to the patient: alisporivir in an amount of about 200 mg to about 400 mg twice a day, preferably of about 400 mg twice per day in the absence of
15 interferon.

Additional embodiments of the present disclosure relate to methods of treating hepatitis C genotype 2 and 3 infections in patients who previously failed interferon therapy or who are intolerant or unable to take interferon comprising administering to the patient: alisporivir in an amount of about 200 mg to about 400 mg twice a day in the absence of
20 interferon, preferably of about 400 mg twice per day in the absence of interferon.

Additional embodiments of the present disclosure relate to methods of treating hepatitis C genotype 2 and 3 infections in patients who previously failed interferon therapy or who are intolerant or unable to take interferon comprising administering to the patient: alisporivir in combination with ribavirin in the absence of interferon, wherein alisporivir is administered in an amount of about 200 mg to about 400 mg twice a day and ribavirin is administered in an amount based on the weight of the patient RBV 1000 - 1200 mg/day (1000 mg for patients < 75kg, 1200 mg/day for patients $\geq$ 75 kg of body weight at screening).
25

In one embodiment, the present disclosure further provides alisporivir for use in treatment of a Hepatitis C virus genotype 2 or 3 infected patients who previously failed interferon therapy or who are intolerant or unable to take interferon characterized in that (i) alisporivir is administered in an amount of between about 200 mg twice a day for about 2 weeks in the absence of interferon, and (ii) if HCV RNA in the patient plasma is detectable by a HCV-RNA assay following step (ii), then administering alisporivir in an amount of 200 mg twice a day for up to about 24 weeks in the absence of interferon, and (iii) if HCV RNA in the patient plasma is not detectable by a HCV-RNA assay following step (ii), then administering alisporivir in an amount of 200 mg twice a day for up to about 12 weeks in the absence of interferon.

In one embodiment, the present disclosure further provides alisporivir for use in treatment of a Hepatitis C virus genotype 2 or 3 in patients who previously failed interferon therapy or who are intolerant or unable to take interferon characterized in that (i) alisporivir is administered in an amount of between about 300 mg twice a day for about 2 weeks in the absence of interferon, and (ii) if HCV RNA in the patient plasma is detectable by a HCV-RNA assay following step (ii), then administering alisporivir in an amount of 300 mg twice a day for up to about 24 weeks in the absence of interferon, and (iii) if HCV RNA in the patient plasma is not detectable by a HCV-RNA assay following step (ii), then administering alisporivir in an amount of 300 mg twice a day for up to about 12 weeks in the absence of interferon.

In one embodiment, the present disclosure further provides alisporivir for use in treatment of a Hepatitis C virus genotype 2 or 3 infected patient who previously failed interferon therapy or who is intolerant or unable to take interferon characterized in that (i) alisporivir is administered in an amount of between about 400 mg twice a day for about 2 weeks in the absence of interferon, and (ii) if HCV RNA in the patient plasma is detectable by a HCV-RNA assay following step (ii), then administering alisporivir in an amount of 400 mg twice a day for up to about 24 weeks in the absence of interferon, and (iii) if HCV RNA in the patient plasma is not detectable by a HCV-RNA assay following step (ii), then administering alisporivir in an amount of 400 mg twice a day for up to about 12 weeks in the absence of interferon.

In one embodiment, the present disclosure further provides alisporivir for use in treatment of a Hepatitis C virus genotype 2 or 3 infected patient who previously failed interferon therapy or who is intolerant or unable to take interferon characterized in that (i) alisporivir is administered in an amount of between about 200 mg twice a day in combination with ribavirin for about 2 weeks in the absence of interferon, and (ii) if HCV RNA in the patient plasma is detectable by a HCV-RNA assay following step (ii), then administering alisporivir in an amount of 200 mg twice a day in combination with ribavirin for up to about 24 weeks in the absence of interferon, and (iii) if HCV RNA in the patient plasma is not detectable by a HCV-RNA assay following step (ii), then administering alisporivir in an amount of 200 mg twice a day in combination with ribavirin for up to about 12 weeks in the absence of interferon.

In one embodiment, the present disclosure further provides alisporivir for use in treatment of a Hepatitis C virus genotype 2 or 3 infected patient who previously failed interferon therapy or who is intolerant or unable to take interferon characterized in that (i) alisporivir is administered in an amount of between about 300 mg twice a day in combination with ribavirin for about 2 weeks in the absence of interferon, and (ii) if HCV RNA in the patient plasma is detectable by a HCV-RNA assay following step (ii), then administering alisporivir in an amount of 300 mg twice a day in combination with ribavirin for up to about 24 weeks in the absence of interferon, and (iii) if HCV RNA in the patient plasma is not detectable by a HCV-RNA assay following step (ii), then administering alisporivir in an amount of 300 mg twice a day in combination with ribavirin for up to about 12 weeks in the absence of interferon.

In one embodiment, the present disclosure further provides alisporivir for use in treatment of a Hepatitis C virus genotype 2 or 3 infected patient who previously failed interferon therapy or who is intolerant or unable to take interferon characterized in that (i) alisporivir is administered in an amount of between about 400 mg twice a day in combination with ribavirin for about 2 weeks in the absence of interferon, and (ii) if HCV RNA in the patient plasma is detectable by a HCV-RNA assay following step (ii), then administering alisporivir in an amount of 400 mg twice a day in combination with ribavirin for up to about 24 weeks in the absence of interferon, and (iii) if HCV RNA in the patient plasma is not detectable by a HCV-RNA assay following step (ii), then administering alisporivir

in an amount of 400 mg twice a day in combination with ribavirin for up to about 12 weeks in the absence of interferon.

In one aspect, the present disclosure further provides use of alisporivir in the manufacture of a medicament for treatment of a Hepatitis C virus genotype 2 or 3 infected patient who previously failed interferon therapy or who is intolerant or unable to take interferon wherein alisporivir is administered during an initial phase in an amount of about 200 mg to about 400 mg twice per day for between about 12 weeks to about 24 weeks and wherein the alisporivir may be administered in combination with ribavirin in the absence of interferon.

In one aspect, the present disclosure further provides use of alisporivir in the preparation of a pharmaceutical composition for treatment of a Hepatitis C virus genotype 2 or 3 infected patient who previously failed interferon therapy or who is intolerant or unable to take interferon wherein alisporivir is administered during an initial phase in an amount of about 200 mg to about 400 mg twice per day for between about 12 weeks to about 24 weeks and wherein the alisporivir may be administered in combination with ribavirin in the absence of interferon.

In one aspect, the present disclosure further provides a therapeutic regimen characterized in that that (i) alisporivir is administered in an amount of between about 200 mg twice a day for about 2 weeks in the absence of interferon, and (ii) if HCV RNA in the patient plasma is detectable by a HCV-RNA assay following step (ii), then administering alisporivir in an amount of 200 mg twice a day for up to about 24 weeks in the absence of interferon, and (iii) if HCV RNA in the patient plasma is not detectable by a HCV-RNA assay following step (ii), then administering alisporivir in an amount of 200 mg twice a day for up to about 12 weeks in the absence of interferon.

In one aspect, the present disclosure further provides a therapeutic regimen characterized in that that (i) alisporivir is administered in an amount of between about 300 mg twice a day for about 2 weeks in the absence of interferon, and (ii) if HCV RNA in the patient plasma is detectable by a HCV-RNA assay following step (ii), then administering alisporivir in an amount of 300 mg twice a day for up to about 24 weeks in the absence of interferon, and (iii) if HCV RNA in the patient plasma is not detectable by a HCV-RNA

assay following step (ii), then administering alisporivir in an amount of 300 mg twice a day for up to about 12 weeks in the absence of interferon.

5 In one aspect, the present disclosure further provides a therapeutic regimen characterized in that that (i) alisporivir is administered in an amount of between about 400 mg twice a day for about 2 weeks in the absence of interferon, and (ii) if HCV RNA in the patient plasma is detectable by a HCV-RNA assay following step (ii), then administering alisporivir in an amount of 400 mg twice a day for up to about 24 weeks in the absence of interferon, and (iii) if HCV RNA in the patient plasma is not detectable by a HCV-RNA assay following step (ii), then administering alisporivir in an amount of 400 mg twice a
10 day for up to about 12 weeks in the absence of interferon.

In one aspect, the present disclosure further provides a therapeutic regimen characterized in that that (i) alisporivir is administered in an amount of between about 200 mg twice a day in combination with ribavirin for about 2 weeks in the absence of interferon, and (ii) if HCV RNA in the patient plasma is detectable by a HCV-RNA assay following step (ii),
15 then administering alisporivir in an amount of 200 mg twice a day in combination with ribavirin for up to about 24 weeks in the absence of interferon, and (iii) if HCV RNA in the patient plasma is not detectable by a HCV-RNA assay following step (ii), then administering alisporivir in an amount of 200 mg twice a day in combination with ribavirin for up to about 12 weeks in the absence of interferon.

20 In one aspect, the present disclosure further provides a therapeutic regimen characterized in that that (i) alisporivir is administered in an amount of between about 300 mg twice a day in combination with ribavirin for about 2 weeks in the absence of interferon, and (ii) if HCV RNA in the patient plasma is detectable by a HCV-RNA assay following step (ii), then administering alisporivir in an amount of 300 mg twice a day in combination with
25 ribavirin for up to about 24 weeks in the absence of interferon, and (iii) if HCV RNA in the patient plasma is not detectable by a HCV-RNA assay following step (ii), then administering alisporivir in an amount of 300 mg twice a day in combination with ribavirin for up to about 12 weeks in the absence of interferon.

In one aspect, the present disclosure further provides a therapeutic regimen characterized
30 in that that (i) alisporivir is administered in an amount of between about 400 mg twice a

day in combination with ribavirin for about 2 weeks in the absence of interferon, and (ii) if HCV RNA in the patient plasma is detectable by a HCV-RNA assay following step (ii), then administering alisporivir in an amount of 400 mg twice a day in combination with ribavirin for up to about 24 weeks in the absence of interferon, and (iii) if HCV RNA in the patient plasma is not detectable by a HCV-RNA assay following step (ii), then administering alisporivir in an amount of 400 mg twice a day in combination with ribavirin for up to about 12 weeks in the absence of interferon.

In one aspect, the present disclosure further provides pharmaceutical compositions comprising alisporivir for uses as defined above. In still other aspects, the present disclosure provides a package comprising the pharmaceutical composition comprising alisporivir for uses as defined above in combination with instructions to administer said composition.

In one aspect, the present disclosure further provides a use of alisporivir for the manufacture of a medicament for the treatment of a Hepatitis C virus genotype 2 or 3 infected patient who previously failed interferon therapy or who is intolerant or unable to take interferon wherein the medicament is formulated at a dosage comprising one, two, three, four or five dose of about 50 mg to about 200 mg. In still other aspects, the present disclosure provides use of alisporivir for the manufacture of a medicament for the treatment of a Hepatitis C virus genotype 2 or 3 infected patient who previously failed interferon therapy or who is intolerant or unable to take interferon wherein the medicament is formulated at a dosage comprising one, two, three or four dose of about 100 mg or about 200 mg in the absence of interferon. In still other aspects, the medicament is formulated at a dosage comprising one, two, three, four or five dose of about 50 mg to about 200 mg, further comprising ribavirin.

In one aspect, the present disclosure further provides use of alisporivir for the manufacture of a medicament for the treatment of a Hepatitis C virus genotype 2 or 3 infected patient who previously failed interferon therapy or who is intolerant or unable to take interferon wherein the medicament is formulated at a dosage comprising one, two, three, four or five dose of about 50 mg to about 200 mg in the absence of interferon, further comprising ribavirin, wherein the content of ribavirin in the medicament is at

between about 800 to about 1200 mg per day, e.g., 1000 mg to 1200 mg per day mg per dosage unit.

In one aspect, the present disclosure further provides a pharmaceutical composition comprising alisporivir for any use as defined above.

5 In one aspect, the present disclosure further provides a kit comprising

a) a pharmaceutical composition comprising alisporivir for use in the treatment of a Hepatitis C virus genotype 2 or 3 infected patient who previously failed interferon therapy or who is intolerant or unable to take interferon, optionally in combination with one or more pharmaceutically acceptable excipients, and

10 b) instructions describing how to administer said pharmaceutical composition for the treatment of a Hepatitis C virus genotype 2 or 3 infected patient who previously failed interferon therapy or who is intolerant or unable to take interferon, wherein the administration is characterized by

(i) alisporivir is administered in an amount of between about 200 mg to
15 about 400 mg twice a day in combination with ribavirin for about 2 weeks in the absence of interferon, and (ii) if HCV RNA in the patient plasma is detectable by a HCV-RNA assay following step (ii), then administering alisporivir in an amount of about 200 mg to about 400 mg twice a day in combination with ribavirin for up to about 24 weeks in the absence of interferon, and (iii) if HCV RNA in the patient plasma is not detectable by a
20 HCV-RNA assay following step (ii), then administering alisporivir in an amount of about 200 mg to about 400 mg twice a day in combination with ribavirin for up to about 12 weeks in the absence of interferon.

The terms "co-administration" or "combined administration" or "administered in combination with" or the like as utilized herein are meant to encompass administration of
25 the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time. Fixed combinations are also within the scope of the present disclosure. The administration of a pharmaceutical combination of the disclosure results in a beneficial effect, e.g. a synergistic or additive therapeutic effect, compared to
30 a monotherapy applying only one of its pharmaceutically active ingredients or as

compared to the current standard of care therapy. The treatment used in the methods described herein may be administered by any conventional route. One or more components may be administered parentally, e.g., in the form of injectable solutions or suspensions, or in the form of injectable deposit formulations. Preferably, alisporivir will be administered orally in the form of solutions or suspensions for drinking, tablets or capsules. Pharmaceutical compositions for oral administration comprising alisporivir typically further comprise one or more pharmaceutically acceptable carrier substances. Typically, these compositions are concentrated and need to be combined with an appropriate diluent, e.g., water, prior to administration. Pharmaceutical compositions for parenteral administration typically also include one or more excipients. Optional excipients include an isotonic agent, a buffer or other pH- controlling agent, and a preservative. These excipients may be added for maintenance of the composition and for the attainment of preferred ranges of pH (about 6.5-7.5) and osmolarity (about 300 mosm/L).

The administration of alisporivir as described herein is in a single dose form or in more than one dosage form; one or more oral dosage forms may be administered at each time per day. In some embodiments, alisporivir is administered in doses of 200 mg to 1000 mg.

The efficacy of the therapy regimen may be monitored using standard protocols. Treatment may be followed by determinations of HCV in serum and measurement of serum ALT levels. For example, the patients may be assessed for the presence of HCV RNA in their plasma. HCV RNA (IU/mL) can be measured at regular intervals during the treatment, e.g., at Day 1 (pre-dose and 4, 8, and 12 hours post-dose) and pre-dose at Day 2, Day 3, Day 8, Day 15, Day 29, and at Week 12, Week 24, Week 36, Week 48, Week 72 (when applicable), and at follow up. In addition, the HCV strains in the patient can be sequenced and assessed for identification of mutations selecting for resistance.

As used herein, LOD means limit of detection (serum HCV RNA is less than 10 IU/mL) and LOQ means limit of quantification (serum HCV RNA is less than 25 IU/mL). HCV RNA levels can be measured using commercially available methods.

The endpoint of treatment is a virological response, i.e., the absence of HCV at the end of a treatment course, several months after initiation of treatment, or several months after completion of treatment. HCV in serum may be measured at the RNA level by methods such as quantitative RT-PCR or northern blots or at the protein level by enzyme immunoassay or enhanced chemiluminescence immunoassay of viral proteins. The endpoint may also include a determination of a serum ALT level in the normal range.

The virological response parameters are: rapid virologic response at treatment week 4 (RVR 4) defined by undetectable serum HCV-RNA at treatment week 4; early virological response (EVR), defined by at least 2 log₁₀ IU/mL reduction in HCV-RNA compared to baseline (partial EVR) or undetectable serum HCV-RNA (complete EVR) at treatment week 12; sustained virological response (SVR24), defined as absence of HCV-RNA from serum by a sensitive Polymerase Chain Reaction (PCR) assay 24 weeks following end of therapy or the HCV RNA is undetectable (by LOD) 24 weeks after end of treatment; End of Treatment Response (ETR): HCV RNA undetectable (by LOD) at treatment end (completed or prematurely discontinued).

Exemplary therapeutic regimens are given in the Examples. In one exemplary protocol a subject in need of treatment is provided with about 200 mg to about 400 mg alisporivir orally twice daily for 2 weeks, followed by about 200 mg to about 400 mg alisporivir orally twice daily for up to 12 weeks.

The following Examples illustrate the embodiments of the disclosure described hereinbefore.

EXAMPLES

1. Compounds

Ribavirin is a synthetic nucleoside analogue and is also commercially available, e.g., as COPEGUS® from Roche.

Alisporivir gelatin capsules.

Example 1 – DEB025A2233: A Phase II, multicenter, open-label, randomized, 2 arms, dose exploration phase II study.

A total of approximately 60 G2 and 3 patients who have previously failed interferon therapy or are intolerant or unable to take interferon will be randomized into one of the 2 treatment groups (A or B) in a 1:1 ratio.

Randomization will be stratified by the following parameters measured at screening:

Viral load at screening ($\geq 800,000$ IU/mL ($5.903 \log_{10}$) or $< 800,000$ IU/mL ($5.903 \log_{10}$))

Study epoch: The total planned duration of the study is up to 48 weeks from randomization as shown in Figure 1. The main study includes 3 epochs: screening, treatment period 1(DEB025/RBV treatment), and post treatment follow-up 1.

1. **Screening epoch:** with duration of 1 to 42 days during which study eligibility will be confirmed.

2. **Treatment period 1(DEB025/RBV treatment) epoch (12 or 24 weeks):** Patients will be randomized into one of three parallel treatment arms:

Arm A: Dual-therapy with a response-guided treatment duration with DEB025 400 mg BID and RBV 1000 - 1200 mg/day (1000 mg for patients < 75 kg, 1200 mg/day for patients ≥ 75 kg of body weight at screening) for 12 or 24 weeks based on week 2 HCV RNA results.

DEB025/RBV Response-guided treatment duration:

- A1: Patients with a viral load $< \text{LLOQ}$ at week 2 will stop DEB025/RBV study treatment after 12 weeks.
- A2: Patients with a viral load $\geq \text{LLOQ}$ at week 2 will complete 24 weeks DEB025/RBV study treatment.

Arm B: Dual-therapy with a response-guided treatment duration with DEB025 300 mg BID and RBV 1000 - 1200 mg/day (1000 mg for patients < 75 kg, 1200 mg/day for patients ≥ 75 kg of body weight at screening) for 12 or 24 weeks based on week 2 HCV RNA results.

DEB025/RBV Response-guided treatment duration:

- B1: Patients with a viral load < LLOQ at week 2 will stop DEB025/RBV study treatment after 12 weeks.
- B2: Patients with a viral load $\geq$ LLOQ at week 2 will complete 24 weeks DEB025/RBV study treatment.

5

3. **Follow up epoch** during which patients do not receive any study medication. The duration of the follow-up epoch is 24 weeks.

10 **Example 2 Rationale of Dose/Regimen, Mode of Administration, and Duration of Treatment with DEB025**

The doses/regimens have been chosen based on inferences made from available clinical data, including the use of modeling and simulation. Recently available on-treatment results from the ongoing study CDEB025A2210 were also considered.

15 Clinical observations from multiple early studies administering DEB025 with peg-IFN α 2a with or without RBV revealed a relationship between Cmin (“trough” exposure) and various measures of antiviral effect, including change from baseline at week 1, RVR, EVR, and SVR. With the data from ESSENTIAL study (Debio 025-HCV-205), categorical observations based on Cmin quintiles suggested a trend for higher response rates with higher Cmin regardless of treatment duration.

20 In vitro sub-genomic replicon EC50 values (unadjusted for protein binding) ranged from 31 to 70 nM in GT1a, 1b, 2a, and 3a replicons. The highest protein binding-adjusted IC50 estimated from GT1a and 1b replicons was 371 ng/mL (305 nM) for GT1a, and 366 ng/mL for GT1b. Analysis of the clinical data revealed that the Cmin associated with the best treatment responses (>411 ng/mL) is consistent with the protein-binding adjusted IC50 estimated from GT1a and 1b replicons. It is assumed that the concentration-response relationship for cyclophilin inhibition is independent of HCV genotype. The clinical experience with DEB025 to date corroborates the assumption. Consequently, the target Cmin of 371 ng/mL is the basis for the therapeutic regimen of DEB025 in the treatment of GT1-4 HCV, including treatment-naïve and –experienced patients.

30

Accounting for the distribution of exposure (i.e., PK variability) as well as variability in viral susceptibility (i.e., variation in the required C_{min} for individual patients), the BID regimens included cover the efficacious dose range based on previously investigated regimens (i.e., 600 mg QD and 400 mg BID). Although the time to steady-state is less critical for DEB025 relative to a DAA, particularly considering the higher barrier to resistance, twice daily administration does increase in vivo exposure faster than once daily administration and most importantly maintains a higher C_{min}. The efficacy and safety of the highest proposed dose, 400 mg BID, has been confirmed in a recent interim analysis from the CDEB025A2210 study. The antiviral activity of the 400 mg BID regimen of DEB025 with peg-IFN α 2a and RBV (i.e., triple therapy) in treatment-experienced GT1 patients over the first 12 weeks of treatment was greater than that observed with the once daily regimens (including 800 mg dosed QD) or the peg-IFN α 2a /RBV control as shown in Figure 2.

At the on-treatment week 12 time point, the rate of HCV-RNA undetectable was superior in the 400 mg BID group (cEVR 72%; $p < 0.01$ for all comparisons) compared with peg-IFN α 2a /RBV dual therapy (cEVR 33%) as well as triple therapy regimens in which DEB025 was administered as 600 mg (cEVR 46%) or 800 mg (cEVR 61%) once daily.

Although the safety profile was generally similar across the BID and QD regimens when DEB025 was administered with peg-IFN α 2a /RBV, the 400 mg BID regimen was associated with increased frequencies of certain adverse events, notably a higher incidence of benign, reversible jaundice, nausea, vomiting, and neutropenia. Determining the safety and/or tolerability profile of alternative BID regimens of DEB025 will be important in determining the best dosing regimen for IFN free treatment in GT2/3 for future phase III and in planning future combinations with DAA in interferon free regimens. This is particularly relevant in that IFN likely contributes to the nausea, vomiting and neutropenia and alternative BID dosing not been explored in an IFN-free regimen.

The available clinical evidence continues to agree with the modeled relationships for exposure and response (efficacy) and the predictions made based on them, specifically that a higher C_{min} based on dose administered translates into better efficacy. A regimen

less than 200 mg BID was not included because it would be predicted to fail to keep the median steady-state trough exposure above that of 600 mg QD .

5 The IFN-free regimens of DEB025 + RBV in the planned study are approximately equal to or higher than the DEB025 regimens investigated in the phase 2 study in patients with GT2/3 HCV (VITAL-1), which included 1,000 mg QD, but do not exceed the highest doses/regimens investigated in GT1 HCV patients. The regimens are expected to comprehensively characterize the antiviral activity and short-term safety (without concomitant peg-IFN α 2a) of DEB025-based dual therapy to further inform and ultimately refine the dose justification for DEB025 based on PK/PD relationships for both safety/tolerability and efficacy.

RBV weight based dose

15 RBV is recommended as a fixed dose of 800mg daily for HCV G2 or 3 treatment-naïve patients in combination with pegIFN for 24 weeks. For treatment failure HCV G2 or 3 patients, the recommended dose of RBV is 1000-1200 mg/day (weight-based) with pegIFN over 48 weeks of treatment. When used in combination with interferon, ribavirin dosing has primarily been toxicity limited (anemia) with higher responses seen with greater ribavirin exposure. For therapy of G1 patients it has been common practice to utilize weight-based ribavirin when used in combination with interferon, direct acting anti-virals or in combination with both. In the VITAL-1 study, which used a flat dose of 20 800 mg/d for all patients, a logistic regression analysis showed that a higher RBV concentration was significantly associated with better efficacy (SVR), with higher weight inversely correlated to efficacy. Therefore, in this study we propose to use appropriate weight-based RBV in combination with DEB025 to ensure all patients receive a similar and higher mg/kg RBV dose.

25 The safety of RBV without the marrow suppressive effects of pegIFN is should be markedly better than with pegIFN, nevertheless, anemia is the primary abnormality to be expected.

Combination DEB025 + RBV

30 The rationale of including RBV with DEB025 comes from combination studies with IFN which have shown that RBV substantially increases SVR rates, mainly by preventing

relapse (McHutchison JG et al, (1998) Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. N Engl J Med, 339(21):1485-92). RBV was also effective in preventing viral breakthrough and relapse in combination treatments with peg-IFN α 2a and the protease inhibitor telaprevir (Hézode C, Forestier N, Dusheiko G, et al. (2009) Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. N Engl J Med.; 360 :1839-50) or boceprevir (Kwo PY, Lawitz EJ, McCone J, et al.(2010) Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. Lancet 2010; 376:705-16).

Interim analysis from the VITAL-1 study demonstrated higher response rates in the DEB025 arms containing RBV compared to the DEB025 monotherapy at a higher dose. To date, all studies with single or dual oral anti-HCV agents seem to indicate the need for concomitant RBV therapy and subsequently the development of DEB025 is currently intended to include RBV in the therapeutic regimen. The performance of the three different doses of DEB025 will be investigated with concomitant administration of weight based RBV in this study.

Treatment duration

One of the areas under attention in the clinical development of anti-HCV drugs is the shortening of overall treatment duration. Therefore, a response guided approach guided by on-treatment responses to DEB025/RBV treatment will be investigated in this study. The treatment duration of 12 or 24 weeks is based on a Pharmacokinetic-Viral kinetic (PKVK) model that was developed using the data obtained from the Phase II study in GT2/3 treatment naive patients (VITAL-1). In this model predicts that for patients treated with DEB025/RBV without interferon, patients who achieve undetectable HCV RNA by treatment week 2 will achieve very high rates of sustained virologic response with only 12 weeks of therapy. This model suggests that with 400 mg BID DEB025 plus ribavirin 26% of patients will be viral negative by week 2 of therapy. In the VITAL-1 study, approximately half of patients treated with DEB025/RBV achieved unquantifiable HCV-RNA levels by treatment week 6 or earlier. The majority of patients who still had

detectable virus had viral loads that were several logs lower than baseline. The curves of viral load decreases during the first 6 weeks were clearly differentiated among the doses.

CLAIMS

1. A method of treating a hepatitis C genotype 2 and 3 infections in a patient who has previously failed interferon therapy or is intolerant or unable to take interferon, the method comprising the step of administering to the patient alisporivir in combination with ribavirin, wherein alisporivir is administered in an amount of about 200 mg to about 400 mg twice a day.
2. A method according to claim 1, wherein 1000 mg/day of ribavirin is administered for patients having body weight less than 75kg and 1200 mg/day of ribavirin is administered for patients having body weight greater than or equal to 75 kg.
3. A method according to claim 1, wherein about 200 mg of alisporivir is administered twice a day.
4. A method according to claim 1, wherein about 300 mg of alisporivir is administered twice a day.
5. A method according to claim 1, wherein about 400 mg of alisporivir is administered twice a day.
6. A method of treating a hepatitis C virus genotype 2 or 3 infection in a patient who has previously failed interferon therapy or is intolerant or unable to take interferon characterized in that (i) alisporivir is administered in an amount of between about 200 mg to about 400 mg twice a day in combination with ribavirin for about 2 weeks, and (ii) if HCV RNA in the patient plasma is detectable by a HCV-RNA assay following step (ii), then administering alisporivir in an amount of about 200 mg to about 400 mg twice a day in combination with ribavirin for up to about 24 weeks in the absence of interferon, and (iii) if HCV RNA in the patient plasma is not detectable by a HCV-RNA assay following step (ii), then administering alisporivir in an amount of about 200 mg to about 400 mg twice a day in combination with ribavirin for up to about 12 weeks in the absence of interferon.
7. A method according to claim 6, wherein about 200 mg of alisporivir is administered twice a day.

8. A method according to claim 6, wherein about 300 mg of alisporivir is administered twice a day.

9. A method according to claim 6, wherein about 400 mg of alisporivir is administered twice a day.

5 10. Alisporivir for use in treatment of a Hepatitis C virus genotype 2 or 3 in a patient who has previously failed interferon therapy or is intolerant or unable to take interferon characterized in that (i) alisporivir is administered in an amount of between about 200 mg to about 400 mg, twice per day in combination with ribavirin in the absence of interferon.

10 11. Alisporivir for use according to claim 10 wherein alisporivir is administered in an amount of about 200 mg twice per day.

12. Alisporivir for use according to claim 10 wherein alisporivir is administered in an amount of about 300 mg twice per day.

13. Alisporivir for use according to claim 10 wherein alisporivir is administered in an amount of about 400 mg twice per day.

15 14. A therapeutic regimen for treating a hepatitis C virus genotype 2 or 3 in a patient who has previously failed interferon therapy or is intolerant or unable to take interferon characterized in that (i) alisporivir is administered in an amount of between about 200 mg to about 400 mg twice a day in combination with ribavirin for about 2 weeks in the absence of interferon, and (ii) if HCV RNA in the patient plasma is detectable by a HCV-
20 RNA assay following step (ii), then administering alisporivir in an amount of about 200 mg to about 400 mg twice a day in combination with ribavirin for up to about 24 weeks in the absence of interferon, and (iii) if HCV RNA in the patient plasma is not detectable by a HCV-RNA assay following step (ii), then administering alisporivir in an amount of about 200 mg to about 400 mg twice a day in combination with ribavirin for up to about
25 12 weeks in the absence of interferon.

15. A therapeutic regimen according to claim 14, wherein about 200 mg of alisporivir is administered twice a day.

16. A therapeutic regimen according to claim 14, wherein about 300 mg of alisporivir is administered twice a day.

17. A therapeutic regimen according to claim 14, wherein about 400 mg of alisporivir is administered twice a day

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18. A pharmaceutical composition comprising alisporivir for use according to any of the claims 10 to 13.

19. A package comprising the pharmaceutical composition according to claim 18 in combination with instructions to administer the composition.

10

Figure 1 Study Design

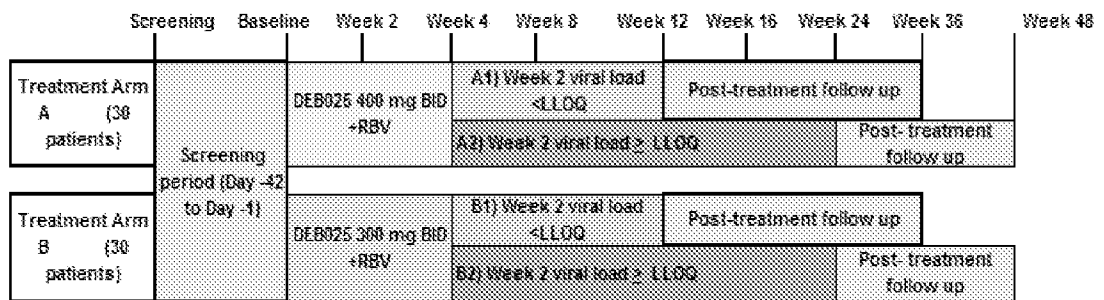
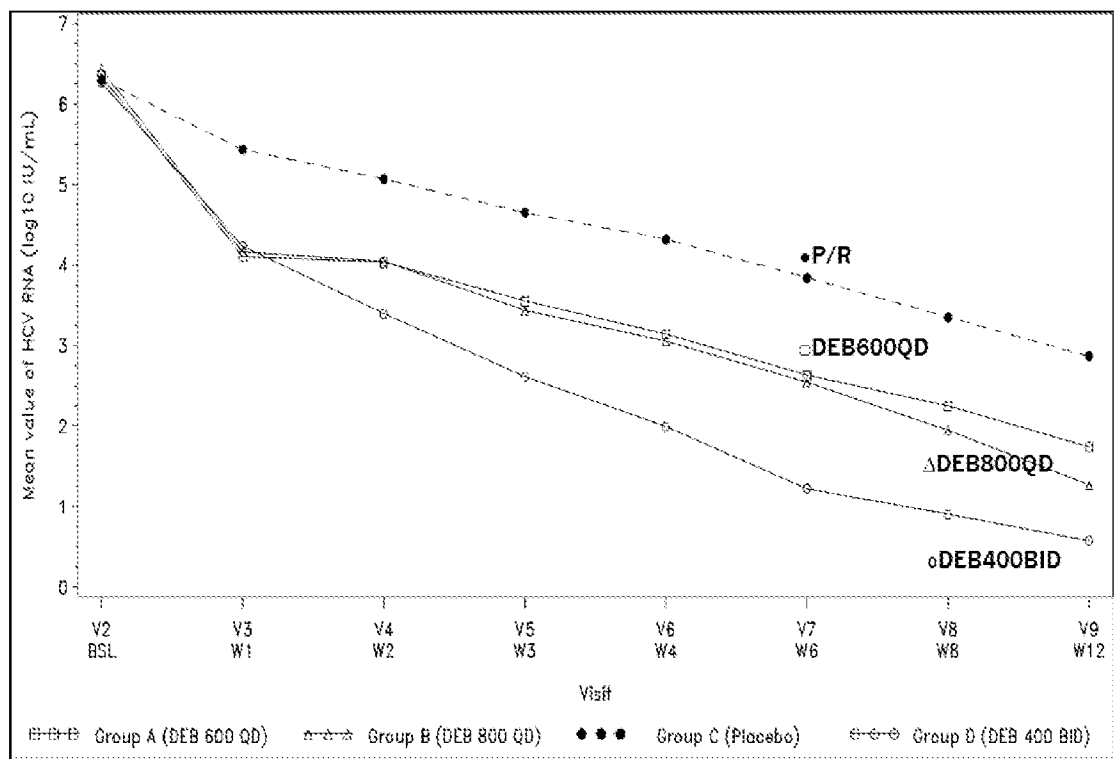


Figure 2 HCV RNA decline during the first 12 weeks of treatment (triple therapy with DEB025+ peg-IFN α 2a +RBV) in treatment-experienced GT1 patients

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/051761

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/708 A61K38/13 A61P1/16 A61P31/20
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 A61P

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)

EP0-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C.



See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search

9 April 2015

Date of mailing of the international search report

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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

Weisser, Dagmar

INTERNATIONAL SEARCH REPORT

International application No
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International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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