EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 November 2013
EMA/797185/2013

Summary on compassionate use for

Daclatasvir, Bristol-Myers Squibb Pharma EEIG

International non-proprietary name: Daclatasvir

Procedure No. EMEA/H/K/003867/CU

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

An agency of the European Union

Product Information

Name of the medicinal product for Compassionate Use:	Daclatasvir
Company:	Bristol-Myers Squibb
Active substance:	daclatasvir
International Nonproprietary Name:	
Target Population:	Daclatasvir for the use in combination with sofosbuvir +/- ribavirin, for genotype 1 patients above 18 years of age and are at a high risk of decompensation or death within 12 months if left untreated
Pharmaceutical form:	Film coated tablet
Strength:	30 and 60 mg
Route of administration:	oral use
Packaging:	High-density polyethylene (HDPE) bottles
Package sizes:	33 tablets

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1. Background information on the procedure

1.1. Submission of the dossier

Sweden notified the European Medicines Agency (EMA) on 16 July 2013 and requested a CHMP opinion on the compassionate use for the above mentioned medicinal product in accordance with Article 83(3) of Regulation (EC) No 726/2004 of the European Parliament and of the council (31 March 2004).

The legal basis for this application refers to:

Article 83(3) of Regulation (EC) No 726/2004 of the European Parliament and of the council (31 March 2004)

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bengt Ljungberg Co-Rapporteur: Joseph Emmerich

1.2. Steps taken for the assessment of the product

- The timetable for the procedure was agreed upon by CHMP on 25 July 2013
- The dossier was received by the EMA on 28 August 2013
- The Rapporteur's preliminary Assessment Report was circulated to all CHMP members on 8 November 2013
- The Rapporteur's updated Assessment Report was circulated to all CHMP members on 15 November 2013
- The CHMP opinion was adopted on 21 November 2013

2. General conditions for the manufacturer

2.1. Manufacturers

Manufacturer of the active substance

Name: Bristol-Myers Squibb Company

Address: One Squibb Drive New Brunswick, New Jersey 08903-0191

Country: United States of America

Manufacturer(s) of the finished product

Name: Bristol-Myers Squibb Company

Address: One Squibb Drive New Brunswick, New Jersey 08903-0191

Country: United States of America

Manufacturer responsible for import and batch release in the European Economic Area

Name: Bristol-Myers Squibb International Corporation

Address: Chaussée de la Hulpe

185 - 1170 Bruxelles

Country: Belgium

Name: Bristol-Myers Squibb Pharmaceuticals Ltd.

Address: Reeds Lane

Moreton

Wirral CH46 1QW

Country: England

2.2. Conditions of distribution

Medicinal product subject to restricted medical prescription.

2.3. Conditions for update of Compassionate Use to be implemented by the manufacturer

In accordance with Article 83(4) of Regulation (EC) No 726/2004, any change or new data having an impact on the CHMP compassionate use opinion as adopted by the CHMP on 24 October 2013, related to the conditions of use, distribution and targeted population of daclatasvir, shall be communicated to the Agency (EMA) in order to update the CHMP Compassionate Use opinion as appropriate.

2.4. Conditions for safety monitoring to be implemented by the manufacturer

In accordance with Article 83(6) of Regulation (EC) No 726/2004, the pharmacovigilance rules and responsibilities defined in Articles 28(1) and 28(2) of the Regulation (EC) No 726/2004 are applicable to medicinal products for which an opinion on the conditions for compassionate use has been adopted. The manufacturer will ensure that these pharmacovigilance obligations are fulfilled.

2.5. Conditions for safety monitoring to be implemented by the Member States.

In accordance with Article 83(6) of Regulation (EC) No 726/2004, the pharmacovigilance rules and Responsibilities defined in Article 28(1) of the Regulation (EC) No 726/2004 are applicable to medicinal products for which an opinion on the conditions for compassionate use has been adopted. The Member State(s) will ensure that these pharmacovigilance obligations are fulfilled.

3. Scientific Discussion

3.1. Introduction

As requested by the CHMP in July 2013, the company submitted a dossier to support the compassionate use of product. The dossier was presented in specify dossier format (CTA).

There are currently no likely effective approved treatment options for patients that have failed to reach SVR when treated with a first generation NS4/4A protease inhibitor (telaprevir [TVR] or boceprevir [BOC]) in combination with peginterferon and ribavirin. In most cases, such patients will have selected for resistant variants that are likely to exhibit cross resistance among presently available agents of the NS3/4A inhibitor class. Many such patients have advanced liver disease and are in urgent need of therapy that induces a sustained virological response (SVR) in order to cease the progression of liver injury. Given their treatment history, such patients would be considered "difficult to cure"; i.e. the sum potency and barrier to resistance of a likely effective regimen needs to be high.

Furthermore, this unmet medical need extends generally to patients with very advanced liver disease that have portal hypertension, as evidenced, e.g., by thrombocytopenia, and patients with hepatic impairment or a history of clinical decompensation. For such patients, regardless of viral genotype, interferon based treatment alternatives are either ill tolerated with low effectiveness, or downright contraindicated due to the risk of precipitating further hepatic deterioration or serious bacterial infections.

Daclatasvir is a first-in-class HCV NS5A (hepatitis C virus nonstructural protein 5A) replication complex inhibitor, and sofosbuvir is a nucleotide NS5B (nonstructural protein 5B) polymerase inhibitor. These drugs have been studied in combination, with or without ribavirin, in a clinical trial (AI444040) including genotype 1 infected patients who previously failed telaprevir or boceprevir treatment. This trial is indicative of high efficacy in such patients, including patients with an urgent medical need and without likely effective approved treatment options.

Therefore, this article 83 application considers the compassionate use of daclatasvir in combination with sofosbuvir, with or without ribavirin. The applicant proposed that the target population be defined as follows:

Daclatasvir for the combination use with sofosbuvir +/- ribavirin, for genotype 1 patients who previously failed on boceprevir or telaprevir based therapy, above 18 years of age and are in urgent need of effective treatment defined by the company as having a life expectancy of < 12 months if the HCV infection is left untreated.

The applicant proposed the following posology and regimen:

"The recommended dose of daclatasvir is 60 mg in combination with sofosbuvir 400 mg once daily for duration of 24 weeks."

To this, the applicant has added the following reflection:

"While the data to date in study AI444040 indicate that the addition of ribavirin to the daclatasvir/sofosbuvir combination did not impact the efficacy in the populations studied, this data are limited. Compared to daclatasvir/sofosbuvir, the inclusion of ribavirin to this combination led to a greater decline in haemoglobin, and in some cases required dose reduction of ribavirin in the later group. Thus, while daclatasvir/sofosbuvir + ribavirin can be used to treat telaprevir or boceprevir failures, the use of the combination of daclatasvir /sofosbuvir (without ribavirin) should be considered as adequate treatment."

3.2. Quality aspects

Introduction

Daclatasvir for compassionate use is formulated as 30mg and 60mg film-coated tablets and packed in HDPE bottles. The excipients used are anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, silicon dioxide, magnesium stearate and the film-coating agent Opadry

Green 03B110007. An application for the marketing of a drug product containing daclatasvir as active substance is planned via the Central Procedure in the EU.

Drug Substance

Daclatasvir is "methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate dihydrochloride" with the CAS number [1009119-65-6]. The molecular formula is C40H50N8O6×2 HCl and the molecular weight is 811.80 (738.88 as free base).

Daclatasvir is a white to yellow powder with poor solubility in water and ethanol at neutral pH. The solubility is strongly pH-dependent and the solubility is high at low pH values. The drug substance exhibits polymorphism and the thermodynamically stable, solvent-free crystal form N-2 is manufactured by the applicant. The drug substance is slightly hygroscopic.

Control of Drug Substance

The drug substance specification covers appearance, identification, colour, identity, assay, related substances (eight specified, individual unspecified, total), residual solvents, water content, HCl content, acetamide, 2-hydroxypyridine-1-oxide, EDAC and total inorganic impurities. The impurities and the limits associated therewith have been evaluated and found to be acceptable. Adequate batch analyses of the active substance are included. The control of drug substance can be accepted.

Stability

The drug substance is stored in double polyethylene bags. A retest period of one year is proposed with the recommended storage condition of 25 °C and protected from light. Stability data of one batch over 12 months at long-term conditions 25 °C /60% RH and accelerated stability data at 40 °C/75% RH is available. A re-test period of one year can be accepted.

Drug Product

Pharmaceutical Development

The drug product is described as plain, green, biconvex, pentagonal film-coated tablets packed in white HDPE bottles. The excipients are commonly used in drug development.

Adventitious Agents

Neither the excipients nor the active substance are derived from human or animal origin with the exception of lactose anhydrous. The vendor of lactose anhydrous certifies that the milk is sourced from healthy animals in the same condition as milk fit for human consumption. The magnesium stearate is obtained from vegetable sources.

Manufacture of the Product

The drug product is manufactured by a standard manufacturing process. In-process controls include weight variation, friability, disintegration time, tablet weight and hardness during tablet compression and weight gain during film coating.

Product Specification

The specification presented is considered appropriate and covers appearance, identity, content uniformity, potency (LC and percent of label), individual unspecified impurities, total impurities and dissolution. The analytical procedures are described and validated. One batch analysis of the 30 mg tablet and two of the 60 mg tablet are included. The batch analyses conform to the

specification. The impurity profile of the drug product is consistent with the impurity profile observed in the drug substance; there are no degradation impurities of the drug product.

Stability of the Product

Stability data is presented for 30 mg and 60 mg tablets. Long-term stability results are available covering 18 months at 25 °C/60% RH for the 30 mg tablets and 24 months at 25 °C/60% RH for the 60 mg tablets. The parameters covered in the stability program are appearance, potency, impurities, dissolution, hardness, disintegration time and water content.

No trend in degradation can be seen. A use-period of 30 months for the 30 mg tablets and 36 months for the 60 mg tablets is proposed by the applicant when stored at 15–25 ºC in a tightly closed container. The stability data and use-period can be accepted.

Overall assessment on Quality

The overall assessment has taken into consideration the purpose of compassionate use. Daclatasvir has previously been approved for use in clinical studies. All relevant information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results indicate acceptable consistency and uniformity of all the important quality characteristics of the product. It can be reasonably concluded that the product should have a satisfactory and uniform performance in the clinic. The Quality documentation can be accepted and is not expected to have a negative impact on the Benefit Risk balance of the product in the context of this procedure.

3.3. Non-clinical aspects

Daclatasvir (DCV, BMS-790052) is an inhibitor of HCV genotype 1a and 1b replication in cell-based replicon assays with effective concentration (50% reduction, EC50) values of 0.003-0.050 and 0.001-0.009 nM, respectively, depending on the assay method. Furthermore, daclatasvir has replicon EC50 values of 0.003-1.25 nM for genotypes 3a, 4a, 5a, and 6a, and 0.034-19 nM for genotype 2a as well as 0.020 nM for infectious genotype 2a (JFH-1) virus.

The major HCV variants observed in clinical studies were at amino acid positions identified previously in resistance studies using the in vitro replicon system.

The pharmacokinetic (PK) characteristics of DCV were evaluated in mice, rats, dogs, and monkeys. In rats, orally administered [14C]DCV was rapidly absorbed and widely distributed; concentrations were detectable in all the tissues analyzed and were highest in the adrenal gland, bile, liver, and alimentary tract tissues; there was little distribution of DCV or its metabolites to brain tissue. DCV and BMS-805215 (M2) were the only circulating drug-related components in human plasma. No glutathione conjugate of DCV was detected. The metabolite M2-to-total drug area under the concentration time curve (AUC) ratio was approximately 5% after single dose and remained less than 5% following multiple doses indicating no accumulation of the metabolite (preliminary results). There were no unique human DCV metabolites detected in vitro or in vivo. In humans, feces (87.7%) was the main route of DCV elimination with little renal excretion (6.6%).

DCV has been evaluated in oral single-dose (mice, rats, monkeys, dogs) and repeat-dose (rats, dogs, monkeys) toxicity studies, as well as phototoxicity, safety pharmacology, genetic, reproductive, combination, and investigative toxicity studies. Dogs did not tolerate DCV at a dose of 100 mg/kg/day (AUC = 158 µgxh/mL), which was associated with mortality due to bone marrow and hepatic toxicity. In contrast, with the exception of a single monkey (150 mg/kg/day; AUC = 80.3 µgxh/mL) euthanized with signs of hepatic and bone marrow toxicity, monkeys tolerated DCV dosed for up to 9 months (up to 300 mg/kg/day; AUC up to 41.2 µgxh/mL). The findings for this 1

decedent monkey were not consistent with findings in other monkeys dosed for up to 9 months; however, a relationship to DCV could not be excluded. Target organs in both rats (up to 6 months) and monkeys (up to 9 months) included the liver (monkeys) and adrenal gland (rats and monkeys). Hepatic effects included minimal to slight bile duct hyperplasia, a response likely related to hepatic inflammation, and, at higher DCV doses, altered composition of bile and/or increased hepatic DCV levels. In rats, reversible adrenal cortical hypertrophy was associated with increased urine corticosterone levels at 100 mg/kg/day (AUC = 107 µg•h/mL). Adrenal gland changes in monkeys were characterized as reversible minimal to marked decreases in cytoplasmic vacuolation in the cortical zona fasciculata, and in males, increases in adrenal-gland weight at ≥ 30 mg/kg/day (AUC ≥ 11.6 µgxh/mL), and at a dose of 300 mg/kg/day (AUC = 41.2 µgxh/mL) slight cortical hyperplasia in the zona reticularis. With repeat dosing across species and study durations up to 9 months, no observed effect level (NOEL) or no observable adverse effect level (NOAEL) doses and AUC values were generally consistent indicating little potential for cumulative or new toxicities to emerge with long-term administration.

In cardiac ion channels assays, DCV and its M4 metabolite displayed mild to moderate inhibitory effects toward the cardiac hERG/IKr potassium channel, sodium channel, and L-type calcium currents. In anaethestized rabbits, single oral doses of DCV at 30 mg/kg induced moderate increase in QRS duration, mild increase in PR, AH, and HV intervals, and mild increases in blood pressure, with no effects on QT intervals observed at any dose. A dose of 10 mg/kg was identified as the NOEL in the rabbit electrophysiologic study. In telemetered dogs, a single dose of 100 mg/kg induced reversible increases in systemic pressures, and small decreases in an index of left ventricular cardiac contractility (+dP/dt), whereas 15 mg/kg was the NOEL.

Central nervous system (CNS) and respiratory safety pharmacology assessments were conducted as part of the pivotal single- and repeat-dose studies in rats, dogs, and monkeys. There were no clear DCV-related CNS or respiratory effects observed in these studies, except for changes (increased body temperature and/or heart rate in early death animals in the 1-month study in dogs or 9-month study in monkeys that were considered secondary to other DCV-related effects.

DCV was not genotoxic (in vitro or in vivo) or phototoxic (in vivo). Carcinogenicity assessments are ongoing (2-year rat and 6-month transgenic mouse). DCV was not a selective developmental toxicant, nor was administration associated with maternal or developmental toxicity at doses of 50 mg/kg in rats (AUC = 70.1 µgxh/mL) 40/20 mg/kg in rabbits (AUC = 245 µgxh/mL). At doses ≥ 200 mg/kg/day in rats (AUC ≥ 375 µg•h/mL) and ≥ 200/99 mg/kg in rabbits (AUC ≥ 1080 µg•h/mL), maternal and developmental (teratogenicity) toxicities were evident in both species. In a study of fertility and early embryonic development in male and female rats, there were no effects on female reproductive parameters and the NOEL for reproductive toxicity in females was 200 mg/kg/day (AUC = 267 µgxh/mL). In male rats, the NOEL for reproductive toxicity was 50 mg/kg/day (AUC = 51.8 µgxh/mL). Reproductive effects in males occurred only at a high AUC value (290 µgxh/mL, 200 mg/kg/day) that produced overt toxicity (reduced prostate/seminal vesicle weights and minimally increased dysmorphic sperm).

Potential toxicologic interactions were assessed for DCV in combination with ASV and/or BMS-791325 (other BMS small molecule direct acting antivirals [DAAs]) in rats, monkeys and dogs and with pegIFNα/RBV in monkeys. There was no evidence of toxicologic interaction in dual small molecule combination studies or in combination with pegIFNα/RBV. In a DCV/ASV/BMS-791325 Triple combination study in dogs, morphologic changes in the liver (liver Kupffer cell hyperplasia/hypertrophy) were observed. These changes were also observed in studies with DCV alone. Although the DCV-related liver findings in the DCV/ASV/BMS-791325 Triple combination study occurred at a lower exposure suggesting a lower threshold for potential hepatic effects, the findings were considered non-adverse because of the minimal nature and low incidence.

Overall, nonclinical assessment of DCV as a single agent, of DCV in combination with ASV and/or BMS-791325, and of DCV/pegIFNα/RBV supports the continued evaluation of DCV as a single agent or in combination in humans.

Pregnancy and contraception requirements

There are no data from the use of daclatasvir in pregnant women.

Studies of daclatasvir in animals have shown reproductive toxicity.

Daclatasvir is not recommended during pregnancy or in women of childbearing potential not using contraception.

Breast-feeding

Available pharmacokinetic and toxicological data in animals have shown excretion of daclatasvir and metabolites in milk.

It is not known whether daclatasvir is excreted in human milk. Mothers should be instructed not to breastfeed if they are taking daclatasvir.

Fertility

Available toxicological data in animals have not shown effects of daclatasvir or metabolites on fertility.

No human data on the effect of daclatasvir on fertility are available.

Carcinogenesis and mutagenesis

Daclatasvir was not carcinogenic in CByB6F1/Tg rasH2 hemizygous mice in a 6 month study at AUC values 8.7 times the exposure at the recommended human dose of 60 mg/day. A 2 year carcinogenicity study in rats is ongoing. No evidence of mutagenic or clastogenic activity was observed in in vitro mutagenesis (Ames) tests, mammalian mutation assays in Chinese hamster ovary cells, or in an in vivo oral micronucleus study in rats.

Impairment of fertility

Daclatasvir had no effects on fertility in male or female rats at any dose tested. The highest AUC values in unaffected females were 18 fold those in humans at the recommended dose of 60 mg/day. In male rats, effects on reproductive endpoints were limited to reduced prostate/seminal vesicle weights, and minimally increased dysmorphic sperm at 200 mg/kg/day; however, neither finding adversely affected fertility or the number of viable conceptuses sired. The AUC associated with this dose in males is 19.2 fold the exposure at the recommended human dose of 60 mg/kg/day.

Embryo-fetal development

Daclatasvir was not a selective developmental toxicant when administered to pregnant rats or rabbits during organogenesis. Neither maternal nor developmental toxicities were observed at maternal daclatasvir doses associated with AUC values 4.6-fold (rat) and 16-fold (rabbit) the recommended human dose of 60 mg/day. At higher doses, concomitant maternal and developmental toxicities were noted in both species; AUC values associated with these doses were 25-fold (rat) and 72-fold (rabbit) those in humans at 60 mg/day. Maternal toxicity included mortality, adverse clinical signs, and decreases in body weight and food consumption. Developmental toxicity consisted of increases in embryofoetal lethality, reduced foetal body weights, and increased incidence of foetal malformations of the ribs and variations, notably affecting the developing head and skull.

In a study of pre- and postnatal development in rats, there was neither maternal nor developmental toxicity at doses up to 50 mg/kg/day, associated AUC values 2.6-fold the human AUC at the recommended dose. At the highest dose (100 mg/kg/day), maternal toxicity included mortality and dystocia; developmental toxicity included slight reductions in offspring viability in the peri- and neonatal periods; and reductions in birth weight that persisted into adulthood. The AUC value associated with this dose is 4.7-fold the AUC in humans at 60 mg/day.

Excretion into milk

Daclatasvir was excreted into the milk of lactating rats with concentrations 1.7 to 2-fold maternal plasma levels.

Discussion on non-clinical aspects

The non-clinical data presented adequately describes the primary pharmacological and toxicological properties of daclatasvir. In monkey and dog studies hepatic effects were evident and the compound was not tolerated in dog due to liver and bone marrow toxicity. Also adrenal glands appeared affected in rat and monkey studies. Liver effects included minimal to slight bile duct hyperplasia, a response likely related to hepatic inflammation, and, at higher doses, altered composition of bile and/or increased hepatic daclatasvir levels. In general, at the NOAELs identified in repeat dose toxicity studies margins of exposure to expected clinical levels at proposed doses, were less than 1. The clinical safety data is limited, but has not to date indicated liver adverse effects. Daclatasvir was potentially phototoxic in vitro, but not in a single dose study in rat administered doses up to 100 mg/kg corresponding to systemic exposure levels of up to 107 µgxh/ml.

The toxicological profile of sofosbuvir and daclatasvir indicates that a concern for enhanced toxicological reactions due to combination treatment likely is limited.

The non-clinical studies are sufficient in scope and extent to support the proposed 24 week duration of clinical use.

The information relevant to non-clinical aspects presented in the Applicant´s proposal for recommendations for health professionals is considered acceptable.

3.4. Clinical aspects

Introduction

Pharmacokinetics

Absorption

Peak daclatasvir concentrations were generally observed approximately 1 to 2 hours post-dose. Administration of a high-fat meal reduced Cmax and AUC by 28% and 23%, respectively. Administration of a light meal did not influence daclatasvir exposure. Daclatasvir exposure HCV infected subjects appeared to be lower than those observed in healthy volunteers at repeated doses from 1 to 30 mg, but similar at 60 mg.

Distribution

The protein binding of daclatasvir was estimated to 95.6%. Daclatasvir is transported by Pgp based on in vitro data.

Elimination and Excretion

Elimination of daclatasvir occurs mainly through faeces (88%) whereas 7% was recovered in urine predominantly as parent drug. After repeated administration the half-life of daclatasvir was between 12 to 15 hours.

Drug Interactions

Daclatasvir is a substrate of cytochrome P450 enzyme 3A4 (CYP3A4) and P-glycoprotein transporter (P-gp). Therefore, strong inducers of CYP3A4 or P-gp may decrease the plasma levels and therapeutic effect of daclatasvir. Strong inhibitors of CYP3A4 or P-gp (eg, amiodarone, clarithromycin, erythromycin, itraconazole, ketoconazole, quinidine, ranolazine, ritonavir) may increase the plasma levels of daclatasvir.

The availability of the 30 mg tablet formulation allows a dose reduction to 30 mg QD in the presence of a strong CYP3A4/P-gp inhibitor and a dose increase to 90 mg QD in the presence of a moderate CYP3A4/P-gp inducer.

There was a modest effect on the PK of daclatasvir with famotidine and no clinically meaningful effect on DCV PK with omeprazole; co administration is allowed.

Daclatasvir is also an inhibitor of P-gp, organic anion transporting polypeptide (OATP) 1B1 and 1B3 and breast cancer resistance protein (BCRP). Administration of daclatasvir may increase systemic exposure to medicinal products that are substrates of P-gp, OATP 1B or 1B3, or BCRP, which could increase or prolong their therapeutic effect and adverse reactions. Caution should be used if the medicinal product has a narrow therapeutic range.

There was no pharmacokinetic interaction with tacrolimus or ciclosporin.

Daclatasvir is contraindicated when combined with medicinal products that strongly induce CYP3A4 or P-gp, e.g. phenytoin, carbamazepine, phenobarbital, rifampicin, dexamethasone, and the herbal product St John's wort (Hypericum perforatum), and thus may lead to lower exposure and loss of efficacy of daclatasvir.

Data indicated that exposure to the major circulating metabolite of sofosbuvir is unchanged with coadministration with daclatasvir. No data is available for daclatasvir.

Special populations

Hepatic impairment
The pharmacokinetics of daclatasvir following a 30 mg single dose were studied in non-HCV infected subjects with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment compared with unimpaired subjects. Total (free + protein bound drug) daclatasvir C_{max} and AUC were lower in subjects with mild, moderate and severe hepatic impairment relative to subjects with normal hepatic function however, hepatic impairment did not have a clinically significant effect on the free drug concentrations of daclatasvir.

Renal impairment
Exposure of daclatasvir (AUC) was 26.4% higher in subjects with ESRD relative to healthy subjects while C_{max} was similar. This increase in exposure is considered not clinically significant.

Clinical efficacy

Daclatasvir is a first-in-class HCV NS5A (hepatitis C virus nonstructural protein 5A) replication complex inhibitor, and sofosbuvir is a nucleotide NS5B (nonstructural protein 5B polymerase inhibitor.

The combination of daclatasvir plus sofosbuvir has been evaluated in study AI444-040, with or without ribavirin in a clinical trial, in treatment-naïve, genotype 1, 3 infected patients, and in genotype 1 infected patients who failed telaprevir (TVR) or boceprevir (BOC) treatment.

The study included non-cirrhotic patients aged 18-70, with chronic HCV genotype 1-, 2-, or 3-infection. Treatment-experienced patients had confirmed virologic failure: non-response (HCV RNA detectable at end of treatment), breakthrough (>1 log increase from nadir in HCV RNA or HCV RNA quantifiable after being undetectable on treatment), or relapse (HCV RNA quantifiable during follow-up after being undetectable at end of treatment) during or following TVR (750 mg three times daily) or BOC (800 mg three times daily) plus peginterferon and ribavirin. Patients who discontinued TVR or BOC due to adverse events were excluded from the AI444040 study.

This open label study initially randomized 88 treatment-naïve patients 1:1:1 to sofosbuvir for 7 days, then daclatasvir and sofosbuvir for 23 weeks; daclatasvir and sofosbuvir for 24 weeks; or daclatasvir, sofosbuvir, and ribavirin for 24 weeks. The sofosbuvir lead in examined whether initial HCV suppression with sofosbuvir would reduce emergence of daclatasvir resistant variants. An additional 123 genotype 1 patients were randomized 1:1 to daclatasvir plus sofosbuvir with or without ribavirin for 12 weeks (treatment naïve, n=82) and 24 weeks (prior HCV protease inhibitor failures, n=41).

Daclatasvir and sofosbuvir were administered orally at 60 mg once daily and 400 mg once daily, respectively. Ribavirin was administered orally twice daily at 1000 1200 mg/day based on weight (<75 kg: 1000 mg; ≥75 kg: 1200 mg) in genotype 1 patients, and at 800 mg/day in genotype 2/3 patients. Ribavirin dose reduction to 600 mg daily was permitted if haemoglobin decreased below 10 g/dl.

Baseline demographic and disease characteristics were as follows:

Table 1 Baseline Demographics and Disease Characteristics

Parameter	Genotype 2/3			Genotype 1						
	Treatment naive			Treatment naive					Prior telaprevir or boceprevir failures	
	B SOF lead-in + DCV n=16	D DCV + SOF n=14	F DCV + SOF + Ribavirin n=14	A SOF lead-in + DCV n=15)	C DCV + SOF n=14	E DCV + SOF + Ribavirin n=15	G DCV + SOF 12-Wk n=41	H DCV + SOF + Ribavirin 12 wk n=41	I DCV + SOF n=21	J DCV + SOF + Ribavirin n=21
Age,median years	51	50	52	56	54	54	55	54	59	57
Male gender, n(%)	11 (69)	6 (43)	5 (36)	7 (47)	9 (64)	7 (47)	20 (49)	21 (51)	13 (62)	12 (60)
Race,[a] n(%)										
White	16(100)	10(71)	12(86)	11(73)	11(79)	12(80)	33(81)	33(81)	19(91)	18(90)
Black	0	2(14)	0	4(27)	3(21)	2(13)	5(12)	7(17)	2(10)	1(5)
HCV RNA,mean log_{10}	6.5	6.8	6.6	6.5	6.6	6.7	6.2	6.4	6.3	6.3

IU/mL(SD)	(0.7)	(0.5)	(0.6)	(0.5)	(03.)	(0.6)	(0.5)	(0.6)	(0.4)	(0.4)
HCV genotype,[b] n(%) 2//1a 3//1b	9(56) 7(44)	8(57) 6(43)	9(64) 5(36)	11(73) 4(27)	10(71) 4(29)	11(73) 4(27)	34(83) 7(17)	33(80) 8(20)	16(76) 5(24)	17(85) 3(15)
IL28B genotype,n(%) CC	8(50)	5(36)	7(50)	4(27)	8(57)	4(27)	9(22)	15(37)	1(5)	0
Fibrosis (Metavir score), [cd] n(%) Minimal/absent (F0-F1) Moderate F2-F3 Significant >F3F4	6(38) 7(44) 3(19)	6(43) 7(50) 1(7)	6(43) 6(43) 2(14)	4(27) 8(53) 3(20)	6(43) 7(50) 1(7)	6(40) 6(40) 2(13)	15(37) 19(46) 6(15)	13(32) 22(54) 5(12)	2(10) 14(67) 3(14)	3(15) 11(55) 6(30)

HCV, hepatitis C virus; ribavirin, 1000-1200 mg/day, weight-based, for genotype 1 patients, and 800 mg/day for genotype 2/3 patients. DCV, daclatasvir; SOF, sofosbuvir; RBV, ribavirin.
a "Other" included the following: D, n=2; F, n=2; E, n=1; G, n=3; H, n=1; J, n=1.
b Genotypes 2 and 3 are indicated for groups B, D, and F, and genotypes 1a and 1b for groups A, C, E, and G-J.
c The METAVIR score was derived from a FibroTest score (BioPredictive.com) and classified based on the FibroTest manufacturer's web site. Patients with F4 scores were required to have a liver biopsy showing the absence of cirrhosis.
d "Missing" included the following: E, n=1; G, n=1; H, n=1; I, n=2.

Among patients with NS3/4A inhibitor experience, prior exposure and treatment response was as follows:

Prior Treatment History of Patients Who Failed Telaprevir or Boceprevir (Groups I and J, n=41)

	Group I DCV + SOF (n=21)	**Group J DCV + SOF + RBV (n=20)**
Prior treatment[a]		
Telaprevir	15 (71)	18 (90)
Boceprevir	7 (33)	2 (10)
Prior failure type[b]		
Breakthrough	7 (33)	8 (40)
Relapse	10 (48)[b]	3 (15)
Nonresponse	5 (24) [b]	9 (45)
Median time from end of prior treatment, weeks	152	71

DCV, daclatasvir; SOF, sofosbuvir; RBV, ribavirin. [a] One patient in group I was reported to have been treated with both telaprevir and boceprevir. [b] One patient in group I was reported to have relapsed following treatment with boceprevir, and subsequently had nonresponse during treatment with telaprevir.

Overall, 211 patients were treated. By intention-to-treat analysis, SVR12 (sustained virologic response for 12 weeks after the last dose of study drug) was achieved by 98% of genotype 1 (treatment-naïve and HCV protease inhibitor virologic failure) and 91% of genotype 2/3 patients.

Confirmed virologic failure was not observed in any of 193 patients with genotype 1 or 2 infection whereas 1 of 18 genotype 3-infected patients experienced viral relapse. High response rates were observed across patients with HCV subtypes 1a and 1b, with CC and non-CC interleukin-28B (IL28B) genotypes, and in patients treated with and without ribavirin.

Among all genotype 1-infected treatment groups, no patient experienced virologic breakthrough, and all had HCV RNA<25 IU/ml at end of treatment. Post-treatment, no genotype 1 patient had confirmed virologic relapse across treatment groups. Overall, 98% (164/167) of genotype 1 patients achieved SVR12, including 84/85 treated for 24 weeks (44/44 treatment-naïve; 40/41 protease inhibitor-experienced) and 80/82 treated for 12 weeks.

Of three GT-1 infected patients not achieving SVR12, two achieved SVR24 (sustained virologic response for 24 weeks after the last dose of study drug) after missing the SVR12 visit, and one was lost to follow-up. SVR rates were similar in subgroups defined by viral subtype (1a vs 1b), IL28B genotype, ribavirin use, or history of failure on protease inhibitors.

Table 2 Virologic response during and after treatment

HCV RNA	N (%)											
	Genotype 2/3				Genotype 1							
	Treatment naive				Treatment naive						Prior Telaprevir or Boceprevir failures	
	B SOF lead-in + DCV	D DCV + SOF	F DCV + SOF + RBV	Total (B,D, F)	A SOF lead-in + DCV	C DCV + SOF	E DCV + SOF + RBV	G DCV + SOF	H DCV + SOF + RBV	Total (A,C, E,G, H)	I DCV + SOF	J DCV + SOF + RBV
	N= 16	N= 14	N= 14	N= 44	N= 15	N= 14	N= 15	N= 41	N= 41	N= 126	N= 21	N= 20
Week2												
<25IU/ mL	13 (81)	12 (86)	12 (86)	37 (84)	10 (67)	11 (79)	10 (67)	36 (88)	34 (83)	101 (80)	19 (91)	16 (80)
Undetectable	5 (31)	4 (29)	4 (29)	13 (30)	7 (47)	2 (14)	3 (20)	12 (29)	13 (32)	37 (29)	3 (140	3 (15)
Week4												
<25IU/ mL	16 (100)	14 (100)	14 (100)	44 (100)	15 (100)	14 (100)	15 (100)	39 (95)[a]	41 (100)	124 (98)	21 (100)	19 (95)[b]
Undetectable	14 (88)	11 (79)	9 (64)	34 (77)	13 (87)	13 (93)	11 (73)	31 (76)[a]	32 (78)	100 (79)	17 (81)	14 (70)[b]
End of treatment												
<25IU/ mL	15 (94)[d]	14 (100)	14 (100)	43 (98)	15 (100)	14 (100)	15 (100)	41 (100)	41 (100)	126 (100)	21 (100)	20 (100)
Undetectable	15 (94)[d]	13 (93)	14 (100)	42 (95)	15 (100)	14 (100)	15 (100)	41 (100)	41 (100)	126 (100)	19 (91)	19 (95)
Post-treatment week 4												
<25IU/ mL	14 (88)[g]	14 (100)	12 (86)[hi]	40 (91)	15 (100)	14 (100)	15 (100)	40 (98)[a]	39 (95)[af]	123 (98)	21 (100)	20 (100)
Undetectable	14 (88)[g]	14 (100)	11 (79)[hi]	39 (89)	15 (100)	14 (100)	15 (100)	40 (98)[a]	39 (95)[af]	123 (98)	21 (100)	19 (95)
Post-treatment week 12												
<25IU/ mL	14 (88)	14 (100)	12 (86)	40 (91)	15 (100)	14 (100)	15 (100)	41 (100)	39 (95)[j]	124 (98)	21 (100)	19 (95)
Undetectable	14 (88)	13 (93)	12 (86)	39 (89)	15 (100)	14 (100)	15 (100)	41 (100)	39 (95)[j]	124 (98)	21 (100)	19 (95)
Post-treatment week 24												
<25IU/ mL	14 (98)	14 (100)	13 (93)	41 (93)	14 (93)[k]	14 (100)	15 (100)	39 (95)[l]	38 (93)[m]	120 (95)	-	-
Undetectable	14 (88)	10 (100)	13 (93)	41 (93)	14 (93)[k]	14 (100)	15 (100)	39 (95)[l]	38 (93)[m]	120 (95)	-	-

DCV, daclatasvir 60 mg once daily; SOF,sofosbuvir 400 mg once daily;LI, lead-in:SOF monotherapy for 7 days;mIIT:modified intent to treat, RBV,ribavirin twice daily,1000-1200 mg/day weight based for genotype 1 patients and 800mg/day for genotype2/3 patients. Group G and H received 12 weeks of treatment, all other groups received 24 weeks of treatment.HCV RNA assay limit of detection 10IU/mL.

[a]Two patients with missing HCV RNA measurements-both had HCV RNA <25IU/mL at week 3. [b] One patient missing an HCV measurement [c]End of treatment analysis (week 24 for groups A-F. week 12 for groups G and H) includes patients who discontinued early, with last HCV RNA measurement considered end of treatment. [d] 1 patient with protocol defined virologic breakthrough (HCV RNA ,25 IU/mL and detectable) [e]1 patient with missing HCV RNA measurement achieved SVR12 [f]HCV RNA 54 IU/mL (not confirmed) at post-treatment week 4, later achieved SVR12. [G] 1 relapse [h] 1 patient lost to follow-up [I] patient with missing HCV RNA measurement, later achieved SVR24. [J] 1 patient with missing HCV RNA measurement, later achieved SVR24 and 1 patient lost to follow-up. [K] 1 patient with likely re-infection [l] 2 patients with missing HCV RNA measurement both achieved SVR24 [m] 2 patients with missing HCV RNA

Among patients with baseline polymorphisms impacting daclatasvir susceptibility, responses were as follows:

Number of Patients	HCV Genotype	Polymorphism(s) at NS5A Amino Acid Positions	Virologic Outcome
1	1a	30H/R	SVR_{48}
1	1a	M28T	SVR_{24}
1	1a	Q30H-Y93H	SVR_{12}
1	1a	Q30E, Y93N	SVR_{48}
1	1a	Y93C	SVR_{36}
1	1a	Q30H	SVR_{36}
1	1a	L31M	SVR_4, then lost to follow-up
1	1a	Q30H-L31M	SVR_{36}
1	1a	Y93N	SVR_{48}
1	1b	R30Q-L31M	SVR_{48}
2	1b	L31M	SVR_{12}, SVR_{36}
1	1b	Y93H	SVR_{36}
13	2	L31M	SVR_{48} (all)
1	2	L31M-P58S	SVR_{24}
1	3	A30K	Relapse
1	3	A30K, L31M	SVR_{48}
3	3	Y93H	SVR_{48} (all)

Discussion on clinical efficacy

The AI444040 showed very high SVR rates in patients with genotype 1 infection, including SVR in 40/41 patients with prior virological failure on boceprevir or telaprevir based regimens. Furthermore, data are indicative that the tested regimens also have high efficacy against genoypes 2 and -3. In the full study population, there was no apparent impact of the lead in procedure, treatment duration or co-administration of ribavirin. While the only patient in the study with definitive virological failure (relapse) did have a baseline polymorphism impacting daclatasvir susceptibility, overall this did not seem to impact outcomes. Regarding the patients with previous

experience of virological failure with TVR or BOC, all patients received 24 weeks of therapy. Half of the patients received ribavirin and half did not. While this did not result in different outcomes, the sample size is not large enough to conclusively decide whether the addition of ribavirin may increase efficacy in difficult to treat patients.

The main limitation in the knowledge of the efficacy of the daclatasvir+sofosbuvir is due to the fact that the study did not include any patients with cirrhosis. It is noted, however, that for each drug there is experience of use in cirrhotics in other combinations, and for neither drug are dosing adjustments required in hepatic impairment.

While the exact magnitude of effect in patients with cirrhosis and advanced liver disease is therefore unknown, it is, given the outcomes of the AI444040 study and the totality of available evidence of efficacy for each agent, reasonable to infer that this drug combination has the potential of delivering high SVR rates also in patients with advanced liver disease.

Overall conclusion on clinical efficacy

The combination of daclatasvir and sofosbuvir for 24 weeks has shown very high efficacy in a non-cirrhotic population, including 167 patients with genotype 1, 41 of whom had previously failed boceprevir- or telaprevir based therapy, and 44 patients with genotypes -2 and -3. The addition of ribavirin made no apparent difference to efficacy; however, the sample size is not large enough for a definite conclusion. While data are lacking in cirrhotic patients, it is reasonable to infer that the combination likely has substantial efficacy also in such patients.

Clinical safety

Most adverse events in the AI444040 study were mild or moderate and did not lead to treatment discontinuation or interruption. The most common adverse events were fatigue, headache, and nausea.

DCV (60 mg QD)/SOF Summary of safety- Treated Subjects (AI444040)

Number (%) of Subjects					
	DCV/SOF with RBV		DCV/SOF without RBV		Total
	12 Weeks (N=41)	24 Weeks (N=49)	12 Weeks (N=41)	24 Weeks (N=80)	N=211
Adverse Events					
SAEs	1 (2.4)	6 (12.2)	1 (2.4)	7 (8.8)	15 (7.1)
AEs leading to discontinuation	0	1 (2.00	0	1(1.3)	2 (0.9)
Grade 3/4 AEs	1 (2.4)	3 (6.1)	1 (2.4)	2 (2.5)	7 (3.3)
Most common AEs (≥ 10% total)					
Fatigue	15 (36.6)	18 (36.7)	16 (39.0)	29 (36.3)	78 (37.0)
Headache	9 (22.0)	18 (36.7)	14 (34.1)	20 (25.0)	61 (28.9)
Nausea	8 (19.5)	11 (22.4)	8 (19.5)	14 (17.5)	41 (19.4)
Arthralgia	3 (7.3)	4 (8.2)	5 (12.2)	9 (11.3)	21 (10.0)
Diarrhoea	4 (9.8)	7 (14.3)	2 (4.9)	8 (10.0)	21 (10.0)
Measured Grade 3 Laboratory abnormalities					
Total subjects[a]	5 (12.2)	5 (10.2)	1 (2.4)	4 (5.0)	15 (7.1)
Haemoglobin	0	1 (2.0)	0	0	1 (0.5)
Lymphocytes	0	1 (2.0)	0	0	1 (0.50
Phosphorus (inorganic)	3 (7.3)	1 (2.0)	0	1 (1.3)	5 (2.4)
Fasting serum glucose (high)[b]	0	1 (2.0)	1 (2.4)	2 (2.5)	4 (1.9)
Serum glucose	0	2 (4.9)	0	1 (1.6)	3 (1,6)
Total cholesterol	1 (2.6)	0	0	1 (1.6)	2 (1.0)
Uric acid	1 (2.4)	0	0	0	1 (0.5)

AEs- adverse events, DCV: daclatasvir, SAEs: serious adverse events, RBV:ribavirin, SOF:sofosbuvir

[a] No Grade 4 values were reported. Two subjects had Grade 3 values for 2 different laboratory parameters; one subject had Grade 3 serum glucose and haemoglobin and the other had Grade 3 fasting serum glucose and serum glucose.

[b] All 4 subjects with a Grade 3 fasting serum glucose had a medical history of diabetes mellitus

Two patients discontinued treatment due to adverse events (fibromyalgia 1, cerebrovascular accident 1); both achieved SVR. Serious adverse events on treatment included single events of gastroenteritis, colitis, cerebrovascular accident, acute renal failure (from dehydration; resolved with fluid administration), forearm fracture, anxiety and pleuritic pain, psoriasis exacerbation, and hypokalemia.

Serious Adverse Events on Treatment

Patients with event, N (%)	Treatment naive					Prior Telaprevir or Boceprevir failures	
	24-week treatment			12-week treatment		24-week treatment	
	Group A&B	Group C&D	Group E&F	Group G	Group H	Group I	Group J
	SOF LI+ DCV	DCV+SOF	DCV+SOF +RBV	DCV+SOF	DCV+SOF +RBV	DCV+SOF	DCV+SOF +RBV
	(n=31)	(n=28)	(n=29)	(n=41)	(n=41)	(n=21)	(n=20)
Serious adverse events[a]	2(7)[b]	4(14)[c]	2(7)	1(2)	0	0	1
Anxiety	1(3)	0	1(3)	0	0	0	0
Pleuritic pain	1(3)	0	0	0	0	0	0
Comminuted fracture	1(3)	0	0	0	0	0	0
Cerebro-vascular accident	0	1(4)	0	0	0	0	0
Abdominal pain	0	1(4)	0	0	0	0	0
Suprapubic pain	0	1(4)	0	0	0	0	0
Gastroenteritis	0	1(4)	0	0	0	0	0
Colitis	0	1(4)	0	0	0	0	0
Acute renal failure	0	1(4)	0	0	0	0	0
Breast cancer	0	0	1(3)	0	0	0	0
Psoriasis	0	0	0	1(2)	0	0	0
Hypokalemia	0	0	0	0	0	0	1

DCV, daclatasvir 60 mg once daily; SOF,sofosbuvir 400 mg once dialy;LI, lead-in:SOF monotherapy for 7 days;RBV,ribavirin twice daily,1000-1200 mg/day weight based for genotype 1 patients and 800mg/day for genotype2/3 patients. Patients in Group A,C,E,G and H had genotype 1 infection and patients in groups B,D and F had genotype 2/3 infection.

[a] Five events of overdose (extra study medication doses), classified as serious adverse events, are not included in the Table; C and D, n=1;E and F, n=2;H,n=1, I,J,n=1, no clinically significant effects were reported from any overdoses.

[b] Anxiety and pleuritic pain occurred in the same patient.

[c] Abdominal pain, suprapubic pain and gastroenteritis occurred in the same patient.

The most common grade 3 or 4 laboratory abnormalities were low phosphorous and elevated glucose. The mean change in hemoglobin for ribavirin- vs non-ribavirin-containing regimens was -

2.2 g/dl vs -0.30 g/dl following 24 weeks of therapy and -2.8 g/dl vs -0.90 g/dl following 12 weeks of therapy. Five patients had their ribavirin dose reduced for anemia.

The AI444040 study excluded patients with cirrhosis. The company has reported a safety database of 53 patients with cirrhosis treated with daclatasvir in combination with peginteferon alfa and ribavirin. No apparent differences in the safety profile compared to peginteferon and ribavirin alone were reported. Furthermore, when daclatasvir was used in combination with asunaprevir, adverse events rates were similar in patients with cirrhosis (n=22) compared to patients without cirrhosis.

Discussion on clinical safety

The combination of daclatasvir and sofosbuvir was well tolerated in the AI444040 study, with low rates of serious adverse events and discontinuations due to tolerability issues. The addition of ribavirin clearly impacted the safety profile with primarily, as expected, decreases of haemoglobin. While the study did not contain patients with cirrhosis, no specific side effect profile of concern for this subgroup emerged. Furthermore, for both daclatasvir and sofosbuvir, safety data from other combinations are not indicative of specific safety problems in this population.

According to available data, the occurrence of clinical symptoms (pyrexia, eosinophilia and liver test abnormalities) have emerged in one patient in a Japanese study with daclatasvir in combination with asunaprevir (DCV/ASV dual therapy), which was related to asunaprevir by the sponsor. Further, it should be noted that one case of drug rash with eosinophilia and systemic symptoms was reported in study AI444-052 evaluating daclastavir versus telaprevir both in combination with peginterferon alfa 2a and ribavirin. This case concerned a 62- year-old male French patient who experienced general pruritus with erythema, which progressed to oedema of the face, arms and legs, desquamation of the scalp, pyrexia, lymphadenopathy and radiological changes in the lungs described as interstitial syndrome despite ribavirin dose reduction and treatment with hydroxyzine and glycerol+white soft paraffin, approximately 10 weeks after commencing study therapy with daclatasvir, peginterferon alfa 2a and ribavirin. The event resolved after therapy discontinuation and the relationship with daclatasvir was deemed possible by the investigator and sponsor. Utilizing intense monitoring for eosinophilia and concurrent pyrexia or rash, no additional cases have been identified across the daclatasvir clinical program.

Overall conclusion on clinical safety

The safety profile of daclatasvir and sofosbuvir when used in combination is favourable. Furthermore, while the population in study AI444040 was non-cirrhotic, no particular safety concerns have emerged precluding the compassionate use of this combination in patients with advanced liver disease.

The sponsor will be requested to pay special attention to hypersensitivity reactions, including DRESS in the periodic safety reports.

3.5. Pharmacovigilance

In order to ensure the safety monitoring of the patients, the following conditions have been adopted and are annexed to the CHMP opinion on compassionate use for daclatasvir as follows:

Conditions for safety monitoring to be implemented by the company

In accordance with Article 83(6) of Regulation (EC) No 726/2004, the pharmacovigilance rules and responsibilities defined in Articles 28(1) and 28(2) of the Regulation (EC) No 726/2004 are applicable to medicinal products for which an opinion on the conditions for compassionate use in accordance with Article 83(4) of Regulation (EC) No 726/2004 has been adopted.

The manufacturer will ensure that these pharmacovigilance obligations are fulfilled.

Conditions for safety monitoring to be implemented by the Member States

In accordance with Article 83(6) of Regulation (EC) No 726/2004, the pharmacovigilance rules and Responsibilities defined in Article 28(1) of the Regulation (EC) No 726/2004 are applicable to medicinal products for which an opinion on the conditions for compassionate use has been adopted. The Member State(s) will ensure that these pharmacovigilance obligations are fulfilled.

3.6. Risk-benefit assessment and recommendation

For patients that have previously failed boceprevir- or telaprevir based antiviral therapy, there is presently no likely effective licensed treatment option. A subset of this population has advanced liver disease and is at a considerable short term risk of progression to decompensation or death. Furthermore, there are many patients that have advanced liver disease, as evidenced by signs and symptoms of portal hypertension, with or without past or present clinical decompensation. For such patients, interferon based treatment alternatives are at best ill tolerated with low effectiveness, or, in case of hepatic impairment/decompensation, outright contraindicated. These patients are in urgent need of effective therapy that can induce SVR.

In the AI444040 study, a total of 211 patients with genotype 1, -2 or -3 infection, including 41 patients with a history of failure on NS3/4A inhibitor therapy, without cirrhosis, were treated with daclatasvir+sofobuvir +/- ribavirin, for 24 weeks. Nominal SVR12 rates varied from 88.9-100% in different treatment arms, with only one confirmed virological failure (relapse in a patient with genotype 3 infection). In 40/41 protease inhibitor experienced patients SVR12 was reached; the remaining patient had missing data at that time of follow up, but later was shown to have reached SVR.

While it is recognised that no patients with cirrhosis were included in the study, and that a precise estimate of efficacy is not available for such patients, it is reasonable to infer that this drug combination will show substantial efficacy also in such patients. There is no need of dose adjustment for either agent in hepatic impairment.

While the sample size is not large enough to draw definite conclusions in the NS3/4A inhibitor experienced subgroup, overall the addition of ribavirin did not increase efficacy, while as expected, it did impact the safety profile negatively.

Apart from side effects typical of ribavirin, no signature safety issues have emerged with the drug combination, which was generally well-tolerated with few serious side effects or discontinuations due to adverse events. While data for the combination are limited to non-cirrhotic patients, data from the study as well as for each drug when used in other combinations are not indicative of safety concerns specific for patients with advanced liver disease, which would preclude the compassionate use of this combination in patients with an urgent need of effective therapy, and that do not have the opportunity of participating in clinical trials.

In the notification to the CHMP of the potential compassionate use of daclatasvir in combination with sofosbuvir, the efficacy shown in patients with prior failure on NS3/4A inhibitors was particularly noted.

The company proposes to further define the target population for compassionate use, among those patients "having a life expectancy of < 12 months if the HCV infection is left untreated".

Regarding the treatment history, the CHMP recognises that the urgent medical need extends also to patients with very advanced liver disease that have not been exposed to boceprevir or telaprevir, either because they did not have the opportunity, or because they were not able to tolerate the necessary interferon co-medication. Therefore, the CHMP proposes that the indication

for compassionate use be extended to encompass patients with genotype 1 virus regardless of prior treatment experience, provided that there is an urgent medical need of viral clearance.

Furthermore, the CHMP acknowledges that there are also patients with non-genotype 1 infection subject to the aforementioned medical urgency. For such patients, the anticipated effectiveness of available treatment options may differ from case to case. Therefore, for patients with non-genotype 1 infection that are deemed unlikely to respond to or tolerate licensed and available treatment options, compassionate use of daclatasvir in combination with sofosbuvir, +/- ribavirin, may also be relevant.

As life expectancy may be difficult to precisely ascertain in the individual case, it is proposed that the clinical indication for compassionate use of daclatasvir in combination with sofosbuvir be redefined as to include those deemed by their treating physician to be "at a high risk of decompensation or death within 12 months if left untreated". In practice, this would primarily encompass patients with signs or symptoms of portal hypertension, as well as those with present or past episodes of clinical decompensation/hepatic impairment.

The value of adding ribavirin to this combination remains unclear. However, there is a growing body of evidence indicating that the addition of ribavirin when sofosbuvir is used in combination with another potent direct acting antiviral may not result in higher SVR rates, while yielding increasing side effects. In this context, the approach proposed by the company, not to primarily recommend the addition of ribavirin, but to leave this open as an option to the treating physician, is supported.

In summary, the benefit-risk of the compassionate use of daclatasvir+sofosbuvir for 24 weeks in patients that are at a high risk of decompensation or death within 12 months if left untreated, is deemed positive

Recommendation

As part of the Opinion, the CHMP adopted conditions of use, conditions for distribution, patients targeted and conditions for safety monitoring addressed to Member States for daclatasvir available for compassionate use (see appendix 1).