20 November 2014
EMA/768319/2014
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

Exviera

International non-proprietary name: dasabuvir

Procedure No. EMEA/H/C/003837/0000

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# List of abbreviations

| | |
|---|---|
| Ab | antibody |
| ALT | alanine aminotransferase |
| APTT | activated partial thromboplastin time |
| AST | aspartate aminotransferase |
| BID | twice daily |
| BMI | body mass index |
| CYP3A | cytochrome P450 3A |
| DAA | direct-acting antiviral agent |
| Disc | premature discontinuation |
| DNA | deoxyribonucleic acid |
| EC50 | half-maximal effective concentration |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDTA | ethylenediaminetetraacetic acid |
| EOT | end of treatment |
| GCP | Good Clinical Practices |
| GGT | gamma glutamyl transferase |
| GT | genotype |
| HBsAg | hepatitis B surface antigen |
| HCV | hepatitis C virus |
| HCVPRO | hepatitis C virus patient-reported outcome |
| HIV | human immunodeficiency virus |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IFN | interferon |
| IL28B | interleukin 28B |
| INR | international normalized ratio |
| ITT | intent-to-treat |
| LLN | lower limit of normal |
| LLOD | lower limit of detection |
| LLOQ | lower limit of quantitation |
| LTFU | lost to follow-up |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NS5A | nonstructural protein 5A |
| pegIFN | pegylated interferon |
| pM | picomolar |
| PRO | patient-reported outcome |
| PT | post treatment |
| QD | once daily |
| RBC | red blood cell |
| RBV | ribavirin |
| RNA | ribonucleic acid |
| SC | subcutaneous |
| SOC | system organ class |
| SVR | sustained virologic response |
| ULN | upper limit of normal |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant AbbVie Ltd. submitted on 6 May 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Exviera, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 July 2013.

The applicant applied for the following indication Exviera is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults (see sections 4.2, 4.4 and 5.1). For hepatitis C virus (HCV) genotype specific activity, see sections 4.4 and 5.1.

**The legal basis for this application refers to:**

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that dasabuvir was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

***Information on Paediatric requirements***

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0314/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0314/2013 was not yet completed as some measures were deferred.

***Information relating to orphan market exclusivity***

***Similarity***

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

**New active Substance status**

The applicant requested the active substance dasabuvir (sodium) contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

***Scientific Advice***

The applicant received Scientific Advice from the CHMP between 24 June 2010 and 21 November 2013. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

***Licensing status***

A new application was filed in the following country: United States of America.

The product was not licensed in any country at the time of submission of the application.

**Manufacturer responsible for batch release**

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
GERMANY

## *1.2. Steps taken for the assessment of the product*

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

Rapporteur: Filip Josephson Co-Rapporteur: Johann Lodewijk Hillege

CHMP Peer reviewer(s): Robert James Hemmings

- The application was received by the EMA on 6 May 2014.
- Accelerated Assessment procedure was agreed-upon by CHMP on 25 April 2014.
- The procedure started on 28 May 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 August 2014 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 21 August 2014. During the meeting on 25 September 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 September 2014. The applicant submitted the responses to the CHMP consolidated List of Questions on 07 October 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 31 October 2014PRAC RMP Advice and assessment overview, adopted on 6 November 2014
- During the meeting on 20 November 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Exviera.

# 2. Scientific discussion

## *2.1. Introduction*

Hepatitis C virus (HCV) infection is a major European public health challenge, with a prevalence of 0.4-3.5% in different EU member states. It is the most common single cause of liver transplantation in the Union.

HCV is divided into six major genotypes and numerous subtypes, which are based on phylogenetic relationship. Genotype 1 is the most common genotype in Europe, comprising approximately 70 % of infections. Genotype 3 is second most common, followed by genotype 2. Genotype 4 is predominant in Egypt, the nation in the world with the highest documented HCV prevalence. Genotypes 5 and -6 are uncommon in Europe and the US, but are more common in South Africa and South-East Asia, respectively (Simmonds et al, Hepatology 2005). HCV genotype does not clearly impact the rate of disease progression. Treatment response, however, with available regimens, differs between genotypes.

The goal of antiviral therapy against HCV is to reach sustained virological response (SVR), which is traditionally defined as the absence of quantifiable virus in plasma at least 24 weeks after the end of therapy. However, most relapses occur within 4 weeks of treatment discontinuation, and a 98-99% concordance has been shown between absence of quantifiable virus 12 weeks after therapy, and SVR24 (Florian et al, AASLD 2011). Therefore the absence of measurable virus 12 weeks post end of treatment (SVR12) is presently accepted by European and US regulators as the primary endpoint in clinical trials. Though occasional late relapses occur, in general the durability of SVR has been amply demonstrated (see e.g., Ng and Saab, Clin Gastroenterol Hepatol 2011).

Up until the European commission approval of sofosbuvir, all approved therapeutic regimens for hepatitis C virus infection contained an interferon. For the treatment of genotype 1 infection, the addition of either one of the NS 3/4A protease inhibitors telaprevir or boceprevir, approved in 2011, was considered standard-of-care. For genotypes other than -1 there were no direct-acting antivirals (DAA) approved, bi-therapy with pegIFN/RBV being the standard. Interferon-based therapies are associated with potentially serious side effects that are important in limiting real life effectiveness. These include a risk of hepatic decompensation and septicaemia in patients with advanced liver disease, as well as bone marrow suppression. Also, there are psychiatric side effects such as depression, which considerably limits eligibility to treatment in the target population (see e.g., Bini et al, Am J Gastroenterol 2005).

Recent years have seen a very rapid drug development for hepatitis C. There are numerous further drugs in the pipeline, and the anticipation is that within short interferon-free therapies with very high antiviral efficacy will be approved and recommended for most or all patients with hepatitis C, regardless of genotype and clinical status.

The applicant has developed an IFN-free regimen containing 3 DAAs with distinct mechanisms of action and non-overlapping resistance profiles for the treatment of chronic HCV infection:

- ABT-450 is a nonstructural protein [NS] 3/4A protease inhibitor, which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication. ABT-450 is metabolized primarily by cytochrome P450 (CYP) 3A4 and is dosed with ritonavir (r), a potent CYP3A4 inhibitor used as a pharmacokinetic enhancer in order to achieve efficacious exposures (the combination of ABT-450 and ritonavir is denoted ABT-450/r);

- Ombitasvir (ABT-267) is an inhibitor of HCV NS5A, which is essential for viral replication;
- Dasabuvir (ABT-333) is a non-nucleoside inhibitor of the HCV RNA-dependent RNA polymerase encoded by the NS5B gene.

Exviera contains dasabuvir.

## *2.2. Quality aspects*

### 2.2.1. Introduction

The finished product is presented as immediate release film-coated tablets containing 250 mg of dasabuvir (as sodium salt monohydrate) as active substance.

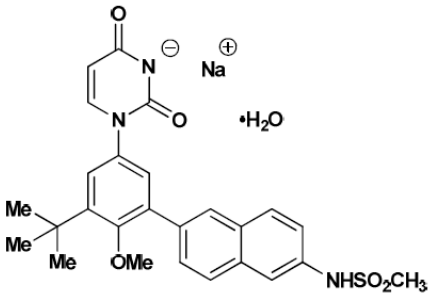
Other ingredients are: microcrystalline cellulose (E460(i)), lactose monohydrate, copovidone, croscarmellose sodium, colloidal anhydrous silica (E551), magnesium stearate (E470b), polyvinyl alcohol (E1203), titanium dioxide (E171), polyethylene glycol 3350, talc, iron oxide yellow (E172), iron oxide red (E172) and iron oxide black (E172), as described in section 6.1 of the SmPC.

The product is available in in clear Polyvinylchloride/Polyethylene/Polychlorotrifluoroethene – Aluminium blisters (PVC/PE/PCTFE-Al), as described in section 6.5 of the SmPC.

### 2.2.2. Active Substance

#### *General information*

The chemical name of the active substance dasabuvir sodium monohydrate is sodium 3-(3-tert-butyl-4--methoxy-5-{6-[(methylsulfonyl) amino] naphthalen-2-yl} phenyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ide hydrate (1:1:1), corresponding to the molecular formula $C_{26}H_{26}N_3O_5SNa.H_2O$ and has a relative molecular mass 493.57 (free acid), or 533.57 (salt, hydrate). It has the following structure:




The structure of the active substance has been confirmed by mass spectrometry, infrared spectroscopy, $^{1}H$- and $^{13}C$-NMR spectroscopy and X-ray crystallography, all of which support the chemical structure.

Dasabuvir sodium monohydrate appears as a white to pale yellow to pink, non-hygroscopic crystalline powder. It is practically insoluble in 0.1 N HCl pH 1, slightly soluble in water and very slightly soluble in methanol. The solubility of the free acid of dasabuvir in various pH buffer solutions is pH dependent and ranges from 0.13 to 910 µg/ml. The dissociation constants of dasabuvir sodium were determined to be pK1 = 8.2 and pK2 = 9.2.

It does not show stereoisomerism. As a result of polymorphic screen studies several crystal forms have been identified; five of them are most relevant to the proposed manufacture. The active substance is consistently manufactured as monosodium salt monohydrate (Form I), which is also the thermodynamically stable form.

The active substance is packaged in material which complies with the EC directive 2002/72/EC and EC 10/2011.

### *Manufacture, characterisation and process controls*

The active substance is manufactured in six chemical synthetic steps followed by salt formation. The proposed starting and raw materials used in the synthesis and intermediates are well-defined and controlled by suitable methods and specifications. The synthesis has been described in sufficient detail and critical process parameters, yields and in-process controls (IPCs) have been reported and are considered satisfactory. The desired active substance particle size is ensured by sufficient IPC of the critical wet milling step and by controlling the critical process parameter (stoichiometry) of salt formation. Sufficient evidence has been presented that the desired polymorph is consistently manufactured.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities and degradation products have been characterised and toxicologically qualified as appropriate.

Any potential genotoxic impurities (GTIs) and their precursors are controlled through material attributes (input materials and intermediates) and processing conditions, or decompose in-process due to their reactivity under the reaction conditions. The overall control strategy including any GTIs is therefore considered satisfactory.

The proposed commercial process has been used in clinical trials and in the manufacture of the primary stability batches. Two slightly different processes have been used in batches for earlier clinical trials; differences have been presented but raised no concerns regarding the comparability of the active substance quality.

Process validation will be performed as per the presented and agreed protocol on three consecutive production-scale batches at the commercial manufacturing facilities.

### *Specification*

The active substance specification includes appropriate tests and limits for: appearance and colour (visual), clarity and colour of solution (Ph. Eur.), identity (dasabuvir: IR, HPLC; Na counterion: Ph. Eur.), crystal form (X-ray powder diffraction), assay (HPLC), impurities (HPLC), residual solvents (GC) and microbiological quality (Ph. Eur.).

The omission of certain tests from the specification of the active substance such as control of GTIs, some residual solvents, heavy metals, particle size, crystal morphology and water content has been adequately justified on the basis of upstream control (IPCs), batch analysis data and physicochemical properties of the substance.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.

Batch analysis data for 22 batches manufactured using the proposed commercial process have been provided. In addition, batch analysis results of another 15 batches manufactured using the two slightly different processes used in early development were also presented. Additional characterisation details were provided for these batches on heavy metals, optical microscopy, particle shape, crystallinity, particle size, water content, sodium content and additional residual solvents.

The submitted batch analysis data confirm that the manufacture is sufficiently robust and provide reassurance that the process yields active substance of consistent quality, complying with the designated specification.

***Stability***

Stability data on four commercial size batches of active substance stored in the intended commercial package for up to nine months under long term conditions at 25 °C/60% RH and for up to six months under accelerated conditions at 40 °C/75% RH according to the ICH guidelines were provided. In addition, one full scale batch was stored at 50 °C/75% RH. In addition, data from another three smaller than commercial scale batches from a different site used in development were also presented for up to 12 months under long term conditions at 25 °C/60% RH a and for up to six months under accelerated conditions at 40 °C/75% RH. The batches were stored in the packaging configuration intended for marketing. The stability parameters tested were appearance, identification, assay, related substances and microbial controls. Crystal form and water content were monitored on the three smaller scale batches. The methods used were the same as those used for release and are considered stability indicating.
No significant changes were observed in any of the monitored parameters through the stability study period, compared to the initial values, for any of the tested storage conditions. The commercial site batches were found comparable to the smaller batches from the different site.

Photostability testing following the ICH guideline Q1B was performed on one batch. Furthermore, the active substance was exposed to acid, base, oxidation, heat, heat with moisture and light (exposure to high intensity UV light) stress conditions. Results for the stress stability samples indicated that dasabuvir sodium is potentially susceptible to base and oxidative degradation, and to a much lesser extent, acid and ultraviolet radiation degradation whereas it appears stable to heat, heat with moisture and light stress conditions.
Finally, the data generated at 50 °C/75% RH support temperature excursions during shipping of up to 50 °C for 1 month.

Based on presented stability data, the proposed re-test period and storage conditions for dasabuvir sodium are acceptable.

## 2.2.3. Finished Medicinal Product

***Description of the product and pharmaceutical development***

Pharmaceutical development was conducted in line with recommendations in ICH Q8/9/10. The approach to the pharmaceutical development can be considered a mix of the traditional and more enhanced approach, although no design space or PAT tools are utilised and multivariate experiments were only performed to understand the manufacturing process.

The objective of the pharmaceutical development was to develop a product with a quality target product profile (QTPP) defined as follows: 250 mg film-coated immediate release tablet, less than 1000 mg total tablet weight and of acceptable appearance, meeting the relevant compendial requirements for this pharmaceutical form comprised of known excipients and stable in different climatic zones. Following the definition of the QTPP an initial risk assessment was performed upon selection of the commercial formulation which led to the identification of formulation attributes and manufacturing process parameters that could potentially impact final product quality. Subsequently, using design of experiments, statistical analysis, simulations and mathematical models and the relationship of the material attributes and process parameters to the drug product CQAs were defined. After determining the CQAs, critical process parameters (CPPs), and in-process controls (IPCs), the control strategy was determined to ensure final product quality and manufacturability. A final risk assessment was then completed to demonstrate risks previously identified are mitigated using the proposed control

strategy. Taking into account the QTTP, the CQAs identified for dasabuvir tablets are: identity, purity, assay, degradation products, uniformity of dosage units, description (appearance), water content, dissolution and microbiological quality.

Dasabuvir free acid is a weak acid with relatively low solubility at bio-relevant pH values. Consequently, a crystalline sodium salt in the form of a monohydrate having a higher apparent aqueous solubility and a much faster dissolution rate was selected for product development. The permeability by Caco-2 assay indicates it is Class II (low solubility and high permeability) compound according to the Biopharmaceutics Classification Systems (BCS).

The particle size range which is acceptable for product manufacture and clinical performance was defined; this is controlled in the active substance manufacturing process. The choice of all excipients has been satisfactorily justified and their function has been adequately described. In addition it has been shown that the crystal form of dasabuvir sodium is not changed by the tablet manufacturing process or upon storage.

An overview of the different formulations used throughout the clinical and formulation development programme has been provided. Originally a low strength capsule formulation was developed for Phase I and IIa clinical studies. As soon as it was realised that a higher dose would be required, a 400 mg tablet was developed using largely the same excipients as the first capsules for the Phase I and II clinical studies. During optimisation of this formulation it was possible to reduce the dose form 400 to 250 mg – the proposed strength for marketing. Bioequivalence between the proposed commercial optimised 250 mg film coated tablet and the 400 mg Phase II tablet was confirmed in a bioequivalence study. The tablets were further optimised to add a cosmetic non-functional film coating that has no significant impact on drug release.

Given the low aqueous solubility of the active substance, a pH 6.8 buffered medium with surfactant is proposed as a dissolution method for release testing. Several surfactants at various concentrations were studied before selecting a medium with 15 mM cetyl trimethylammonium bromide (CTAB) able to achieve sink conditions. The rotation speed was also optimised to avoid coning.
The discriminating power of the dissolution method was investigated with regard to the tablet hardness and active substance particle size. Although no changes to the dissolution profile were found for the tested wide ranges, indicating robust performance, the proposed method was able to discriminate tablets with varying levels of binder and disintegrant as well as stability related changes. Therefore the dissolution method is considered sufficiently discriminatory.
A summary of the manufacturing process development history has been presented and a discussion on each individual unit operation was provided assessing their impact to content uniformity, uniformity of dosage units, appearance, assay and dissolution. Design of experiments (DoE) were utilised to define the operating parameters for the dry granulation and coating steps particularly.

Exviera film-coated tablets are packaged in polyvinyl chloride/polyethylene/ polychlorotrifluoroethylene blisters with aluminium foil lidding (PVC/PE/PCTFE-Al). The material complies with the Ph. Eur. requirements. The choice of the container closure system is supported by stability data and is adequate for the intended use of the product.

***Manufacture of the product and process controls***

The manufacturing process for dasabuvir tablets consists of the following separate manufacturing steps: blending, dry granulation, blending, tableting, and coating, followed by bulk and subsequently primary packaging; it has been described in sufficient detail. The manufacturing process of the finished product follows conventional pharmaceutical practices and is therefore considered a standard process. Holding times for bulk tablets have been defined and are supported by data. The control strategy was based upon the CPPs, IPCs, raw material and final product specifications. The designed control strategy ensures that the manufacturing process consistently delivers a product that meets the defined criteria for all CQAs.
The manufacturing process for Exviera tablets will be validated before commercialisation of the product on three consecutive production-scale batches manufactured at the commercial manufacturing facilities in accordance with the agreed protocol.

Overall it is considered that the manufacture is sufficiently robust to provide reassurance that the process produces the finished product Exviera 250 mg film-coated tablets of consistent quality, complying with the designated specification.

***Product specification***

The finished product release and shelf life specifications include appropriate tests and limits for appearance (visual), identification (HPLC, IR), assay (HPLC), degradation products (HPLC), uniformity of dosage units (Ph. Eur.), water content (Ph. Eur.), dissolution (Ph. Eur.- HPLC) and microbial limits (Ph. Eur.).
A statistical evaluation for water content showed the appropriateness of the specification limits for this parameter. Because the microbial risks of this solid oral dosage product are low, testing is only planned until additional confirmatory data are obtained. As per ICH Q6A Specifications, Decision Tree #8, based on the results of these confirmatory batches (development and commercial ones) meeting the acceptance criteria, the test for microbial quality will be removed from the commercial specification and the testing will no longer be applied.

Batch analysis results are provided for 16 production scale batches. Results confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

***Stability of the product***

Stability data of three production scale batches of Exviera tablets from the proposed site, stored under long term conditions for six months at 30 °C/75% and under accelerated conditions for six months at 40 °C/75% RH according to the ICH guidelines were provided. The same three batches were stress tested at -20 °C, 5 °C, 50 °C, and one of them was tested for photostability as per the ICH guideline. An additional batch was exposed to oxidative conditions, heat, heat and moisture, and light.

Three further production scale batches manufactured in a different facility using the same process were studied under the same conditions for up to 15 and 9 months respectively. The stability batches were packed in the primary packaging proposed for marketing.

Parameters tested were: description, assay, dissolution, water content, degradation products, microbiological quality and water activity (selected time points). The methods used for stability testing were the same as for release and were shown to be stability indicating.

No meaningful changes were seen in any of the batches tested under long term and accelerated conditions and all results remained within specification. The product is not sensitive to light.

In addition to the real time stability data a statistical analysis was performed showing that the assay results would be met at the end of the shelf life.

The open dish study showed that if tablet water content exceeds a certain level, then drug release might not meet the acceptance criteria. Therefore an appropriate water content limit has been set for the release and shelf life.

Based on the packaged stability data, statistical analyses, blister permeability water content model and interpretation of the open dish stability data, the shelf life as stated in the SmPC is acceptable.

***Adventitious agents***

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

### 2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

### 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

### 2.2.6. Recommendation(s) for future quality development

Not applicable.

## *2.3. Non-clinical aspects*

### 2.3.1. Pharmacology

***Primary pharmacology***

Dasabuvir is a non-nucleoside inhibitor of the hepatitis C virus (HCV) RNA-dependent RNA polymerase, encoded by the non-structural protein 5B (NS5B) gene. For a further discussion of the primary pharmacology, see below, section on pharmacodynamics.

***Secondary pharmacology***

In assays including 75 receptors, ion channels and transporters, dasabuvir (0,1-10 µM) showed an inhibition of binding by > 50% at the V1a (82%) receptor, the Cl–channel (109%), the A3 receptor (76%), the BZD (peripheral, 69%), the CCKA receptor (78%), the 5-HT1B receptor (60%) and the glucocorticoid receptor (69%). In another assay including 79 receptors, ion channels and transporters, metabolite M1 (10 µM) displayed an inhibition of binding by > 50% at the V1a receptor (57%).

According to the study reports results showing an inhibition higher than 50% are considered to represent significant effects of the test compounds. Even so, in the pharmacology written and tabulated summaries the applicant has only presented results showing an inhibition higher than 80%. Clearly, several other targets were showing an inhibition higher than 50% and several targets were showing inhibition of 20 to 50% (mild to moderate effect). A functional assay was performed only for the V1a receptor (no activity found). A comment regarding the large amount of targets showing a moderate to high inhibition would have been desirable. However, the possible secondary targets have been taken into account when evaluating the results of the toxicology studies.

***Safety pharmacology programme***

Cardiovascular effects of dasabuvir were evaluated *in vitro* and *in vivo*.

In a GLP hERG assay the $IC_{50}$ of dasabuvir was 0.3 µg/mL, to be compared with the clinical plasma concentration at the maximum recommended human dose, 1.03 µg/mL. This indicates a possible effect of dasabuvir on hERG. No prolongation of dog Purkinje fiber action potential duration was seen up to and including the highest concentration tested, 14.9 µg/mL. In anesthetized dogs, dasabuvir produced a modest increase in mean arterial blood pressure (7 mmHg) and a shortening of the QT interval (maximum 14 ms) at plasma concentrations of 0.23 and 1.84 µg/mL, respectively. When administered in a low-dose study over a slower range of escalating infusion dasabuvir did not produce an effect on mean arterial blood pressure at concentrations as high as 0.7 µg/mL suggesting that the pressor effect observed at high infusion rates was mediated by the rate of rise in dasabuvir concentration. In conscious dogs, 10 mg/kg dasabuvir (exposure = 6 µg/mL) produced a slight decrease in blood pressure (13 mmHg at two hours after dosing). Clinically, in First-In-Human studies on dasabuvir no effects on blood pressure were observed. Furthermore, the effect of dasabuvir on cardiovascular safety was evaluated in a thorough QT study. The 3DAA (direct acting antivirals, combination of ABT-450, ABT-267 and dasabuvir) regimen, at dasabuvir doses of 250 mg and 500 mg, did not result in QTc prolongation in humans. Taken together, dasabuvir does not appear to have a potential for adverse QT-effects.

Safety studies on the central nervous system included a primary observation study (Irwin, doses up to 100 mg/kg), a pro-/anticonvulsant study (doses up to 100 mg/kg), a study on nociception and spontaneous locomotor activity (doses up to 100 mg/kg) and a functional observational battery (FOB, doses up to 30 mg/kg). In all of the studies, performed in rat, the plasma exposures were exceeding the highest clinical plasma concentration ($C_{max}$ =1.03 µg/mL). No relevant effects were found in any of the studies.

Effects of dasabuvir on the respiratory function were evaluated in conscious rats. Oral administration of dasabuvir did not produce any physiologically relevant effects on respiratory rate, tidal volume or minute volume up to and including 30 mg/kg, a dose associated with plasma levels of 4.7 µg/mL (clinical $C_{max}$ =1.03 µg/mL).

The safety aspects of the gastrointestinal system were studied in ferrets and rats. No emesis or nausea was observed in ferrets up to and including the highest oral dose of 15 mg/kg, corresponding to a plasma concentration of 1.1 µg/mL. In rats dasabuvir had no significant effects on gastrointestinal transit up to and

including the highest oral dose of 30 mg/kg, corresponding to a plasma concentration of 3.6 µg/ml (clinical $C_{max}$ =1.03 µg/mL).

In rats, dasabuvir did not affect latency to sodium barbital (159 mg/kg, intraperitoneal)-induced sleep, sleep duration, or number of rats sleeping through the highest dose tested, 100 mg/kg, p.o. Neither did dasabuvir induce sleep when given with ethanol (2000 mg/kg, i.p.), through the highest dose tested, 100 mg/kg, p.o.

In conclusion, no concerns were raised in the safety pharmacology studies on dasabuvir and no further studies are considered needed.

### 2.3.2. Pharmacokinetics

The species used for studies on absorption, distribution, metabolism and excretion of dasabuvir were mouse, rat, dog, rabbit and monkey.

Dasabuvir, as the free acid has minimal solubility in aqueous solutions. The sodium salt has greater solubility in water and a faster in vitro dissolution rate, enabling administration of a simple aqueous suspension at high doses (up to 12000 mg/kg/day) for toxicology testing. The applicant has submitted results from product development studies, presenting pharmacokinetics data on different formulations of dasabuvir (R&D/14/0041, R&D/07/1144, R&D/13/785). In general, the data on pharmacokinetics are presented by the applicant in an unstructured way with several different formulations used, which makes comparison of data e.g. between different species difficult to assess. For the rat no results on absorption using the final formulation, the sodium salt suspension, were presented and only limited data on the dog. This is considered a shortcoming, since rat and dog are the main species used in the pivotal toxicity studies. Furthermore, the only data on bioavailability were measured using the solution formulation of free acid in 10% DMSO in PEG-400. The final formulation was not used in any of the studies on metabolism, distribution and excretion. This is, however, considered acceptable by the CHMP (see also below the comment regarding the distribution studies).

A study in fasted dogs after a single dose of dasabuvir administered as the sodium salt suspension in 0.2% HPMC and as the solution of free acid in DMSO: PEG-400 demonstrated comparable exposures. In study R&D/13/785, data regarding exposure after administration of different formulations in rat is included. The data described in the report is ambiguous and unclear. Since rat is a main species used in the toxicology studies and since other formulations of dasabuvir than the final formulation have been used in most of the pharmacokinetics studies and the initial GLP toxicity studies in rat, a clarification of the stated comparability in plasma exposure in rats after treatment with the final sodium salt formulation and the formulations of the free acid would have been desirable. However, since the final sodium salt formulation is used in all pivotal toxicity studies, thereby enabling estimation of adequate exposure margins in these studies, an explanation of the ambiguous data is considered not to be needed.

Dose proportionality and gender differences were not studied in the pharmacokinetic studies but were addressed in the toxicokinetic analysis.

Dasabuvir was rapidly absorbed with $T_{max}$ values being around two hours in in rats, dogs and rabbits and around one hour in mice and somewhat higher in monkey. The oral bioavailability values from studies using the solution formulation of free acid in 10% DMSO in PEG-400, were wide-ranging, with values high in dog (96%), moderate in rat (21%) and very low in monkey (4.5%).

According to the study report R&D/07/1144 the bioavailability from studies using the suspension of the sodium salt in fasted dogs was comparable to that obtained from a solution formulation of the free acid (~2.5 mg/kg

doses). Regarding comparison between bioavailability of the different formulations following oral dosing in rat, a study is referred to in the study report, but this is not enclosed in the documentation.

In all of the distribution studies presented the formulation of dasabuvir used was the solution of the free acid in DMSO: PEG-400, i.e. not the final formulation. Since the absorption of the free acid formulation can be assumed to be lower than of the sodium salt formulation it is not certain that the distribution of dasabuvir using the free acid in DMSO:PEG-400 would be fully representative of the distribution of the suspension of the sodium salt in 0.2% HPMC. However, the CHMP agreed that the presented results can be considered sufficient for the purpose of these studies.

Protein binding of dasabuvir and the M1 metabolite was independent of the 0.1 to 10 µM concentrations tested in mouse, rat, dog, monkey or human plasma, a concentration range which encompasses the average clinical concentrations. Dasabuvir was highly protein bound with fraction unbound <0.01 in all species tested, showing no significant differences across species. The M1 metabolite was less highly protein bound (fraction unbound <0.1) in all species when compared to dasabuvir.

When incubated in whole blood, [$^{3}$H]dasabuvir distributed preferentially into the plasma compartment, with a blood-to-plasma concentration ratios ranging from 0.6 and 0.7 in rat, dog, monkey and human, independent of the 0.3 to 30 µM concentration evaluated.

In a tissue distribution study in rats the highest concentration of [$^{14}$C]dasabuvir was found in the liver, but [$^{14}$C]dasabuvir-derived radioactivity was not shown to be distributed to tissues protected by the blood brain barrier (brain, spinal cord) or the lens of the eye. [$^{14}$C]dasabuvir-derived radioactivity did not selectively associate with tissues containing melanin (pigmented tissues of the eye, pigmented skin). Peak [$^{14}$C]dasabuvir-derived radioactivity distributed to most tissues by 0.5-1 hours after drug administration. Tissue concentrations declined below the limits of quantitation in most tissues within 24 hours after dosing and concentrations of radioactivity were not detectable in any tissues 168 hours post-dose (R&D/12/152). After 96 hours radioactivity was still detectable in the pigmented skin. The Applicant referred to clinical data, showing that there were no serious adverse events and no discontinuation of treatment due to a photosensitivity event. Based on this, the Applicant concluded that no risk minimization measures were warranted for the 3DAA or 2DAA combinations to prevent phototoxicity-related adverse events in humans. Based on the submitted information, CHMP concluded that there was no large concern regarding a risk for photosensitivity reactions associated with treatment using the 3DAA regimen (see also section on phototoxicity below).

Following oral administration of [$^{14}$C]dasabuvir to pregnant Sprague-Dawley rats, there was a lack of drug-derived radioactivity in the amniotic fluid and detectable foetal levels only in the liver. This indicates that only small amounts of [$^{14}$C]dasabuvir-related material are crossing the placenta.

Dasabuvir metabolite identification across species showed that metabolism primarily occurred on the *t*-butyl group to form the active metabolite M1, followed by secondary oxidation to M4 and M5, followed by secondary glucuronidation of M1 and M5 to M3 and M6, respectively, as well as sulfation of M1 to M2. Seven metabolites were identified in human plasma, including M1, M2, M3, M4, M5, M6 and a trace amount of the desmethyl metabolite, M11. Unchanged parent drug was the most abundant component in plasma in animals (46 to 100%) and humans (59%). Metabolite M1 was the only major (>10% of total drug related materials in plasma) metabolite in plasma in TgHras mice (30 %), CD1-mice (34 %) and human (18%). In rats all metabolites including M1 (3 %) was considered minor (<10% of total drug related materials in plasma). In dogs only unchanged parent drug was detected. Thus, M1 was not detected in the dog plasma, but detectable levels were found in the faeces and urine. The M1 metabolite was shown to have similar activity against genotype 1 HCV infection as dasabuvir.

In rats (bile duct cannulated Sprague-Dawley, single i.v. dose) the most significant metabolite in bile was M3 (~50% of the dose), followed by M1 (8% of the dose) and M5 (5% of the dose). Other metabolites included M2, M4 and M6. In urine, M1 was the primary component (2.5% of dose) (similar metabolite profiles observed following single oral doses). In dogs, unchanged parent drug was the major species in faeces, representing 53.9% of the administered oral [$^{14}$C]dasabuvir dose, followed by M1. Other metabolites included M4, M12, M13 and some small uncharacterized radiochemical components, each representing <2% of dose.

Studies in human liver microsomes and studies with recombinant CYP and FMO enzymes have demonstrated that dasabuvir is predominantly metabolized by CYP2C8 and to a lesser extent CYP3A4.

Following single oral administration of dasabuvir to mice, rats, dogs and humans, parent drug and metabolites were mainly cleared via biliary excretion and fecal elimination, with minimal renal clearance. In CD-1 mouse, a majority of radioactivity was recovered in the faeces (>98%), with the fraction of dose recovered in urine <1%. In bile-duct cannulated male Sprague-Dawley rats, most of the radioactivity was observed in faeces (58.7% of dose), followed by 32.1% in bile and 0.9% in urine, with an overall recovery of 92.0%. In dogs, 82.3% of the dose was recovered in the faeces, with minimal recovery in the urine (~0.6% of dose). In human, 94.4% of the dasabuvir dose was found in faeces and 2.2% in urine, with an overall 96.6% recovery of radioactivity during the 240 hour collection period.

Rats and dogs are the species used in the pivotal repeated toxicology studies. The choice of nonclinical species can be considered acceptable. The active metabolite M1 was the only major human metabolite. In dogs, M1 was not detected in plasma. In rats, dispite the low level of M1 detected in plasma (3%), the plasma exposure level in the repeat-dose toxicity and the reproductive toxicity studies was exceeding the human maximal clinical exposure. The only carcinogenicity study included in the documentation was performed in TgHras mouse (a study in rat is ongoing) and also in this study the plasma exposure level of M1 was exceeding the human maximal clinical exposure. Thus the M1 metabolite can be considered to be covered in the pivotal toxicology studies in rats and mice (see also the toxicokinetics section).

## 2.3.3. Toxicology

The toxicological profile of dasabuvir has been evaluated in a set of non-clinical studies including repeat-dose toxicity studies up to 3 months in mice, 6 months in rats and 9 months in dogs; combination repeat dose toxicity studies with ribavirin (RBV) and/or pegylated interferon-α (pegIFN) up to 1 month in monkeys and 3 months in rats; genotoxicity; carcinogenicity studies (Tg-rasH2 mice, Sprague-Dawley rats); fertility and pre- and postnatal development (rat) and embryo-fetal development (EFD) (rat and rabbit) studies; and impurity qualifying studies. The rat carcinogenicity study is in the reporting phase.

The rat (Sprague-Dawley) and dog (Beagle) were selected as the main rodent and non-rodent toxicology species. In general, the non-clinical toxicology program has been performed according to relevant guidelines.

### Single dose toxicity

No single-dose toxicity studies were conducted with dasabuvir, which was deemed acceptable by CHMP.

### Repeat dose toxicity

Dasabuvir has been evaluated in repeat-dose toxicity studies in wild type TgHras mice (up to 1 month), CD-1 mice (up to 3 months), Sprague Dawley rats (up to 6 months with 1 month recovery) and Beagle dogs (up to 9

months with 1 month recovery). Treatment with dasabuvir was well tolerated in rats and dogs. No dose-limiting effects were noted in the chronic rat and dog studies and therefore, the toxicology of dasabuvir is not considered fully explored. However, based on the 18-/47-fold (males/females) exposure margins in the 6-month rat study, and the 120-fold exposure margin in the 9-month dog study, this is considered acceptable. Adverse effects including mortality and GI tract effects were observed in mice. Findings in rat (lung and small intestine) and dogs (liver, adrenal gland and lymphoid tissue) were not considered adverse.

*Preterminal mortalities and GI tract effects in mice*

CD-1 and wild-type TgHras mice were terminated for welfare reasons at ~ 29- and 110-fold clinical exposure based on AUC, respectively. At necropsy, the presence of semisolid luminal material presumed to represent unabsorbed dasabuvir was observed in the stomach of mice. Microscopic findings included hyperplasia of the mucosal epithelium, mucus metaplasia of gastric glands and increased inflammation in the glandular stomach and hyperkeratosis and squamous metaplasia in the non-glandular stomach. The deaths and GI tract effects were attributed to the administration of large amounts of dasabuvir locally, rather than a systemic effect. This is supported by the lack of similar GI tract findings in the dog at equivalent exposures and the increased incidence/severity of the findings in the mouse at 12000 compared to 6000 mg/kg/day despite a similar exposure at these two dose levels. As the total daily dose of dasabuvir in humans, 500 mg/day corresponding to ~8 mg/kg/day in a 60 kg patient, is considerably less than 6000 mg/kg/day, the findings in mice are not anticipated in humans.

Non-adverse intestinal findings were noted at high dosages and after long term administration (6-months) in the rodent. In the 6-months TgHras carcinogenicity study, there was refractile foreign material presumed to represent precipitated dasabuvir accompanied by infiltrates of neutrophils and macrophages (≥ 600 mg/kg/day; ≥ 119 µg·hr/mL) but not at lower dosages. The refractile material with associated inflammation is considered to be secondary to local effects of a high drug load rather than a systemic effect.

In the 6-months rat study, similar refractile foreign material was present accompanied by granulomatous inflammation in the ileum at 800 mg/kg/day; 119 µg·hr/mL in males and 319 µg·hr/mL in females. While the inflammation and crystals were still present at the end of the 1-month recovery period, there was no evidence of progression. Support for this conclusion is based on the lack of findings at a lower drug load (200 mg/kg/day) in the 6-month rat study (female rats at 200 mg/kg/day achieved a higher systemic exposure than the males at 800 mg/kg/day) and the lack of findings in the 9-month dog study at a lower drug load (60 mg/kg/day) but high systemic exposure (828 µg·hr/mL).

*Lung effects in rats*

Non-adverse findings in the 6-month rat study included alveolar histiocytosis (≥ 50 mg/kg/day; ≥ 31 µg·hr/mL). Alveolar histiocytosis was not observed in other species (mouse, dog or monkey) and evidence of reversibility was noted at the end of the 1-month recovery period.

*Liver effects in dogs*

In the 9-month dog study, microscopic changes in the liver were limited to minimal to mild diffuse hepatocellular vacuolation in males given 60 mg/kg/day correlating with mildly increased liver enzyme values (ALT, SDH, GGT and total bilirubin) and increased liver weights. These effects were not noted at the end of the 1-month recovery period.

*Lymphoid tissue and adrenal gland effects in dogs and mice*

In the 9-month dog study, there was an increase in incidence and severity of thymic lymphoid depletion in the male high dose group (60 mg/kg/day) with a corresponding decrease in mean thymus weight. In addition, some dogs in this group exhibited lymphoid depletion in the spleen (mild), Peyer's patches (minimal to moderate), and lymph nodes (minimal to mild). However, there were no effects on peripheral lymphocyte counts. The affected males also had increased adrenal gland weights and mild diffuse adrenal cortical hypertrophy/hyperplasia, suggestive of a stress response. There were no effects in females despite similar exposures in males (829 µg·hr/mL) and females (848 µg·hr/mL) at 60 mg/kg/day. The lymphoid effects in the high dose males were reversible. No adverse clinical findings related to lymphoid depletion were noted during the study and there were no effects on peripheral lymphocyte counts. Thus, the effects in the high dose males were not considered adverse.

Effects on lymphoid tissues in other studies were limited to the 1-month study in wild-type TgHras mice where a minimal to moderate thymic lymphoid depletion/necrosis was noted in female mice administered 6000 and 12000 mg/kg/day. This finding was considered to be secondary to stress based on the presence of adrenal cortical hyperplasia and deaths in these groups. Similar findings were not apparent in the 6-month carcinogenicity study in TgHras mice at dosages up to 2000 mg/kg/day.

## Combination repeat-dose toxicity

Co-administration of ribavirin (rat and monkey) and pegIFN (monkey) with dasabuvir did not exacerbate any toxicities associated with ribavirin/pegIFN and did not induce any new combinatorial toxicities. Additionally, there were no apparent effects on the toxicokinetic parameters (dasabuvir, ribavirin, or pegIFN) with the co-dosing paradigms in either species.

According to the SmPC, dasabuvir is indicated for combination therapy with ombitasvir (ABT-267) and ABT-450/ritonavir with or without ribavirin for up to 24 weeks. No non-clinical combination toxicity studies have been conducted with the 3 DAAs; this was deemed agreeable by CHMP.

## Genotoxicity and carcinogenicity

Dasabuvir was tested negative in a complete package of genotoxicity studies, including test for gene mutations and chromosomal aberrations *in vitro* and chromosomal aberrations *in vivo*.
The carcinogenic potential of dasabuvir was evaluated in a 26-week study in TgHras transgenic mice with no statistically significant increases in neoplastic changes due to dasabuvir treatment. Therefore, dasabuvir was considered not carcinogenic up to the highest dosage tested (2 g/kg/day) corresponding to 39-fold clinical exposure based on AUC. The 2-year carcinogenicity study in Sprague Dawley rats is in the reporting phase.

## Reproduction and developmental toxicity

In the fertility and early embryonic development study in rats, there were no significant effects on male or female fertility parameters when tested up to doses of 800 mg/kg/day (400 mg/kg BID) corresponding to 29- and 36-fold the expected clinical AUC in males and females, respectively. In addition, dasabuvir did not affect reproductive organ weights, or caused macroscopic or histopathological findings in reproductive organs in any of the investigated species in repeat-dose toxicity studies.

Embryofoetal developmental studies were performed in rats and rabbits. There were no dasabuvir-related changes in maternal or foetal parameters in either of the species. In rats, the NOAEL for maternal and foetal toxicity was 800 mg/kg/day (400 mg/kg BID) corresponding to 48-fold clinical exposure based on AUC and in

rabbits, the NOAEL for maternal and foetal toxicity was 400 mg/kg/day corresponding to 12-fold clinical exposure based on AUC.

In the pre- and post-natal study in rats, oral administration of dasabuvir up to doses of 800 mg/kg/day (400 mg/kg BID) from the period of implantation to weaning of offspring no significant effects on maternal function such as maintenance of pregnancy, delivery and nursing were observed. In the $F_1$ generation rats, there were no significant effects on survival, growth, sexual maturation, motor activity, acoustic startle, learning and memory, mating and fertility, male reproductive organ weights or ovarian and uterine parameters. The NOAEL was 800 mg/kg/day corresponding to 44-fold clinical exposure based on AUC. On Day 14 post-partum, the mean dasabuvir plasma concentration in $F_1$ pups were between 10 to 15% of that in maternal animals indicating that dasabuvir is transferred to the pups via milk.

## Toxicokinetic data

### *Immunotoxicity*

No independent immunotoxicity studies were conducted. However immunotoxicity was evaluated by the standard parameters in repeat-dose toxicity studies. The evaluations did not identify direct dasabuvir-related immunotoxicity concerns.

### *Local Tolerance*

No local tolerance studies were submitted which is acceptable. Local irritating properties of dasabuvir in the GI tract have been observed in mice after administration of ≥6000 mg/kg/day (110-fold above the clinical AUC exposure). This is not considered a concern in the clinical situation.

## Other toxicity studies

### *Phototoxicity*

Dasabuvir absorbs light within the range of natural sunlight (290 to 700 nm) with a MEC exceeding the threshold of 1000 L $mol^{-1}cm^{-1}$ as cited in ICH S10 Step 4 Guideline. In rat QWBA studies, [$^{14}$C] dasabuvir-derived material was widely distributed following an oral dose, with concentrations in skin and eye comparable to blood. The [$^{14}$C] dasabuvir-derived material was not selectively associated with melanin-containing tissues. Tissue concentrations declined below the limits of quantitation in most tissues, including non-pigmented skin and eye, within 24 hours after dosing. However, radioactivity was still detectable in pigmented skin at 96 hours. No *in vitro* or *in vivo* phototoxicity studies were performed with ABT-333. The Applicant refers to clinical data, showing that there were no serious adverse events and no discontinuation of treatment due to a photosensitivity event. Based on this, the Applicant concludes that no risk minimization measures are warranted for the 3DAA or 2DAA combinations to prevent phototoxicity-related adverse events in humans.

The performed Phase 2 or 3 clinical trials with the 3DAA regimen were primarily conducted over the period of November 2012 through November 2013, and included the summer months in the Northern Hemisphere. In the clinical trials, there were no restrictions on sun exposure or requirements for sun protection or use of sunscreen and the percentage of subjects with rash-related treatment-emergent events following treatment with the 3DAA regimen (13.9%) was comparable to that observed for placebo subjects (15.7%), suggesting that the higher frequency of rash-related events in the 3DAA + RBV treatment groups (28.6%) was primarily due to the presence of RBV. In addition, utilizing a company MedDRA query (CMQ) for photosensitivity reactions a search

was performed which identified a low and comparable incidence of photosensitivity preferred terms (0.9% for the ABT-450/r, ABT-267 and ABT-333 + RBV group, 1.0% for ABT-450/r, ABT-267 and ABT-333 and 0.8% for the placebo group) for the 3DAA+RBV regimen and placebo. According to the Applicant, all events in the three groups were non-serious, mild in severity and did not lead to study drug discontinuation.

Approximately 88% of the patients in the Phase 2/3 trials (2309 patients) is reported to have been treated for at least 28 days during the time period from Spring equinox to Fall equinox per hemisphere (approximately six months with at least 12 hours of day light per day and 52% (1372 patients) were treated for at least 28 days during the time period from Summer solstice to Fall equinox per hemisphere (approximately three months of summer). Using exact binomial probability calculations, the Applicant estimate the probability to be at least 95% to observe a photosensitivity reaction in at least one subject in the 6 month period or the 3 month period if the rates of these reactions were 0.0013 and 0.0022, respectively.

Based on the above information, CHMP concluded that there is no large concern regarding a risk for photosensitivity reactions associated with treatment using the 3DAA regimen.

***Dependence***

No drug dependence studies were submitted. CHMP considered this as acceptable, as neither dasabuvir, nor its metabolites have no distribution to the brain and there was no evidence of effects on the central nervous system in toxicology studies.

***Metabolites***

No dedicated studies were conducted with dasabuvir metabolites. In humans, metabolite M1 was characterized as a major metabolite (21.4% of total plasma radioactivity). M1 is also a major metabolite in CD-1 and TgHras mouse and a minor metabolite in rats. However, based on the high exposure in rats, adequate exposure of M1 has been achieved in the evaluation of general toxicity, carcinogenicity, *in vivo* genotoxicity and embryo-foetal development.

***Impurities***

The toxicological qualifications of the specified ABT-333 impurities as suggested by the applicant are endorsed.

## 2.3.4. Ecotoxicity/environmental risk assessment

The risk to the terrestrial compartment needs to be further evaluated and refined in an updated ERA. The applicant has indicated that the final reports and the updated ERA will be provided in April 2015.

## 2.3.5. Conclusion on the non-clinical aspects

The non-clinical documentation is comprehensive and studies have been conducted in accordance with relevant guidelines and GLP. The Applicant has sought scientific advice for the non-clinical program and followed the recommendations received.

The non-clinical part of the dossier is considered to be sufficient. No major deficiencies have been identified. A final Environmental risk assessment cannot be made at present, which needs to be addressed by the Applicant.

## *2.4. Clinical aspects*

### 2.4.1. Introduction

***GCP***

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

| Type of Study | Study ID | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| BA | M11-030 | 5.3.1.1 | BA | Open-label | ABT-333 tablet: 400 mg single dose; PO<br>$^{14}$C-ABT-333 solution: 84-85 µg; IV | 8 | Healthy subjects | Single dose | Complete, Full |
| BA | M13-330 | 5.3.1.1 | Food effect on BA | Open-label, randomized, 3-period crossover | ABT-333 optimized tablet: 250 mg single dose; PO | 18 | Healthy subjects | Single dose per treatment period | Complete, Full |
| BA | M12-995 | 5.3.1.2 | Dosage form effect on BA | Open-label, randomized, 3-period crossover | ABT-333: 400 or 300 mg optimized tablet or 400 mg reference tablet; PO | 18 | Healthy subjects | Single dose per treatment period | Complete, Full |
| BA | M13-331 | 5.3.1.2 | Dosage form effect on BA | Open-label, randomized, 2-period crossover | ABT-333: 250 mg optimized tablet or 400 mg Phase 2b tablet; PO | 32 | Healthy subjects | Single dose per treatment period | Complete, Full |
| BA | M14-196 | 5.3.1.2 | Dosage form effect on BA | Open-label, randomized, 2-period crossover | ABT-333: 250 mg commercial tablet or 250 mg clinical Phase 3 tablet; PO | 32 | Healthy subjects | Single dose per treatment period | Complete, Full |
| PK | M10-351 | 5.3.3.1 | Safety, tolerability, PK, resistance, food effect | Double-blind (or open-label [Substudy 3]), randomized, placebo-controlled | Substudy 1: ABT-333 capsule: 10 to 2000 mg or placebo; PO<br>Substudy 2: ABT-333 capsule: 100 or 600 mg or placebo QD or BID; PO<br>Substudy 3: ABT-333 capsule: 100 mg; PO | 133 | Healthy and HCV GT1-infected subjects | Substudy 1: single dose<br>Substudy 2: QD or BID for 2 days<br>Substudy 3: single dose | Complete, Full |
| PK | M10-687 | 5.3.3.1 | Safety, tolerability, PK; PK impact of ketoconazole | Blinded, randomized, placebo-controlled | ABT-333 capsule: 200 to 1000 mg or placebo BID; PO<br>ABT-333 capsule: 200 mg QD PO;<br>Ketoconazole tablet: 200 mg; PO | 45 | Healthy subjects | 10 days | Complete, Full |

| Type of Study | Study ID | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| PK | M11-031 | 5.3.3.1 | Safety, tolerability, PK | Double-blind, randomized, placebo-controlled | ABT-333 tablet: 1200 or 1600 mg or placebo BID; PO | 24 | Healthy subjects | 7 days | Complete, Full |
| BA | M11-032 | 5.3.3.1 | Dosage form effect on BA, safety, tolerability, and PK | Open-label (Part 1) and double-blind (Part 2) randomized, 2-period crossover | Part 1: ABT-333: one 400 mg tablet or 8 × 50 mg capsules; PO<br>Part 2: ABT-333: 3 × 400 mg tablets/placebo or 4 × 400 mg tablets/placebo; PO | 34 | Healthy subjects | Single dose per treatment period | Complete, Full |
| ADME | M13-329 | 5.3.3.1 | ADME | Open-label | [$^{14}$C]ABT-333 powder for oral suspension: 400 mg; PO | 4 | Healthy subjects | Single dose | Complete, Full |
| PK/PD | M12-990 | 5.3.3.1 | Tolerability, PK, QTc prolongation | Double-blind, randomized, placebo-controlled, 2-period crossover | ABT-450 tablet: 400 or 300 mg or placebo; PO<br>Ritonavir SGC: 100 mg or placebo; PO<br>ABT-267 tablet: 100 mg or placebo; PO<br>ABT-333 tablet: 800 mg or placebo; PO | 24 | Healthy subjects | Single dose per treatment period | Complete, Full |
| PK | M11-603 | 5.3.3.1 | Safety, PK | Open-label | ABT-450 HGC: 200 mg QD; PO<br>Ritonavir SGC: 100 mg; PO<br>ABT-333: 100 mg capsule or 400 mg tablet BID; PO | 26 | Healthy subjects | 17 days (ABT-450/r) or 15 days (ABT-333) | Complete, Full |

| Type of Study | Study ID | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| PK | M12-187 | 5.3.3.1 | PK, safety | Open-label, randomized | ABT-450 SDD tablet: 150 or 250 mg QD; PO<br>ABT-267 SDD tablet: 25 mg QD; PO<br>ABT-267 HME tablet: 200 mg QD; PO<br>ABT-333 tablet: 400 mg BID; PO<br>ABT-072 SDD tablet: 400 mg QD; PO<br>Ritonavir SGC: 100 mg QD; PO | 51 | Healthy subjects | 21 days | Complete, Full |
| PK | M10-380 | 5.3.3.2 | Safety, tolerability, antiviral activity, PK, resistance | Blinded, randomized, placebo-controlled | Part 1: ABT-333 capsule: 300 or 600 mg BID or 1200 mg QD; PO<br>pegIFN: 180 µg QW; SC<br>RBV tablet: 1000 to 1200 mg BID, or placebo; PO<br>Part 2: ABT-333 capsule: 2400 to 3200 mg QD; PO (not performed) | 30 | Treatment-naïve, HCV-infected subjects | 28 days | Complete, Full |
| PK | M11-602 | 5.3.3.2 | Safety, tolerability, PK, antiviral activity, quality of life | Blinded, randomized, placebo-controlled | ABT-450 HGC: 50, 100, or 200 mg or placebo QD; PO<br>ABT-072 tablet 100, 300, or 600 mg or placebo QD; PO<br>ABT-333 tablet: 400 or 800 mg or placebo BID; PO<br>pegIFN: 180 µg QW; SC<br>RBV tablet: 500 to 600 mg BID; PO<br>Ritonavir SGC: 100 mg QD; PO | 74 | Treatment-naïve, HCV-infected subjects | 3 days of DAA monotherapy, 81 days of combination DAA and pegIFN/RBV therapy, followed by up to an additional 36 weeks of pegIFN/RBV therapy | Complete, Full |

| Type of Study | Study ID | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| PK | M12-221 | 5.3.3.3 | Safety, PK | Open-label, randomized | ABT-450 tablet: 150, 200, or 250 mg QD; PO<br>ABT-267 HME tablet: 25 mg QD; PO<br>ABT-333 tablet: 400 mg BID; PO<br>Ritonavir SGC: 100 mg QD; PO | 90 | Healthy subjects | 21 days | Complete, Full |
| PK | M12-215 | 5.3.3.3 | PK, safety | Open-label | ABT-450 SDD tablet: 200 mg; PO<br>ABT-267 HME tablet: 25 mg; PO<br>ABT-333 tablet: 400 mg; PO<br>Ritonavir SGC: 100 mg; PO | 24 | Healthy subjects or subjects with chronic hepatic insufficiency | Single dose | Complete; Full |
| PK | M12-193 | 5.3.3.3 | Safety, PK | Open-label, randomized, 2-period crossover | ABT-450/r tablet: 150/100 mg; PO<br>ABT-267 HME tablet: 25 mg; PO<br>ABT-333 tablet: 400 mg; PO | 24 | Subjects with normal renal function or with mild to severe renal impairment | Single dose | Complete; Full |
| PK | M11-023 | 5.3.3.3 | Safety, tolerability, PK | Blinded, randomized, placebo-controlled | ABT-333 tablet: 400 to 1600 mg or placebo; PO | 39 | Healthy subjects | Single dose | Complete, Full |
| DDI | M12-196 | 5.3.3.4 | PK effect by gemfibrozil | Open-label | ABT-450 tablet: 150 mg QD; PO<br>ABT-333 tablet: 400 mg QD; PO<br>Ritonavir SGC: 100 mg QD; PO<br>Gemfibrozil tablet: 600 mg QD; PO | 12 | Healthy subjects | ABT-450/r and ABT 333: 2 days; Gemfibrozil: 5 days | Complete, Full |

| Type of Study | Study ID | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| DDI | M12-198 | 5.3.3.4 | 2- or 3-DAA regimen coadministered with warfarin; safety, tolerability, PK | Open-label | ABT-450 tablet: 150 mg QD; PO<br>ABT-267 tablet: 25 mg QD; PO<br>ABT-333 tablet: 400 mg BID; PO<br>Ritonavir SGC: 100 mg QD; PO<br>Warfarin tablet: 5 mg; PO<br>Vitamin K tablet: 10 mg PO | 24 | Healthy subjects | ABT-450/r, ABT-267 and ABT-333: 24 days; Warfarin and Vitamin K: single dose | Complete, Full |
| DDI | M12-199 | 5.3.3.4 | 2- or 3-DAA regimen coadministered with omeprazole; safety, tolerability, PK | Open-label, randomized | ABT 450/r/ABT-267 tablet: 150/100/25 mg QD; PO<br>ABT-333 tablet: 250 mg BID; PO<br>Omeprazole capsule: 40 mg QD; PO | 24 | Healthy subjects | ABT-450/r/ ABT-267 and ABT-333: 19 days; Omeprazole: 1 day with washout and 5 days | Complete, Full |
| DDI | M12-189 | 5.3.3.4 | 2- or 3-DAA regimen coadministered with ketoconazole; safety, tolerability, PK | Open-label, randomized | ABT-450/r/ABT-267 tablet: 150/100/25 mg QD; PO<br>ABT-333 tablet: 250 mg QD; PO<br>Ketoconazole tablet: 400 mg QD; PO | 24 | Healthy subjects | ABT-450/r/ ABT-267 and ABT-333: single dose twice after washout; Ketoconazole: 6 days | Complete, Full |
| DDI | M14-027 | 5.3.3.4 | 2- or 3-DAA regimen coadministered with carbamazepine; safety, tolerability, PK | Open-label | ABT-450/r/ABT-267 tablet: 150/100/25 mg; PO<br>ABT-333 tablet: 250 mg; PO<br>Carbamazepine tablet: 200 mg QD or BID; PO | 12 | Healthy subjects | ABT-450/r/ ABT-267: 2 doses with washout; Carbamazepine: 24 days | Complete, Full |

| Type of Study | Study ID | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| DDI | M12-201 | 5.3.3.4 | 2- or 3-DAA regimen coadministered with digoxin; safety, tolerability, PK | Open-label | ABT-450 tablet: 150 mg QD; PO<br>ABT-267 tablet: 25 mg QD; PO<br>ABT-333 tablet: 400 mg BID; PO<br>Ritonavir SGC: 100 mg QD; PO<br>Digoxin tablet: 0.5 mg; PO | 24 | Healthy subjects | ABT-450, ritonavir, ABT-267, and ABT-333: 19 days; Digoxin: 2 doses with washout | Complete, Full |
| DDI | M12-200 | 5.3.3.4 | 2- or 3-DAA regimen coadministered with rosuvastatin or pravastatin; safety, tolerability, PK | Open-label | ABT-450 tablet: 150 mg QD; PO<br>ABT-267 tablet: 25 mg QD; PO<br>ABT-333 tablet: 400 mg BID; PO<br>Ritonavir SGC: 100 mg; PO<br>Rosuvastatin tablet: 5 mg QD; PO<br>Pravastatin tablet: 10 mg QD; PO | 48 | Healthy subjects | ABT-450, ritonavir, ABT-267, and ABT-333: single dose followed by 14 days; rosuvastatin or pravastatin: 17 days | Complete, Full |
| DDI | M13-492 | 5.3.3.4 | 2- or 3-DAA regimen coadministered with LPV/r; safety, tolerability, PK | Open-label, randomized | ABT-450 SDD tablet: 150 mg QD; PO<br>ABT-267 HME tablet: 25 mg QD; PO<br>ABT-333 tablet: 400 mg QD; PO<br>Ritonavir SGC: 100 mg QD; PO<br>LPV/r tablet: 400/100 mg BID; PO | 60 | Healthy subjects | 28 days | Complete, Full |

| Type of Study | Study ID | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| DDI | M14-013 | 5.3.3.4 | 2- or 3-DAA regimen coadministered with LPV/r; safety, tolerability, PK | Open-label, randomized | ABT-450/r tablet: 150/100 mg QD; PO<br>ABT-267 tablet: 25 mg QD; PO<br>ABT-333 tablet: 400 mg QD; PO<br>LPV/r tablet: 800/200 mg QD; PO | 48 | Healthy subjects | 28 days | Complete, Full |
| DDI | M13-506 | 5.3.3.4 | 2- or 3-DAA regimen coadministered with darunavir; safety, tolerability, PK | Open-label, randomized | ABT-450 tablet: 150 mg QD; PO<br>ABT-267 tablet: 25 mg QD; PO<br>ABT-333 tablet: 400 mg BID; PO<br>Ritonavir SGC: 100 mg QD; PO<br>Darunavir tablet: 600 or 800 mg BID; PO | 72 | Healthy subjects | 28 days | Complete, Full |
| DDI | M12-202 | 5.3.3.4 | 2- or 3-DAA regimen coadministered with darunavir; safety, tolerability, PK | Open-label, randomized | ABT-450/r/ABT-267 tablet: 150/100/25 mg QD; PO<br>ABT-333 tablet: 250 mg BID; PO<br>Ritonavir SGC: 100 mg QD; PO<br>Darunavir tablet: 800 mg QD; PO | 24 | Healthy subjects | 28 days | Complete, Full |
| DDI | M13-394 | 5.3.3.4 | 2- or 3-DAA regimen coadministered with atazanavir; safety, tolerability, PK | Open-label, randomized | ABT-450/r tablet: 150/100 mg QD; PO<br>ABT-267 tablet: 25 mg QD; PO<br>ABT-333 tablet: 400 mg BID; PO<br>Ritonavir SGC: 100 mg QD; PO<br>Atazanavir capsule: 300 mg QD; PO | 72 | Healthy subjects | 28 days | Complete, Full |

| Type of Study | Study ID | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| DDI | M13-783 | 5.3.3.4 | 2- or 3-DAA regimen coadministered with emtricitabine and tenofovir disoproxil fumarate; PK, safety, and tolerability | Open-label, randomized | ABT-450 tablet: 150 mg QD; PO<br>ABT-267 tablet: 25 mg QD; PO<br>ABT-333 tablet: 400 mg BID; PO<br>Ritonavir SGC: 100 mg QD; PO<br>Emtricitabine capsule: 200 mg QD; PO<br>Tenofovir disoproxil fumarate tablet: 300 mg QD; PO | 36 | Healthy subjects | 21 days | Complete, Full |
| DDI | M13-104 | 5.3.3.4 | 2- or 3-DAA regimen coadministered with efavirenz, emtricitabine, and tenofovir disoproxil fumarate (Atripla); PK, safety, and tolerability | Open-label, randomized | ABT-450 tablet: 150 mg QD; PO<br>ABT-333: 400 mg BID; PO<br>Ritonavir SGC: 100 mg; PO<br>Efavirenz, emtricitabine, and tenofovir disoproxil fumarate tablet: 600/200/300 mg QD; PO | 16 | Healthy subjects | 17 or 3 days | Complete, Full |
| DDI | M13-782 | 5.3.3.4 | 3-DAA regimen coadministered with rilpivirine; PK, safety, and tolerability | Open-label, randomized | ABT-450/r tablet: 150/100 mg QD; PO;<br>ABT-267 tablet: 25 mg QD; PO;<br>ABT-333 tablet: 400 mg BID; PO;<br>Rilpivirine tablet: 25 mg QD; PO | 60 | Healthy subjects | 28 days | Complete, Full |

| Type of Study | Study ID | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| DDI | M13-392 | 5.3.3.4 | 2- or 3-DAA regimen coadministered with raltegravir; PK, safety, and tolerability | Open-label, randomized | ABT-450 SDD tablet: 150 mg QD; PO<br>ABT-267 HME tablet: 25 mg QD; PO<br>ABT-333 tablet: 400 mg BID; PO<br>Ritonavir SGC: 100 mg QD; PO<br>Raltegravir tablet: 400 mg BID PO | 36 | Healthy subjects | ABT-450, ritonavir, ABT-267, and ABT-333: 14 days; Raltegravir: 17 days | Complete, Full |
| DDI | M13-103 | 5.3.3.4 | 2- or 3-DAA regimen coadministered with cyclosporine; PK, safety, and tolerability | Open-label, randomized | ABT-450 SDD tablet: 150 mg QD; PO<br>ABT-267 HME tablet: 25 mg QD; PO<br>ABT-333 tablet: 400 mg BID; PO<br>Ritonavir SGC: 100 mg QD; PO<br>Cyclosporine SGC or solution: 10, 30, and 100 mg single and multiple dose; PO | 36 | Healthy subjects | ABT-450, ritonavir:, ABT-267, and ABT-333: 21 days; Cyclosporine: 2 days with washout | Complete, Full |
| DDI | M13-491 | 5.3.3.4 | 2- or 3-DAA regimen coadministered with tacrolimus; PK, safety, and tolerability | Open-label, randomized | ABT-450 SDD tablet: 150 mg QD; PO;<br>ABT-267 HME tablet: 25 mg QD; PO;<br>ABT-333 tablet: 400 mg BID; PO;<br>Ritonavir SGC: 100 mg QD; PO<br>Tacrolimus capsule: 0.5 or 2 mg; PO | 36 | Healthy subjects | ABT-450, ritonavir: ABT-267, and ABT-333: 28 days; Tacrolimus: 2 days with washout | Complete, Full |

| Type of Study | Study ID | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| DDI | M12-997 | 5.3.3.4 | 2- or 3-DAA regimen administered in setting of stable methadone maintenance therapy; PK, PD, safety, and tolerability | Open-label, randomized | ABT-450 SDD tablet: 150 mg QD; PO;<br>ABT-267 HME tablet: 25 mg QD; PO;<br>ABT-333 tablet: 400 mg BID; PO;<br>ABT-450/r/ABT-267 tablet: 150/100/25 mg QD; PO;<br>Ritonavir SGC: 100 mg QD; PO<br>Methadone: QD per physician instruction | 36 | Healthy subjects on stable methadone therapy | ABT-450, ritonavir, ABT-267, ABT-333, and ABT-450/r/ ABT-267: 14 days;<br>Methadone: 25 days | Complete, Full |
| DDI | M13-100 | 5.3.3.4 | 2- or 3-DAA regimen administered in setting of stable buprenorphine/ naloxone maintenance therapy; PK, safety, and tolerability | Open-label, randomized | ABT-450 SDD tablet: 50 mg QD; PO;<br>ABT-267 HME tablet: 25 mg QD; PO;<br>ABT-333 tablet: 400 mg BID; PO;<br>ABT-450/r/ABT-267 tablet: 75/50/12.5 mg QD; PO<br>Ritonavir SGC: 100 mg QD; PO<br>Buprenorphine/ naloxone: QD per physician instruction | 36 | Healthy subjects on stable buprenorphine/ naloxone therapy | ABT-450, ritonavir, ABT-267, ABT-333, and ABT-450/r/ ABT-267: 14 days;<br>Buprenorphine/ naloxone: 25 days | Complete, Full |
| DDI | M12-205 | 5.3.3.4 | 2- or 3-DAA regimen coadministered with oral contraceptives; PK, safety, and tolerability | Open-label, randomized | ABT-450/r/ABT-267 tablet: 150/100/25 mg QD; PO<br>ABT-333 tablet: 250 mg BID; PO<br>EE/NGM tablet: 35/250 µg; PO<br>NET tablet: 0.35 mg; PO<br>EE/NET tablet: 35 µg/0.4 mg; PO | 34 | Healthy subjects | ABT-450/r/ ABT-267: 8, 19, or 21 days<br>ABT-333: 19 or 21 days<br>EE/NGM: 21 days<br>NET: 17 days<br>EE/NET: 15 days | Complete; Full |

| Type of Study | Study ID | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| DDI | M12-204 | 5.3.3.4 | 2- or 3-DAA regimen coadministered with escitalopram or duloxetine; PK, safety, and tolerability | Open-label | ABT-450/r/ABT-267 tablet: 150/100/25 mg QD; PO<br>ABT-333 tablet: 250 mg BID; PO<br>Escitalopram tablet: 10 mg; PO<br>Duloxetine capsule: 60 mg; PO | 48 | Healthy subjects | ABT-450/r/ ABT-267: 16 or 20 days<br>ABT-333: 16 or 20 days<br>Escitalopram: single dose;<br>Duloxetine: single dose | Complete, Full |
| DDI | M14-324 | 5.3.3.4 | 3-DAA regimen coadministered with alprazolam or zolpidem tartrate; PK, safety, and tolerability | Open-label | ABT-450/r/ABT-267 tablet: 150/100/25 mg QD; PO<br>ABT-333 tablet: 250 mg BID; PO<br>Alprazolam tablet: 0.5 mg; PO<br>Zolpidem tartrate tablet: 5 mg; PO | 24 | Healthy subjects | ABT-450/r/ ABT-267 and ABT-333: 16 days<br>Alprazolam and zolpidem tartrate: 2 days with washout | Complete, Full |
| DDI | M14-325 | 5.3.3.4 | 3-DAA regimen coadministered with furosemide or amlodipine besylate; PK, safety, and tolerability | Open-label | ABT-450/r/ABT-267 tablet: 150/100/25 mg QD; PO<br>ABT-333 tablet: 250 mg BID; PO<br>Furosemide tablet: 20 mg with 20 mEq potassium bicarbonate tablet; PO<br>Amlodipine besylate tablet: 5 mg; PO | 26 | Healthy subjects | ABT-450/r/ ABT-267 and ABT-333: 16 days or 24 days<br>Furosemide or amlodipine besylate: 2 days with washout | Complete; Full |

| Type of Study | Study ID | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| PD | M12-680 | 5.3.4.1 | 3-DAA QTc prolongation potential | Double-blind, randomized, placebo- and active-controlled | ABT-450 SDD tablet: 200 or 350 mg or placebo; PO<br>ABT-267 HME tablet: 25 or 50 mg or placebo; PO<br>ABT-333 tablet: 250 or 500 mg or placebo; PO<br>Ritonavir SGC: 150 mg or placebo; PO<br>Moxifloxacin tablet: 400 mg; PO | 60 | Healthy subjects | Single dose per treatment period | Complete; Full |
| Efficacy and Safety | M13-386 | 5.3.5.1 | Safety, tolerability, antiviral activity, PK | Open-label | ABT-450 tablet: 150 mg QD; PO;<br>ABT-267 tablet: 1.5 to 50 mg QD; PO;<br>ABT-333 tablet: 400 mg BID; PO;<br>Ritonavir SGC: 100 mg QD; PO<br>RBV tablet: 1,000 or 1,200 mg QD (divided BID); PO | 12 | HCV GT1-infected treatment-naïve subjects | ABT-450, ritonavir, ABT-333, and RBV: 12 weeks; ABT-267: 2 days + 12 weeks | Complete, Full |
| Efficacy and Safety | M11-652 | 5.3.5.1 | Efficacy, safety, and PK of 2 or 3 DAAs with and without RBV | Open-label, randomized | ABT-450 tablet: 100, 150, or 200 mg QD; PO;<br>ABT-267 tablet: 25 mg QD; PO;<br>ABT-333 tablet: 400 mg BID; PO<br>Ritonavir SGC: 100 mg QD; PO<br>RBV tablet: 1,000 to 1,200 mg QD (divided BID) PO | 580 | HCV GT1-infected treatment-naïve and previous null responder subject | 8, 12, or 24 weeks | Complete, Full |

| Type of Study | Study ID | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| Efficacy and Safety | M13-389 | 5.3.5.1 | Efficacy and, safety with and without RBV; noninferiority to historical SVR rate of telaprevir plus pegIFN and RBV | Open-label, randomized | ABT-450/r/ABT-267 tablet: 150/100/25 mg QD; PO; ABT-333 tablet: 250 mg BID; PO; RBV tablet: 1,000 or 1,200 mg QD (divided BID); PO | 187 | PegIFN/RBV treatment-experienced, noncirrhotic, HCV GT1b-infected adults (prior null responders, non-or partial responders and relapsers) | 12 weeks | Ongoing; Interim |
| Efficacy and Safety | M13-098 | 5.3.5.1 | Efficacy and safety with RBV; noninferiority to historical SVR rate of telaprevir plus pegIFN and RBV | Double-blind, randomized, placebo-controlled | ABT-450/r/ABT-267 tablet: 150/100/25 mg or placebo QD; PO ABT-333 tablet: 250 mg or placebo BID; PO RBV tablet: 1,000 or 1,200 mg or placebo QD (divided BID); PO | 395 | Noncirrhotic, HCV GT1-infected adult subjects who are null responders, partial responders or relapsers to prior pegIFN/RBV treatment | 12 weeks | Ongoing; Interim |
| Efficacy and Safety | M11-646 | 5.3.5.1 | Efficacy and, safety with RBV; noninferiority to historical SVR rate of telaprevir plus pegIFN and RBV | Double-blind, randomized, placebo-controlled | ABT-450/r/ABT-267 tablet: 150/100/25 mg or placebo QD; PO ABT-333 tablet: 250 mg or placebo BID; PO RBV tablet: 1,000 or 1,200 mg or placebo QD (divided BID); PO | 636 | Treatment-naïve, noncirrhotic HCV GT1-infected adults | 12 weeks | Ongoing; Interim |
| Efficacy and Safety | M13-961 | 5.3.5.1 | Efficacy and, safety with and without RBV; noninferiority to historical SVR rate of telaprevir plus pegIFN and RBV | Double-blind, randomized | ABT-450/r/ABT-267 tablet: 150/100/25 mg QD; PO ABT-333 tablet: 250 mg BID; PO; RBV tablet: 1,000 to 1,200 mg or placebo QD (divided BID); PO | 419 | Treatment-naïve, HCV GT1b-infected adults | 12 weeks | Ongoing; Interim |

| Type of Study | Study ID | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| Efficacy and Safety | M14-002 | 5.3.5.1 | Efficacy and, safety with and without RBV; noninferiority to historical SVR rate of telaprevir plus pegIFN and RBV | Double-blind, randomized | ABT-450/r/ABT-267 tablet: 150/100/25 mg QD; PO;<br>ABT-333 tablet: 250 mg BID; PO;<br>RBV tablet: 1,000 to 1,200 mg or placebo QD (divided BID); PO | 305 | Treatment-naïve, noncirrhotic HCV GT1a-infected adults | 12 weeks | Ongoing; Interim |
| Efficacy and Safety | M12-746 | 5.3.5.2 | Efficacy and safety with RBV | Open-label | ABT-450: 150 mg QD; PO;<br>ABT-333: 400 mg BID; PO;<br>Ritonavir: 100 mg QD; PO<br>RBV: 1,000 or 1,200 mg QD (divided BID); PO | 50 | HCV-infected subjects who are treatment-naïve or previous nonresponders to pegIFN/RBV | 12 weeks | Complete, Full |
| Efficacy and Safety | M13-099 | 5.3.5.2 | Efficacy and, safety with RBV; noninferiority to historical SVR rate of telaprevir plus pegIFN and RBV | Open-label, randomized | ABT-450/r/ABT-267 tablet: 150/100/25 mg QD; PO<br>ABT-333 tablet: 250 mg BID; PO<br>RBV tablet: 1,000 to 1,200 mg or placebo QD (divided BID); PO | 381 | HCV GT1-infected, treatment-naïve and previous pegIFN/RBV treatment-experienced adults with compensated cirrhosis | 12 or 24 weeks | Ongoing; Interim |
| Efficacy and Safety | M14-103 | 5.3.5.2 | Efficacy and, safety with RBV | Open-label | ABT-450/r/ABT-267 tablet: 150/100/25 mg QD; PO<br>ABT-333 tablet: 250 mg BID; PO;<br>RBV tablet: 1,000 to 1,200 mg or placebo QD (divided BID); PO | 38 | Noncirrhotic, HCV GT1a-infected adults on a stable opioid replacement therapy with methadone or buprenorphine ± naloxone | 12 weeks | Ongoing; Interim |

## 2.4.2. Pharmacokinetics

Dasabuvir has a major metabolite, M1, which has antiviral activity, albeit 7-8 fold lower than the parent compound (see below). M1 has been measured in almost all pharmacokinetic studies. M1 is present at plasma concentrations about half those of dasabuvir. However, due to differences in protein binding, the unbound M1 concentration is 6.5-fold higher than the concentration of dasabuvir and thus the contribution of M1 to efficacy is significant. Active moiety calculations have been performed but are difficult to use as M1 in contrast to dasabuvir may have higher liver distribution due to active uptake. In the calculations the applicant has used a relative activity factor of 10 instead of 7-8. Thus, M1 contributes slightly more to the active moiety and efficacy than estimated by the applicant.

**Table 1. Activity of ABT-333 and its M1 Metabolite in Genotype 1a-H77 and 1b-Con1 Subgenomic Replicons**

| | | | Genotype 1a | | Genotype 1b | |
|---|---|---|---|---|---|---|
| | | | $EC_{50}$ (nM) | | | |
| A-Number | Name | N | 0% Human Plasma | 40% Human Plasma | 0% Human Plasma | 40% Human Plasma |
| A-998821.0 | ABT-333 | 3 | 6 | 103 | 1 | 15 |
| A-1041392.0 | M1 metabolite | 3 | 39 | 143 | 8 | 26 |

***Absorption***

Dasabuvir as the free acid, is a moderate molecular weight (mw 493.58), lipophilic compound (logD 4.3), with minimal solubility in aqueous solutions (~0.15 µg/mL at pH 7.4). The solubility is not pH dependent at physiological pH:s. The absorption of dasabuvir was moderate with Tmax occurring at ca. 3 hours post-dose. Different formulations have been used during development and the PK bridging is sufficient. In the last part of development an optimized tablet was used that had a higher, almost complete, bioavailability than the earlier formulations and therefore the dose was reduced from 400 to 250 mg to maintain the same exposure. Dasabuvir is a substrate of Pgp in MDR-1 over-expressing MDCK cells. The permeability *in vitro* has not been well determined but seems to be high *in vivo* based on the high bioavailability.

Dasabuvir should be administered with food. In most studies dasabuvir has been administered 30 minutes after the start of a moderate meal. The administration of dasabuvir 30 minutes after starting a moderate-fat breakfast resulted in a ca. 40% increase in dasabuvir AUC and a 54% increase in Cmax. The corresponding parameters for M1 increased ca. 54 and 30%, respectively. Administration with a high-fat breakfast resulted in somewhat lower food-effect. A quite marked difference in exposure between morning and evening dose was observed in many studies and may be caused by differences in food intake.

***Distribution***

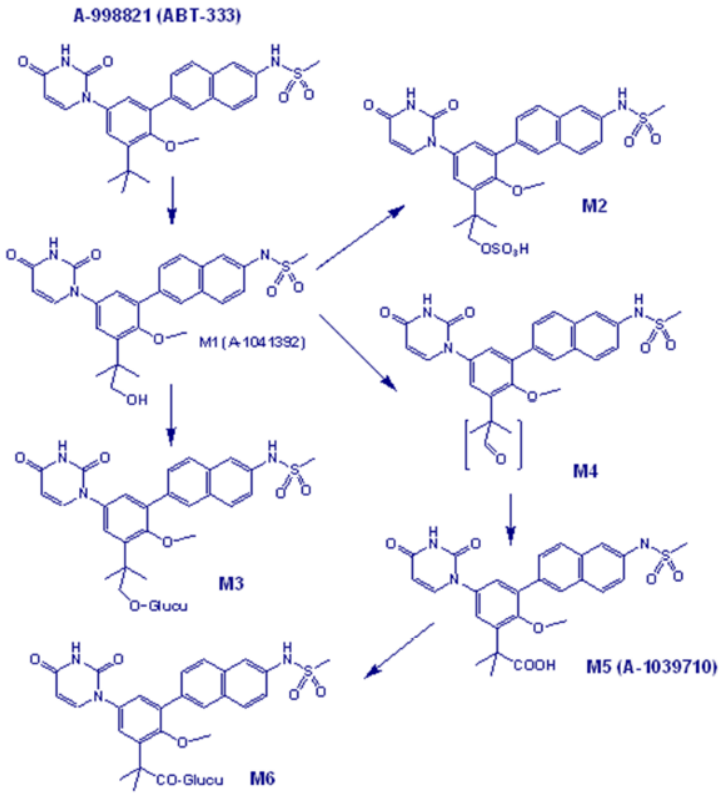
The volume of distribution of dasabuvir is approximately 400 L after iv administration. Dasabuvir is extensively protein bound, fu values in human ranged from 0.0030-0.0054. The metabolite M1 is less bound with an fu of about 0.05. This means that the free concentration of M1 is ca. 6.5-fold the free concentration of dasabuvir (using 0.57 in molar M1/dasabuvir ratio) and thus the M1 contribution to efficacy (assuming similar distribution) could be significant. In contrast to dasabuvir, M1 is a substrate to hepatic uptake transporters (OATP1B1, 1B3 and OCT-1) and may reach higher concentrations in the liver as compared to plasma. The liver/plasma

concentration ratio of radioactivity after a radiolabelled dasabuvir dose to rat was ca 23-46 at different time points. M1, but not dasabuvir, is substrate to OATP1 and 3. The blood to plasma ratio of dasabuvir was 0.67.

***Elimination***

In the mass-balance study, 94% of the radioactivity was excreted in faeces up to 240 hours postdose and 2.2% (± 0.57%) was excreted in urine. Unchanged dasabuvir contributed to 26% of the radioactivity in faeces while excretion of dasabuvir in urine is negligible. As the unchanged drug in faeces likely is unabsorbed drug based on the expected bioavalability of an early formulation (no information found on which formulation was used in this study), biliary and renal excretion seems not to be significant elimination pathways of unchanged drug. Dasabuvir is eliminated mainly through formation of M1. M1 was the most abundant component in faeces, accounting for 32% of total dose, followed by unchanged dasabuvir (26%), M2 (15%), M5 (11%) and some minor metabolites (M8-10). The total amount of M1-related conjugates in human urine and faeces was 24% of dose. Secondary oxidative metabolite of M1 and subsequent conjugates comprised 14% of dose, indicating M1 is mainly cleared through direct faecal elimination or M1 conjugates; subsequent oxidation of M1 plays a secondary role. M1 is the only "major metabolite" present in plasma after dasabuvir dosing.

This is the proposed elimination schedule of dasabuvir (and M1)




The formation of M1 is catalysed by CYP2C8 and CYP3A4 *in vitro* and their roles have been confirmed *in vivo* in the drug interaction study with the 2C8 inhibitor gemfibrozil and the 3A inhibitor ketoconazole. As dasabuvir always will be given with ritonavir, which is a time-dependent inhibitor of CYP3A and possibly also an inducer of CYP2C8, the role of CYP2C8 in relation to CYP3A becomes even more marked at steady state in the 3-DAA combination. The applicant has not fully investigated which transporters and enzymes are involved in the elimination of M1. M1 seems to be partly biliary excreted (ca 45%), partly glucuronidated (35%) and to a lesser extent – oxidized (20%). The uptake transporters OATP1B1 and 1B3, as well as OCT-1 are likely involved and as

M1 can be transported by Pgp and BCRP, these may be involved in hepatic efflux. UGT1A4, 1A9 and 2B7 are capable of performing the glucuronidation. CYP2C8 and 3A4 has been proposed to catalyse the oxidation. There are no in vivo data indicating involvement of a certain enzyme/transporter.

If the active uptake of M1 would be in vivo relevant, OAT1B1 and 1B3 inhibitors could give rise to increased M1 exposure. However, the lack of increase in M1 exposure in the DDI studies with cyclosporine and atazanavir (see below) indicate that OATP uptake is of limited importance for M1 elimination. It is possible that OCT-1 is more relevant.

**Pharmacogenetics**

CYP2C8 is a polymorphic enzyme. The transporters OCT-1, BCRP and OATP1B1 are also subject to polymorphisms. The applicant has analysed the impact of pharmacogenetics on ABT-450 and dasabuvir pooling data from many PK studies. No association was found between genotype of genes coding enzymes and transporters and drug exposure. The variability in drug exposure may have been too large for effects to be detected with this method.

The applicant has also analysed the relationship between BSEP genotype and elevation in transaminases generally in the file as well as elevation of transaminases in oestrogen treated patients (the OC DDI study). (*Genetic studies have identified that mutations in BSEP that lead to premature truncation of the protein or missense mutations in patients are responsible for hereditary cholestasis. In addition, a relatively common polymorphism in exon 13 (rs2287622) may be associated with higher incidences of pregnancy and contraceptive-induced cholestasis.*) No relationship between BSEP genotype and raised transaminases was found but looking at the subjects in the OC DDI study, there was a correlation. However, this is a very small data set (see Table 1).

**Table 1.** BSEP gene analysis for rs2287622 in Subjects on Estradiol in Studies M11-652, M12-205 and M12-998 (CC has a lower expression)

| Genotype | Grade 3 or Above | Under Grade 3 | % of Subjects with Grade 3 or Above |
|---|---|---|---|
| C/C | 3 | 9 | 25% |
| C/T | 3 | 15 | 17% |
| T/T | 1 | 17 | 6% |
| Total | 7 | 41 | 15% |

The applicant has been asked by CHMP to investigate as a post-authorisation measure whether concomitant use of drugs that are BSEP inhibitors is associated with increased transaminases.

***Dose proportionality and time dependencies***

Single dose pharmacokinetics using early formulations is linear up to doses of 800-1200 mg, where absorption starts to decrease, possibly due to solubility. There is no single-dose vs. multiple-dose comparison, thus, it cannot be properly assessed whether there is any change over time in clearance. There is an *in vitro* induction signal and in some of the DDI studies, the results could be interpreted as dasabuvir mediating a small induction. There is also a signal of CYP3A4 TDI *in vitro*. The accumulation ratio of dasabuvir and M1 are about 2 and 1.5, respectively. Based on the short half-life of dasabuvir (ca. 6 hrs), a somewhat smaller accumulation would be expected. In conclusion, there seems to be no marked time-dependency. Steady state for both substances was reached approximately on the third day of treatment.

***Special populations***

Population pharmacokinetic analyses of PhaseI/II and Phase III data suggested cirrhosis, sex, creatinine clearance and body weight to be statistically significant predictors of dasabuvir CL. However these effects were not considered clinically relevant and no dose adjustment based on gender, age, weight and race is warranted. Females had higher exposures (AUC24,ss) of the DAAs compared to males. The dasabuvir exposure was ≤ 30% higher. There were no indications of an altered DAA exposure in Asians; Black and Hispanic/Latinos. Body weight was a significant covariate on CL/F, Vc/F and Vp/F. A < 10% change in exposure with a change of ± 10 kg from 76 kg of body weight was estimated. The difference is deemed as clinically not relevant. Age was a significant covariate on CL/F. A ≤ 10% change in exposures with a change of ± 10 years from 54 years of age was predicted for dasabuvir.

*Hepatic impairment*

The AUC of dasabuvir was 17% increased, 16% decreased and 4.2-fold increased, respectively in patients with mild, moderate and severe hepatic impairment. M1 was unchanged, decreased by 57% and increased by 76%. There was no increase in fu vs degree of impairment. Due to lack of clinical data, a posology for moderate hepatic impairment is not given in the Exviera SmPC.

*Renal impairment*

The AUC of dasabuvir was 97, 38 and 47% (increased in mild, moderate, and severe renal impairment), respectively. For M1 the AUC was 39 and 28 decreased in mild and moderate renal impairment while it was 34% decreased in severe impairment.

No information about the effect of age on the PK of dasabuvir is available in truly elderly patients (>75 years) and limited information is available in elderly patients >65 years. Possible differences in exposure in elderly are thereby difficult to predict. However, based on safety data, no dose adjustments appear necessary.

**Exposure associated with clinical response**

ABT-333 monotherapy data did not suggest a significant difference in efficacy between 300 mg BID (~25% lower exposure), 400 mg BID (~Phase 3 exposure) and 600 mg BID dosing. A logistic-regression analyses using GT1a data from Phase 3 studies (including cirrhotic and non-cirrhotic, treatment-naïve and treatment-experienced subjects), indicated that ABT-333 exposures were not a significant predictor of SVR. In addition, a simulation study using a semi-mechanistic model of viral dynamics (ABT-450/r, ABT-267 and

ABT-333 Exposure-Viral Load Response Report R&D/13/1069) did not show a significant difference in SVR when all components (ABT-450, ABT-267and ABT-333) were reduced by 50%.

Multivariate logistic regression did not suggest a significant correlation between ABT-333 exposure and safety (Rash-related events, ALT elevations, Total bilirubin elevations and Low hemoglobin levels) at the dose 400 mg BID.

***Pharmacokinetic interaction studies***

The applicant has submitted an extensive DDI data package with *in vitro* and *in vivo* studies. Both dasabuvir and M1 has been screened for enzyme and transporter inhibition *in vitro.* The DDI potential has been investigated with 17 drugs, sometimes in more than one study. In the *in vivo* studies, all DAAs are included and the net effect is gained. This is satisfactory as it reflects the clinical situation, but it sometimes hinders mechanistic conclusions, in particular when combining with such a DDI prone drug as ritonavir. The DDIs with ritonavir are time-dependent and the drug affects a multitude of proteins. Thus, mutual, time dependent interactions are expected. However, the study designs do not always take this into account and the estimated interaction effect may be slightly different at steady state.

*Dasabuvir as perpetrator – in vitro studies*

Dasabuvir inhibits several enzymes and transporters. The results and possible *in vivo* relevance based on Ki or $EC_{50}$ and, the "Relevant in vivo concentration" which here includes the estimated exposure at the site of the enzyme and a safety factor, is presented below:

| Enzyme/Transporter | IC50 (uM) | Ki (uM) | Relevant in vivo konc (uM)# | Inhibition indicated?* |
|---|---|---|---|---|
| D: CYP2C9¤ | 3.4 | 1.7 | 1.0 | no |
| D: CYP2C8¤ | 1.3 | 0.65 | 1.0 | yes |
| D: CYP2C19¤ | 1.8 | 0.9 | 1.0 | yes |
| D: CYP2D6¤ | 13.5 | 6.8 | 1.0 | no |
| D: CYP3A4 | TDI | TDI | 202 / 1.0 | unknown |
| M1: CYP3A4 | TDI | TDI | 196 / 1.0 | unknown |
| D: UGT1A1 | 0.92 | 0.46 | 1.0 | yes |
| M1: UGT1A1 | 6.53 | 3.26 | 3.2 | no (?) |
| D: UGT1A4 | 3.78 | 1.89 | 1.0 | yes (see below) |
| M1: UGT1A4 | 10.2 | 5.1 | 3.2 | no |
| D: UGT1A6 | 3.37 | 1.7 | 1.0 | yes (see below) |
| M1: UGT1A6 | >50 | >25 | 3.2 | no |
| D: UGT1A9 | 6.51 | 2.6 | 1.0 | no |
| M1: UGT1A9 | 46.6 | 23.3 | 3.2 | no |
| D: UGT2B7 | 41.9 | 21.0 | 202 / 1.0 | yes / no |
| M1: UGT2B7 | >50 | >25 | 196 / 3.2 | ? / no |
| D: Pgp | 16.7 | n.d | 202 / 1.0 | yes / no |
| D: BCRP | 15.6 | n.d | 202 / 1.0 | yes / no |
| M1 BCRP | 22 | n.d | 196 / 3.2 | yes / no |
| D: MRP-2 | 39 | n.d | 1.0 | no |

*#Including safety factor*

**If two concentrations and evaluations are given this relates to intestinal / systemic inhibition.*

As can be seen from the table, the Ki's of UGT1A4 and 1A6 are close to the cut-off. The EC50's were not well determined and are likely over-predicted. Thus, the signals are considered positive.

When relevant, enzyme inhibition parameters were corrected for non-specific binding and metabolism. Based on the in vitro information, potential for in inhibition in vivo can be concluded for dasabuvir and intestinal Pgp, dasabuvir and M1 on intestinal BCRP, dasabuvir and M1 on OATP1B1 and 1B3, dasabuvir on CYP2C8 and 2C19 dasabuvir on UGT1A2, 1A4, 1A6 and 2B7. Possibly also CYP3A4 through TDI but here data is lacking to perform the IVIVC assessment.

The *in vitro* enzyme induction study results indicate PXR mediated (CYP3A) induction as well as CYP1A2 down regulation or toxicity. Toxicity was observed at the highest concentration. Again the influence of metabolism/degradation during the 24h 37°C incubations and well as non-specific binding is unknown. If there are toxicity issues, the full study could have had reduced sensitivity. However, as ritonavir will give induction of PXR inducible proteins unless they are sufficiently inhibited by ritonavir, or one of the 3-DAA components, this will not be further pursued. The net effect of the combination is available on a number of enzymes. In some of the studies comparing 3-DAA and 2-DAA (with and without dasabuvir), the results actually indicate that dasabuvir give rise to some additional induction.

*Dasabuvir as perpetrator – in vivo studies*

*Mutual interactions in vivo between the components of the 3-DAA combination.*

Dasabuvir give rise to increased plasma concentrations of ABT-450. In a DDI study 400 mg dasabuvir increased the ABT-450 exposure by ca 50%. The ritonavir exposure was slightly decreased. ABT-450/r 200/100 mg decreased the exposure of dasabuvir by approx. 50% along with a minor to similar decreases in M1 exposure. The mechanisms of the DDI effects on ABT-450 and dasabuvir may be BCRP+OATP1B1 inhibition and CYP induction, respectively. This study was not designed for investigating time-dependent processes and the ABT-450/r dose was higher than the one recommended. The pharmacokinetics of ABT-450 is markedly dose dependent and thus extrapolation between doses is difficult. There is no study investigating the mutual interaction between all substances of the combination. However, DDIs affecting ABT-267 exposure are rare.

*In vivo interaction studies with 3-DAA as perpetrator drugs*

CYP3A4: alprazolam

The 3-DAA combination at steady state and alprazolam was given alone and in combination. Alprazolam AUC was increased by 34%, the increased exposure alprazolam is probably due to CYP3A4 inhibition by ritonavir and possible also ABT-450. As compared to midazolam, alprazolam is not a very sensitive CYP3A4 substrate due to its limited first-pass metabolism. Thus, the effect on a more sensitive substrate may be higher. In the SmPC clinical monitoring of alprazolam is recommended. A decrease in alprazolam dose can be considered based on clinical response.

CYP3A4: amlodipine

When multiple doses of 3-DAAs were co-administered with a single oral dose of amlodipine besylate a 157% increase in amlodipine AUC, while amlodipine harmonic mean t1/2 increased from 42 hours to 104 hours. Cmax increased by 26% for amlodipine. No change in DAAs was observed. There is some CYP3A4 metabolism of amlodipine but it is not very sensitive to inhibition. The very strong CYP3A4 inhibitory combination indinavir/r 800/100 gave rise to a 89% increase in amlodipine AUC (Glesby et al Clin Pharmacol Ther. 2005). A dose reduction by 50% and extra monitoring is recommended in the SmPC.

CYP2C9: warfarin

3-DAA at steady state did not significantly affect the exposure of warfarin. 3-DAA decreased the AUC of S- and R warfarin by approx. 15%, most likely due to induction. INR should be monitored. Clinically significant drug-drug interactions are not expected with other CYP2C9 substrates.

CYP2C19: Omeprazole and escitalopram

Omeprazole is metabolised by CYP2C19 and CYP3A4. 3DAA slightly (38%) reduced omeprazole exposure. This is expected due to the induction by ritonavir. If dasabuvir was removed from the DAA regimen, there was a 55% increase in omeprazole exposure. This would indicate that dasabuvir inhibit CYP2C19. This is also indicated by the in vitro data. There was no effect of omeprazole 40 mg qd on the exposure of the DAAs.

Escitalopram is metabolised by CYP2C19 and CYP2D6. 2-DAA gave rise to a 25% reduction in the AUC of escitalopram, while there was no effect on escitalopram if dasabuvir was included in the treatment. This part is thus in contrast to the possible effects of dasabuvir indicated by the omeprazole study. However, based on the omeprazole data the DAA regimens appears to induce CYP2C19. The net effect could be higher if a drug is more metabolized by CYP2C19 than omeprazole, which is also metabolized by the inhibited CYP3A4. The formation of the active metabolite from clopidogrel is catalyzed by CYP2C19 and CYP3A4. Thus, the net effect on active metabolite exposure is unknown.

P-glycoprotein: digoxin

In a drug interaction study with digoxin, 2DAA gave rise to a higher effect (36%) than 3-DAA (16%) with dasabuvir). Renal CL of digoxin was slightly decreased by 14% and by 19% with 3-DAA and 2-DAA, respectively. The reason for the smaller effect when adding dasabuvir is unknown. Monitoring is recommended.

OATP1B1: pravastatin

Pravastatin exposures (AUC24) were increased by 82% by concomitant 3DAA treatment. A similar effect was obtained with 2DAA. *In vitro* data indicate that dasabuvir (and M1) are OATP1B1 inhibitors *in vivo*. ABT-450, ritonavir and ABT-267 are also inhibitors. This study indicates that the 3DAA combination also inhibits these transporters *in vivo*. Pravastatin multiple dose treatment increased the exposure to ABT-450 and ritonavir (approx. 30-40%) during 2DAA but not 3DAA treatment. A pravastatin dose-reduction is recommended.

BCRP and OATP1B1: rosuvastatin

The exposure to rosuvastatin increased by ~160% and by ~30% when co-treated with 3-DAA and 2-DAA, respectively. The study was performed with a Viekirax formulation that gave rise to only 60% of the exposure obtained with the final formulation. Effects up to 4-fold are expected with the 3-DAAs. Rosuvastatin increased ritonavir exposure by approx. 50 % during the 3DAA regimen and less so during 2DAA. The 2-DAA and 3-DAA differences shows the BCRP inhibitory potential of dasabuvir and ABT-450 *in vivo*. The dose of rosuvastatin is limited to 5 mg together with the 3DAA and 10 mg with the 2-DAA treatment.

Other statins: The possible DDI with pitavastatin and fluvastatin has not been investigated. Increased exposure is expected. Therefore a temporary suspension of these statins is recommended during treatment with the DAAs. If statin treatment is required, pravastatin may be used at reduced dose.

CYP3A metabolized statins (simvastatin, lovastatin, atorvastatin) are contraindicated.

*Antiretroviral drugs:*

Rilpivirine

The 3-DAA regimen increases the exposure of rilpivirine (administered as 75 mg qd) 3-fold. The effect by the DAAs was higher than expected as the most pronounced effect reported by a CYP3A4 inhibitor in the SPC so far (by darunavir/r, a 2.3-fold increase). Rilpivirine should be used cautiously, in the setting of repeated ECG monitoring.

Raltegravir

Raltegravir is eliminated through UGT1A1 catalysed metabolism. Treatment with 3-DAA gave rise to a 2-fold increase in raltegravir exposure (400 mg bid). UGT1A1 was inhibited in vitro by dasabuvir, ABT-267 and ABT-450. The background induction is evident if dasabuvir or ABT-267 is excluded, then the exposure increases 2.2-fold or more initially (due to inhibition) followed by induction becoming more prominent over time, counteracting the inhibition leading to a gradual reduction in exposure and a net ca 40% increase in raltegravir exposure. No dose adjustment is necessary.

Dolutegravir

Based on the effects observed on raltegravir, it seemed likely that the dolutegravir exposure would have a similar increase. However, the specific UGT enzyme involvement in the elimination of the two drugs has not been confirmed by in vivo DDI studies. Preliminary in vivo DDI data indicate that the effect on dolutegravir is less pronounced than observed for raltegravir. The applicant will submit the study report when available. Meanwhile, dolutegravir will not be included in the SmPC.

Lopinavir/r

Lopinavir/r (steady state 800/200 mg QD and 400/100 mg BID) was investigated with two 2-DAA regimens and the 3-DAA regimen. The exposure to dasabuvir and M1 was reduced by 46% and 28%, respectively, when lopinavir/r was dosed QD in the evening. There were no marked effects of the 3-DAA regimen on lopinavir. In all three DAA regimens, lopinavir/r increased the exposure to ABT-450. The effect of lopinavir/r at steady state was considerable greater in the ABT-450/r+ombitasvir regimen (~6-fold increase in AUC) compared to the ABT-450/r+dasabuvir and the 3-DAA regimen (2-3-fold increase in AUC). In all DAA regimens, there was an increase in plasma concentrations of ABT-450 (second peak) following the evening dose of lopinavir/r. Use of lopinavir/r is contraindicated.

Darunavir/r

The effect of the 3 DAAs (ABT-450/r+ombitasvir+dasabuvir), the 2 DAAs (ABT-450/r+ombitasvir) and the 2-DAAs (ABT-450/r+dasabuvir) on darunavir (800 mg QD and 600 mg BID) and vice versa was investigated. In an additional study, the effect of ABT-450/r/ombitasvir ± dasabuvir on darunavir/r (800/100 mg QD in the evening) and vice versa was investigated. The mutual interactions were investigated when all study drugs were at steady state. The effects on darunavir (small decrease in exposure) were concluded not to be clinically relevant unless there is extensive PI resistance development. The exposure to ombitasvir, dasabuvir and M1 were either comparable or decreased upon co-administration with darunavir. The greatest effects were observed on the exposure to ABT-450. If darunavir was dosed bid, there was a second peak of ABT-450 following the evening dose of darunavir/r (similar to lopinavir/r). Darunavir can be taken (without ritonavir) unless there is extensive PI resistance.

Atazanavir

The effect of ABT-450/r+ombitasvir±dasabuvir on atazanavir (300 mg QD in the morning and 300/100 mg in the evening) and vice versa was investigated when all study drugs were at steady state. Atazanavir increased

the exposure to ABT-450 between 2- and 3-fold. The recommended dose of atazanavir is 300 mg, without ritonavir, in combination with the 3-DAAs. (Combination not recommended without dasabuvir.)

*HIV protease inhibitors other than atazanavir and darunavir are not recommended, for reasons of interactions/lack of data.*

Emtricitabine/tenofovir disoproxil fumarate

The effect of ABT-450/r+ombitasvir±dasabuvir on emtricitabine/tenofovir disoproxil fumarate (200/300 mg QD) and vice versa was investigated with all study drugs being at steady state. The exposure to emtricitabine was unchanged, whereas the exposure to tenofovir was slightly increased. Based on what is known about the inhibitory effects on transporters by the DAA combinations, the increased tenofovir exposure could possibly be caused by inhibition of intestinal P-gp or possibly BCRP (increasing absorption of the prodrug tenofovir disoproxil fumarate).

*The 3DAA combination including dasabuvir as victim for DDIs*

CYP2C8 inhibition: gemfibrozil

The effect of 600 mg gemfibrozil bid on a single dose of ABT-450/r + dasabuvir was investigated. AUC tom dasabuvir increased approx. 11-fold. The metabolism to M1 was inhibited showing in a 78% reduction of M1 AUC. The effect is probably different at steady state and there are some design issues adding variability to the DDI investigation. There was a 38% increase in the AUC of ABT-450 but no change in ritonavir. Gemfibrozil is contraindicated.

CYP3A inhibition: ketoconazole

The effect of the strong CYP3A4 inhibitor ketoconazole (at steady state; 400 mg QD for six days) on the pharmacokinetics of the 3- and 2- DAA/r combinations (single dose) and vice versa was investigated. Ketoconazole increased the exposure to ABT-450, ritonavir and ombitasvir by approximately 2-fold, 1.5-fold and 1.2-fold, respectively. The exposure (AUC) of dasabuvir increased 42%. M1 was unaffected. The exposure to ketoconazole increased 2-fold. The net effect at steady state on all substances is likely somewhat more pronounced as the ritonavir/ the3-DAA regimen shows time dependent CYP3A4 inhibition likely affecting also ketoconazole exposure. CYP3A4 inhibitors are contraindicated. The reason for the contraindication is not only the somewhat higher effect expected at steady but also the observed marked effects of lopinavir/r and atazanavir/r proposed to be caused by dual CYP3A and transporters. Many potent CYP3A inhibitors are also transporter inhibitors. The elimination of ABT-450 is not well characterised and as such mechanistic interpretation is difficult.

Enzyme induction: Carbamazepine

The effect of carbamazepine, 200 mg BID on a single dose administration of the 3-DAAs decreased the exposure by 65% for ABT-450, 32% for ABT-267, by 70% for dasabuvir and 38% for M1. The ritonavir exposure decreased by approx. 85%. The carbamazepine study may not be worst case due to the use of single dosing of the DAA as there will be a time dependent inhibition and induction mediated by the DAA regimens (probably due to ritonavir) potentially affecting the carbamazepine exposure. Strong as well as moderate inducers are

contraindicated in the SmPC. Induction may both reduce the systemic exposures to sub therapeutic levels as well as increase the production of a reactive metabolite potentially leading to hepatotoxicity (see below).

Enzyme induction: Efavirenz

This interaction was investigated in the DDI study together with emtricitabine and tenofovir (Atripla). The study was terminated early due to increased transaminases. When it was terminated, the DAAs had been administered for 14 days alone and co-treatment with Atripla has occurred for 3 days. Terminated DDI studies between CYP3A inducers (efavirenz and rifampicin) due to adverse events (ALT elevations in particular) have previously been reported in literature: (Schmitt et al. Arch Drug Info. 2009. Jamois. Arch Drug Info. 2009. Nijland, et al. AIDS. 2008;22:931-5.) This is further discussed in the clinical safety section. Strong as well as moderate inducers are contraindicated in the SmPC.

OATP, Pgp and likely BCRP inhibition: Cyclosporine

The effect of cyclosporine A (single dose; 10 mg or 30 mg) on the exposure to three various DAA combinations (at steady state) and vice versa was investigated. The DAA combinations were: 2-DAA (ABT-450/r+dasabuvir), 2-DAA (ABT-450/r+ombitasvir) and 3-DAA (ABT-450/r+ombitasvir+dasabuvir) regimens. The exposure to ABT-450 was increased by approximately 1.5-fold in the two DAA regimens included in the current application, and there was an approximate 30% reduction in the exposure dasabuvir (~20% reduction of its metabolite M1). The effect by CyA at steady state may be markedly higher. The reduced exposure to dasabuvir could possibly be caused by inhibited intestinal uptake transporters. The effect of the 3-DAA and 2-DAA on cyclosporine (CyA) single-dose PK was investigated. The DAAs was dosed to steady state. The dose normalised AUC of CyA was increased 4.3-fold by 2-DAA and 5.8-fold by 3-DAA. The effect of C24 was 3-fold higher that the effect on AUC. The half-life was increased from 8.7 to 9.8 hrs (2-DAA) indicating that the major part of the DDI is at absorption/1st pass using this regimen. The half-life was increased from 7.3 to 24.5 when the 3-DAA regimen was administered.

A reduction of the initial CyA dose to 1/5 of the normal daily dose is proposed in the SmPC but with a dosing frequency of once daily instead of twice daily. This was considered acceptable by CHMP.

*Other commonly used medicinal products:*

Oral contraceptives

The interaction between ABT-450/r/ABT-267 with or without dasabuvir and the COC EE + NGM (Ortho-Cyclen tablets) was investigated as well as 3-DAA with POP containing NET (Jolivette) and 3-DAA with COC containing EE + NET (Balziva) . Ortho Cyclen was administered for 21 days, Jolivette for 17 days and Balziva for 21 days. On the $10^{th}$, 4 th and $8^{th}$ day, respectively, the DAA treatment started and was continued for 19,21 and 8 (discontinued) days, respectively. The first and last contraceptive investigations were prematurely discontinued due to increased transaminases.

ORTO CYCLEN (EN/NGM)

The AUC24 of ABT-450 were ca. 30% reduced as 2-DAA and unchanged as 3-DAA (day 21 vs day 28) when combined with the COC. The exposure of ritonavir was 20-29% lower when used concomitantly with the COC (day 21). Ombitasvir was unaffected. AUC12 of dasabuvir were ca. 50% lower when dosed with the COC. Correspondingly, M1 were similarly 37-46% reduced.

The exposure of Norelgestromin was increased by ca 160% when co-administered by 2-DAA or 3-DAA, respectively. AUC of norgestrel (NG) was increased by ca.150% regardless of dasabuvir co-administration. The

pharmacokinetics of ethinyl estradiol was unaffected. This treatment was discontinued. The mechanism of the increase in progestin is unknown (it could be UGT inhibition) as well as the reason for the lower dasabuvir, M1 and ABT-450 exposure.

JOLIVETTE (NET)

The exposure values of ABT-450 were approximately 25% higher (day 17 vs 24) when administering NET (Jolivette) POP. The pharmacokinetics of ritonavir, ombitasvir and dasabuvir was largely unaffected. The exposure of norethindrone was somewhat reduced during the 3-DAA treatment.

BALZIVA (EE/NET)

This treatment was again discontinued early due to adverse events and thus the pharmacokinetic data set is imcomplete. Through concentration comparisons of ritonavir indicated no marked change in exposure. The sparse C24 data on dasabuvir and M1 did not indicate a marked increase in exposure.

The sparse C24 data on EE did not indicate a marked change in exposure. AUC24 was increased by 22%, from day 7 to day 8 (only 1 day together). The effect that would be obtained at steady state is unknown. The exposure of norethindrone was increased (AUC at day 4 29% increased) but the full extent is unknown.

*Based on the DDI study and on clinical safety data analyses, use of EE is contraindicated. Based on avaiable safety data, use of other estrogens is not restricted.*

Knowing the mechanism of the decrease in DAA exposure would enable prediction of similar DDIs. At present, the mechanism is unknown. Up-regulation of hepatic uptake transporters and thereby increased hepatic exposure (possibly saturation of efflux transporters), with or without increased formation of a reactive metabolite, could explain both reduced DAA exposure and higher risk of hepatic safety issues. Other mechanisms such as BSEP inhibition/down-regulation are also possible.

*Interactions causing increased transaminases:*

Increased transaminases were observed both in the efavirenz and OC interaction studies. Inhibitors of BSEP, such as glybenclamide, troglitazone and oestrogen have been associated with liver cholestasis (Paulis Magnus et al 2010). See also the pharmacogenetics section. Both ABT-450 and ritonavir have been shown to be inhibitors of BSEP *in vitro at in vivo relevant concentrations*. Dasabuvir and is also an inhibitor *in vitro* but at 30-fold higher than clinically relevant concentrations. Oestrogen and progesterone metabolites are trans-inhibitors of BSEP (Vallejo et al 2006).

Testing of bile acids was performed in order to explore a possible relationship between changes in the levels of various bile acids in plasma and the observed changes in ALT levels. Total bile acid levels were measured as were the levels of ursodeoxycholic, cholic, chenodeoxycholic and deoxycholic acids. This testing was performed using available samples from subjects in Arms 1 and 2 and all subjects in Arm 4. Evaluation of these data did not demonstrate any trend. See also the section on pharmacogenetics. The CHMP agreed on the need to request a safety analysis of the risk of raised transaminases if the 3DAAS are combined with a BSEP inhibitor within a post-authorisation measure. The analysis of the clinical safety data with respect to concomitant use of drugs that may inhibit BSEP based on the EU DDI guideline criteria ($50*Cmax_u/Ki \geq 1$) should be submitted by the Applicant by March 2015.

Tacrolimus

A single dose of tacrolimus gave rise to a small to moderate reduction of the exposure of all substances coadministered but ombitasvir. This study was not designed to investigate a full mutual interaction, i.e. obtaining steady state for all substances. An extensive accumulation is expected at multiple dose conditions of tacrolimus due to the quite long half-life. Dose normalised tacrolimus AUC was increased between 57- to 86 fold by the 3-DAA depending on the study design. The half-life increased up to 230 h. The applicant recommends administration of tacrolimus every week instead of the recommended bid. This is the starting dose and will be followed by TDM based dose titration. The resulting plasma concentration-time course of tacrolimus will be very different from the usual one and the exposure level may also be very different. However, there is clinical data on this combination.

Methadone

A DDI study was conducted with subjects who were on stable methadone therapy. The study showed a minimal effect on the methadone exposure. Compared to historical controls presented by the applicant initially, ABT-450 AUC was up to 90% lower. However, after gaining more pk data with the (final) formulation used in the study and therefore changing the historical control data, there was no clear difference in exposure as compared to the controls. Methadone seemed to have minimal impact on ritonavir, ABT-267, dasabuvir or M1 exposures. There is a marked inter-study difference in DAA exposure and using historical controls is not a satisfactory approach for these drugs. Methadone is an auto-inducer in vivo. Due to the difficulty in performing studies there is little in vivo DDI data. In conclusion nothing may be concluded regarding the potential effects of methadone on the DAAs. One question was posed regarding which arms to use in the comparison. This is now considered resolved. It is difficult to study this interaction without having historical controls. There is some clinical data on the combination but the population was 95% treatment naïve, quite young and non-cirrhotic.

Buprenorphine/naloxone

ABT-450/r and ABT267 with or without dasabuvir increased buprenorphin AUC by ca 40% (3-DAA) or 60% (2-DAA). The AUC of the metabolite norbuprenorphin increased by 82% by 3-DAA and 111% by 2-DAA. No dose adjustment of buprenorphine is considered necessary. Comparison of DAA exposure was made with historical controls. This approach is not adequate for this kind of high variability situation. No marked differences in DAA exposure were observed.

Zolpidem

A single dose of zolpidem decreased the ABT-450 exposure (after 3-DAA multiple doses) by up to 37%. The mechanism behind this interaction is not known. There is conflicting data in the literature on whether or not zolpidem is a PXR activator in vitro. If the mechanism of the DDI is time dependent there might be a larger effect on ABT-450 when at steady state. However, the mechanism is unknown.

Duloxetine

A single dose of duloxetine exposures were 17% to 25% lower when co-dosed with the 2 DAA and 3-DAA regimen respectively at steady state. Duloxetine is eliminated through oxidative metabolism via CYP1A2 and, to a lesser degree, CYP2D6. The effect of DAAs on duloxetine might be the mild CYP1A2 induction by ritonavir.

Furosemide

The effect of 2-DAA and 3-DAA on furosemide pharmacokinetics (single dose) was investigated. There was no effect on furosemide AUC but Cmax was increased by 40%. With the earlier and higher furosemide peak

concentration, caution is warranted when co-administering furosemide with the 3-DAA regimen and monitoring of the clinical response is recommended.

Ribavirine

While the effects of DAAs on ribavirin and vice versa was not evaluated in Phase 1 studies, the effects were characterized in Phase 2 and 3 studies and analysed in the population PK analysis. The results indicated that DAAs did not affect ribavirin pharmacokinetics and vice versa.

Spironolactone

Spironolactone may be a reasonably common co-medication if 3-DAA is used in patients with advanced liver disease (not recommended at present). There is no DDI study with spironolactone. There are few indications of a marked effect by the ABTs on spironolactone as no CYPs are involved in its elimination. However spironolaktone is a PXR ligand and in vitro inducer (El-Sankary et al 2001, Horita et al 2014). Induction has also been observed in vivo in an old but well performed study (Huffman et al 1973). Furthermore spironolactone is a Pgp inhibitor in vivo (Volpe et al 2013, Waldorf et al 1978, Fenster et al 1984). Spironolactone also inhibits estrogen metabolism in vivo and it has been stipulated that this is the cause of the gynecomastia observed with spironolactone (Satog et al 2003). Induction could cause both reduced efficacy and possibly increased active metabolite formation. However, the CHMP agreed that since the paper was old and that since no induction has been indicated during the clinical use in all these years, this issue will not be further pursued.

## 2.4.3. Pharmacodynamics

***Mechanism of action***

Dasabuvir (ABT-333) is a non-nucleoside inhibitor of the HCV NS5B RNA-dependent RNA polymerase which is an enzyme that catalyses the replication of the viral RNA. ABT-333 displays a novel mechanism of action, as the previously approved inhibitor of NS5B is a nucleotide analogue.

ABT-450 (ABT-450) is an inhibitor of HCV NS3/4A protease which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication.

Ombitasvir (ABT-267) is an inhibitor of HCV NS5A which is essential for viral replication.

Based on EC50s, no activity against HBV or HIV is anticipated for any of these three drugs.

Exviera contains dasabuvir (ABT-333).

***Primary and Secondary pharmacology***

***2.4.3.1. The in vitro activity of ABT-333***

**Activity in biochemical assays**

ABT-333 is an inhibitor of the RNA-dependent RNA polymerase encoded by the NS5B gene of HCV. This compound inhibited purified recombinant NS5B polymerases derived from HCV genotype 1a and 1b isolates with IC50 values between 2.2 and 10.7 nM.

ABT-333 had IC50 values of 900 nM or greater against purified polymerases derived from HCV genotypes 2a, 2b, 3a, and 4a isolates. Thus, the activity of ABT-333 appears specific to genotype 1. For this reason, the drug has not been evaluated for use in other genotypes than this.

**Activity in the replicon assay**

ABT-333 inhibited replication of HCV subgenomic replicons in cell culture assays with EC50 values of 7.7 and 1.8 nM against genotype 1a-H77 and 1b-Con1, respectively. The M1 metabolite of ABT-333 has antiviral activity, albeit 7-8 fold lower than the parent compound, and shows appreciable plasma exposures (30% to 60% of the parent drug).

ABT-333 had a TD50 of 10,360 nM in an MTT cytotoxicity assay, producing a therapeutic index that exceeded 1345-fold.

### *2.4.3.2. The in vitro activity of ABT-450*

**Activity in biochemical assays**

ABT-450 is an inhibitor of the protease encoded by the NS3 and NS4A (cofactor) genes of HCV. This compound inhibited activity of purified NS3/4A protease enzymes from genotypes 1a, 1b and 4a with IC50 values between 0.16 and 0.43 nM.

For the purified NS3/4A protease enzymes derived from HCV genotypes 2a, 2b and 3a isolates, the IC 50 values were 2.4 to 14.5 nM.

**Activity in the replicon assay**

ABT-450 inhibited replication of HCV subgenomic replicons in cell culture assays with EC50 values of 1.0 and 0.21 nM against genotype 1a-H77 and 1b-Con1, respectively. The EC50 value of ABT-450 against stable cell line replicons containing the NS3 genes from HCV genotype 3a, 4a or 6a was 19 nM, 0.09 nM or 0.68 nM, respectively; and the EC50 against the 2a JFH-1 strain replicon was 5.3 nM. The lower activity seen for macrocyclic NS3/4A inhibitors against genotype 3 is likely due to a conserved polymorphism at 168 position in NS3/4A which confers lower viral susceptibility.

ABT-450 had a median toxic dose (TD50) of 37,000 nM in an MTT cytotoxicity assay, producing a therapeutic index that exceeded 37,000-fold.

### *2.4.3.3. The in vitro activity of ABT-267*

As there is no known enzymatic function of NS5A, no studies with biochemical assays were reported.

**Activity in the replicon assay**

ABT-267 inhibited replication of HCV subgenomic replicons in cell culture assays with EC50 values of 14 pM and 5 pM against genotype 1a-H77 and 1b-Con1, respectively.

The EC50 value of ABT-267 against stable cell line replicons containing NS5A from HCV genotypes 2a, 2b, 3a, 4a, 5a or 6a was 12.4, 4.3, 19.3, 1.7, 3.2 or 366 pM, respectively.

The relatively similar EC50 values for all major HCV genotypes are noted. It is likely that ABT-267 might have been a valuable drug for the treatment of genotype 3; however, it will only be available co-formulated with a

NS3/4A inhibitor with significantly reduced activity against this genotype (see above). Also, the lower activity against genotype 6a is noted. The molecular background for this has not been clarified.

ABT-267 had a TD50 of > 32,000,000 pM in an MTT cytotoxicity assay, producing a therapeutic index that exceeded 2 million-fold.

#### *2.4.3.4. In vitro selection of drug resistance*

HCV subgenomic replicon cell lines were passaged in the presence of ABT-450, ABT-267 or ABT-333. The resistance variants selected in HCV genotype 1a-H77 or 1b-Con1 cell lines by these compounds were cloned into the respective subgenomic replicon, and the EC50 and EC90 values of ABT-450, ABT-267 or ABT-333 were evaluated. In addition, variants reported as being selected by other NS3/4A protease, NS5A or NS5B polymerase inhibitors were also analysed.

**Resistance selection in genotypes 1a and -1b**

The following major variants in HCV NS3 were observed in HCV subgenomic replicon cell lines treated with ABT-450: R155K, D168E, and D168N in 1a-H77; and R155Q, A156T, A156V, D168H and D168V in 1b-Con1. As is typical for a macrocyclic inhibitor of NS3/4A, ABT-450 selects for resistant variants at positions 155 and 168, which confer significant fold-changes in susceptibility (see below). This confirms that the virology of ABT-450 is relatively similar to that of simeprevir.

Notably, the substitutions at positions 155 and 168 confer higher fold-changes 37-fold for R155K;13-219-fold for mutations in 168 position and likely significant resistance. The prevalent Q80K mutation in genotype 1a confers a fold-change of 3. For simeprevir, another macrocyclic inhibitor of NS3/4A, the fold-change for Q80K was less than 10; still this variant was associated with lower clinical efficacy, presumably due to an impaired barrier to further resistance.

The following major variants in HCV NS5A were observed in HCV subgenomic replicon cell lines treated with ABT-267: M28T, M28V, Q30R, Y93C, and Y93H in 1a-H77; and L28T, L31F, L31V and Y93H alone or in combination with L28M, R30Q or L31F/V in 1b-Con1. The selection of variants at positions 28, 30, 31 and 93, as well as the susceptibility changes seen indicate full cross resistance between ABT-267 and daclatasvir and ledipasvir. The high fold-changes for resistance associated mutations at 28, 30 and 93 in genotype 1a is a feature shared with daclatasvir and ledipasvir. Further, similar to these drugs, the barrier to resistance is higher in genotype 1b compared to 1a, with two mutations required to conceive very high fold-changes in -1b versus one in -1a.

The following major variants in HCV NS5B were observed in HCV subgenomic replicon cell lines treated with ABT-333: C316Y, M414T, Y448H and S556G in both genotypes 1a-H77 and 1b-Con1 replicons. Based on the fold-changes for single mutations (up to 5000-fold), ABT-333 is anticipated to be a drug with a low barrier to resistance in both genotype 1a and -1b. The lack of impact on susceptibility of the S282T mutation is notable, and indicative of the anticipated lack of cross resistance with nucleos(t)ide analogue inhibitors of NS5B.

#### *2.4.3.5. Clinical drug resistance*

The main method used to detect resistant variants was population sequencing. No next-generation sequencing data has been presented; this, however, is no regulatory requirement. The regions encoding NS3 amino acids 1 – 360, NS5A amino acids 1 – 215, and NS5B amino acids 300 – 591 were sequenced.

The primary virologic failure (PVF) population consists of patients in the phase 2 and 3 program who were randomized to active therapy and who experienced on-treatment virological failure (failure to suppress, or on-treatment virological rebound) or who relapsed after end of therapy were included. As a control group, to assess the impact of baseline polymorphic variants on outcome, there were baseline samples sequenced from patients achieving SVR in the large phase IIb AVIATOR study (M11-652) as well as some other phase II studies. For the six phase 3 studies, samples were sequenced from baseline and time of failure for those who had rebound or relapse. In addition to that additional baseline samples were included from a subset of patients who achieved SVR (i.e. 2 SVR-achieving patients for every 1 PVF patient matched for HCV subtype, IL28B genotype, baseline HCV RNA, and sex to the extent possible).

**Resistance variants (RAVs) seen at baseline**

Below follow summary tables of all baseline RAVs detected by population sequencing in the population described above, first genotype 1a next genotype 1b.

**Table 2. Prevalence of BL NS3, NS5A and NS5B RAVs (Pop Sequencing), GT1a-infection**

| NS3 | | | NS5A | | | NS5B | | |
|---|---|---|---|---|---|---|---|---|
| Variant | n (N = 532)[a] | Fold Change in $EC_{50}$[b] | Variant | n (N = 502)[a] | Fold Change in $EC_{50}$ | Variant | n (N = 558)[a] | Fold Change in $EC_{50}$ |
| V36A | 3 | 3 | M28I | 1 | nd | C316Y | 2 | 1472 |
| V36L | 8 | 2 | M28T | 3 | 8965 | M414T | 1 | 32 |
| V36M | 6 | 2 | M28V | 37 | 58 | E446D | 1 | nd |
| Q80H | 1 | nd | Q30E | 1 | 1326 | E446Q | 1 | 17 |
| Q80K | 219 | 3 | Q30G | 1 | nd | Y448H | 2 | 975 |
| Q80L | 21 | 2 | Q30H | 8 | 3 | C451Y | 5 | nd |
| Q80N | 2 | nd | Q30R | 6 | 800 | A553G | 1 | nd |
| Q80R | 5 | 2 | L31I | 1 | nd | S556G | 16 | 30 |
| Q80S | 1 | nd | L31M | 5 | 2 | S556N | 1 | nd |
| R155G | 1 | 14 | L31V | 1 | 155 | S556R | 1 | 261 |
| R155K | 4 | 37 | H58C | 1 | nd | Any | 29 | |
| D168A | 1 | 50 | H58D | 1 | 243 | | | |
| E357A | 4 | nd | H58L | 1 | nd | | | |
| E357D | 3 | nd | H58P | 16 | 0.5 | | | |
| E357G | 9 | nd | H58Q | 3 | nd | | | |
| E357Q | 3 | nd | H58R | 6 | nd | | | |
| E357T | 1 | nd | H58S | 1 | nd | | | |
| Any | 265 | | H58Y | 1 | nd | | | |
| | | | Y93C | 2 | 1675 | | | |
| | | | Y93F | 1 | nd | | | |
| | | | Y93H | 7 | 41383 | | | |
| | | | Y93L | 1 | 3006 | | | |
| | | | Y93N | 4 | 66740 | | | |
| | | | Any | 88 | | | | |

nd = not determined;

The high frequency of NS3 Q80K is anticipated, particularly in US patients with genotype 1a. Baseline mutations at positions 155 and 168 are rare. The reported frequency of NS5A mutations at baseline is roughly similar to that seen in other DAA development programs (approx. 15%). Approximately 5% of samples showed baseline resistance relevant to ABT-333.

**Table3. Baseline Prevalence of Variants at Signature NS3, NS5A and NS5B Resistance-Associated Amino Acid Positions by Population Sequencing in HCV Genotype 1b-Infected Subjects**

| NS3 | | | NS5A | | | NS5B | | |
|---|---|---|---|---|---|---|---|---|
| Variant | n (N = 203)[a] | Fold Change in $EC_{50}$[b] | Variant | n (N = 214)[a] | Fold Change in $EC_{50}$[b] | Variant | n (N = 206)[a] | Fold Change in $EC_{50}$[b] |
| Q80L | 11 | nd | L28M | 1 | 2 | C316H | 4 | 229 |
| R155Q | 1 | NA | R30H | 1 | nd | C316K | 1 | nd |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| A156T | 1 | 7 | R30Q | 20 | 0.4 | C316N | 35 | 5 |
| D168A | 1 | 27 | L31I | 4 | nd | C316W | 4 | NA |
| D168E | 1 | 4 | L31M | 11 | 0.9 | S368A | 2 | nd |
| D168K | 1 | 882 | P58A | 2 | nd | M414L | 2 | nd |
| D168N | 1 | nd | P58L | 1 | nd | C445F | 3 | nd |
| D168T | 1 | 49 | P58R | 1 | nd | S556G | 31 | 11 |
| Any | 13 | | P58S | 7 | 0.8 | Any | 59 | |
| | | | P58T | 4 | 0.4 | | | |
| | | | Y93H | 16 | 77 | | | |
| | | | Any | 54 | | | | |

nd = not determined; NA = not available due to low replication capacity of the variant, $EC_{50}$ could not be determined.

As anticipated, baseline NS3 resistance in genotype 1b is rare. The frequency of NS5A Y93H is similar to previous reports. Mutations impacting the susceptibility to ABT-333 are relatively common (>18%).

**BL RAVs and impact on outcome**

As the virological failure rate was very low in genotype 1b, the following discussion focuses on genotype 1a.

No strong correlations between baseline resistant variants and outcomes were found, as shown in the following table. Please note that this table is an extract only including patients of the PVF population who were treated with the 3DAA regimen, +/- RBV. Also note that the table indicates the proportion of patients with a certain mutation among those failing virologically and those achieving SVR, respectively.

**Table 4. Frequencies of RAVs in PVF population vs in those achiving SVR, GT1a-infection.**

| | Variant | 3DAAs | | | 3DAAs + RBV | | |
|---|---|---|---|---|---|---|---|
| | | PVF | SVR | P value | PVF | SVR | P value |
| GT1a NS3 | V36L | 2/21, 9.5 | 0/57 | 0.07 | 0/46 | 4/248, 1.6 | 1.0 |
| | V36M | 1/21, 4.8 | 0/57 | 0.269 | 1/46, 2.2 | 2/248, 0.8 | 0.401 |
| | Q80K | 13/21, 61.9 | 23/57, 40.4 | 0.125 | 27/46, 58.7 | 85/248, 34.3 | 0.003** |
| | Q80L | 0/21 | 3/57, 5.3 | 0.559 | 1/46, 2.2 | 9/248, 3.6 | 1.0 |
| | Q80R | 0/21 | 1/57, 1.8 | 1.0 | 1/46, 2.2 | 2/248, 0.8 | 0.401 |
| | R155K | 1/21, 4.8 | 0/57 | 0.269 | 1/46, 2.2 | 1/248, 0.4 | 0.289 |
| | D168A | 0/21 | 0/57 | N/A | 1/46, 2.2 | 0/248 | 0.156 |
| | E357G | 1/21, 4.8 | 1/57, 1.8 | 0.469 | 1/46, 2.2 | 2/248, 0.8 | 0.401 |
| GT1a NS5A | M28T | 1/21, 4.8 | 0/62 | 0.253 | 0/46 | 1/248, 0.4 | 1.0 |
| | M28V | 2/21, 9.5 | 5/62, 8.1 | 1.0 | 5/46, 10.9 | 11/248, 4.4 | 0.146 |
| | Q30E | 1/21, 4.8 | 0/62 | 0.253 | 0/46 | 0/248 | N/A |
| | Q30R | 1/21, 4.8 | 2/62, 3.2 | 1.0 | 1/46, 2.2 | 2/248, 0.8 | 0.401 |
| | L31M | 0/21 | 1/62, 1.6 | 1.0 | 1/46, 2.2 | 2/248, 0.8 | 0.401 |
| | H58D | 0/21 | 0/62 | N/A | 1/46, 2.2 | 0/248 | 0.156 |
| | H58P | 0/21 | 4/62, 6.5 | 0.568 | 3/46, 6.5 | 8/248, 3.2 | 0.387 |
| | Y93C | 0/21 | 1/62, 1.6 | 1.0 | 1/46, 2.2 | 0/248 | 0.156 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Y93F | 0/21 | 0/62 | N/A | 1/46, 2.2 | 0/248 | 0.156 |
| | Y93H | 0/21 | 0/62 | N/A | 1/46, 2.2 | 5/248, 2.0 | 1.0 |
| | Y93L | 0/21 | 0/62 | N/A | 1/46, 2.2 | 0/248 | 0.156 |
| | Y93N | 2/21, 9.5 | 1/62, 1.6 | 0.156 | 1/46, 2.2 | 0/248 | 0.156 |
| | C316Y | 1/21, 4.8 | 1/65, 1.5 | 0.431 | 0/46 | 0/268 | N/A |
| | C451Y | 1/21, 4.8 | 0/65 | 0.244 | 0/46 | 2/268, 0.7 | 1.0 |
| | S556G | 1/21, 4.8 | 2/65, 3.1 | 1.0 | 0/46 | 8/268, 3.0 | 0.609 |

Notably, the Q80K mutation (very prevalent with GT1a-infection) was overrepresented in baseline samples from patients who did not achieve SVR in the population. However, response rates were still above 90% among patients receiving at least 12 weeks of therapy (see table below).

**Table 5. Observed Data $SVR_{24}$ Rate Among HCV Genotype 1a-Infected Subject by Q80K Polymorphism at Baseline**

| | Number of Subjects with $SVR_{24}$, %[a] | | | |
|---|---|---|---|---|
| **M11-652 Arms** | **Q80K** | **Q80** | **Total (ITT)** | ***P* value** |
| 3-DAA ± RBV | 78/89, 87.6% | 122/130, 93.8% | 240/259, 92.7% | 0.143 |
| 3-DAA ± RBV (without 8-week arm) | 64/70, 91.4% | 96/100, 96.0% | 193/203, 95.1% | 0.321 |

a. Number of subjects achieving $SVR_{24}$ out of the total number of subjects who have sequence available.

Note: Observed data $SVR_{24}$ rates exclude subjects who do not achieve $SVR_{24}$ due to premature discontinuation of study drug or missing data in the $SVR_{24}$ window as Q80K variants at baseline are unlikely to contribute to premature discontinuation from study drug or study.

All in all, as most patients that failed virologically did not have RAVs at baseline conferring significant resistance to the DAAs, one may speculate further on the reasons for failure. For instance, one may wonder whether a more sensitive assay for detecting baseline RAVs might yield further prognostic information. This issue was raised during the approval procedure of another macrocyclic NS3/4A inhibitor showing a similar resistance pattern as that of ABT-450, and therefore being essentially virologically similar. However, next generation sequencing with a sensitivity threshold of 1% (as opposed to approximately 20% for population sequencing), did not identify a substantial further proportion of patients with detectable resistant variants at baseline. Furthermore, for another NS5A inhibitor, there was no impact on outcome of resistant variants at baseline detectable by next generation sequencing at a population proportion of less than 20%. In summary, baseline resistance testing is not anticipated to be of utility for guiding the use of the present DAA combo.

**Resistance at time of failure**

The following table is a summary for resistance at time of failure, for patients with rebound or relapse in the phase 3 studies. The vast majority failing therapy had genotype 1a (those with genotype 1b are indicated in column 3).

The table only includes RAVs that would be considered as primary (i.e. RAVs with more profound effects on susceptibility), to somewhat simplify. Therefore, when no RAVs are indicated, this may be either none detected,

or RAVs associated with a low FC (or where the FC has not been determined). Hence, the table somewhat underestimates treatment emergent resistant variants.

**Table 6. Primary RAVs for the 3 classes seen at time of failure (rebound/relapse) in phase 3.**

| Study | Type failure | ID | NS3/4A | NS5A | NS5B |
|---|---|---|---|---|---|
| SAPPHIRE 1 TN (1a + 1b) | Rebound | 108203 | R155K, D168D/V | Q30R | S556G/S, D559D/N |
| | | 110203 | R155K+ T449I | Y93C | S556G |
| | | 302202 (1b) | D168V | Y93H | C316N + S556G |
| | Relapse | 300203 | D168D/V | Q30R | Y561H/Y |
| | | 302206 | D168V | M28T | S556G |
| | | 384209 | D168V | M28T | E446Q |
| | | 405206 | D168V | Y93N | S556G |
| | | 561210 (1b) | D168V | L31M + Y93H | S556G |
| | | 120212 | - | M28V | - |
| | | 381211 | D168V | Q30R | - |
| PEARL-4, TN (1a) | Rebound | 105401 | D168A/D/I/N/T/V | M28T | S556G |
| | | 100408 | R155K+ A156G | Q30E/G/, Q30Q/R | C316C/Y |
| | Relapse | 108405 | D168V | Y93N | S556G |
| | | 123401 | R155K | M28M/T, H58D/H | M414M/T, S556G/S |
| | | 144402 | D168Y | Y93N | G554S |
| | | 114402 | D168V | Q30R | S556G |
| | | 116405 | D168D/V | M28V, Q30Q/R | S556G |
| | | 122404 | D168V | M28T | S556G/R/S |
| | | 132406 | D168V | Q30R | S556G |
| | | 109403 | - | Q30R | - |
| | | 101405 | R155K/R, D168A/D | M28M/T, Q30Q/R | - |
| | | 139405 | D168V | M28T | - |
| | | 102419 | D168A/D/V | M28V | - |
| | | 106413 | D168D | M28T + H58R | - |
| | | 116403 | D168F/V | H58D | - |
| | | 116409 | D168H | M28V + Q30R | - |
| | | 133402 | D168V | Q30E | - |
| | | 136402 | D168V | Q30R | - |
| PEARL-3, TN (1b) | Rebound | 232506 (1b) | - | Y93H | C316H |
| SAPPHIRE-2 TN (1a + 1b) | Relapse | 561303 (1b) | D168A | - | - |
| | | 107304 (1b) | - | - | - |
| | | 131311 | D168Y | M28V | S556G |
| | | 700307 | D168V | M28V, Q30R, | S556G, |
| | | 114304 | D168D/V | Q30R | - |
| | | 123304 | - | M28V | - |
| | | 108308 | - | - | - |
| TURQUOISE-2 TN/TE (1a + 1b) - Cirrhotics - | Rebound | 101102 | D168V | M28T | C316Y |
| | | 126103 | D168A/V | - | S556R/S |
| | | 101111 | D168Y | M28T | - |
| | | 103101 | D168H | Q30R | - |
| | Relapse | 105111 | D168V | Q30R | M414M/T, |
| | | 127128 | D168V | Q30R | S556G |
| | | 109101 | D168V | M28V, Q30R | - |
| | | 127123 | D168D/V | Q30R | - |
| | | 135104 | D168D/H/L/V | - | - |
| | | 129101 | - | - | - |

Note: All these cases are GT1a if not otherwise indicated in column 3.

This table demonstrates that close to all patients fail with resistance to both the NS3A/4 and the NS5A class, and around half of the patients fail with a virus also resistant to dasabuvir. The lower frequency of dasabuvir resistance is likely due to a lower selective pressure due to lower potency; a similar phenomenon is seen if

comparing the risk of NS3/4A resistance on failure with telaprevir and boceprevir. The primary NS3/4A- and NS5A-RAVs that are seen confer cross resistance to other available agents of these classes.

**Persistence of selected resistant variants**

The persistence of emerged variants was evaluated in Phase 2 Studies M12-998, M13-386, M12-746, and M11-652. The table below shows RAVs associated with a larger FC (i.e. those shown in the preceding tables). Data is lacking for genotype 1b due to the low number of such treatment failures.

**Table 7. Persistence of Emerged RAVs over 48 weeks of follow-up (clonal sequencing)**

| Target | Emerged Variant[a] | Prior to PTW24[b] | PTW24 | PTW48 |
|---|---|---|---|---|
| | | n/N, %[c] | | |
| **NS3/4A**, GT 1a | R155K | 7/47, 14.9 | 5/30, 16.7 | 1/13, 7.7 |
| | D168A | 5/47, 10.6 | 2/30, 6.7 | 0/13 |
| | D168V | 24/47, 51.1 | 4/30, 13.3 | 0/13 |
| | D168Y | 5/47, 10.6 | 0/30 | 0/13 |
| **NS5A**, GT 1a | M28T | 7/32, 21.9 | 5/24, 20.8 | 4/20, 20.0 |
| | M28V | 2/32, 6.3 | 2/24, 8.3 | 4/20, 20.0 |
| | Q30R | 13/32, 40.6 | 12/24, 50.0 | 8/20, 40.0 |
| **NS5B**, GT 1a | M414T | 5/34, 14.7 | 1/16, 6.3 | 1/12, 8.3 |
| | S556G | 11/34, 32.4 | 7/16, 43.8 | 5/12, 41.7 |
| | H58D | 0/32 | 1/24, 4.2 | 2/20, 10.0 |

As can be seen, while the proportion of follow up sample with detectable NS3/4A mutations decline over 48 weeks of post treatment follow-up, the proportion of samples with NS5A and NS5B resistance remains stationary. The findings of NS3/4A as well as NS5A are in accordance with previous reports after non-curative exposure to these classes. The persistence of selected resistance mutations to non-nucleoside NS5B inhibitors has previously been less well characterised.

All in all, these data illustrate the problem of what would be the appropriate retreatment regimen in those few patients that fail virologically on a combination of three drugs from different classes, all of which have a low barrier to resistance.

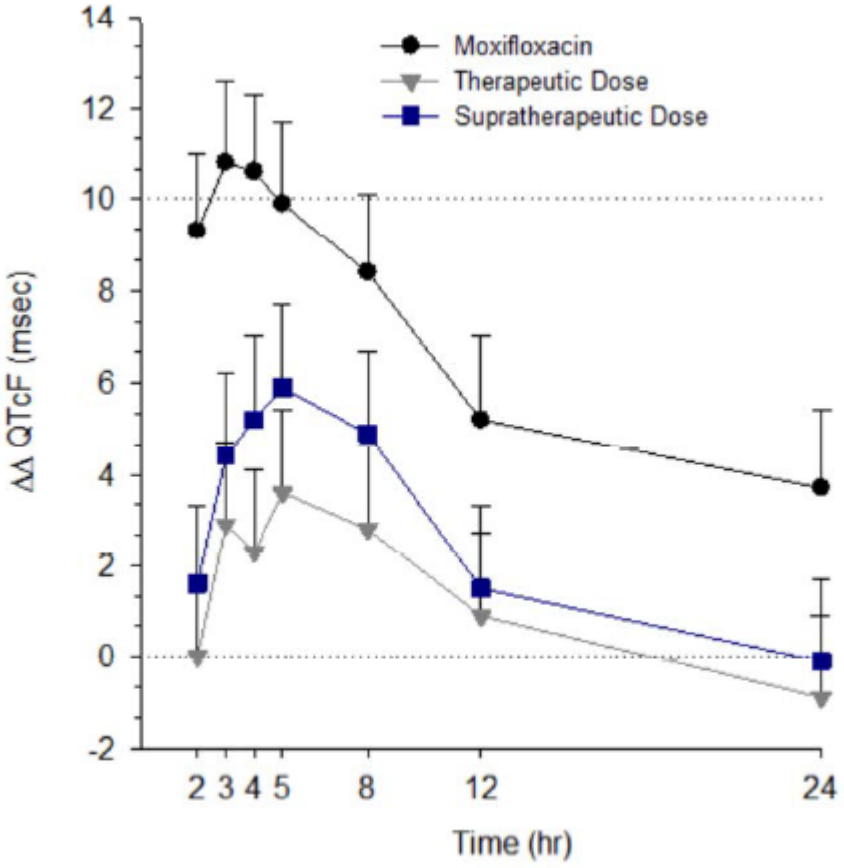
### *2.4.3.6. Thorough QT study*

Study M12-680 was a thorough QT study of the combination of ABT-450, ritonavir, ABT-267, and ABT-333 in healthy adults conducted to support the Phase 3 program. This placebo- and positive-controlled (moxifloxacin 400 mg) study evaluated therapeutic and supratherapeutic doses of the DAAs, as shown below:

- Therapeutic doses: ABT-450 200 mg SDD + ritonavir 150 mg + ABT-267 25 mg + ABT-333 250 mg
- Supratherapeutic doses: ABT-450 350 mg SDD + ritonavir 150 mg + ABT 267 50 mg + ABT-333 500 mg

Mean Cmax values with the supratherapeutic doses were 6.3-fold (ABT-450), 1.8-fold (ABT-267), and 2-fold (ABT-333) compared to Cmax values from the to-be-marketed formulation of ABT-450/r/ABT-267 150/100/25 mg + ABT-333 250 mg. No subject in this study experienced QT interval corrected for heart rate using

Fridericia's correction formula (QTcF) interval values > 450 msec or changes from baseline > 30 msec when receiving a therapeutic or supratherapeutic dose of the 3-DAA combination.




te: Change from time-matched baseline and placebo.

There is a minor QTc effect which is not considered clinically relevant. As discussed below, in the context of the dose ranging of ABT-333, this effect is likely due to that particular DAA.

## 2.4.4. Discussion on clinical pharmacology

**Basic PK characteristics**

Dasabuvir has a high bioavailability and a moderate absorption rate. Intake of food increases the absorption and dasabuvir should be taken 30 minutes after starting a meal. This is the same recommendation as used in the majority of studies. The formulation development is bridged well through bioequivalence studies.

Dasabuvir is eliminated through metabolism to M1 catalysed by CYP2C8 and, to some extent CYP3A4. The CYP3A4 is likely reduced when dasabuvir is administered as 3-DAA. The metabolite M1 is active and likely contributes to the target pharmacological effects obtained with dasabuvir. The metabolite is present at about half the plasma concentration of dasabuvir but is much less protein bound and therefore its free exposure is

6-fold higher than the free exposure of dasabuvir. M1 is eliminated through biliary excretion, glucuronidation and, to a minor extent, oxidation.

**Intrinsic factors affecting 3-DAA exposure**

There are few intrinsic factors identified that affect the exposure of the DAAs to a clinically relevant extent.

The AUC of dasabuvir was 4.2-fold increased in severe hepatic impairment but was not much affected by mild and moderate disease. M1 was 57% decreased and 76% increased in moderate and severe hepatic impairment, respectively. There was no increase in fu vs degree of impairment. Due to lack of clinical data, a posology for moderate hepatic impairment is not given in the SPC.

The AUC of dasabuvir was 97, 38 and 47% increased in mild moderate and severe renal impairment, respectively. For M1 the AUC was 39 and 28 decreased in mild and moderate renal impairment while it was 34% decreased in severe impairment.

There is little data in patients older than 65 years and no PK data in patients over 75 years. Women had ca. 30% higher exposures than men. The applicant has performed extensive pharmacogenetic analysis on PK related genes but no polymorphism was identified as important. The analysis may not be sensitive enough due to the high inter-study variability. Polymorphism in the gene coding for BSEP and the relation to increased transaminases has also been investigated. The results were unclear.

**Extrinsic factors affecting 3-DAA exposure**

The applicant has submitted an extensive DDI data package with *in vitro* and *in vivo* studies. In the in vivo DDI studies, all DAAs are included and the net effect is observed. This is satisfactory as it is the clinical situation, but sometimes hinders mechanistic conclusions, in particular combining with such a DDI prone drug as ritonavir. The DDIs with ritonavir are time-dependent and the drug affects a large number of proteins. Thus, mutual time dependent interactions are expected. However, the study design does not always takes this into account and the estimated steady state effects and their uncertainty needs to be discussed.

Dasabuvir interactions

The available in vitro data indicate that dasabuvir (or M1) may inhibit UGT1A1, OATP1B1 and OATP1B3, BCRP and Pgp. In the in vivo studies these proteins are also all inhibited by the 3-DAA combination. However, there are other components in the 3-DAA regimen which also inhibits these proteins. Thus, dasabuvir may contribute and not be solely responsible for these effects. Sometimes, the effect of ABT-450 and ombitasvir has been investigated with and without dasabuvir. In this situation, an indication about the effect of dasabuvir could be observed although it should be remembered that introducing dasabuvir also gives rise to an about 50% increase in ABT-450.

The applicant has tabled some of the differing results below.

**Table 12. Changes in AUC of Interacting Drugs when Dosed with the 2-DAA or 3-DAA Regimens**

| Drug | 3-DAA Regimen | 2-DAA Regimen | Probable Cause |
|---|---|---|---|
| Raltegravir | 130% ↑ | 20% ↑ | Greater effect with the 3-DAA regimen due to UGT1A inhibition by dasabuvir in addition to UGT1A inhibition by ABT-450 and ombitasvir. |
| Digoxin | 16% ↑ | 36% ↑ | Unknown[a] |
| Rosuvastatin | 160% ↑ | 30% ↑ | Greater effect with the 3-DAA regimen due to BCRP inhibition by dasabuvir in addition to BCRP inhibition by ABT-450 and ombitasvir. |
| Cyclosporine | 469% ↑ | 274% ↑ | Greater effect with the 3-DAA regimen due to inhibition of efflux transporters by dasabuvir in addition to that by ABT-450 and ombitasvir. |
| Tacrolimus | 5610% ↑ | 8480% ↑ | See discussion below |
| Buprenorphine | 107% ↑ | 51% ↑ | Greater effect with the 3-DAA regimen due to UGT1A inhibition by dasabuvir in addition to UGT1A inhibition by ABT-450 and ombitasvir. |
| Omeprazole | 39% ↓ | 54% ↓ | Weak CYP2C19 inhibition by dasabuvir. |

2-DAA regimen: ABT-450/r + ombitasvir; 3-DAA regimen: ABT-450/r + ombitasvir + dasabuvir

a. AUC differences are smaller than the 25% cutoff, but $C_{max}$ differences were > 25%. As digoxin is a narrow therapeutic index drug this is highlighted.

The results in the DDI rosuvastatin study indicates that it is dasabuvir which gives the major part of the BCRP inhibition effect. This effect is probably causing the interaction effect on dasabuvir on ABT-450 as well.

3-DAA interactions

The available *in vitro* and *in vivo* studies indicate the following effects of the 3-DAA combination: time-dependent CYP3A inhibition, CYP2C19 induction, UGT1A1 inhibition, BCRP inhibition, P-gp inhibition, OATP1B1 and 1B3 inhibition, induction of PXR inducible enzymes is also expected. Effects by other drugs on the DAAs are expected by BCRP inhibitors and CYP3A4 inhibitors and enzyme inducers (ABT-450) and CYP2C8 inhibitors and enzyme inducers (dasabuvir). The elimination of ombitasvir seems to be mainly biliary excretion. The interaction effects observed affecting ombitasvir exposure are very small and involved transporters not identified.

Increased transaminases have been observed in the DDI study with oral contraceptives in arms containing ethinyl estradiol (EE). There is also a signal of increased hepatotoxicity in EE treated patients in phase III. Furthermore, increased transaminases have been observed in a DDI study with efavirenz. BSEP inhibition may be one mechanism, hepatic accumulation of a toxic metabolite another possibility. A post-authorisation measure has been performed to follow up one of the theories (the analysis of clinical safety data when combined with BSEP inhibitors). Available phase III data does not indicate a raised risk of increased transaminases in patients treated with other systemic oestrogens (see section on clinical safety).

In the submitted drug interaction study with ketoconazole only a single dose of 3DAA is administered. Potent CYP3A4 inhibition was reached as the ketoconazole exposure was increased by the 3DAAs. A somewhat higher effect could be reached as steady state but the net effect is difficult to predict. More marked effects (up to a 6-fold change instead of the 2-fold increase observed with ketoconazole) have been observed by lopinavir/r and

atazanavir/r. This may be due to dual inhibition of CYP3A and transport proteins (such as OATP1B1 and BCRP).The elimination of ABT-450 has not been elucidated and two post-authorisation measures are present to clarify the major elimination pathways (see CHMP AR for Viekirax).

There is no drug interaction study with the usually recommended probe drug midazolam. The studies submitted involve less sensitive CYP3A substrates. Thus classification, which is usually based on the effect on midazolam, is not straight forward, neither of course how potent effects should be expected by 3-DAA on CYP3A4 metabolised drugs. The 3-DAA combination is classified as strong CYP3A inhibitor.

Other important issues involve specific drug combinations and the clinical relevance interpretation of observed effects of darunavir, atazanavir, methadone, weak and moderate enzyme inducers, etc. Potent CYP3A inhibitors are contraindicated due to expected marked increases in exposure and inducers can give rise to both subtherapeutic levels and increased hepatotoxicity (This is discussed in more detail in the Viekirax AR.)

Spironolactone may be a common co-medication if 3DAA is used in patients with advanced liver disease. Some indications of spironolactone being an inducer were observed in the literature but there is no signal from the long therapeutic use and therefore this will not be further pursued.

ABT-333 is the first non-nucleoside inhibitor of the viral NS5B polymerase to undergo European regulatory evaluation. It has nanomolar EC50s against genotype 1, but is likely not effective against other genotypes. It has a low barrier to resistance. The primary NS5B variant selected on failure is S556G.

ABT-450 shows protein binding adjusted EC50 values in replicon assays for genotypes 1a, -1b and 4 in the low nanomolar range. Similar to other macrocyclic NS3/4A inhibitors, it selects for resistance at positions 155 and 168 in the protease. ABT-450 has a low to moderate barrier to resistance; in case of virological failure, treatment emergent resistant variants are seen in most patients.

ABT-267 shows picomolar EC50s across genotypes. As typical of its class, this drug has a low barrier to resistance and selects for resistant variants at NS5A positions 28, 30 and 93.

A combination through QTc study including supratherapeutic doses of each DAA did not show any clinically relevant impact on the QTc interval.

## 2.4.5. Conclusions on clinical pharmacology

There are no major issues on pharmacokinetics. An important aspect is the DDI with ethinyl estradiol and efavirenz giving rise to increased transaminases – both regarding what treatment recommendations are important and what could be a likely mechanism, attempting to predict other scenarios at risk. A post-authorisation measure has been requested to follow up one of the theories (the analysis of clinical safety data when combined with BSEP inhibitors, to be submitted by the Applicant by March 2015).

Multiple class resistance in patients failing therapy with this regimen may have important consequences on any further treatment attempts. This is a major risk associated with the use of this 3DAA combination, which should be followed prospectively as specified in the RMP. The clinical consequence of treatment failure is a most important issue to integrate to the discussion of optimal regimens and treatment durations, in particular for patients with cirrhosis (discussed further in the efficacy section).

## *2.5. Clinical efficacy*

### 2.5.1. Dose response study(ies)

**Formulation issues**

As a preamble, it is noted that the formulations used in earlier trials and in phase III were not fully bioequivalent. The following introduction serves to clarify this background to the dose selection process. The doses and formulations of the DAAs used for all Phase 3 studies are presented in the table below.

**Table 67. DAA Doses and Formulations Used in Phase 3 Studies**

| DAA | Dose | Formulation |
|---|---|---|
| ABT-450/r | 150/100 mg QD | ABT-450/r/ABT-267 Coformulated Tablet |
| ABT-267 | 25 mg QD | |
| ABT-333 | 250 mg BID | Tablet |

ABT-450/r/ABT-267 coformulated tablet = ABT-450, ritonavir and ABT-267 coformulated tablet

The formulations of the 3 DAAs used in Phase 2 studies were different than those used in Phase 3 studies. The doses and formulations of the DAAs used for the Phase 2 studies are presented in Table 68.

**Table 68. DAA Doses and Formulation Used in Phase 2 Studies**

| DAA | Dose | Formulation |
|---|---|---|
| ABT-450/r | 100/100 to 250/100 mg QD | ABT-450 SDD tablets and ritonavir SGC |
| | 50/100 mg to 200/100 mg QD | ABT-450 HGC and ritonavir SGC |
| ABT-267 | 25 mg QD | HME tablets |
| ABT-333 | 400 mg BID | Tablet |

HGC = Hard Gelatin Capsule (also referred to as capsules); SGC = Soft Gelatin Capsule (also referred to as capsules); SDD = Spray Dried Dispersion; HME = Hot-Melt Extrusion

ABT-450 exposure was about 60% higher with the phase III formulation compared to that used in phase II. Note that ABT-450 kinetics are non-linear with a non-proportional increase in exposure with increased dose.

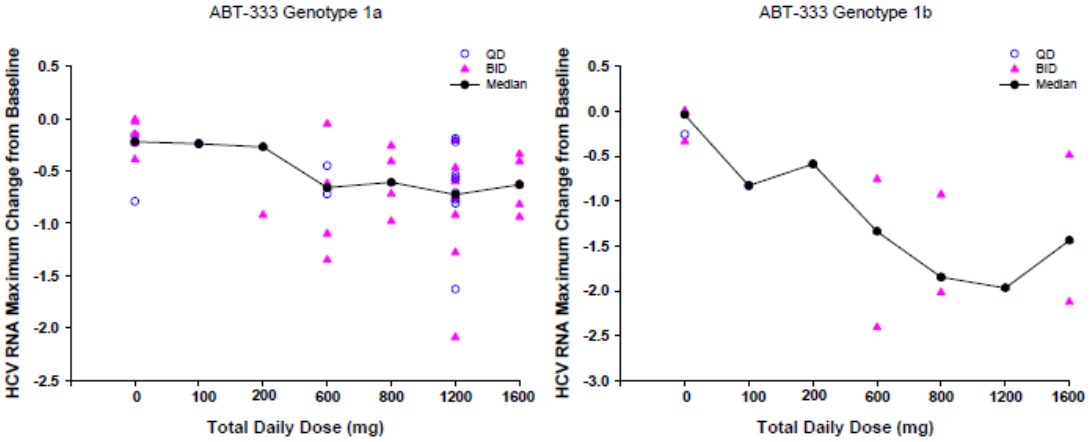
ABT-267, ABT-333 and ritonavir exposures from the Phase 3 formulations were comparable to the formulations used in Phase 2 studies. However, the dose of ABT-333 in the phase 3 formulation was lower, as bioavailability of ABT-333 was higher compared to the phase 2 formulation. ABT-333 exposures from the ABT-333 250 mg tablet formulation used in the Phase 3 studies were bioequivalent to the ABT-333 400 mg tablets used in the Phases 2 studies. It is furthermore notable that the phase 2 formulation of ABT-333 differed from that used in the monotherapy study (see below).

**The dose selection of ABT-333**

The antiviral activity of ABT-333 as monotherapy and in combination with pegIFN and RBV has been evaluated in three Phase 1b/2 studies (Studies M10-351, M10-380, and M11-602). Monotherapy doses of 100, 600, and 1200 mg QD and 100, 300, 400, 600, and 800 mg BID were assessed. In combination with pegIFN and RBV,

doses of 300 and 600 mg BID and 1200 mg QD were evaluated for up to 4 weeks while doses of 400 and 800 mg BID were evaluated for up to 12 weeks followed by pegIFN and RBV for up to 48 weeks.

**Figure 15. Maximum Change in Log HCV Viral Load from Baseline Versus ABT-333 Dose Following ABT-333 Monotherapy for 2 Days from Studies M10-351, M10-380, and M11-602**




In Study M10-380, ABT-333 doses of 300 mg BID (N = 8), 600 mg BID (N = 8), and 1200 mg QD (N = 8) showed similar antiviral activity when dosed as monotherapy for 2 days (1.01, 0.78, 0.68 log10 IU/mL decline at 300 mg BID, 600 mg BID and 1200 mg QD, respectively), followed by 26 days of coadministration with pegIFN and RBV (3.65, 3.96, and 3.59 log10 IU/mL decline at 300 mg BID, 600 mg BID, and 1200 mg QD, respectively). The potency of ABT-333 is low relative to DAAs of other classes. It does not appear possible to reach a drug exposure that covers the fold-change in EC50 of treatment-emergent single mutants (also see pharmacodynamics section above).

In combination with pegIFN and RBV, the 800 mg BID dose was associated with a greater mean hemoglobin reduction (4.2 g/dL decrease at Week 12) compared to the 400 mg BID dose (2.4 g/dL at Week 12) and placebo plus pegIFN and RBV (2.3 g/dL decrease at Week 12). Thus, higher doses of ABT-333 caused an additive effect to the anaemia seen with peginterferon+RBV. Furthermore, higher ABT-333 exposures were associated with a higher QT interval (corrected for heart rate using Fridericia's formula [QTcF]) in the first-in-human study (Study M10-351). Thus, ABT-333 likely exerts an exposure-dependent impact on the QTc interval, and is likely responsible for the small QT increase seen in the combination QT study. (see above section on pharmacodynamics for the discussion). However, the magnitude of this effect at the selected dose is not clinically relevant.

ABT-333 has an elimination half-life of about 5 to 8 hours, conducive to BID dosing. All in all, it appears that the selected dose should yield exposures at the proximal end of the Emax plateau, in terms of effect against virus with wild-type susceptibility.

**The dose selection of ribavirin**

The daily dose of RBV used in Phase 3 studies was 1,000 or 1,200 mg, divided BID, and based on subject weight. This dose is approved for treatment of adult patients with chronic HCV infection in combination with pegIFN by itself and pegIFN with telaprevir or boceprevir and others. The selection of the dose of 1000/1200 mg ribavirin

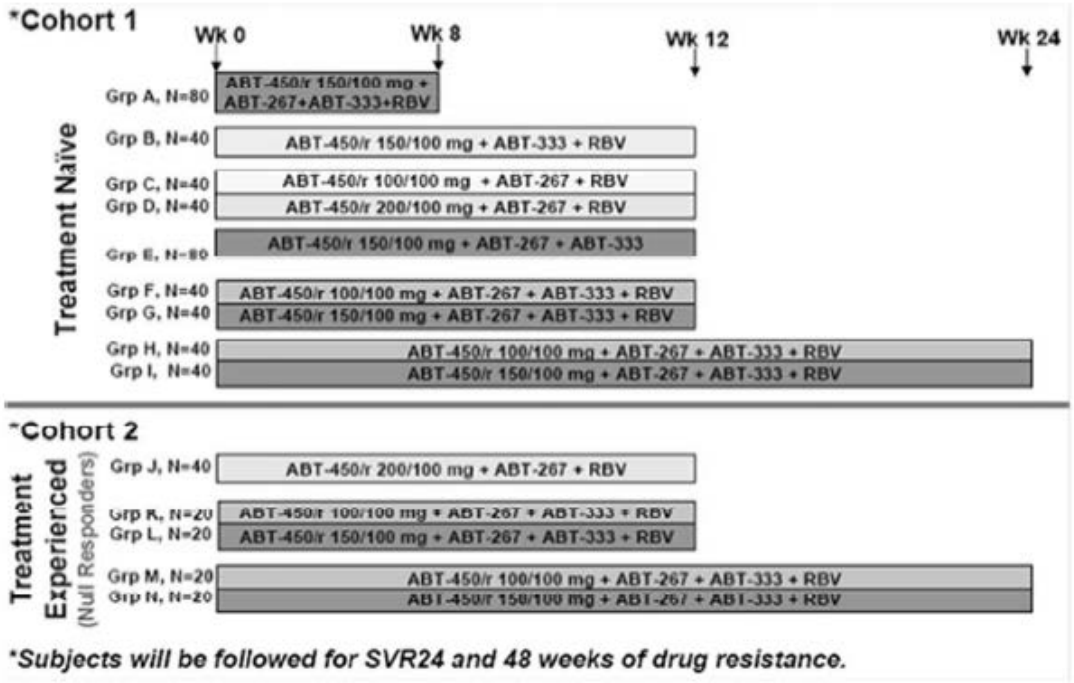
when used in interferon-free DAA combinations has become standard. This dose has previously been shown to have a generally acceptable safety profile and to provide the possibility of dose reduction in case of significant anaemia without any loss of efficacy.

## *2.6. The selection of treatment regimens for phase III*

The main study to inform regimen selection for phase III was M11-652, also termed AVIATOR.
This was a Phase 2, open-label, randomized, combination treatment study of multiple doses of ABT-450/r, and ABT-267 and/or ABT-333 with or without RBV in non-cirrhotic HCV genotype 1-infected treatment-naïve subjects and previous null responders to pegylated interferon (pegIFN) and RBV treatment.

The study consisted of a Treatment Period of 8, 12, or 24 weeks and a Follow-up Period for sustained viral response and resistance monitoring for 48 weeks.

**Figure 4. Study Schematic (Study M11-652)**




For each arm, dosing was as follows:

**Table 1. Dosing Schematic**

| Cohort | Group | N | Treatment | Duration |
|---|---|---|---|---|
| 1 | A | 80 | ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + RBV | 8 weeks |
| 1 | B | 40 | ABT-450/r 150/100 mg QD + ABT-333 400 mg BID + RBV | 12 weeks |
| 1 | C | 40 | ABT-450/r 100/100 mg QD + ABT-267 25 mg QD + RBV | 12 weeks |
| 1 | D | 40 | ABT-450/r 200/100 mg QD + ABT-267 25 mg QD + RBV | 12 weeks |
| 1 | E | 80 | ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID | 12 weeks |
| 1 | F | 40 | ABT-450/r 100/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + RBV | 12 weeks |
| 1 | G | 40 | ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + RBV | 12 weeks |
| 1 | H | 40 | ABT-450/r 100/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + RBV | 24 weeks |
| 1 | I | 40 | ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + RBV | 24 weeks |
| **Cohort** | **Group** | **N** | **Treatment** | **Duration** |
| 2 | J | 40 | ABT-450/r 200/100 mg QD + ABT-267 25 mg QD + RBV | 12 weeks |
| 2 | K | 20 | ABT-450/r 100/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + RBV | 12 weeks |
| 2 | L | 20 | ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + RBV | 12 weeks |
| 2 | M | 20 | ABT-450/r 100/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + RBV | 24 weeks |
| 2 | N | 20 | ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + RBV | 24 weeks |

Ribavirin was dosed at 1000/1200 mg per day depending on body weight below or above 75 kg.

Subjects were HCV-infected, non-cirrhotic, treatment-naïve or prior null responders to pegIFN+RBV. Patients with HBV or HIV coinfection were excluded. For a definition of null response, see below under the heading "main efficacy studies". The selection of previous null responders provides an enrichment of patients known to be on the difficult to cure end of the scale; thus, the population is presumed to bracket the range of innate host responses to support direct acting antiviral effects.

In terms of defining the appropriate regimen the study contains comparisons of

- Duration: 8 versus 12 versus 24 weeks of therapy.
- ABT-450 doses: 100 versus 150 versus 200 mg of ABT-450 used for 12 weeks, and 100 versus 150 mg of ABT-450 used for 24 weeks.

- Combinations of drugs: ABT-450+ABT-333+RBV versus ABT-450+ABT-267+RBV versus ABT-450+ABT-267+ABT-333 versus ABT-450 +ABT-267 + ABT-333+RBV when used for 12 weeks.

Thus, the AVIATOR study forms quite a complex investigation of different regimen possibilities. In terms of regimens not studied, it is notable that there are no 2DAA regimens without RBV. Thus, there is no way, within this study, of directly assessing the impact of the third agent on overall regimen efficacy.

Overall, SVR24 was achieved in 89.7% of treatment-naïve subjects and 92.5% of prior null responders overall. The further analysis of this study, however, is conducted along the lines of its informing on adequate regimens in genotypes 1a and -1b respectively.

**Table 8. SVR12 rates by subgroup and subgenotype (ITT population)**

| Population | Treatment naive | | | | | | Prior null responders | | |
|---|---|---|---|---|---|---|---|---|---|
| Treatment duration | 8 Weeks | 12 weeks | | | | 24 weeks | 12 weeks | | 24 weeks |
| Arm | A | B | C+D | E | F+G | H+I | J | K+L | M+N |
| Regimen | 450<br>267<br>333<br>RBV | 450<br>-<br>333<br>RBV | 450<br>267<br>-<br>RBV | 450<br>267<br>333<br>- | 450<br>267<br>333<br>RBV | 450<br>267<br>333<br>RBV | 450<br>267<br>-<br>RBV | 450<br>267<br>333<br>RBV | 450<br>267<br>333<br>RBV |
| SVR GT 1a n/N<br>% | 47/56<br>83.9 | 22/29<br>75.7 | 43/52<br>82.7 | 43/52<br>82.7 | 51/54<br>94.4 | 48/54<br>88.9 | 21/26<br>80.8 | 25/28<br>89.3 | 26/27<br>96.3 |
| SVR GT 1b n/N<br>% | 23/24<br>95.8 | 12/12<br>100 | 27/27<br>100 | 25/25<br>100 | 25/25<br>100 | 24/25<br>96 | 19/19<br>100 | 17/17<br>100 | 15/16<br>93.8 |

While the response rates are generally impressive, the lower efficacy in genotype 1a compared to -1b is notable. This is due to a lower potency and/or barrier to resistance for all the three DAAs against genotype 1a.

**Conclusions regarding treatment duration**

Comparison of relapse rates between arms is particularly relevant when assessing the impact of treatment duration. Among treatment-naïve subjects receiving 3 DAAs + RBV, 10/80 relapsed following 8 weeks of treatment in Group A, compared with 1/79 following 12 weeks of treatment in Groups [F + G] and 3/78 following 24 weeks of treatment in Groups [H + I], 2 of which discontinued treatment prematurely. The difference in response rates between 8 and 12 weeks' duration was driven primarily by the subjects with genotype 1a infection, as there was only 1 virologic failure in Group A and none in Groups [F + G] among subjects with genotype 1b infection. There were no relapses among null responders treated with 3 DAAs+RBV for 12 [K + L] or 24 [M + N] weeks.

Based on the higher relapse rate with 8 weeks duration, and the lack of a difference between 12 and 24 weeks, 12 weeks was chosen as the standard duration in the phase III studies. 24 weeks of therapy was also studied in the TURQUOISE-II trial, dedicated to compensated cirrhotics. Such patients are now known to require a longer treatment duration on average than do non-cirrhotics. Furthermore, there were no cirrhotics in the AVIATOR study.

**Conclusions regarding the dose of ABT-450**

No significant differences were seen in SVR12 rates among subjects treated with the same regimen, but with different ABT-450/r doses (100/100 mg versus 150/100 mg or 100/100 mg versus 200/100 mg). Overall efficacy was therefore not a driver of ABT-450/r dose selection for Phase 3. Instead, selection of the ABT-450/r dose was based on resistance and safety analyses. These concerns are described above, under the heading on dose selection.

**Conclusions regarding the contribution of ABT-267 to regimen efficacy**

The comparison of the SVR24 rate in Group B (no ABT-267) and groups treated with 3 DAAs + RBV for 12 weeks was used to assess the contribution of ABT-267 to the treatment response. When Group B was compared with Group G (same ABT-450/r dose), the difference of 11.64% was not statistically significant (P = 0.141). When Group B was compared with Groups [F + G], the difference of 13.15% showed a trend toward statistical significance (P = 0.056). The difference in response rates was driven by the subjects with genotype 1a infection, as there were no virologic failures in these groups among subjects with genotype 1b infection.

**Conclusions regarding the contribution of ABT-333 to regimen efficacy**

Comparison of the SVR24 rate in groups that did not receive ABT-333 and groups treated with 3 DAAs + RBV for 12 weeks was used to assess the contribution of ABT-333 to the treatment response. When Group C was compared with Group F (treatment-naïve, same ABT-450/r dose), the difference of 13.31% showed a trend toward statistical significance (P = 0.090), which persisted when Groups [C + D] were compared with Groups [F + G] (P = 0.090) and when Groups [C + D + J] were compared with Groups [F + G + K + L] (P = 0.065). Once again, the difference in responses was driven by genotype 1a –infected subjects, as there were no failures in these groups among genotype 1b-infected subjects.

**Conclusions regarding the contribution of ribavirin to regimen efficacy**

The comparison of the SVR24 rate in Group E (no RBV) and groups treated with 3 DAAs + RBV for 12 weeks was used to assess the contribution of RBV to the treatment response. When Group E was compared with Group G (same ABT-450/r dose), the difference of 6.88% was not statistically significant (P = 0.262). When Group E was compared with Groups [F + G], the difference of 8.03% showed a trend toward statistical significance (P = 0.089). Again, the difference in response rates was driven by the subjects with genotype 1a infection, as there were no virologic failures in these groups among subjects with genotype 1b infection.

**Comments on the selection of the combination regimen**

ABT-450 is the most potent antiviral agent in the combination, but cannot be used as monotherapy due to its insufficient barrier to resistance.

In a very small sample in study M12-998, the SVR rate with ABT-450(r)+ABT267 given without ribavirin to patients with genotype 1a virus was 5/8 (62.5%). Data from the AVIATOR study indicate the contribution of each of the 3DAAs to regimen efficacy against genotype 1a.

Concerning genotype 1b, the dual DAA combo of ABT-450(r) + ABT-267 is being studied in the ongoing PEARL-1 (M13-393) study, as well as in the M12-539 study. The virological failure rate seen when only ABT-450(r) + ABT267 was given to treatment experienced patients with genotype 1b infection, under two different study protocols, is reported at 6.6% (5/76).

**Table 9. HCV GT1b-Infected Treatment-Experienced Subjects: Contribution of Each Agent to the Regimen**

| Without: | Regimen | Study (Group) | Virologic Failures n/N per Study | Total n/N (%) |
|---|---|---|---|---|
| -- | 3-DAA + RBV | M11-652[a] (K + L) | 0/17 | 2/228 (0.9) |
| | | M13-098 (A) | 2/123 | |
| | | M13-389 (1) | 0/88 | |
| ABT-333 | ABT-450/r + ABT-267 + RBV | M11-652 (J) | 0/19 | 0/19 (0) |
| ABT-267 | ABT-450/r + ABT-333 + RBV | M12-746 (3) | 1/1 | 1/1 (100) |
| RBV | 3-DAA | M13-389 (2) | 0/91 | 0/91 (0) |
| ABT-333 + RBV | ABT-450/r + ABT-267 | M13-393 (3) | 4/40 | 5/76 (6.6) |
| | | M12-536[b] (1 + 2) | 1/36 | |

a. 12-week arm only.

b. Including 12-week arms with ABT-450/r 100/100 and 150/100 mg doses.

In the PEARL-1 study, there were no virological failures with this combination among 42 treatment naïve, non-cirrhotic patients. Despite the latter, these outcomes would further support an incremental effect of a third agent also in an unselected treatment naïve population with genotype 1b, as a wide such group would be anticipated to contain such patients as in a peginterferon+ribavirin cohort, the only difference being that these have not been exposed to these drugs (about half of a treatment naïve genotype 1 cohort would not be cured if treated with peginterferon+ribavirin only, and 10-20% would be “null responders”).

The preliminary data on the efficacy of the dual combination in genotype 1b receive external support from an analogous drug development program, indicating that the efficacy of this combination would likely be considerable, though not optimised. A similar argument goes for the combination of ABT-450+ABT-333, though due to the lower potency of ABT-333, the efficacy of this combination would likely be lower than for the ABT-450+ABT-267 combination.

Based on such considerations, as well as the apparent tolerability of the regimen, the company proceeded to study only the triple DAA combination in phase III. The value of the addition of ribavirin was studied in three trials including non-cirrhotic patients. The choice of comparing 3DAA versus 3DAA + RBV, rather than, e.g., ABT-450 + ABT267+ RBV versus 3DAA+RBV was informed by safety data indicating a favourable safety profile of ABT-333 compared to RBV (see discussion of clinical safety) Furthermore, in the phase III trial (TURQOUISE-II) dedicated to compensated cirrhotics, all patients received RBV, and a comparison was made between 12 and 24 weeks of therapy.

## 2.6.1. Main studies

The applicant has performed six phase III studies in patients with genotype 1a and -1b virus. Five of these were in non-cirrhotic patients, whereas one was dedicated to patients with compensated cirrhosis. Furthermore, the applicant has submitted four supportive studies performed in post-transplant patients with genotype 1 virus that

do not have advanced fibrosis, in patients with genotype 1 virus that are on opiate substitution, and in patients with genotype 1 infection that have HIV co-infection.

**Table 10. Overview of the Pivotal Phase 3 and Supportive Studies**

| Study | GT | Population | Cirrhosis Y/N | regimen | N |
|---|---|---|---|---|---|
| **Phase 3** | | | | | |
| M11-646 (SAPPHIRE-1) | 1 | TN | N | 3-DAA + RBV vs. placebo for 12 weeks | 630 |
| M13-098 (SAPPHIRE-2) | 1 | TE | N | 3-DAA + RBV vs. placebo for 12 weeks | 393 |
| M13-389 (PEARL-2) | 1b | TE | N | 3-DAA +/- RBV for 12 weeks | 186 |
| M13-961 (PEARL-3) | 1b | TN | N | 3-DAA +/- RBV for 12 weeks | 419 |
| M14-002 (PEARL-4) | 1a | TN | N | 3-DAA +/- RBV for 12 weeks | 305 |
| M13-099 (TURQUOISE-II) | 1 | TN/TE | Y (all patients, Child-Pugh A) | 3-DAA + RBV for 12 vs. 24 weeks | 380 |
| **Supplementary studies** | | | | | |
| M12-999 | 1 | Post Tx | N | 3DAA +RBV for 24 weeks | 34 |
| M14-103 | 1 | TN/TE (on opiate substitution) | N | 3-DAA + RBV for 12 weeks | 38 |
| M14-004 (TURQUOISE-I) | 1 | TN/TE (With HIV coinfection | N+Y | 3DAA+RBV for 12 or 24 weeks | 63 |

In this table, 3-DAA refers to ABT-450/r/ABT-267 (150/100/25 mg QD) + ABT-333 (250 mg BID). In all studies, ribavirin was dosed at 1000/1200 mg per day with body weight below or above 75 kg.

### *2.6.1.1. General design features for the phase 3 studies*

There are two studies where 12 weeks of 3DAA+RBV therapy is compared to placebo (SAPPHIRE I and –II). As the anticipated SVR rate in the placebo group is 0, the purpose of this comparison is exclusively the evaluation of safety.

There are three studies where 12 weeks of 3DAA+RBV is compared to 12 weeks of 3DAAs (PEARL-II, PEARL-III, PEARL-IV)

The above studies included non-cirrhotic patients with genotype 1a or -1b infection. Requirements for prior treatment history varied (see below). Patients with prior exposure to other direct acting antivirals were not studied.

There is one study where 12 weeks and 24 weeks of 3DAA+RBV are compared in patients with compensated cirrhosis (TURQUOISE-II). These patients could have genotype 1a or -1b virus, and could either be treatment naïve or having previously failed on pegIFN+RBV therapy.

The following stratification factors were used in the studies:

- HCV genotype (1a vs. 1b) when applicable
- IL-28 genotype (CC vs. non-CC) for the treatment naïve groups.
- Type of prior response (null – or partial responders, or relapse), and referring to prior therapy with peg-IFN + RBV.

The definitions of prior response to peginterferon+ribavirin where those generally accepted and in accordance with regulatory guidance:

- Null responder: failed to achieve a 2 log10 reduction in HCV RNA (IU/mL) at Week 12; or > 1 log10 reduction at Week 4 (≥ 25 days).
- Partial responder: achieved ≥ 2 log10 IU/mL reduction in HCV RNA at Week 12, but still had detectable HCV-RNA at end of treatment (minimum 20 weeks).
- Relapser: undetectable at or after the end of at least 36 weeks of treatment, but relapsed within 52 weeks of treatment follow-up.

**Main inclusion/exclusion criteria**

The major inclusion/exclusion criteria are implied in each of the study titles. These pertain to the subgenotype of the virus and to the patient being treatment naïve or having previously been treated with peginterferon+RBV. Furthermore cirrhosis was either an exclusion criterion or an inclusion criterion for each of the pivotal studies. These are the definitions used to determine cirrhosis as an inclusion criterion (study M13-099), or to exclude cirrhosis (the other five pivotal trials).

**Table 11. Definitions of cirrhosis as inclusion/exclusion criterion in phase 3.**

| | Defining cirrhosis (inclusion criterion), - study M13-099 | Defining absence of cirrhosis (exclusion criterion), - all other studies |
|---|---|---|
| Liver biopsy (within 24 months) | Metavir score of > 3 (including 3/4 or 3–4) or Ishak score of > 4 | Metavir score ≤3 or Ishak score ≤4 |
| Fibroscan (within 6 months) | ≥ 14.6 kPa | < 9.6 kPa |
| Fibrotest and APRI-scores (screening) | Method not used (M13-099) | ≤ 0.72 and ≤ 2 |
| Child-Pugh score (screening) | ≤ 6 (i.e. compensated cirrhosis) | Not applicable |

*Note: 1 method was sufficient. A non-qualifying FibroTest/APRI or FibroScan could be overruled by a qualifying liver biopsy.*

The methods and limits used to determine cirrhosis status have been accepted by regulators. Any of the three methods could be used to rule out cirrhosis (in accordance with local practice). With regards to fibroscan results, a kPA of <9.6 kPa would in fact also rule out many patients with METAVIR F3, creating an enrichment of patients with mild or moderate fibrosis in the non-cirrhosis studies.

Apart from cirrhosis (above), the same main exclusion criteria applied in all studies, namely:

- Previous use of any investigational or commercially available anti-HCV therapy (excepting peginterferon+RBV in those studies targeting “treatment experienced” patients.
- (other than interferon and/or pegIFN/RBV)
- HIV- and HBV co-infection
- A large number of other medications (listed in tables below). Strong CYP3A inhibitors or inducers were also disallowed within 2 weeks prior to the study
- Use of any herbal supplements
- Cause of liver disease other than HCV infection
- Recent (within 6 months) history of drug or alcohol abuse

For the studies in non-cirrhotics, screening laboratory analyses showing any of the following abnormal laboratory results:

- ALT or AST > 5 × upper limit of normal (ULN);
- albumin < lower limit of normal (LLN);
- INR > 1.5
- indirect bilirubin > 1.5 × ULN and direct bilirubin > ULN
- haemoglobin < LLN;
- platelets < 120,000 cells/mm3;
- neutrophil count < 1,500 cells/µL (< 1,200 cells/µL for black patients)
- calculated creatinine clearance (CG) < 60 mL/min;

For the turquoise II study (M13-099) in patients with compensated cirrhosis, the following laboratory limits were used

- ALT or AST > 7 × upper limit of normal (ULN);
- albumin < 2.8 g/dL;
- INR > 2.3
- Total bilirubin > 3 mg/dL
- haemoglobin < LLN;
- platelets < 60,000 cells/mm3;
- neutrophil count < 1,500 cells/µL (< 1,200 cells/µL for black patients)
- calculated creatinine clearance (CG) < 60 mL/min;

Furthermore, patients could not have a present or past Child-Pugh B/C classification, or have a history of hepatic decompensation, including variceal bleeding events.

Due to the potential for DDIs of this ritonavir-boosted triple DAA regimen, a considerable number of medications were prohibited.

**Lists of specifically disallowed medications**

| | | |
|---|---|---|
| Alfuzosin | Fusidic acid | Quercetin |
| Amiodarone | Gemfibrozil | Quinidine |
| Astemizole | Itraconazole | Rifabutin |
| Bepridil | Ketoconazole | Rifampin |
| Bosentan | Lovastatin | Rosiglitazone |
| Buprenorphine | Methadone | Salmeterol |
| Clarithromycin | Midazolam (oral) | Simvastatin |
| Carbamazepine | Mifepristone | St. John's Wort |
| Cisapride | Modafinil | Telithromycin |
| Conivaptan | Montelukast | Terfenadine |
| Dronedarone | Nefazodone | Triazolam |
| Efavirenz | Phenobarbital | Trimethoprim |
| Eleptriptan | Phenytoin | Troglitazone |
| Eplerenone | Pimozide | Troleandomycin |
| Ergot derivatives | Pioglitazone | Voriconazole |
| Everolimus | Propafenone | Hormonal contraceptives[a] |

| | |
|---|---|
| Alfentanil | Mexiletine |
| Budesonide | Perphenadine |
| Colchicine | Risperadone |
| Cyclosporine | Sildenafil |
| Digoxin | Sirolimus |
| Disopyramide | Tacrolimus (topical use was permitted) |
| Divalproex | Tadalafil |
| Erythromycin | Thioridazine |
| Ethosuximide | Vardenafil |
| Fentanyl | Vinblastine |
| Fluticasone | Vincristine |
| Lamotrigine | Warfarin |
| Lidocaine (use for local anesthesia was permitted) | |

### *2.6.1.2. Results of the main studies*

The following is a summary of the main demographics of the phase III trials

**Table 12. Main demographics/characteristics in the phase 3 studies**

- **Numbers concern total number of patients randomized to active therapy**

| | SAPPHIRE-1 (GT-1)<br>3-DAA + RBV<br>(N=473) | PEARL-4 (GT1a)<br>3-DAA +/- RBV<br>(N=305) | PEARL-3 (GT1b)<br>3-DAA +/- RBV<br>(N=419) | Sapphire-2 (GT1)<br>3-DAA + RBV<br>(N=297) | PEARL-2 (GT1b)<br>3-DAA +/- RBV<br>(N=186) | TURQUOISE-2 (GT1)<br>3-DAA + RBV<br>(N=380) |
|---|---|---|---|---|---|---|
| | 12 weeks of therapy | | | | | 12/24 weeks |
| Male | (57.3) | 199 (65.2) | 192 (45.8) | 167 (56.2) | 102 (54.8) | 267 (70.3) |
| White race | (90.5) | 257 (84.3) | 394 (94.3) | 269 (90.6) | 170 (91.4) | 360 (94.7) |
| Age, mean ± SD | 49 | 54.0 | 50.0 | 54 | 54 | 58 |
| ≥ 65 | 19 (4.0) | 23 (7.5) | 33 (7.9) | 20 (6.7) | 31 (16.7) | 49 (12.9) |
| IL28-CC | 144 (30.4) | 94 (30.8) | 88 (21.0) | 44 (21.0) | 17 (9.1) | 69 (18.2) |

| | | | | | | |
|---|---|---|---|---|---|---|
| BL Fibrosis F0-F1 | 363 (76.7) | 195 (63.9) | 291 (69.6) | 202 (68.0) | 125 (67.2) | All cirrhotic (F4) |
| F2 | 70 (14.8) | 56 (18.4) | 85 (20.3) | 53 (17.8) | 34 (18.3) | |
| F3 | 40 (8.5) | 54 (17.7) | 42 (10.0) | 42 (14.1) | 27 (14.5) | |
| Plasma HCV-RNA (mean log10) | 6.42 | 6.57 | 6.31 | 6.55 | 6.52 | 6.47 |
| Platelets < 60 | These studies only concern patients without cirrhosis | | | | | 5 (1.3) |
| 60 - < 90 | | | | | | 51 (13.4) |
| 90- < 120 | | | | | | 82 (21.6) |
| TN | All | | | None | | 160 (42.1) |
| TE | None | | | All | | 220 (57.9) |
| prior response | NA | | | | | |
| Null | | | | 193 (49) | 53 (28.5) | 137 (36.1) |
| Partial | | | | 86 (21.8) | 68 (36.6) | 31 (8.2) |
| Relapse | | | | 115 (29.2) | 65 (34.9) | 52 (13.7) |

TN: Treatment naïve, TE: treatment experienced

#### 2.6.1.2.1. Treatment naïve (TN) patients without cirrhosis (GT-1)

**Study M11-646 (SAPPHIRE-1)**

Study title: A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 co-administered with ribavirin (RBV) in treatment-naïve adults with genotype 1 chronic hepatitis C virus (HCV) infection (SAPPHIRE-I).

This study was performed at 79 investigative sites in the United States, Australia, Austria, Canada, France, Germany, Hungary, Italy, New Zealand, Spain, Sweden, Switzerland, and the United Kingdom.

The study was a randomised comparison of 3 DAAs + RBV vs. placebo (3:1) for 12 weeks, previously untreated patients with GT1. Patients allocated to placebo were offered the active regimen for 12 weeks OL after the blinded period.

**Table 13. Outcomes with 3DAAs + RBV, in Sapphire 1**

| | GT1a (322) | GT1b (151) | TOTAL (473) |
|---|---|---|---|
| SVR12 | 307/322 (95.3) | 148/151 (98.0) | 455/473 (96.2) |
| IL28 CC | 103/106 (97.2) | 36/38 (94.7) | 139/144 (96.5) |
| IL28 non-CC | 204/216 (94.4) | ...112/113 (99.1) | 316/329 (96.0) |
| Non-response | 15/322 | 3/151 | 18/473 (3.8) |
| On-treatment virologic failure | | | 1/473 (0.2) |
| Rebound | 1 | 0 | 1/473 (0.2) |
| Fail to suppress | 0 | 0 | 0/473 |
| Relapse | 6/322 (1.9) | 1/151 (0.7) | 7/463 (1.5) |
| Premature drug discontinuation | 6 | 1 | 7/473 (1.5)[a] |
| Missing $SVR_{12}$ data | 2 | 1 | 3/473 (0.6) |

SVR rates were outstanding with a 95% rate in genotype 1a and a 98% rate in genotype 1b. There were no on-treatment virological failures, and only one relapse in genotype 1b. Six patients with genotype 1a virus relapsed.

**Study M14-002 (PEARL-IV)**

Study title: A randomized, double-blind, controlled study to evaluate the efficacy and safety of the combination of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 with and without ribavirin (RBV) in treatment-naïve adults with genotype 1a chronic hepatitis C virus (HCV) infection (PEARL-IV).

The study was conducted at 53 investigative sites in United States, Canada, and the United Kingdom.

Patients were randomized to 3 DAAs + RBV or 3 DAAs without RBV (1:2) for 12 weeks.

**Table 14. SVR12 and reasons for non-response, PEARL-IV (TN, GT 1a)**

| | 3-DAA + RBV N = 100 | 3-DAA N = 205 |
|---|---|---|
| SVR12 | 97/100 (97) | 185/205 (90.2%) |
| IL28 CC | 31/31 (100) | 61/63 (96.8) |
| IL 28 non-CC | 66/69 (95.7) | 124/142 (87.3) |
| Non-response | 3/100 | 20/205 (9.8) |
| On-treatment virologic failure | 1/100 | 6/205 (2.9) |
| Rebound | 1 | 6 |
| Fail to suppress | 0 | 0 |
| Relapse | 1/98 | 10/194 (5.2) |
| Premature study drug discontinuation | 0 | 3/205* |
| Missing $SVR_{12}$ data | 1/100 | 1/205 |

**Two patients were lost to follow-up, 1 patient discontinued due to "other" reasons*

Virological rebound occurred from week 2 to week 8 of treatment, and all relapses were seen within 4 weeks of stopping therapy in this study.

It is clear that in patients with genotype 1a virus, also in the absence of advanced liver disease, the 3DAA regimen without ribavirin is associated with a higher risk both of on-treatment virological breakthrough (rebound) and of post-treatment relapse. Thus the 3DAA regimen is in fact not optimized in an unselected population with genotype 1a. The apparent impact of IL28B genotype on the likelihood of SVR, particularly in the RBV-free arm, is noted. Regarding baseline resistance in this study, while the Q80K mutation, which does not confer high level resistance to ABT-450, was apparently more common in those failing virologically in the ribavirin-free arm, the impact of detectable high level baseline resistance does not explain the increased failure rates (see above section on pharmacodynamics).

**Study M13-961 (PEARL-III)**

Study title: A randomized, double-blind, controlled study to evaluate the efficacy and safety of the combination of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 with and without ribavirin (RBV) in treatment-naïve adults with genotype 1b chronic hepatitis C virus (HCV) infection (PEARL-III). Thus, this study

is analogous to PEARL-IV, described above, except that its target population have genotype 1b rather than -1a virus.

The study was conducted at 50 investigative sites in Austria, Belgium, Spain, Hungary, Israel, Italy, Poland, Portugal, Romania, Russian Federation, and the United States.

Patients were randomized to 3 DAAs + RBV or 3 DAAs without RBV (1:1) for 12 weeks.

**Table 15. Outcomes in PEARL-III (TN, GT 1b)**

| | 3-DAA + RBV N = 210 | 3-DAA N = 209 |
|---|---|---|
| SVR12 | 209/210 (99.5) | 207/209 (99.0) |
| Non-response | 2/210 | 2/210 |
| On-treatment virologic failure | 1 | 0 |
| Rebound | 1 | 0 |
| Fail to suppress | 0 | 0 |
| Relapse | 0 | 0 |
| Premature study drug discontinuation | 0 | 0 |
| Missing $SVR_{12}$ data | 0 | 2 |

The efficacy of the 3DAA without ribavirin regimen was outstanding in genotype 1b. There was no room for additive efficacy with RBV.

#### 2.6.1.2.2. Treatment experienced (TE) patients without cirrhosis (GT-1)

It has been noted above that patients with prior experience of direct acting antiviral therapy were not included in the TE studies; thus TE exclusively refers to experience of peginterferon+ribavirin. As exposure to this regimen does not select for resistance, and thus does not alter the activity of drugs in a subsequent regimen, such a TE population is understood as an enrichment of that more difficult to treat subgroup of a treatment naïve population, who would not have been cured on peginterferon+ribavirin therapy alone. In typical trials of genotype 1 infected, treatment naïve subjects with pegIFN/RBV, SVR rates have been approximately 50%. Approximately 10-15% relapse after the end of treatment; 10-15% are partial responders and approximately 20% are null responders.

**Study M13-098 (SAPPHIRE-II)**

Study title: A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 co-administered with ribavirin (RBV) in treatment-experienced adults with genotype 1 chronic hepatitis C virus (HCV) infection (SAPPHIRE-II)

This study was conducted at 76 investigative sites in Australia, Canada, Czech Republic, Denmark, France, Germany, Ireland, Italy, Mexico, The Netherlands, Portugal, Russia, Spain, United Kingdom, and the United States/Puerto Rico.

Patients were randomized to 3 DAAs + RBV or placebo (3:1) for 12 weeks. Patients allocated to placebo were offered the active regimen for 12 weeks open label after the blinded period. As stated above, in the discussion

of SAPPHIRE-I, the anticipated SVR rate in the placebo group is 0. Therefore the placebo comparison is of relevance for safety only.

**Table 16. SVR12 and reasons for non-response, SAPPHIRE-II**

| | 3-DAA + RBV GT1a (173) | 3-DAA + RBV GT 1b (124) | 3-DAA + RBV Total (297) |
|---|---|---|---|
| SVR12 | 166/173 (96.0) | 120/124 (96.8) | 286/297 (96.3) |
| Prior non-response : NULL | 83/87 (95.4) | 56/59 (94.9) | 139/146 (95.2) |
| : PARTIAL | 36/36 (100) | 29/29 (100) | 65/65 (100) |
| : RELAPSE | 47/50 (94.0) | 35/36 (97.2) | 82/86 (95.3) |
| Non-response | 7/173 | 4/124 | 11/297 |
| On-treatment virologic failure | 0 | 0 | 0/297 |
| Relapse | 5/173 (2.9) | 2/124 (1.6) | 7/293 (2.4) |
| Premature study drug discontinuation | 2 | 2 | 4/297 (1.3) |
| Missing SVR12 data | 0 | 0 | 0 |

Of the 7 who relapsed, 6 were male, 6 had the IL28B non-CC genotype, and 3 had F3 fibrosis stage.

When using the 3DAA+RBV, efficacy is very high also in these patients that are enriched “poor responders” to pegIFN+RBV, with virtually similar outcomes regardless of prior response category or viral subgenotype (though the proportion of relapsers was numerically higher in genotype 1a. Further, it is notable that also in such previously defined poor responders to pegIFN+RBV, the addition of RBV to 3DAA prevents on treatment virological breakthrough in patients with genotype 1a virus.

**Study M13-389 (PEARL-II)**

Study title: A randomized, open-label, multicentre study to evaluate the safety and antiviral activity of the combination of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 with and without ribavirin in treatment-experienced subjects with genotype 1b chronic hepatitis C virus (HCV) infection (PEARL–II).

As the efficacy of the 3DAA combination without RBV had been shown to be lower in genotype 1a in the AVIATOR study, the three DAA combination without RBV was studied in phase III in treatment experienced patients with genotype 1b virus, but not with -1a (see also comment above).

This study was conducted at 43 investigative sites in United States, Austria, Belgium, Italy, Portugal, Puerto Rico, Sweden, Switzerland, The Netherlands, and Turkey.

Patients were randomised to 3DAA or 3DAA+RBV, for 12 weeks, at a 1:1 ratio.

None of the patients had a virological failure as the resons for not achieving SVR12, table below:

**Table 17. SVR12 and reasons for non-response, PEARL-II**

| | 3-DAA + RBV | 3-DAA |
|---|---|---|
| SVR12 | 85/88 (96.6) | 91/91 (100) |
| Non-response | 3/88 | 0/91 |
| On-treatment virologic failure | 0 | 0 |
| Rebound | 0 | 0 |
| Fail to suppress | 0 | 0 |
| Relapse | 0 | 0 |
| Premature study drug discontinuation | 2/88 (2.3) | 0 |

| | | |
|---|---|---|
| Missing SVR12 data | 1/88 (1.1) | 0 |

#### 2.6.1.2.3. Patients with genotype 1a or 1b virus and compensated cirrhosis

**Study M13-099 (TURQUOISE-II)**

Study title: A randomized, open-label study to evaluate the safety and efficacy of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 coadministered with ribavirin (RBV) in adults with genotype 1 chronic hepatitis C virus (HCV) infection and cirrhosis (TURQUOISE-II).

This study is remarkable insofar as it is the first registrational study in the field of HCV therapy dedicated exclusively to patients with (compensated) cirrhosis. Thus it counterbalances the fact that most patients in the other phase III studies had minimal fibrosis.

The study was conducted at 78 investigative sites in the United States, Puerto Rico, Canada, Belgium, France, Germany, Italy, Spain, and the United Kingdom.

In contrast to the other phase III studies, this study was providing the treatments open label:

Patients were randomized to 3DAAs + RBV for either 12 weeks or 24 weeks.

Notably, this study included patients with either -1a or -1b viral sub genotype; also, it included both patients that were treatment naïve as well as patients with prior experience of non-curative peginterferon + RBV therapy.

It is presently well known that the mean requirements in terms of drug pressure and/or treatment duration, in order to maximize SVR rates, is higher in patients with cirrhosis compared to those that have less advanced liver disease. Furthermore, the phase II program did not include patients with cirrhosis. Finally, failure to achieve SVR with the 3DAA is likely to be associated with multiple class drug resistance. As compensated cirrhotics may progress to decompensation if SVR is not reached, and as it is presently unclear how to retreat patients with cirrhosis that have preselected for triple class drug resistance, the prudent strategy of adding ribavirin to the regimen of all patients is recognized, even though it leaves the question open of whether cirrhotics with genotype 1b infection might do without it. Furthermore, the need to explore the appropriate treatment duration in cirrhotics in phase III is recognized.

Inclusion/exclusion criteria and stratification factors are delineated at the beginning of this section on the pivotal studies of this application. As a reminder, patients could only be included if they had a prior liver biopsy showing cirrhosis, or a Fibroscan result (within 6 months) of 14.6 kPa, minimum baseline platelets was 60,000. Further, patients had to have a Child-Pugh A classification and no history of clinical decompensation.

Overall, SVR rates were 91.8% (191/208) and 95.9% (165/172) in the 12 and 24 weeks treatment arm, respectively. SVR rates were very high for either treatment duration for patients infected with genotype 1b - only 1/119 did not achieve SVR12. This patient, TE with prior partial response, had a relapse after completing 12 weeks of therapy. For patients with genotype 1a-infection, 24 weeks of therapy yielded an SVR rate of >90% in all subgroups, while 12 weeks of therapy carried higher risk of failure in some subsets.

**Table 18. SVR12 by duration and subtype, and treatment populations, TURQUOISE-2 (ITT)**

| | 3DAAs + RBV<br>12 weeks<br>(N=208) | 3DAAs + RBV<br>24 weeks<br>(N=172) |
|---|---|---|

| | GT1a | GT1b | GT1a | GT1b |
|---|---|---|---|---|
| TN | | | | |
| IL-28 CC | 19/19 (100) | 4/4 (100) | 15/16 (93.8) | 5/5 (100) |
| IL-28 non-CC | 40/45 (88.9) | 18/18 (100) | 37/40 (92.5) | 13/13 (100) |
| ALL | 59/64 (92.2) | 22/22 (100) | 52/56 (92.9) | 18/18 (100) |
| TE | | | | |
| Prior NULL-response | 40/50 (80.0) | 25/25 (100) | 39/42 (92.9) | 20/20 (100) |
| Prior Partial response | 11/11 (100) | 6/7 (85.7) | 10/10 (100) | 3/3 (100) |
| Prior relapse | 14/15 (93.3) | 14/14 (100) | 13/13 (100) | 10/10 (100) |
| ALL | 65/76 (85.5) | 45/46 (97.8) | 62/65 (95.4) | 33/33 (100) |

Thrombocytopenia in cirrhosis is a marker of portal hypertension. Baseline platelet count is one of the main predictors of disease progression in cirrhosis. Low counts are generally associated with more severe disease, where extended treatment durations may be of importance. This is both in terms of required drug pressure to achieve SVR, as well as in terms of the potential clinical consequences of failing to achieve SVR. The number of patients with low platelets was relatively small in this study (a consequence of selection criteria, as the likelihood of meeting other exclusion criteria related to Child-Pugh status and clinical decompensation increases with decreasing platelet counts).

SVR12 rates by baseline platelet counts were presented as below:

**Table 19. SVR12 by baseline platelets, TURQUOISE-2**

| BL platelets | 12 weeks treatment | 24 weeks treatment |
|---|---|---|
| < 90,000 | 25/ 30 (83.3) | 25/ 26 (96.2) |
| >=90,000 | 166/178 (93.3) | 140/146 (95.9) |

*Rebound* (n=4) only occurred in patients with genotype 1a-infection (1 in arm A, 3 in arm B). The risk for rebound is not affected by the treatment duration. The *relapse* frequency, however, may be lowered by increasing the treatment duration.

For genotype 1a there is therefore an interest in scrutinizing the risk for relapse for the two different treatment durations by type of patient population. In the full dataset, the relapse rate among patients with GT1a in the 12 week arm was 11/140 (8%) versus 1/121 (1%) in the 24 week arm. Counting the patient in the 24 week arm with on-treatment breakthrough at day 97 as a “relapse” (as this breakthrough occurred after 12 weeks of therapy), the point estimate would be 2/121 (1.5%).

**Table 20. Relapse frequency by treatment duration in patients with genotype-1a infection**

| | 3DAAs + RBV 12 weeks | 3DAAs + RBV 24 weeks |
|---|---|---|
| TN | | |
| IL-28 CC | 0/19 | 0/16 |
| IL-28 non-CC | 4/45 | 1/40 |
| TE | | |
| Prior NULL-response | 7/50 | 0/42 |

| | | |
|---|---|---|
| Prior Partial response | 0/11 | 0/10 |
| Prior relapse | 0/15 | 0/13 |

In an attempt to further understand the determinants of relapse after 12 weeks, in order to identify those cirrhotic GT1a patients most suitable for 12 or 24 weeks of therapy, the applicant further analysed this dataset by logistic regression. Some traditional prognostic factors, such as age and baseline HCV RNA, were unrelated to relapse. Former injection drug use identified 10 of the 11 relapsers, but the biological plausibility of this marker is uncertain. IL28b genotype was also associated with relapse, but only when comparing TT genotype with non-TT genotype. Male sex was marginally associated with relapse.

Higher AFP, lower platelets, and lower albumin, all factors identifying patients with more advanced cirrhosis, were each significantly associated with relapse. These variables collectively identified all of the prior null responders who relapsed and 3 of the 4 treatment-naïve subjects who relapsed.

**Table 21. Relapse by Baseline Values of AFP, Platelets, and Albumin (12 weeks treatment groups)**

| Group | All | Prior Null Responders | Subjects Without Prior Null Response |
|---|---|---|---|
| Subjects with 1 or more unfavorable values* | 10/48 (20.8%) | 7/25 (28%) | 3/23 (13%) |
| Subjects with all 3 values favorable* | 1/87 (1.1%) | 0/22 (0%) | 1/65 (1.5%) |
| P value | < 0.0001 | 0.01 | 0.05 |

* Unfavorable values defined as AFP ≥ 20 ng/mL, platelets < 90 × $10^9$/L, albumin < 35 g/L.

While it is recognized that GT1a cirrhotics with a higher risk of relapse on 12 weeks of therapy could be identified post hoc using various biologically plausible baseline characteristics, and particularly that data indicate that cirrhosis associated with low platelets or biochemical abnormalities is a risk factor for relapse with a shorter treatment durations, the actual cut-offs presented above are considered clinically arbitrary.

## Supportive studies

### *2.6.1.3. Efficacy in the post-transplant setting*

#### Study M12-999

This was an open-label study to evaluate the safety and efficacy of the combination of ABT-450/ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 with or without ribavirin (RBV) in adult liver transplant recipients with genotype 1 hepatitis C virus (HCV) infection.

The applicant has submitted data from a Cohort 1 (=arm A) of this ongoing study, which is fully enrolled and comprises 34 HCV genotype 1-infected subjects with fibrosis ≤ F2 (Metavir). Subjects were treatment-naïve after transplantation but may have received previous HCV treatment (pegIFN or IFN with or without RBV) prior to liver transplantation.

Patients received 3DAA + RBV for 24 weeks.

RBV dosing was managed at the discretion of the investigator. Previous studies in this population highlight the potential for RBV dose modification, use of erythropoiesis-stimulating agents, such as erythropoietin, and transfusion. Creatinine clearance is commonly reduced in this population, in part due to chronic calcineurin inhibitor (CNI) exposure. The reduced creatinine clearance may augment RBV exposures, increasing the possible risk of RBV toxicity. Consequently, RBV dosing was at the discretion of the investigator and typical weight-based dosing was not required upon initiation of study drug.

The most frequently selected RBV dose range at the initiation of therapy was 600 – 800 mg per day (19/34 subjects; 55.9%). This was also the most common RBV dose at completion of the study regimen (23/34 subjects; 67.6%). Overall, 19 (55.9%) subjects dose modified RBV.

The use of calcineurin inhibitors (CNIs), cyclosporine and tacrolimus, at a stable dose was permitted with the following recommendations for dose adjustment based on data from Phase 1 drug-interaction studies: Tacrolimus: 500 mg once a week taken with the study drugs and with food. Cyclosporine: one-fifth of the pre-study total daily dose taken as a single daily dose with the study drugs and with food. Adjustment of CNI dose and dosing interval was permitted based on the investigator's interpretation of CNI levels.

**Table 22. Baseline disease and demographic characteristics**

| parameter | Arm A (N=34) |
|---|---|
| Male (%) | 79.4 |
| White (%) | 85.3 |
| Age (mean) | 60 |
| Genotype | 1a: 29 (85.3%)<br>1b: 5 (14.7%) |
| IL28B C/C | 8 (23.5%) |
| Baseline HCV-RNA | 6.6 log10 |
| Immunosuppresive medication | Cyclosporine: 5 (14.7%)<br>Tacrolimus: 29 (85.3%) |
| Baseline fibrosis stage | F0-F1: 19 (55.9%)<br>F2: 15 (44.1%) |
| Months since liver transplantation (median, min, max) | 39.5 (12.9-136.4 |
| Baseline creatinine clearance (mean | 90.5 ml/min |

Thus this is a not very advanced post-transplant cohort without significant fibrosis, and with a high mean baseline creatinine clearance. The main limitation of available data from this study is that no patients with advanced fibrosis or cirrhosis were included.

Of the 32 subjects with data available to assess SVR12, 31 (96.9%) achieved SVR12; being 96.3% (26/27) in subjects with genotype 1a infection and 100% (5/5) in subjects with genotype 1b infection.

A single subject with HCV genotype 1a infection, experienced relapse at Post-Treatment Day 3.

#### *2.6.1.4. Efficacy in patients receiving opiate substitution therapy*

**Study M14-103**

This was an open-label, single-arm, phase 2 study to evaluate the combination of ABT-450/r/ABT-267 and ABT-333 coadministered with ribavirin (RBV) in adults with genotype 1 hepatitis C virus (HCV) infection taking methadone or buprenorphine.

From a regulatory perspective, patient with HCV infection taking opiate substitution therapy is not considered a clinically relevant subgroup for which there is a need of a specific demonstration of efficacy and safety, in the absence of clinically relevant drug-drug interactions that would mandate specific studies, e.g., of the appropriateness of proposed dose adjustments. In this case, estimates by cross study comparisons indicate that methadone may lower exposure to ABT-450 substantially. Furthermore, there is an increase in buprenorphine/norbuprenorphine exposure on co-administration with 3DAA. (further discussed in the pharmacokinetics section).

Hepatitis C virus genotype 1-infected adult subjects who were on a stable opioid replacement therapy of methadone or buprenorphine ± naloxone for at least 6 months prior to screening were eligible for the study. Patients were non-cirrhotic and either treatment naïve or had prior pegIFN/RBV treatment experience. Patients with HBV or HIV co-infection were excluded.

All subjects were scheduled to receive 3DAA+RBV for 12 weeks.

The study population comprised 38 patients, 66% of whom were male and 94,7% of whom were white. Mean age was 48 years. 84% had genotype 1a virus and 32% had IL28B C/C genotype. 36/38 patients were treatment naïve. 19 (50%) subjects were on methadone and 19 (50%) subjects were on buprenorphine +/- naloxone.

37/38 patients achieved SVR, with one patient discontinuing the study prematurely.

#### *2.6.1.5. Efficacy in patients with genotype 1 infection and HIV co-infection*

Study M14-004 is an ongoing, randomized, open-label trial to evaluated 3DAA coadministered with RBV for 12 and 24 weeks in HCV GT1-infected subjects with HIV-1 coinfection.

In part a of this study, for which SVR12 and safety data have been submitted, TN or pegIFN/RBV experienced patients with or without cirrhosis were included. Most patients had GT1a infection. Patients were treated with either an atazanavir or a raltegravir based antiretroviral regimen. The SVR rates were 29/31 (93.5%) and 29/32 (90.6%) in the 12 and 24 week arms, respectively. Like previous studies with different interferon-free DAA regimens, these data are indicative that HIV co-infection does not impact the likelihood of SVR:

## 2.6.2. Discussion on clinical efficacy

**Design and conduct of clinical studies**

Each of the drugs were studied in dose ranging monotherapy studies in genotype 1. Subsequently each drug was studied in combination with peginterferon and ribavirin in further phase IIa dose ranging. This is in agreement with the paradigm that has prevailed during the recent transition from interferon based to interferon free anti-HCV therapy.

After a few exploratory combination studies, the company performed the large phase IIa study AVIATOR (M13-652). This trial is crucial for informing on the drug combinations and durations that were subsequently studied in phase III. This drug development program comprises four active drugs – three direct acting antivirals of different classes, as well as ribavirin – and a pharmaco-enhancer. Thus, the number of potential combinations is very large. Adding to these parameters is the fact that also treatment duration was a factor to consider in the selection of the appropriate regimen. It is notable that factorial designs covering all possible combination are not only practically infeasible, but would also have been impossible, as several combinations would be anticipated to provide insufficient efficacy based on pharmacodynamic considerations and/or clinical trial experiences. In this context, it should be noted that all three DAAs select for resistant variants, and that there is therefore a need to protect patients from inadvertent non-curative exposure.

The company has further presented the largest interferon-free phase III program hitherto submitted for regulatory evaluation. There are five studies of the use of 3DAAs with or without ribavirin in non-cirrhotic patients, further classified based on treatment experience (naïve or previously exposed to peginterferon+ribavirin) and on viral sub genotype (1a versus -1b). The company has also performed the first phase III trial dedicated exclusively to (compensated) cirrhotics. The dossier is complemented by interim data from a study of the use of 3DAA+RBV post-transplant in patients with genotype 1 infection that do not yet have advanced fibrosis.

All in all, the rationale for the design of this drug development program is understood and there are no indications of particular deficiencies in its conduct.

**Efficacy data and additional analyses**

In selecting the doses, the applicant has not only, as in the general case, needed to balance sufficient potency and barrier to resistance against exposure dependent safety concerns, but also take into account multi-directional drug-drug interactions between the regimen components and the pharmacokinetic enhancer ritonavir. The company has adequately described this procedure and the rationale for the dose selection is in agreement with the antiviral drug development paradigm. For all three drugs, exposures at the selected dose are anticipated to yield maximal activity against wild-type virus. Dasabuvir appears only to be active against genotype 1 virus.

The AVIATOR study demonstrated that, in non-cirrhotic subjects, 8 weeks of therapy is submaximal and that more than 12 weeks did not add efficacy. These findings are supported by other data on interferon-free treatment regimens that have yielded similar results. Furthermore, this study clearly showed that the optimal regimen might differ between genotypes 1a and -1b.

For genotype 1a, leaving out ombitasvir, dasabuvir or ribavirin from the regimen yielded lower SVR rates. Though perhaps not always statistically compelling, this is supported by PK/PD arguments and in particular by an understanding of differential barriers to resistance, as well as by sparse clinical observations.

For genotype 1b, the additive value of a third agent, be it ombitasvir, dasabuvir or ribavirin is less clear cut. There are two on-going studies – M13-393 (PEARL-1) and M12-536 - in which the use of the dual combination of ABT-450 and dasabuvir is investigated in genotype 1b. While 0/42 treatment naïve non-cirrhotic patients experienced virological failure, data indicate a 6.6% virological failure rate among a total of 76 patients with the dual DAA combination in treatment experienced patients with genotype 1b. Further, there is a numerical over-representation of baseline NS5A RAV Y93H in those that fail. There are similar figures from other programs. Furthermore, it may be that adding a third drug would give some increment in efficacy in patients that are intrinsically "difficult to cure" due to host factors.

It is notable that in weighing the benefit of a third agent, its side effects profile must be considered. Dasabuvir has a favourable side effects profile compared to ribavirin, which is the main driver of symptomatic adverse effects within the regimens tested, as will be clear from the analysis of safety. For such reasons, the company studied the 3DAA regimen without ribavirin in phase III, rather than either of the 2DAA regimens with ribavirin. However, the efficacy of 2DAA+RBV for 12 weeks in non-cirrhotic patients with GT1b is likely to be similar as that of 3DAA, as shown in the AVIATOR study and further supported by a reverse bridging argument (GT4 to GT1b) based on the M13-393 study.

The phase III program has demonstrated excellent efficacy with 99% SVR when 12 weeks of 3DAA is given to non-cirrhotic patients with genotype 1b, regardless of host factors and prior exposure to peginterferon+ribavirin, which does not per se impact response to the DAAs. Patients with prior DAA exposure were not included in this study program, as in most cases these would have previously selected for variants cross-resistant to one of the DAAs in the present regimen).

**Table 23. Summary on outcomes, GT1b-infection, phase 3**

| | 3 DAAs<br>12 weeks | 3 DAAs + RBV<br>12 weeks |
|---|---|---|
| non-cirrhotic patients | | |
| Treatment naive | (PEARL-3) | (SAPPHIRE-1, PEARL-3) |
| SVR12 | 207/209 (99.0) | 357/361 (98.9) |
| Relapse | 0/209 | 1/361 |
| Rebound | 0/209 | 1/361 |
| Treatment experienced | (PEARL-2) | (SAPPHIRE-2, PEARL-2) |
| All | 91/91 (100) | 205/212 (96.7) |
| Prior response (NULL/PARTIAL/RELAPSE) | n=33/27/55 | n=91/55/69 |
| Relapse: | 0/91 | 2/212 |
| Rebound: | 0/91 | 0/212 |
| cirrhotic patients (TURQUOISE-2) | | |
| | 3DAAs + RBV<br>12 weeks | 3DAAs + RBV<br>24 weeks |
| Treatment naïve | | |
| SVR12 | 18/18 (100) | 22/22 (100) |
| Treatment experienced | | |
| SVR12 | 45/46 (97.8) | 33/33 (100) |
| Prior response (NULL/PARTIAL/RELAPSE) | n=25/7/14 | n=20/3/10 |
| Relapse : PARTIAL | 1/46 (prior partial) | 0/22n=3 |

Concerning genotype 1a, the important PEARL-IV study clearly shows the advantage of adding ribavirin to the 3DAA when treating for 12 weeks (and likely also compared to a longer treatment duration, as some

on-treatment virological failure was seen when ribavirin was excluded from the regimen); whereas the SVR rate was 97% with 3DAA+RBV, it was 90% without RBV. These data are supported by results from the AVIATOR study. The numerical difference is somewhat greater in IL28B non C/C genotype, compared to the smaller sample with C/C genotype. Baseline resistance does not clearly identify patients likely to fail without ribavirin; the numerical over-representation of patients with the Q80K variant among failures, however, is noted and should be further discussed.

Based on these data, the company proposes that 3DAA+RBV is the recommended regimen in genotype 1a. This is supported.

**Table 24. Summary on SVR and frequency of relapse/rebound, GT1a-infection, phase 3**

| | | 3 DAAs 12 weeks | 3 DAAs + RBV 12 weeks |
|---|---|---|---|
| non-cirrhotic patients | | | |
| Treatment naive | | (PEARL-4) | (SAPPHIRE-1, PEARL-4) |
| SVR12 All | | 185/205 (90.2) | 404/422 (95.7) |
| IL28 CC | | 61/63 (96.8) | 134/137 (97.8) |
| IL 28 non-CC | | 124/142 (87.3) | 270/285 (94.7) |
| Relapse | | 10/194 (5.2) | 7/420 (1.7) |
| Rebound | | 6/205 (2.9) | 2/422 (0.5) |
| Treatment experienced | | | (SAPPHIRE-2) |
| All | | Not studied | 166/173 (96.0) |
| Prior non-response : NULL | | | 83/87 (95.4) |
| : PARTIAL | | | 36/36 (100) |
| : RELAPSE | | | 47/50 (94.0) |
| Relapse: | | | 5/173 (2.9) |
| Rebound: | | | 0/173 |
| cirrhotic patients (TURQUOISE-2) | | | |
| | | 3DAAs + RBV 12 weeks | 3DAAs + RBV 24 weeks |
| Treatment naïve | | | |
| ALL | SVR12<br>Relapse | 59/64 (92.2)<br>5/64 | 52/56 (92.9)<br>1/56 |
| IL-28 CC | SVR12<br>Relapse | 19/19 (100)<br>0/19 | 15/16 (93.8)<br>0/16 |
| IL-28 non-CC | SVR12<br>Relapse | 40/45 (88.9)<br>5/45 | 37/40 (92.5)<br>1/40 |
| Rebound: | | 0/64 | 0/56 |
| Treatment experienced | | | |
| ALL | SVR12<br>Relapse | 65/76 (85.5)<br>7/76 | 62/65 (95.4)<br>0/65 |
| Prior NULL-response | SVR12<br>Relapse | 40/50 (80.0)<br>7/50 | 39/42 (92.9) |
| Prior Partial response | SVR12<br>Relapse | 11/11 (100)<br>0/11 | 10/10 (100) |
| Prior relapse | SVR12<br>Relapse | 14/15 (93.3)<br>0/15 | 13/13 (100) |
| Rebound: | | 1/76 | 3/65 |

In general rates of virological failure on DAA regimens tend to be somewhat higher in patients with cirrhosis, with 12 weeks of therapy. Furthermore, as more drug pressure is required for maximal efficacy, the differential effect of adding ribavirin may be somewhat greater in such patients. Moreover, there were no cirrhotic patients in the AVIATOR study. Therefore, the TURQUOISE-II study (M13-399) compared 3DAA+RBV for 12 versus 24 weeks in compensated cirrhotic patients with either of the genotype 1 subgenotypes, and with or without treatment experience (peginterferon+ribavirin). Results were again excellent in patients with genotype 1b

infection, with a single relapse among 64 patients treated for 12 weeks (including 46 previously peginterferon+ribavirin treated patients).

For genotype 1a, efficacy was somewhat lower, with 92-93% SVR in treatment naïve patients. In patients with prior peginterferon+ribavirin experience, preselected as a difficult to cure subgroup of a general population, 12 weeks of therapy yielded 85.5% SVR versus 95.5% SVR with 24 weeks. However, it is notable that 10-20% of a treatment naïve genotype 1 population would-be null responders if subjected to peginterferon+ribavirin therapy. Furthermore, a similar trend for 24 weeks is seen in treatment naïve patients with IL28B non C/C genotype (from which null responders are generally selected), as well as in patients with low platelets at baseline, comprising those with most advanced but yet compensated disease.

SVR is considered a clinical imperative in patients with compensated cirrhosis to avoid disease progression with decompensation, which may be imminent. Furthermore, effective retreatment alternatives may not be readily available for cirrhotic patients failing with emergence of resistance to NS3/4A and NS5A inhibitors +/- resistance to dasabuvir.

In the full dataset, the relapse rate among patients with GT1a in the 12 week arm was 11/140 (8%) versus 1/121 (1%) in the 24 week arm. Counting the patient in the 24 week arm with on-treatment breakthrough at day 97 as a “relapse” (as this breakthrough occurred after 12 weeks of therapy), the point estimate would be 2/121 (1.5%).

During the assessment procedure, the applicant proposed different algorithms to identify a subset of GT1a cirrhotic patients for whom 24 weeks of therapy would be indicated, presuming that those not fulfilling criteria might be treated for 12 weeks. These include prior null responder status or, alternatively, having one or more biomarkers of more advanced disease (platelets, alfa-fetoprotein, albumin) with certain cut-offs (see above). Such approaches however, are fraught with uncertainty. Given the similar tolerability of 12 and 24 weeks of therapy (the proportion of patients stopping therapy due to adverse events in the Turquoise study was 4/208 versus 4/172 for the two durations), and the abovementioned uncertainty of the effectiveness of retreatment options, a 24 week course of therapy is considered appropriate for all GT1a patients with compensated cirrhosis. Nevertheless, the CHMP agreed to include the information originating from the post hoc analysis on the risk of relapse in subgroups of GT1a cirrhotics in section 5.1. of the Exviera SmPC.

A further interim analysis has demonstrated high efficacy of 3DAA+RBV in post-transplant patients without advanced fibrosis. Further data from those with more advanced liver disease are eagerly awaited, but not within the approval procedure.

There are no data in patients with decompensated liver disease.

### 2.6.3. Conclusions on the clinical efficacy

Overall 3DAA without ribavirin and 3 DAA+RBV for 12 weeks in non-cirrhotic and cirrhotic patients, respectively, with genotype 1b has demonstrated outstanding efficacy, as has 3DAA+RBV for 12 weeks in non-cirrhotic patients with genotype 1a. In compensated cirrhotic patients with genotype 1a, the relapse rate was higher with 12 compared to 24 weeks. Failure of these regimens is often associated with the selection of dual class resistance, with or without further resistance to dasabuvir; in such cases, appropriate retreatment alternatives may not always be obvious.

Outstanding issues include the appropriate treatment duration in subsets of patients with genotype 1a and compensated cirrhosis, as well as which patients with genotype 1a virus could be suitable for RBV-free therapy if this is needed.

## *2.7. Clinical safety*

The safety database submitted at the time of the application for the 3-DAA regimen contained data from 6 Phase 3 and 2 Phase 2 studies in HCV GT1-infected adult subjects (Phase 3 Studies M11-646, M13-098, M13-099, M13-389, M13-961, and M14-002 and Phase 2 Studies M11-652 and M14-103) that included administration of the 3 DAAs in combination with and without RBV at the proposed doses or higher—ABT-450 150 mg once daily (QD), ritonavir 100 mg QD, ABT-267 25 mg QD, and ABT-333 250 mg twice daily (BID).

In addition, 17 Phase 1 studies that evaluated safety in healthy volunteers who received multiple doses of ABT-450/r + ABT-267 + ABT-333 at the proposed doses or higher of each of the DAAs are included in the provided integrated summary of safety (ISS).

The safety population consisted of the following subjects for each analysis set:

- Placebo-Controlled Analysis Set: all randomized subjects who received at least 1 dose of double-blind study drug in a Phase 3 placebo-controlled study (SAPPHIRE I and –II);
- Regimen-Controlled Analysis Set: all randomized subjects who received at least 1 dose of study drug in a Phase 3 regimen-controlled study (PEARL II, -III and –IV)
- Phase 2 and 3 (All Treated) Analysis Set: all enrolled subjects who received at least 1 dose of active (3-DAA +/-RBV) study drug at the proposed dose or higher in a Phase 2 or 3 study;
- Phase 1 Analysis Set: all healthy volunteers who received multiple doses of the 3-DAA regimen at the proposed dose or higher of each of the DAAs in the regimen in a Phase 1 study. For drug-drug interactions studies, only data from period/days during which the DAAs were administered without the interacting drug were included in the pooled analyses.

Thus 3DAA+RBV was compared with placebo in two randomised phase III trials, whereas 3DAA+RBV was compared with 3DAA in three randomised phase III trials. This allows for some disentanglement of the side effect profile of the 3DAA per se versus that of placebo, through cross study comparison.

**Patient exposure**

A total of 2,632 subjects received at least 1 dose of 3 DAAs ± RBV and were included in the All Treated Analysis Set. The median number of days of treatment for all subjects was 84 days, with greater than 95% of subjects receiving more than 60 days of treatment. The size of the safety database considerably exceeds ICH suggestions.

**Table 25. Duration of Study Drug Exposure (All Treated Analysis Set)**

| Parameter | 3-DAA + RBV (N = 2044) | 3-DAA (N = 588) | Total (N = 2632) |
|---|---|---|---|
| Duration (days) | | | |
| Mean ± SD | 91.3 ± 28.26 | 83.4 ± 6.35 | 89.6 ± 25.30 |
| Median | 84 | 84 | 84 |
| Minimum – maximum | 1 – 171 | 11 – 96 | 1 – 171 |
| Subject-years | 511.4 | 134.4 | 645.9 |
| Duration interval (days), n (%) | | | |
| 1 – 15 | 15 (0.7) | 2 (0.3) | 17 (0.6) |
| 16 – 30 | 5 (0.2) | 1 (0.2) | 6 (0.2) |
| 31 – 60 | 86 (4.2) | 6 (1.0) | 92 (3.5) |
| 61 – 90 | 1711 (83.7) | 578 (98.3) | 2289 (87.0) |
| 91 – 120 | 6 (0.3) | 1 (0.2) | 7 (0.3) |
| 121 – 150 | 3 (0.1) | 0 | 3 (0.1) |
| > 150 | 218 (10.7) | 0 | 218 (8.3) |
| Cumulative duration interval (days), n (%) | | | |
| < 15 | 14 (0.7) | 1 (0.2) | 15 (0.6) |
| ≥ 15 | 2030 (99.3) | 587 (99.8) | 2617 (99.4) |
| ≥ 30 | 2024 (99.0) | 585 (99.5) | 2609 (99.1) |
| ≥ 60 | 1939 (94.9) | 579 (98.5) | 2518 (95.7) |
| ≥ 90 | 228 (11.2) | 2 (0.3) | 230 (8.7) |
| ≥ 120 | 221 (10.8) | 0 | 221 (8.4) |
| ≥ 150 | 218 (10.7) | 0 | 218 (8.3) |

The proposed treatment duration is 84 days in most patients, and 168 days in some compensated cirrhotics.

The majority of subjects in the All Treated Analysis Set were white (90.5% total); 57.3% of all subjects were male and mean age was 51.6 years overall. Overall, a total of 188 (7.1%) subjects were black and 163 (6.2%) subjects were of Hispanic or Latino ethnicity. The majority of subjects participated at sites in the US (45.0%) and European Union (40.7%). The representation of non-white subjects was relatively low, whereas EU representation is considerable.

The majority of subjects were treatment-naïve (68.0%) and had minimal fibrosis (F0 – F1, 59.8%). The proportion of patients with minimal fibrosis is notable; however, the applicant has performed a substantially sized phase III trial dedicated to patients with compensated cirrhosis.

The All Treated Analysis Set included 690 subjects (26.2%) with a history of hypertension, 482 (18.3%) with a past or current history of depression or bipolar disorder, and 169 subjects (6.4%) with a past or current diagnosis of diabetes. The inclusion of a large proportion of patients with prior psychiatric issues is notable, as such medical problems form relative contraindications and often prevent interferon-based therapy.

The all treated analysis set included 385 patients with compensated cirrhosis, 383 of whom were treated with 3DAA+RBV.

### Adverse events

The 3DAA combination of ABT-450(r), ombitasvir and dasabuvir was investigated in combination with ribavirin, in two randomised, placebo controlled phase III trials; furthermore this combination was studied with or without ribavirin in three randomised, controlled trials. Notably, the side effect profile of ribavirin is well understood, and includes primarily haemolytic anaemia, secondary hyperbilirubinaemia, pruritus, rash, dry skin, fatigue, cough and neuropsychiatric side effects such as insomnia and irritability.

**Table 26.Overview of Treatment-Emergent Adverse Events (Placebo-Controlled and Regimen-Controlled Analysis Sets)**

| | Treatment Group, n (%) | | | |
|---|---|---|---|---|
| | Placebo-Controlled Analysis Set | | Regimen-Controlled Analysis Set | |
| Category | 3-DAA + RBV (N = 770) | Placebo (N = 255) | 3-DAA + RBV (N = 401) | 3-DAA (N = 509) |
| Any adverse event | 685 (89.0) | 196 (76.9) | 332 (82.8) | 383 (75.2) |
| Any adverse event with a reasonable possibility of being related to DAA[a] | 564 (73.2) | 145 (56.9) | 248 (61.8) | 276 (54.2) |
| Any adverse event with a reasonable possibility of being related to RBV[a] | 579 (75.2) | 140 (54.9) | 261 (65.1) | 222 (43.6) |
| Any severe adverse event | 27 (3.5) | 1 (0.4) | 4 (1.0) | 6 (1.2) |
| Any grade 3 or 4 adverse event | 30 (3.9) | 2 (0.8) | 12 (3.0) | 10 (2.0) |
| Any serious adverse event (i.e., grade 4) | 16 (2.1) | 1 (0.4) | 9 (2.2) | 7 (1.4) |
| Any adverse event leading to discontinuation of study drug | 6 (0.8) | 1 (0.4) | 2 (0.5) | 2 (0.4) |
| Any adverse event leading to interruption of study drug | 7 (0.9) | 0 | 8 (2.0) | 2 (0.4) |
| Any adverse event leading to RBV dose modifications | 45 (5.8) | 1 (0.4) | 34 (8.5) | 1 (0.2) |
| Any fatal adverse event | 1 (0.1) | 0 | 0 | 0 |
| Deaths, including nontreatment-emergent | 1 (0.1) | 0 | 0 | 0 |

a. As assessed by the investigator.

The frequency of any side effect or any side effect considered reasonably attributable to a DAA was similar in placebo-treated patients and patients treated with 3DAA without ribavirin. The frequency of severe or serious side effects, however, was numerically somewhat higher with 3DAA compared to placebo, though still relatively low (1.4% versus 0.4% for serious AEs). The side effect burden was clearly higher when ribavirin was added to the 3DAAs. Similar to previous observations in other settings, dose modifications of ribavirin (mostly due to anaemia) were not associated with lower efficacy.

In the all-treated analysis set, the frequency of serious adverse events when using the 3DAA regimen with or without ribavirin was 2.5%, the frequency of AEs leading to drug discontinuation was 1%. The all treated analysis set contains one fatal adverse event, discussed further below under the section on hepatic safety.

**Table 27. Treatment-Emergent Adverse Events Reported for ≥ 5.0% of Subjects in Either Treatment Group (Placebo-Controlled Analysis Set)**

| | Treatment Group, n (%) | | |
|---|---|---|---|
| **Preferred Term** | **3-DAA + RBV (N = 770)** | **Placebo (N = 255)** | **Risk Difference (%)[a]** |
| Any adverse event | 685 (89.0) | 196 (76.9) | 12.1 |
| Pruritus | 121 (15.7) | 11 (4.3) | 11.4 |
| Fatigue | 263 (34.2) | 67 (26.3) | 7.9 |
| Nausea | 172 (22.3) | 38 (14.9) | 7.4 |
| Asthenia | 104 (13.5) | 17 (6.7) | 6.8 |
| Insomnia | 108 (14.0) | 19 (7.5) | 6.6 |
| Anaemia | 41 (5.3) | 0 | 5.3 |
| Dry skin | 49 (6.4) | 4 (1.6) | 4.8 |
| Headache | 264 (34.3) | 76 (29.8) | 4.5 |
| Diarrhoea | 104 (13.5) | 23 (9.0) | 4.5 |
| Decreased appetite | 56 (7.3) | 7 (2.7) | 4.5 |
| Dyspnoea | 75 (9.7) | 14 (5.5) | 4.3 |
| Dizziness | 64 (8.3) | 11 (4.3) | 4.0 |
| Rash | 77 (10.0) | 15 (5.9) | 4.1 |
| Cough | 67 (8.7) | 13 (5.1) | 3.6 |
| Vomiting | 44 (5.7) | 6 (2.4) | 3.4 |
| Dyspepsia | 43 (5.6) | 10 (3.9) | 1.7 |
| Abdominal pain upper | 45 (5.8) | 11 (4.3) | 1.5 |
| Nasopharyngitis | 54 (7.0) | 15 (5.9) | 1.1 |
| Irritability | 41 (5.3) | 12 (4.7) | 0.6 |
| Arthralgia | 42 (5.5) | 16 (6.3) | –0.8 |
| Myalg ia | 44 (5.7) | 18 (7.1) | –1.3 |

b. Risk difference was calculated as the percentage of subjects in the 3-DAA + RBV treatment group minus the percentage of subjects in the placebo treatment group.

Notes: Order is by decreasing risk difference.

Fatigue, asthenia, headache, nausea, diarrhoea, pruritus and rash were the most common treatment-emergent adverse events when using 3DAA+RBV. Also, anaemia was only reported among patients treated with 3DAA+RBV, but not with placebo.

The following table compares the frequency of common adverse events when using 3DAA with or without RBV:

**Table 28. Treatment-Emergent Adverse Events Reported for ≥ 5.0% of Subjects in Either Treatment Group (Regimen-Controlled Analysis Set)**

| | Treatment Group, n (%) | | |
|---|---|---|---|
| **Preferred Term** | **3-DAA + RBV (N = 401)** | **3-DAA (N = 509)** | **Risk Difference (%)[a]** |
| Any adverse event | 332 (82.8) | 383 (75.2) | 7.5 |
| Nausea | 63 (15.7) | 43 (8.4) | 7.3 |
| Anaemia | 30 (7.5) | 1 (0.2) | 7.3 |
| Insomnia | 49 (12.2) | 26 (5.1) | 7.1 |
| Pruritus | 48 (12.0) | 31 (6.1) | 5.9 |
| Asthenia | 36 (9.0) | 20 (3.9) | 5.0 |
| Blood bilirubin increased | 21 (5.2) | 2 (0.4) | 4.8 |
| Fatigue | 120 (29.9) | 135 (26.5) | 3.4 |
| Rash | 25 (6.2) | 19 (3.7) | 2.5 |
| Dyspepsia | 22 (5.5) | 17 (3.3) | 2.1 |
| Cough | 27 (6.7) | 24 (4.7) | 2.0 |
| Dizziness | 25 (6.2) | 25 (4.9) | 1.3 |
| Headache | 98 (24.4) | 129 (25.3) | –0.9 |
| Diarrhoea | 35 (8.7) | 58 (11.4) | –2.7 |

c. Risk difference was calculated as the percentage of subjects in the 3-DAA + RBV treatment group minus the percentage of subjects in the 3-DAA treatment group.

Notes: Order is by decreasing risk difference.

Anaemia, insomnia, pruritus, asthenia and increased bilirubin are more common when the 3DAA are used with RBV. All of these side effects have previously been associated with ribavirin use. Also nausea is more commonly reported with RBV than without RBV.

With the relevant caveats of cross study comparison, the following table further informs on the contribution of RBV to the side effects profile of the treatment regimen.

**Table 29. Adverse Drug Reactions (Placebo-Controlled and Regimen-Controlled Analysis Sets)**

| | Placebo-Controlled Analysis Set | | | Regimen-Controlled Analysis Set | | |
|---|---|---|---|---|---|---|
| | Treatment Group, n (%) | | | Treatment Group, n (%) | | |
| Preferred Term | 3-DAA + RBV (N = 770) | Placebo (N = 255) | Risk Difference (%)[a] | 3-DAA + RBV (N = 401) | 3-DAA (N = 509) | Risk Difference (%)[a] |
| Any adverse event | 685 (89.0) | 196 (76.9) | 12.1 | 332 (82.8) | 383 (75.2) | 7.5 |
| Pruritus | 121 (15.7) | 11 (4.3) | 11.4 | 48 (12.0) | 31 (6.1) | 5.9 |
| Fatigue | 263 (34.2) | 67 (26.3) | 7.9 | 120 (29.9) | 135 (26.5) | 3.4 |
| Nausea | 172 (22.3) | 38 (14.9) | 7.4 | 63 (15.7) | 43 (8.4) | 7.3 |
| Asthenia | 104 (13.5) | 17 (6.7) | 6.8 | 36 (9.0) | 20 (3.9) | 5.0 |
| Insomnia | 108 (14.0) | 19 (7.5) | 6.6 | 49 (12.2) | 26 (5.1) | 7.1 |
| Anaemia | 41 (5.3) | 0 | 5.3 | 30 (7.5) | 1 (0.2) | 7.3 |

d. Risk difference was calculated as the percentage of subjects in the 3-DAA + RBV treatment group minus the percentage of subjects in the placebo treatment group (Placebo-Controlled Analysis Set) or as the percentage of subjects in the 3-DAA + RBV treatment group minus the percentage of subjects in the 3-DAA treatment group (Regimen-Controlled Analysis Set).

Note: Order is by decreasing magnitude of risk difference in the Placebo-Controlled Analysis Set.

It may be concluded that on cross study comparison none of these common side effects were clearly numerically more frequently reported with the 3DAA regimen compared to placebo, and that the bulk of the treatment emergent AEs arising from the use of 3DAA+RBV are due to RBV and are also characteristic of the known side effects profile of this compound. Risk differences indicate that the 3DAAs may cause fatigue and pruritus. The latter has been seen with other macrocyclic NS3/4A inhibitors, and may be due to the impact of ABT-450 on biliary transporters such as BSEP.

### Serious adverse event / deaths / other significant events

#### Deaths

Three deaths were reported among subjects in the All Treated Analysis Set. Of the 3 deaths, none was considered related to study drug and 2 were due to non-treatment emergent adverse events.

- Subject 112201 in Study M11-646 (3-DAA + RBV) died during the Post Treatment Period, 221 days after the last dose of study drug, due to treatment-emergent adverse events of non-small cell lung cancer and mediastinal mass that began 15 days after the last dose of study drug.
- Subject 5682 in Study M11-652 (3-DAA) died 67 days after the last dose of study drug due to non-treatment-emergent adverse events of coronary artery stenosis and arteriosclerosis.
- Subject 382123 in Study M13-099 (3-DAA + RBV) had severe lactic acidosis in the setting of metformin use and multi-organ failure in the setting of severe hypotension and lactic acidosis. The subject went on to receive a liver transplant 3 days after the last dose of study drug. The subject died 84 days after the last dose of study drug due to non-treatment emergent adverse events including multi-organ failure and septic shock that began 80 days after the last dose of study drug.

No pattern in the type of adverse events leading to death in the All Treated Analysis Set was observed, and the events are considered unlikely to be causally associated with treatment.

**Serious adverse events**

The overall incidence of treatment-emergent serious adverse events was (0.4% to 2.7% across treatment groups in each analysis set (Table 6 and Table 7).

Of the 65 subjects with treatment-emergent serious adverse events in the All Treated Analysis Set (Table 7), 11 subjects experienced treatment-emergent serious adverse events assessed by the investigator as being related or as having a reasonable possibility of being related to DAA treatment

One subject in the Phase 1 Analysis Set experienced a treatment-emergent serious adverse event. One subject 312 from Study M13-782 experienced a spontaneous abortion during the first 12 weeks of gestation, which was considered by the investigator to be moderate in severity and to have a reasonable possibility of relationship to both DAA and RBV treatment. This subject had a risk factor of advanced maternal age (43 years old).

**Table 30. Subjects with Treatment-Emergent Serious Adverse Events Considered Related to DAA (All Treated Analysis Set)**

| Subject Number (Age/Sex/Race)/Study | Treatment Group (Regimen) | Onset Day[a] | Resolution Day | Preferred Term | Severity | Reason Serious |
|---|---|---|---|---|---|---|
| **Treatment-Emergent Serious Adverse Events in both the Placebo-Controlled and All Treated Analysis Sets** | | | | | | |
| 380301 (63/M/W)/M13-098 | 3-DAA + RBV for 12 weeks | 54 | 59 | Cerebrovascular accident | Severe | HOS |
| 383207 (56/M/W)/M11-646 | 3-DAA + RBV for 12 weeks | 12 | 31 | Acute respiratory failure[b] | Severe | HOS |
| | | 12 | 31 | Hypoxia[b] | Severe | HOS |
| 803211 (46/F/W)/M11-646 | 3-DAA + RBV for 12 weeks | 1 | 2 | Abdominal pain[b] | Severe | HOS, IMP |
| | | 1 | 2 | Chills[b] | Severe | HOS, IMP |
| | | 1 | 2 | Diarrhoea[b] | Severe | HOS, IMP |
| | | 1 | 2 | Nausea[b] | Severe | HOS |
| | | 1 | 2 | Sinus tachycardia[b] | Severe | HOS, IMP |
| | | 1 | 1 | Ventricular extrasystoles[b] | Severe | HOS |
| | | 1 | 2 | Vomiting[b] | Severe | HOS |
| **Treatment-Emergent Serious Adverse Events in both the Regimen-Controlled and All Treated Analysis Sets** | | | | | | |
| 237513 (48/F/W)/M13-961 | 3-DAA for 12 weeks | 73 | ongoing | Arthritis | Moderate | HOS |
| 302403 (19/M/W)/M14-002 | 3-DAA + RBV for 12 weeks | 83 | 98 | Pancreatitis[c] | Moderate | HOS |

| Subject Number (Age/Sex/Race)/Study | Treatment Group (Regimen) | Onset Day[a] | Resolution Day | Preferred Term | Severity | Reason Serious |
|---|---|---|---|---|---|---|
| **Treatment-Emergent Serious Adverse Events in the All Treated Analysis Set Only** | | | | | | |
| 109311 (58/F/B)/M13-098 (open-label part of study) | Placebo for 12 weeks followed by 3-DAA + RBV for 12 weeks | 12 | 12 | Angioedema[b,d] | Mild | HOS |
| 111109 (25/F/W)/M13-099 | 3-DAA + RBV for 12 weeks | 8 | 29 | Hepatitis acute[b] | Severe | IMP |
| 116104 (67/F/B)/M13-099 | 3-DAA + RBV for 24 weeks | 152 | 156 | Anaemia[b] | Severe | HOS, IMP |
| 137103 (61/F/W)/M13-099 | 3-DAA + RBV for 24 weeks | 12 | 19 | Chronic obstructive pulmonary disease[b] | Severe | HOS |
| 382123 (64/F/W)/M13-099 | 3-DAA + RBV for 12 weeks | 5 | 12 | Nausea[b] | Mild | HOS |
| | | 5 | 12 | Vomiting[b] | Mild | HOS |
| | | 9 | 12 | Lactic acidosis[b] | Severe | HOS, LT |
| 403101 (53/M/W)/M13-099 | 3-DAA + RBV for 24 weeks | 156 | 200 | Cellulitis | Severe | HOS, IMP |

B = black; F = female; HOS = hospitalization or prolonged hospitalization; IMP = important medical or surgical intervention; LT = life threatening; M = male; W = white

e. Days shown are relative to first dose of 3-DAA + RBV or 3-DAA.

f. Led to premature discontinuation of study drug.

g. This subject had a history of pancreatitis.

h. This subject had swelling to the left side of the mouth and lip and was treated with diphenhydramine and methylprednisolone. Concomitant medications included lisinopril, which has been associated with angioedema.

Note: A treatment-emergent adverse event was considered related if it was considered possibly or probably related to DAA (Study M11-652 and Study M13-389) or to have a reasonable possibility of relationship to DAA (all other Phase 2 and 3 studies), according to the investigator.

The cases of "acute hepatitis" and lactic acidosis are further discussed below, under the heading of hepatic safety. The other events are of a diverse character and no particular pattern seems to emerge.

### Laboratory findings

Treatment emergent abnormalities in liver function test are specifically discussed within the context of hepatic safety, in the section below.

The following table shows the definitions of some important graded laboratory abnormalities.

**Table 2. Definitions of CTCAE Grades for Selected Laboratory Parameters**

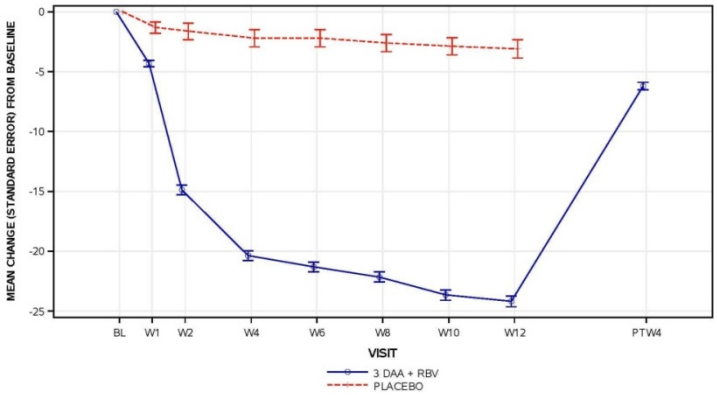
| Test | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| ALT | > ULN – 3 × ULN | > 3 – 5 × ULN | > 5 – 20 × ULN | > 20 × ULN |
| AST | > ULN – 3 × ULN | > 3 – 5 × ULN | > 5 – 20 × ULN | > 20 × ULN |
| Alkaline phosphatase | > ULN – 2.5 × ULN | > 2.5 – 5 × ULN | > 5 – 20 × ULN | > 20 × ULN |
| Total bilirubin | > ULN – 1.5 × ULN | > 1.5 – 3 × ULN | > 3 – 10 × ULN | > 10 × ULN |
| Hemoglobin | < LLN – 100 g/L | < 100 – 80 g/L | < 80 – 65 g/L | < 65 g/L |
| Creatinine clearance | < LLN – 60 mL/min/1.73m$^2$ | < 59 – 30 mL/min/1.73m$^2$ | < 29 – 15 mL/min/1.73m$^2$ | < 15 mL/min/1.73m$^2$ |
| Creatine phosphokinase[a] | > ULN – 2.5 × ULN | > 2.5 – 5 × ULN | > 5 – 10 × ULN | > 10 × ULN |

LLN = lower limit of normal

a. Presented only for the Phase 1 Analysis Set because creatine phosphokinase was not collected in the Phase 2 and 3 studies. Creatine phosphokinase data were collected only in Phase 1 Studies M12-198 and M12-201.

### Haematology

## Mean Change from Baseline in Haemoglobin (g/L) (Placebo-Controlled Analysis Set)




Anaemia is a well-recognized RBV-related toxicity. The magnitude of the mean decrease in haemoglobin seen in the 3DAA+RBV group (compared with placebo, below) is typical of the ribavirin dose used.

The following graph, comparing the impact on haemoglobin of 3DAA+RBV versus 3DAA without ribavirin is indicative that the effect is indeed largely due to RBV, though it may be that the 3DAA (perhaps dasabuvir – see discussion above on dose selection) may provide a very minor contribution to this effect.

## Mean Change from Baseline in Haemoglobin (g/L) (Regimen-Controlled Analysis Set)

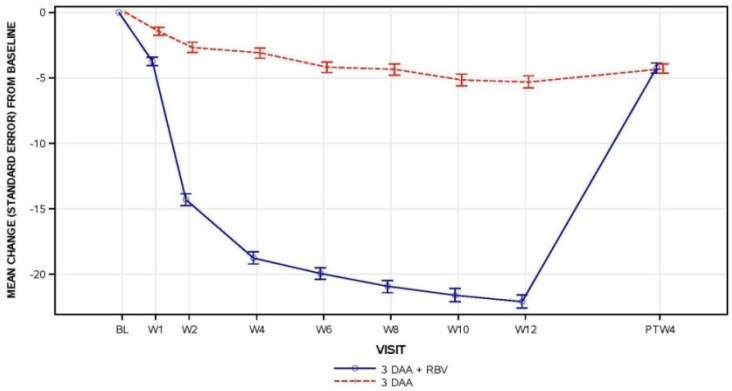



**Table 31. Haemoglobin by Grade During the Treatment Period (Placebo-Controlled and Regimen-Controlled Analysis Sets)**

| | Placebo-Controlled Analysis Set | | Regimen-Controlled Analysis Set | |
|---|---|---|---|---|
| | Treatment Group, n (%) | | | |
| Post baseline Grade | 3-DAA + RBV (N = 765) | Placebo (N = 254) | 3-DAA + RBV (N = 401) | 3-DAA (N = 509) |
| Hemoglobin | | | | |
| Grade 1 (< LLN – 100 g/L) | 377 (49.3) | 6 (2.4) | 209 (52.1) | 34 (6.7) |
| Grade 2 (< 100 – 80 g/L) | 41 (5.4) | 0 | 23 (5.7) | 0 |
| Grade 3 (< 80 – 65 g/L) | 1 (0.1) | 0 | 2 (0.5) | 0 |
| Grade 4 (< 65 g/L) | 0 | 0 | 0 | 0 |
| At least grade 2 | 42 (5.5) | 0 | 25 (6.2) | 0 |

LLN = lower limit of normal

Note: N indicates the number of subjects with a post baseline value. Subjects were counted if the post-baseline haemoglobin value met the criterion regardless of the baseline haemoglobin value.

Four treatment-emergent serious adverse events were reported among these anaemia-related treatment-emergent adverse events. These include 3 subjects who had RBV dose modification (including 1 subject whose nadir haemoglobin was 86 g/L and 1 subject who interrupted study drug) and 3 subjects who had a blood transfusion. The percentage of subjects in the All Treated Analysis Set who received erythropoietin or a blood transfusion was low (< 0.5%). All in all, in terms of anaemia, ribavirin seems roughly similarly tolerated in combination with these DAAs, as seen in other interferon-free studies.

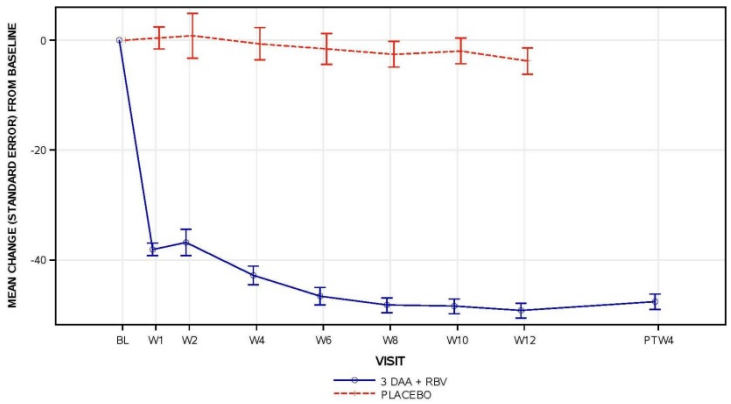
### Clinical chemistry

With the exception of liver function tests, which are further discussed below, the rate of clinically relevant treatment emergent laboratory abnormalities was low. The impact of ribavirin-associated haemolysis on serum bilirubin was apparent – the proportion of patients with bilirubin >2xULN was 12% versus 2% with and without ribavirin.

### 2.7.1. Hepatic safety

As anticipated, in the general case, suppression of HCV replication with direct acting antivirals leads to prompt normalization of ALT due to a reduction of hepatic inflammation. This is demonstrated in the figure below:

**Mean Change from Baseline in ALT (U/L) (Placebo-Controlled Analysis Set)**




However, as discussed above, under the section on dose selection, ABT-450 shows a dose-dependent tendency to cause treatment-emergent increases in transaminases. Furthermore, this drug is an inhibitor of OATP1B1 and –B3. Also, all three DAAs are described as inhibitors of UGT1A1. Therefore, the 3DAA combination is a cause of mechanistic (mainly indirect) hyperbilirubinaemia. This complicates the assessment of potential cases of drug induced liver injury (DILI).

In the Placebo-Controlled Analysis Set, the percentages of subjects (3DAA versus placebo) with at least grade 2 post-baseline ALT values were 2.2% [17/765] versus 16.1% [41/254]) or at least grade 3 (1.2% [9/765] versus 3.9% [10/254]. The higher frequency of low level ALT increases in the placebo group is anticipated, as fluctuating transaminase increases are common in hepatitis C. In general, virological suppression is associated with biochemical response in the form of ALT normalisation.

In the Regimen-Controlled Analysis Set, the percentages of subjects in the 3-DAA + RBV and 3-DAA treatment groups with at least grade 2 (2.0% [8/401] and 1.8% [9/509], respectively) or at least grade 3 (0.7% [3/401] and 0.2% [1/509], respectively) post-baseline ALT values were similar. A similar pattern of results was observed for AST.

In the All Treated Analysis Set, the percentages with at least grade 2 post-baseline ALT values were 2.2% [59/2626]) and at least grade 3 were 1.0% [26/2626]). A similar pattern of results was observed for AST. Six (0.2%) subjects (all 3-DAA + RBV) had a post-baseline grade 4 ALT value. One of these 6 subjects also had a post-baseline grade 4 AST value.

The following table illustrates the relation between ABT-450 dose and ALT increases, as well as the impact of concomitant systemic oestrogen-containing medications:

**Table 32. Summary of Liver Function Test Values by Grade, Oestrogen-Containing Medication Use, and Dose of ABT-450 (Expanded Phase 2 and 3 Analysis Set)**

| | Treatment Group, n (%) | | | | | |
|---|---|---|---|---|---|---|
| | Oestrogen-Containing Medication Use | | | | | |
| | Yes | | | No | | |
| Maximum CTCAE Grade | ABT-450 < 200 mg (N = 103)[a] | ABT-450 ≥ 200mg (N = 9)[a] | Total (N = 112)[a] | ABT-450 < 200 mg (N = 2771)[a] | ABT-450 ≥ 200mg (N = 156)[a] | Total (N = 2927)[a] |
| Post-baseline ALT | | | | | | |
| Grade 1 | 16 (15.5) | 1 (11.1) | 17 (15.2) | 614 (22.2) | 49 (31.4) | 663 (22.7) |
| Grade 2 | 4 (3.9) | 0 | 4 (3.6) | 34 (1.2) | 5 (3.2) | 39 (1.3) |
| Grade 3 | 0 | 1 (11.1) | 1 (0.9) | 21 (0.8) | 6 (3.8) | 27 (0.9) |
| Grade 4 | 5 (4.9) | 1 (11.1) | 6 (5.4) | 1 (< 0.1) | 0 | 1 (< 0.1) |
| At least grade 2 | 9 (8.7) | 2 (22.2) | 11 (9.8) | 56 (2.0) | 11 (7.1) | 67 (2.3) |
| At least grade 3 | 5 (4.9) | 2 (22.2) | 7 (6.3) | 22 (0.8) | 6 (3.8) | 28 (1.0) |

i. Number of subjects with baseline and at least 1 post-baseline value.

Thus, there are two salient aspects of the treatment emergent transaminitis associated with the 3DAA combo. First, as stated above, it is a dose and therefore exposure related side effect of ABT-450. Second, the risk of transaminitis is strikingly increased with concomitant administration of systemic oestrogen-containing medications. Notably, Grade 3 or higher ALT elevations were not observed in subjects receiving progestins only or subjects receiving topical vaginal oestrogen preparations. A logistic regression analysis also identified systemic oestrogen co-medication as a risk factor for grade 3+ ALT increases. Cirrhosis, however, was not identified as a risk factor.

In a further sub analysis, patients on ethinyl oestradiol (rather than other oestrogens such as oestradiol, estriol and conjugated oestrogens) were the driver of the excess transamnitis rates noted above.

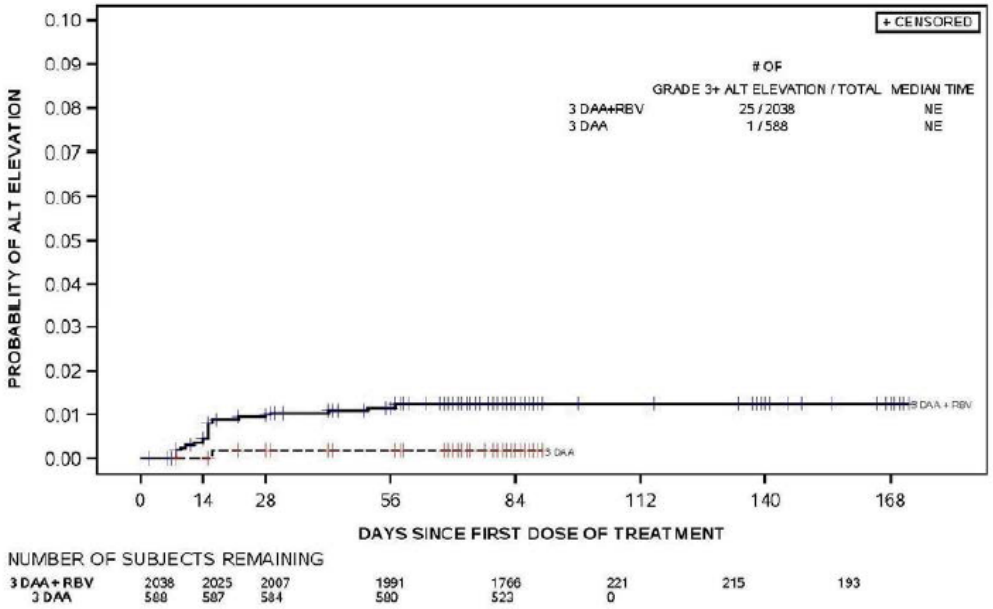
**Table 33. Number and Percentage of Subjects with Maximum Grade 1, 2, 3, or 4 Post-Baseline ALT Grades in EE, Other Estrogen, or Non-Estrogen Users**

| Max Post-Baseline ALT Grade, n (%) | EE N = 23 | Other Estrogens N = 89 | No Estrogen N = 2933 |
|---|---|---|---|
| 1 | 4 (17.4) | 13 (14.6) | 663 (22.7) |
| 2 | 3 (13.0) | 1 (1.1) | 39 (1.3) |
| 3 | 1 (4.3) | 0 | 27 (0.9) |
| 4 | 5 (21.7) | 1 (1.1) | 1 (< 0.1) |
| **At least grade 2** | **9 (39.1)** | **2 (2.2)** | **67 (2.3)** |
| **At least grade 3** | **6 (26.1)** | **1 (1.1)** | **28 (1.0)** |

Non-EE systemic oestrogens were used by 68 patients. Oral oestradiol: 22 Oral conjugated oestrogens: 12. Other oral oestrogens: 6 Depot oestradiol: 2 Transdermal (Oestradiol patch/cream/gel): 26. Vaginal oestrogens were used by 21.

The onset of treatment emergent transaminitis was typically within the first weeks of therapy.

**Figure 9.** **Kaplan-Meier Curve of Time to Onset of Grade 3+ ALT Elevations (All Treated Analysis Set)**




The difference in frequency between those receiving RBV and those that do not, is not significant when systemic oestrogen use is taken into account.

Although the typical signature event observed was an early rise in serum ALT/AST peaking at 2 weeks with subsequent resolution despite continued drug treatment, variations on this theme were observed.

In the phase III studies, the following algorithm was used to manage confirmed ALT increases.

**Table 9.** **Management of Confirmed Transaminase Elevations**

| | |
|---|---|
| ALT ≥ 10 × ULN or<br><br>ALT ≥ 5 × ULN with symptoms and signs of hepatitis present* | Permanently discontinue study drugs. |
| | Complete hepatic questionnaire, update concomitant medications eCRF (if applicable), and obtain appropriate additional testing (e.g., serology for hepatitis A, B, and E, urine for drug screen). |
| | Evaluation and management as medically appropriate. |
| ALT ≥ 5 × ULN but < 10 × ULN without symptoms or signs of hepatitis* | Complete hepatic questionnaire, update concomitant medications eCRF (if applicable), and obtain appropriate additional testing (including serology for hepatitis A, B, and E, urine for drug screen). |
| | Continue study drugs and repeat liver enzymes and INR within 3 days and as clinically indicated until resolution. |
| | If ALT values during follow-up are increased from the prior values, or increasing direct bilirubin, or increasing INR, or symptoms/signs of hepatitis then permanently discontinue study drug. |

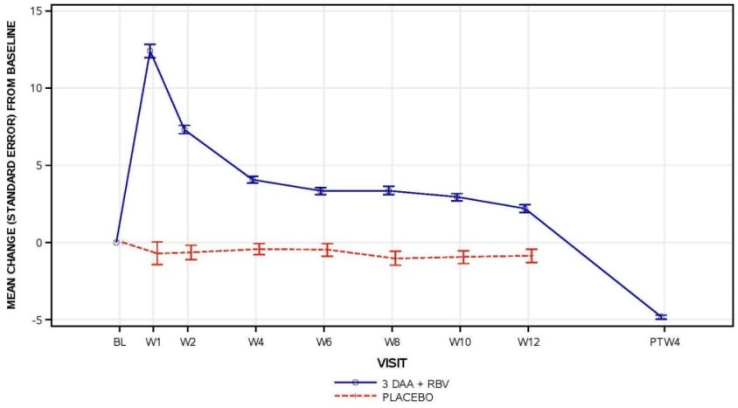
* If another cause is identified based on additional testing, medically manage as appropriate; study drugs may be continued.

In some of the studies this was qualified by a requirement that ALT be >2x baseline.

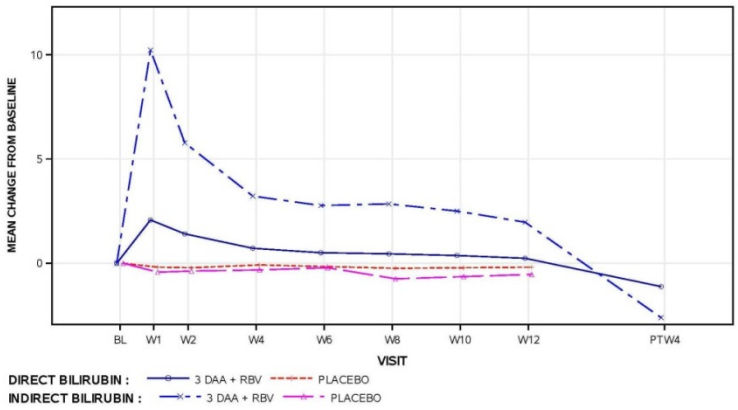
The number of patients discontinuing study therapy due to ALT or transaminase increases was very low – 2/2632 in the all treated analysis set.

The following graphs illustrate the time-course of treatment emergent hyperbilirubinaemia (indirect and direct).

**Figure 1. Mean Change from Baseline in Total, Direct, and Indirect Bilirubin (µmol/L) (Placebo-Controlled Analysis Set)**

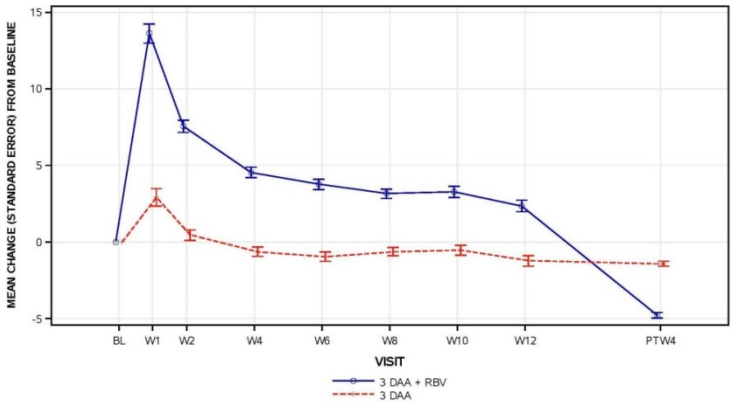



**Total Bilirubin**

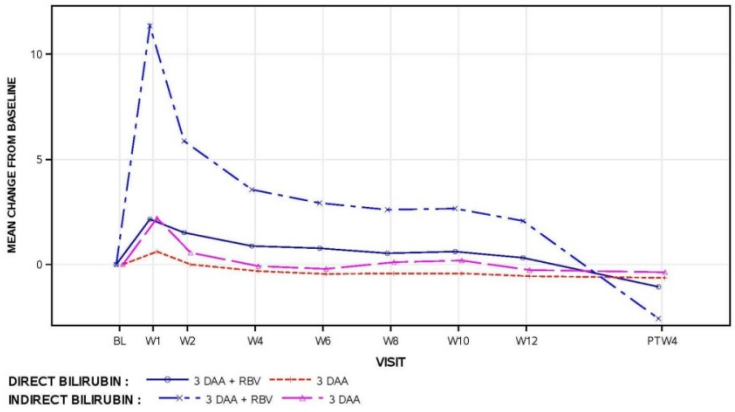



**Direct and Indirect Bilirubin**

**Figure 2. Mean Change from Baseline in Total, Direct, and Indirect Bilirubin (µmol/L) (Regimen-Controlled Analysis Set)**




**Total Bilirubin**




**Direct and Indirect Bilirubin**

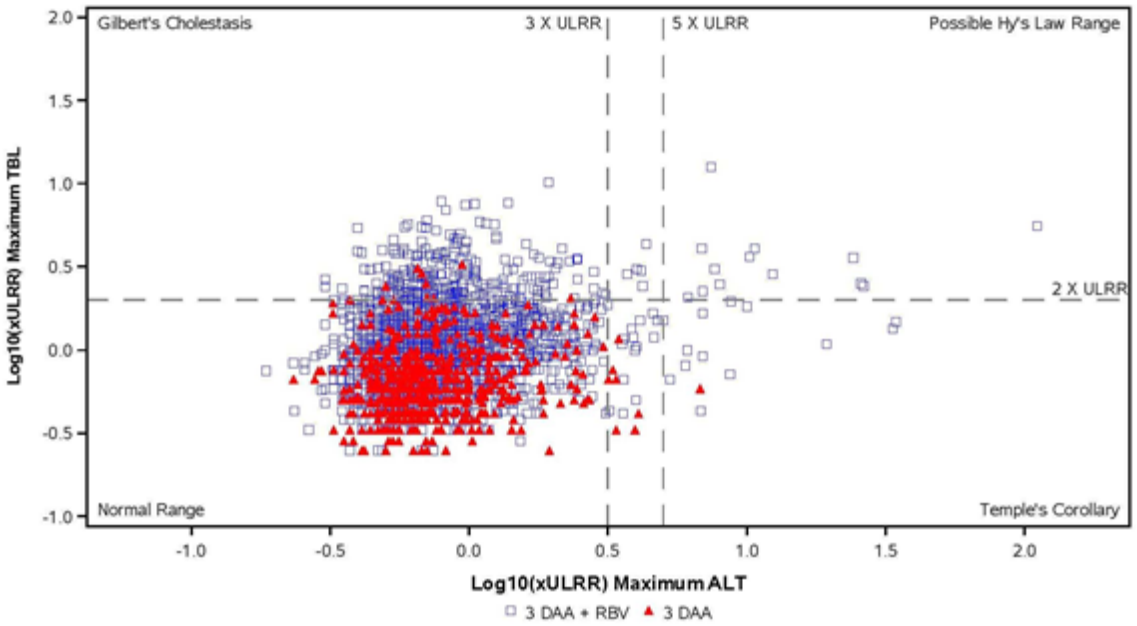
The predominantly indirect hyperbilirubinaemia is apparent, with a maximum occurring at week 1 – that is, typically somewhat earlier than the onset of grade 3+ transaminitis.

The overall incidence of bilirubin-related treatment-emergent adverse events in the All Treated Analysis Set was 3.8%; the incidence of jaundice, ocular icterus, and yellow skin was 1.9%, 0.6%, and 0.1%, respectively. The overall incidence of gallbladder-related treatment-emergent adverse events, including cholecystitis, cholecystitis acute, cholecystitis chronic, and cholelithiasis, in the All Treated Analysis Set was 0.2%.

**Potential Hy's law cases and the company expert adjudication panel**

An "eDISH" representation of subjects who received the 3-DAA regimen, with or without RBV, has been provided for the All Treated Analysis Set. In this, ALT is plotted versus total bilirubin, and patients in the upper right quadrant are identified as possibly fulfilling Hy's law.

**Figure 3. eDISH Plot (All Treated Analysis Set)**




Approximately 1% of patients are found in the Hy's law quadrant. Notably, all were also treated with ribavirin, which causes indirect hyperbilirubinaemia due to haemolysis.

The applicant convened an external hepatic expert panel that was not provided treatment assignment reviewed hepatic laboratory and clinically relevant data from all subjects whose ALT and total bilirubin values were in the Hy's quadrant of the eDISH plot, and any subject with a post-baseline serum ALT > 5 × upper limit of normal (ULN) without a total bilirubin elevation ≥ 2 × ULN (subset of Temple's corollary quadrant). The panel concluded that none of these 32 subjects met criteria for Hy's law, as the elevations in total bilirubin in these cases were temporally inconsistent with Hy's law in that they preceded the peak serum ALT elevations, a result consistent with inhibition of bilirubin transporters by ABT-450 (see above). Moreover, the peak total bilirubin elevations were predominantly indirect bilirubin, a finding inconsistent with Hy's law, and again consistent with inhibition of bilirubin transporters and exacerbation by RBV-induced haemolysis.

Of the 32 subjects evaluated by the external hepatic expert panel, treatment-emergent adverse events led to interruption of study drug in 3 subjects and discontinuation of study drug in 2 subjects. In all cases, serum ALT improved or resolved by end of treatment.

The majority of these 32 subjects completed study drug with ALT levels that had declined from the peak value and that were normal or grade 1 by the Final Treatment Visit or by Post-Treatment Week 4.
Seven of the 32 subjects were taking systemic oestrogen-containing medication and 5 of these subjects also discontinued the hormones. Two of these 5 subjects interrupted the study drug regimen. All 5 subjects had improvement and normalization of ALT. Among the remaining 2 subjects, 1 subject discontinued study drug with return to baseline of serum ALT and 1 subject continued both study drug and the hormonal contraceptive with resolution of serum ALT by Post-Treatment Week 2.

There was one case of on treatment liver failure in the safety database. This was a 64 year old white female with CPT-A cirrhosis, metformin-treated diabetes type II and hypertension. This patient was hospitalised shortly after starting therapy for treatment of oedema of unknown cause. On day 9 after starting therapy the patient experienced circulatory shock and lactic acidosis, which was possibly metformin-related. Subsequently there was multiorgan-failure, including liver failure. In this case it appears that circulatory shock preceded liver failure and a causal relation to 3DAA treatment does not seem likely. During the review procedure, the company was asked for an update on total exposure to paritaprevir and on any serious liver related adverse events. Among a total of 4,589 patients exposed, there were no further on-treatment hepatic failure reported.

**Safety in special populations**

**Sex**

A greater percentage of females versus males had at least 1 post-baseline grade 2 haemoglobin result (10.3% versus 1.8%). The somewhat lower tolerability of ribavirin in women has been seen in other studies also, and is presumably due to lower baseline haemoglobin counts.

The frequency of at least grade 2 ALT elevations was 2.3% in males and 2.1% in females; the frequency of at least grade 3 elevations was 1.1% and 1.2% respectively.

**Age and race**

There were fewer subjects ≥65 years of age (N = 62 for the Placebo-Controlled Analysis Set, N = 87 for the Regimen-Controlled Analysis Set) and fewer black subjects (N = 70 for the Placebo-Controlled Analysis Set, N = 69 for the Regimen-Controlled Analysis Set) compared with subjects < 65 years of age. That stated, within each age group (< 65 years, ≥ 65 years) or each race group (black, non-black), the treatment-group differences in the incidence of treatment-emergent adverse events and the percentage of subjects with haemoglobin and liver function test values by maximum grade were generally consistent with those observed in the overall analysis.

**Cirrhosis**

The most frequent treatment-emergent adverse events were similar to those observed in noncirrhotic subjects. The overall incidence of treatment emergent serious adverse events (5.5%) and treatment emergent adverse events leading to premature discontinuation of study drug was 2.1% and thus somewhat higher than observed in subjects without cirrhosis. There was no commonality evident among these events.

A greater frequency of total bilirubin elevations and anaemia-related events was observed in cirrhotics compared with Phase 3 clinical studies of AbbVie DAAs with RBV in subjects without cirrhosis. This is in line with previous experiences of the use of ribavirin in cirrhotics. No subject discontinued due to symptomatic hyperbilirubinaemia.

Importantly, the safety of ABT-450(r), ombitasvir and dasabuvir in patients with HCV and decompensated cirrhosis (Child-Pugh B and –C) has not been described.

**Post transplant**

The applicant has submitted interim results from the M12-999 study of 3DAA+RBV for 24 weeks in a post-transplant population that do not have advanced fibrosis. Overall safety was as follows.

**Table 8. Overview of Treatment-Emergent Adverse Events (Safety Population)**

| Category | Arm A N = 34 n (%) |
|---|---|
| Any adverse event | 33 (97.1) |
| Any adverse event with a reasonable possibility of being related to DAA[a] | 27 (79.4) |
| Any adverse event with a reasonable possibility of being related to RBV[a] | 28 (82.4) |
| Any severe adverse event | 2 (5.9) |
| Any serious adverse event | 2 (5.9) |
| Any adverse event leading to discontinuation of study drug | 1 (2.9) |
| Any adverse event leading to interruption of study drug | 1 (2.9) |
| Any adverse event leading to RBV dose modifications | 9 (26.5) |
| Any fatal adverse event | 0 |
| Deaths[b] | 0 |

DAA = direct-acting antiviral agent; RBV = ribavirin

a. As assessed by the investigator.

b. Includes nontreatment-emergent deaths.

Anaemia was reported at a higher rate in this post-transplant population than in the general treatment population (20% versus less than 10%). This is anticipated, notwithstanding the lower mean starting dose of ribavirin. The most frequently selected RBV dose range at the initiation of therapy was 600 – 800 mg per day (19/34 subjects; 55.9%). This was also the most common RBV dose at completion of the study regimen (23/34 subjects; 67.6%). Overall, 19 (55.9%) subjects dose modified RBV. No subject received a transfusion. Five subjects received erythropoietin No subject initiating RBV at doses of 800 mg or less per day interrupted RBV for anaemia or required erythropoietin.

CNI levels were monitored closely throughout the study by means of post-dose testing to inform the scheduling of the next dose. No subject had a reported event of rejection. There was no apparent signal of increased hepatotoxicity in this population.

#### *2.7.1.1. HCV/HIV coinfection*

Due to the fact that Exviera is always given in combination with Viekirax, it is relevant to remind that Viekirax contains low dose ritonavir (100 mg qd), which may select for PI resistance in co-infected patients without suppressive antiretroviral therapy. Based on in vitro studies conducted with Viekirax the applicant concluded that that this risk is not relevant. However, since the possibility of bridging from in vitro to in vivo in this particular regard is unclear and in the absence of reassuring in vivo data, the combination of Exviera and ritonavir co-formulated with paritaprevir and ombitasvir should only be given to co-infected patients in the setting of effective antiretroviral therapy.

**Safety related to drug-drug interactions and other interactions**

As described in the section on pharmacokinetics, the drug-drug interaction profile of these ritonavir-boosted combination regimens are very complex. Apart from a considerable range of potentially significant pharmacokinetic drug interactions, two pharmacodynamics interactions have been identified, where the hepatotoxicity of ABT-450, in combination with other agents, appear to be augmented. The drugs implicated are ethinyl estradiol and efavirenz. In the first case, the mechanism is unclear; the same to some extent pertains to the efavirenz interaction, though the applicant argues that this may represent a negative effect of combining ritonavir with a significant inducer, as similar findings as those for efavirenz have been reported in other interaction studies with ritonavir and efavirenz or rifampicin.

Some antiretrovirals are considered acceptable as alternatives for co-treatment, despite the fact that rather substantial exposure effects are seen:

The decrease seen for darunavir exposure (darunavir dosed 800 mg qd) is considered unlikely to affect viral suppression in the absence of extensive PI resistance, during the limited treatment duration in question.

The 2-fold increase in raltegravir exposure is not considered a safety issue, on the basis on what is known for this agent and class. A similar increase in exposure for dolutegravir (not studied) was expected. However, preliminary data suggest a smaller effect on dolutegravir.

Rilpivirine exposure is increased 3-fold, which may have a potential for QT-prolongation. However, a 2-fold increase is deemed safe (seen with rilpivirine in combination with boosted HIV protease inhibitors). Furthermore, in addition to the approved dose of rilpivirine (i.e. 25 mg qd), doses of 75 mg qd and 150 mg qd were studied over 96 weeks in the rilpivirine phase 2 studies, without QTc-problems noted. Therefore, also the combination with rilpivirine is considered acceptable, in the setting of ECG-monitoring.

**Discontinuation due to adverse events**

The overall incidence of treatment-emergent adverse events leading to interruption of study drug was low (0% to 2.0% across treatment groups) in each analysis set. Treatment-emergent adverse events leading to interruption of study drug for at least 2 subjects in the All Treated Analysis Set were diarrhoea, nausea, vomiting, asthenia, fall, alanine aminotransferase increased, and haemoglobin decreased (2 [< 0.1%] subjects each, all 3-DAA + RBV).

Treatment-emergent adverse events leading to RBV dose modification occurred in 6.0% of all subjects in the All Treated Analysis Set. Treatment-emergent adverse events leading to RBV dose modification reported for more than 1.0% of subjects were anaemia (3.3%) and haemoglobin decreased (1.6%).

All in all, this four or five drug combo is very well-tolerated. Transaminase increases are mainly asymptomatic and only prompted treatment discontinuation in two cases. Ribavirin dose reductions were not associated with lower efficacy.

## 2.7.2. Discussion on clinical safety

The primary (“all-treated”) safety database for this application comprises approximately 2600 patients that received at least 1 dose of 3DAAs+/- RBV, and thus exceeds ICH recommendations. The tolerability of this combination is very good, with serious adverse events emerging in approximately 2% of patients treated with

3DAA+RBV and 1.4% in those treated with 3DAA without RBV. Discontinuation rates due to AEs were 0.4% with 3DAA and somewhat higher with 3DAA+RBV.

As for the individual components, ABT-450 has shown an exposure dependent risk of transaminitis, which was considered dose limiting. All in all, in the "all treated" analysis set. 2.2% of patients had at least grade 2 ALT increases and 1% had at least grade 3 increases. Furthermore, ABT-450 is an inhibitor of OATP1B1, -B3 as well as UGT1A1. Therefore, it is a cause of mechanistic hyperbilirubinaemia, which is augmented when given in combination with RBV - exposure to which induces haemolytic anaemia.

As with other NS5A inhibitors, no specific side effects have been associated with ombitasvir.

The development program of dasabuvir indicates that this drug at high exposure may have some negative effect on haemoglobin, and also that it has a dose-dependent, albeit limited, QT-prolonging potential. At the proposed doses, the 3DAA regimen is not anticipated to cause clinically relevant QT prolongation.

As an important part of the rationale to study 3DAA in phase III rather than ABT-450 + ABT-267+RBV, the company considers that the emerging safety profile indicates that dasabuvir is better tolerated than ribavirin. A comparison of symptomatic side effects in the M11-652 (AVIATOR) study, where these two regimens were directly compared, is as follows.

**Table 104. Treatment-Emergent Adverse Events with ≥ 5.0 Percentage Point Difference Between Groups C + D + J and Group E (Study M11-652)**

| | Treatment Group, n (%) | |
|---|---|---|
| Preferred Term | Groups C + D + J (ABT-450/r + ABT-267 + RBV) (N = 124) | Group E (ABT-450/r + ABT-267 + ABT-333) (N = 79) |
| Any adverse event | 113 (91.1) | 68 (86.1) |
| Headache | 38 (30.6) | 15 (19.0) |
| Fatigue | 34 (27.4) | 16 (20.3) |
| Asthenia | 18 (14.5) | 5 (6.3) |
| Cough | 18 (14.5)* | 2 (2.5) |
| Insomnia | 17 (13.7) | 6 (7.6) |
| Pruritus | 14 (11.3) | 3 (3.8) |
| Dyspepsia | 11 (8.9) | 2 (2.5) |
| Myalgia | 10 (8.1) | 2 (2.5) |
| Dry skin | 9 (7.3) | 1 (1.3) |
| Dyspnoea | 8 (6.5) | 1 (1.3) |
| Nasopharyngitis | 6 (4.8) | 8 (10.1) |

* *P* value statistically significant at the 0.05 level based on comparison between groups using Fisher's exact test.

Note: Order is by decreasing frequency in Groups C + D + J.

As anticipated, the incidence of anaemia and hyperbilirubinaemia was higher with ribavirin compared to dasabuvir. Whereas 52.4% of patients on ribavirin had at least a grade 1 decrease in haemoglobin with ribavirin, the same figure with the three DAA was 8.9% Also the frequency of post-baseline at least grade 3 ALT increases was higher with ribavirin - 4.2% versus 0%. Thus, data support the argument of the applicant.

The drug development program as a whole indicates that the 3DAA combination without ribavirin may cause pruritus as a common adverse effect. With the addition of ribavirin, side effects such as anaemia, asthenia, insomnia, rash, dry skin and indirect bilirubinaemia increase in frequency. This is typical of the previously described side effects profile of ribavirin.

Paritaprevir as a component of these regimens is a cause of transaminitis, seen at grade 3 or more in approximately 1% of treated patients. Treatment emergent transaminitis is usually mild and asymptomatic, and is often transient despite treatment continuation; very few patients discontinued therapy due to ALT increases. There is an association of the concomitant use of ethinyl oestradiol-containing drugs and the risk of transaminitis. The risk of at least grade 3 ALT increases was approximately 1% in those not treated with ethinyl oestradiol versus approximately 25% in the somewhat more than 20 patients receiving concomitant therapy. In most cases the ALT increases resolved on continued 3AA therapy, in some cases after discontinuation of the oestrogen. In the phase III studies, a stopping algorithm whereby patients with ALT increases >10xULN or >5xULN if accompanied by signs and symptoms of hepatitis should discontinue antiviral therapy. Only 2 patients were reported to discontinue the 3DAA regimen due to transaminitis. It is notable that stopping therapy would be associated with rebound or relapse with virus resistant to the NS3/4A and/or NS5A classes.

The applicant identified 32 patients either potentially fulfilling Hy's law, or having increases of ALT >5x ULN without fulfilling the bilirubin criteria. In many of these cases, bilirubinaemia is either indirect or clearly precedes ALT increases. There was one on-treatment case of hepatic failure. This has been extensively reviewed and a causal relation with HCV treatment is considered unlikely. Thus, within this drug development program, there is no evidence that paritaprevir or the 3DAA regimen is a causative agent of serious DILI with hepatic failure. This includes a relatively large experience in patients with compensated cirrhosis.

On-treatment monitoring of transaminases is not recommended, as transaminitis is generally transitory with continued therapy, there is no evidence of its development into failure of hepatic function, and there is no information on what level of increase should mandate treatment discontinuation, which may lead to dual or triple class drug resistance with uncertain retreatment options on relapse of previously suppressed virus. The relevant findings on transaminitis and bilirubinemia, however, are described in detail in the product information.

13 out of 23 patients with taking concomitant EE experience on-treatment transaminase increases, while 5 out of 23 patients had grade 4 transaminitis. One patient had grade 4 transaminitis and concomitant nausea, and discontinued under the investigator-reported diagnosis of "acute hepatitis". The concerns raised are supported by findings in a DDI study in healthy volonteers, There two arms with different progestins in combination with EE were discontinued due to transaminase increases. There were no transaminase increases in the progestin only arm. This supports the inference that the interaction is indeed due to the EE component. Progestins when given alone or in combination with other estrogens have not shown the same association. The safety database for concomitant treatment with EE is too small to ascertain acceptable liver safety. If needed, other effective contraceptive measures should be instituted prior to therapy, which is always elective as to its precise timing.

The reasons why a contraindication is preferred to ALT monitoring are the high frequency of grade 3 or more changes, the impossibility of defining an operational cut-off for corrective action (discontinuation of EE or the DAA regimen) and the fact that inadvertent discontinuation of the EE regimen may lead to dual or triple class resistance with unclear retreatment options (see above).

The safety dataset on systemic non-EE oestrogens is considered sufficiently reassuring to support the limitation of the proposed contraindication to ethinyl oestradiol.

ABT-450 exposure is moderately increased in moderate hepatic impairment (62% increase) and increased 9.5-fold in severe hepatic impairment. There are no efficacy and safety data available in these populations. The

applicant proposed that the 3DAA combination should be contraindicated patients with Child-Pugh C, whereas the product information reports that there are no data on efficacy and safety in patients with Child-Pugh B. This is supported.

### 2.7.3. Conclusions on the clinical safety

This triple DAA combination, which also includes ritonavir as a pharmacokinetic enhancer, and furthermore in many cases should be used in combination with ribavirin, has been shown generally well tolerated with low rates of serious adverse events and treatment discontinuations. The drug combination may cause transaminitis and mechanistic hyperbilirubinemia; however an association with progression to serious DILI including hepatic failure has not been established. Due to a high frequency of higher grade transaminitis, the combination with ethinyl oestradiol is contraindicated; forms of effective contraception without this drug must be used when needed. Due to the ritonavir component, there is a high propensity for potentially important drug-drug interactions. This has been extensively addressed in the product information.

## *2.8. Pharmacovigilance*

**Detailed description of the pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

## *2.9. Risk Management Plan*

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 1.2 with the following content:

### *Safety concerns*

| **Summary of Safety Concerns** | |
|---|---|
| Important identified risks | Drug-drug interactions (including based on co-administration with ABT-450/r/ABT-267):<br>– Concomitant use with drugs that are moderate or strong inducers of CYP3A (e.g., carbamazepine, phenytoin, phenobarbital, efavirenz, rifampicin, and St. John's Wort)<br>– Concomitant use with drugs that are moderate or strong inducers of CYP2C8 (e.g., rifampicin)<br>– Concomitant use with drugs that are sensitive CYP3A substrates (e.g., ergotamine, lovastatin and salmeterol)<br>– Concomitant use with drugs that are strong CYP3A4 inhibitors<br>– Concomitant use with drugs that are strong inhibitors of CYP2C8 (e.g., gemfibrozil) |
| | Hepatotoxicity when co-administered with ethinyl estradiol-containing medications |
| Important potential risks | Drug-drug interactions:<br>–Concomitant use with drugs that are primarily metabolized by CYP3A and CYP2C19; drugs that are sensitive substrates of UGT1A1; drugs that are substrates of BCRP, OCT1, OATP1B1/1B3, or P-gp, including antiretroviral regimens that contain ritonavir; or immunosuppressant medications |
| | Hepatotoxicity among non-users of ethinyl estradiol-containing medications |
| | Potential for off-label use including:<br>– use of the DAA regimen in patients with genotypes other than HCV GT1<br>– use in other DAA combinations<br>– use in pediatric patients |
| | Medication errors |
| | Risk of resistance development |
| Important missing information | Safety in patients with hepatic impairment (Child Pugh B) |
| | Safety in patients with renal impairment (creatinine clearance < 60 mL/min) |
| | Safety in post liver transplant patients |
| | Safety in patients co-infected with HIV-1 |
| | Safety in pregnancy in patient using the 3-DAA regimen without RBV |
| | Safety in patients co-infected with HBV |
| | Safety in elderly patients |
| | Safety in patients who have failed prior DAA treatments |

***Pharmacovigilance plan***

| **Study / Activity Type, Title and Category (1 – 3)** | **Objectives** | **Safety Concerns Addressed** | **Status (Planned, Started)** | **Date for Submission of Interim or Final Reports (Planned or Actual)** |
|---|---|---|---|---|
| Study M13-774<br>Study M13-862<br>(Studies comparing 3-DAA + RBV to telaprevir + Peg-IFN and RBV)<br>Category 3 | Assess safety and efficacy of the 3-DAA regimen, comparing 3-DAA + RBV to telaprevir + Peg-IFN and RBV, in treatment-naive and treatment-experienced genotype 1 subjects. | Potential risk of hepatotoxicity | Ongoing | July 2016 |
| Longitudinal cohort safety study in the TARGET registry<br>Voluntary PASS<br>Category 3 | Evaluation of ALT elevations in patients using the 3-DAA AbbVie regimen in real world settings | Potential risks of: hepatotoxicity, off-label use, safety in post liver transplant patients, HIV-1 co-infection, HBV co-infection, elderly patients | Planned;<br>Protocol under development and planned for submission Jan 31, 2015 | To be determined |

| Study / Activity Type, Title and Category (1 – 3) | Objectives | Safety Concerns Addressed | Status (Planned, Started) | Date for Submission of Interim or Final Reports (Planned or Actual) |
|---|---|---|---|---|
| Study M14-222<br>Study M14-423<br>(Long-term efficacy studies with 5-year follow-up)<br>Category 3 | To evaluate the effect of response to treatment (assessed by $SVR_{12}$ status) on the long-term progression of liver disease in adults with chronic HCV GT1 infection who received treatment with ABT-450/r/ABT-267 and ABT-333 with or without RBV, as measured by all-cause death, liver-related death, liver decompensation, liver transplantation, and hepatocellular carcinoma. | Potential risk of hepatotoxicity<br><br>Potential risk of resistance development | Ongoing | 2021 for both studies<br>Yearly interim reports provided in PSURs |
| Study M14-227<br>(Study in Child Pugh B subjects)<br>Category 3 | Evaluate safety and efficacy ($SVR_{12}$) in subjects with Child Pugh B. | Missing information in patients with hepatic impairment | Planned;<br>Protocol final | March 2017 |
| Study M14-226<br>(Study in subjects with renal dysfunction)<br>Category 3 | Evaluate safety and efficacy ($SVR_{12}$) in subjects with CrCl < 60 mL/min | Missing information in patients with renal impairment | Planned;<br>Protocol final | March 2017 |
| Study M12-999<br>(Study in liver transplant patients)<br>Category 3 | Evaluate safety in liver transplant patients | Missing information in post liver transplant patients | Ongoing | To be determined |
| Study M14-004<br>(Study in patients co-infected with HIV-1)<br>Category 3 | Evaluate safety in patients coinfected with HIV-1 | Missing information in patients co-infected with HIV-1 | Ongoing | To be determined |

| Study / Activity Type, Title and Category (1 – 3) | Objectives | Safety Concerns Addressed | Status (Planned, Started) | Date for Submission of Interim or Final Reports (Planned or Actual) |
|---|---|---|---|---|
| Study M13-102<br>(Study to assess resistance and durability of response)<br>Category 3 | Evaluate resistance development in subjects with virologic failure to an AbbVie DAA regimen. | Potential risk of resistance development | Ongoing | October 2017 |
| Study M14-224<br>(Study to evaluate re-treatment of subjects who have failed the 3-DAA regimen)<br>Category 3 | Evaluate safety and efficacy of 3-DAA + sofosbuvir in subjects who have failed treatment with the DAA regimen | -Missing information in patients who have failed prior DAA treatments<br>-Potential risk of resistance development | Under development | To be determined |
| M13-101<br>(Study to evaluate re-treatment of subjects who experienced virologic failure)<br>Category 3 | To re-treat patients who have failed the 3-DAA regimen with a pegIFN-based DAA regimen is ongoing. | -Missing information in patients who have failed prior DAA treatments<br>-Potential risk of resistance development | Ongoing | June 2018 |
| Non-clinical study<br>Category 3 | To investigate interactions with drugs that are BSEP inhibitors, which would be classified as such, based on the EU guidelines; to investigate drug interactions with combined BSEP and MRP inhibitors/relevant genotypes. | Missing nonclinical information for ABT-450 | Being planned | March 2015 |

Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

***Risk minimisation measures***

| Safety Concern | Routine Risk Minimisation Measures | Additional Risk Minimisation Measures |
|---|---|---|
| Identified risk – Drug-drug interactions (including based on co-administration with ABT-450/r/ABT-267):<br>– Concomitant use with drugs that are moderate or strong inducers of CYP3A (e.g., carbamazepine, phenytoin, phenobarbital, efavirenz, rifampicin, and St. John's Wort)<br>– Concomitant use with drugs that are moderate or strong inducers of CYP2C8 (e.g., rifampicin)<br>– Concomitant use with drugs that are sensitive CYP3A substrates (e.g., ergotamine, lovastatin and salmeterol)<br>Concomitant use with drugs that are strong CYP3A4 inhibitors<br>– Concomitant use with drugs that are strong inhibitors of CYP2C8 (e.g., gemfibrozil) | Proposed text in product information:<br>Contraindicated medications and DDIs which require dose adjustments or monitoring will be listed in section 4.3, section 4.4, and section 4.5 of the SmPC.<br><br>Prescription only medicine | None |
| Identified risk – Hepatotoxicity when co-administered with ethinyl estradiol-containing medications | Proposed text in product information:<br>Language concerning elevations in serum ALT and discontinuation of ethinyl estradiol-containing medications will be included in sections 4.3 and 4.4 of the SmPC.<br>The Product Information Leaflet (PIL) will educate patients using the 3-DAA regimen on the common symptoms of hepatitis and the need to self-report to their provider so that treatment decisions can be made in conjunction with his/her health care provider.<br>Prescription only medicine | None |

| Safety Concern | Routine Risk Minimisation Measures | Additional Risk Minimisation Measures |
|---|---|---|
| Potential Risk – Drug-drug interactions<br>– Concomitant use with drugs that are primarily metabolized by CYP3A and CYP2C19; drugs that are sensitive substrates of UGT1A1; drugs that are substrates of BCRP, OCT1, OATP1B1/1B3, or P-gp, including antiretroviral regimens that contain ritonavir; or immunosuppressant medications | Proposed text in product information:<br>Contraindicated medications and DDIs which require dose adjustments or monitoring will be listed in section 4.3, section 4.4, and section 4.5 of the SmPC.<br><br>Prescription only medicine | None |
| Potential risk – Hepatotoxicity among non-users of ethinyl estradiol-containing medications | Proposed text in product information:<br>Language concerning elevations in serum ALT and discontinuation of ethinyl estradiol-containing medications will be included in section 4.4 of the SmPC.<br>The Product Information Leaflet (PIL) will educate patients using the 3-DAA regimen on the common symptoms of hepatitis and the need to self-report to their provider so that treatment decisions can be made in conjunction with his/her health care provider.<br>Prescription only medicine | None |
| Potential risk – Potential for off-label use including:<br>– use of the DAA regimen in patients with genotypes other than HCV GT1<br>– use in other DAA combinations<br>– use in pediatric patients | Proposed text in product information:<br>Section 4.2 of the SmPC will provide guidance on method of administration.<br><br>Prescription only medicine | None |
| Potential risk – Medication errors | Proposed text in product information:<br>Section 4.2 of the SmPC will provide guidance on method of administration. Labeling (immediate and outer packaging) has been designed to minimize medication errors (see Module SVI.4.2).<br><br>Prescription only medicine | None |

| Safety Concern | Routine Risk Minimisation Measures | Additional Risk Minimisation Measures |
|---|---|---|
| Potential risk – Risk of resistance development | Proposed text in product information:<br>Section 4.2 of the SmPC will advise on appropriate dosing and administration to achieve maximal efficacy.<br><br>Prescription only medicine | None |
| Missing information – Safety in patients with hepatic impairment (Child Pugh B) | Proposed text in product information:<br>Section 4.2 and section 4.4 of the SmPC will advise that safety and efficacy have not yet been established in certain populations.<br><br>Prescription only medicine | None |
| Missing information – Safety in patients with renal impairment (creatinine clearance < 60 mL/min) | Proposed text in product information:<br>Section 4.2 and section 4.4 of the SmPC will advise that safety and efficacy have not yet been established in certain populations.<br><br>Prescription only medicine | None |
| Missing information - Safety in post liver transplant patients | Proposed text in product information:<br>Sections 4.4, 4.8 and 5.1 of the SmPC will provide information on currently available data in this population.<br><br>Prescription only medicine | None |
| Missing information - Safety in patients co-infected with HIV-1 | Proposed text in product information:<br>Sections 4.4, 4.8 and 5.1 of the SmPC will provide information on currently available data in this population.<br><br>Prescription only medicine | None |

| Safety Concern | Routine Risk Minimisation Measures | Additional Risk Minimisation Measures |
|---|---|---|
| Missing information – Safety in pregnancy for patients treated with the 3-DAA regimen without RBV | Proposed text in product information:<br>Section 4.6 of the SmPC will provide information with respect to reproductive studies performed in animals.<br><br>Prescription only medicine | None |
| Missing information – Safety in patients co-infected with HBV | Proposed text in product information:<br>Section 4.2 and section 4.4 of the SmPC will advise that safety and efficacy have not yet been established in certain populations.<br><br>Prescription only medicine | None |
| Missing information – Safety in elderly patients | Proposed text in product information:<br>Section 4.4 of the SmPC will inform on the number of subjects ≥ 65 years of age that were included in clinical trials<br><br>Prescription only medicine | None |
| Missing information – Safety in patients who have failed prior DAA treatments | Proposed text in product information:<br>Section 4.4 of the SmPC under Retreatment will state that the efficacy of ABT-333 in patients previously exposed to ABT-333, or to medicinal products anticipated to be cross-resistant, has not been demonstrated.<br><br>Prescription only medicine | None |

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

## *2.10. Product information*

### 2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

# 3. Benefit-Risk Balance

## Benefits

### Beneficial effects

In non-cirrhotic, treatment naive patients with genotype 1a infection, the combination of 3DAA (ritonavir-boosted ABT-450, ombitasvir, dasabuvir) plus ribavirin yielded an SVR (sustained virologic response) rate of 95.7% (404/422) across the SAPPHIRE-I and PEARL-IV studies. In non-cirrhotics, PEGinterferon plus ribavirin experienced patients, the SVR rate was 96% (166/173) (SAPPHIRE-II study). In the PEARL IV study (non-cirrhotic, treatment naïve) 3DAA without RBV gave 90.2% (185/205) SVR rate. Within that study, this was almost 7% higher when RBV was added (SVR rate 97%, 97/100).

In non-cirrhotic, treatment naïve patients with genotype 1b infection, the combination of 3DAA+RBV yielded an SVR rate of 98.9% (357/361) across the SAPPHIRE-I and PEARL-III studies. In non-cirrhotic, pegIFN+RBV experienced patients, the SVR rate was 96.7% (205/212). As opposed to the case with genotype 1a, 3DAA without RBV were shown to be similarly effective as 3DAA with RBV. In the PEARL-II study, the SVR rate with 3DAA was 100% (91/91). This was higher than when RBV was added (96.6%, 85/88). The conclusion that RBV does not add to efficacy in such patients is supported by information from the phase IIb AVIATOR study.

In patients with genotype 1a and compensated cirrhosis (treatment naïve and pegIFN+RBV experienced), 3DAA+RBV for 12 weeks yielded an SVR rate of 88.6% (124/140) (TURQUOISE-II). When treatment was extended to 24 weeks, the SVR rate was 94.2% (114/121). The difference between treatment durations was apparent in subsets of patients classified as prior null responders to pegIFN/RBV, by those with IL28B non C/C genotype and by those with low platelets at baseline.

In contrast to this, when the same regimen (3DAA+RBV) was given for 12 or 24 weeks was given to patients with genotype 1b infection within the same study, there was no apparent impact of treatment duration on the probability of SVR, with 98.5% (67/68, one patient relapsing) SVR with 12 weeks and 100% SVR (51/51) with 24 weeks of therapy.

### Uncertainty in the knowledge about the beneficial effects

It is unclear what precise subsets of patients with compensated cirrhosis and genotype 1a infection would have an equal probability of SVR when given 12 rather than 24 weeks of 3DAA+RBV.

The magnitude of the incremental effect of adding dasabuvir to ABT-450(r) and ombitasvir in genotype 1b is relatively ill defined.

Efficacy in decompensated liver disease has not been studied.

## Risks

### Unfavourable effects

In a total of approximately 2600 subjects receiving at least 1 dose of 3DAA+RBV, the frequency of serious adverse events was 2.5% and the frequency of AEs leading to discontinuation was 1%. Most AEs were consistent with the previously described side effects profile of RBV (anaemia, hyperbilirubinemia, pruritus, rash, insomnia, and asthenia). The 3DAA appear to contribute to pruritus.

Transaminitis has been described as an exposure-dependent AE of ABT-450. The general pattern of ALT normalisation within a few weeks of therapy when HCV replication is suppressed by a potent antiviral regimen, is seen in most treated cases. However, 1% of the treated population experienced an at least grade 3 (≥5xULN) ALT while on treatment. This frequency was higher in patients treated with ethinyl oestradiol-containing medications (6/23, 26%, five of whom had grade 4 transaminitis).

Among those few patients that experienced virological failure, treatment emergent resistance to the NS3/4A + NS5A class was generally seen, and around half the patients showed resistance also to dasabuvir. In the presence of a resistant viral quasispecies that is detectable with population sequencing and is cross-resistant to other agents, impaired retreatment efficacy is anticipated both with the same drug(s) as well as with cross resistant drugs.

#### Uncertainty in the knowledge about the unfavourable effects

The clinical impact of the general emergence of resistance to both the NS3/4A and the NS5A class, as well as in many cases to dasabuvir in case of virological failure is an issue surrounded by considerable uncertainty. As previously reported, there is some degree of reversion of NS3/4A resistance as selection pressure is removed. It is unclear whether retreatment efficacy would still be impaired, e.g., due to “quasispecies memory” after such reversion, as well as the extent of such reversion with time. As previously reported, preselected NS5A resistance does not appear to revert. The potential residual activity of NS5A inhibitors in such patients is not fully characterised.

It is important to consider that in most cases, patients that fail virologically on these very potent regimens are likely to be intrinsically difficult to treat. In such cases, the efficacy of any presently conceivable retreatment regimen is unclear, as the efficacy of other available and investigational NS3/4A and NS5A inhibitors may be compromised. Also, interferons may have poor efficacy or be ill tolerated due to advanced liver disease or significant comorbid conditions. For these reasons, it is difficult to accept submaximal durations or removing RBV from the regimen, if this is anticipated to lower SVR rates or, as in cirrhotics with more advanced disease, be associated with a non-negligible risk of clinical disease progression. Due to these uncertainties, the selection of resistance is considered a major safety concern despite the high efficacy of these combination regimens.

While it is clear that the 3DAA regimen may cause transaminitis (attributable to the paritaprevir component), the extent to which it may be a cause of serious DILI with liver failure is not fully clear. Still, a traditional assessment of Hy’s law is difficult, as patients generally exhibit mechanistic hyperbilirubinaemia. However, it is notable that none of the cases where the 3DAA clearly caused hyperbilirubinaemia and transaminitis progressed to liver failure with signs of hepatic synthesis defects; thus available data, given its limitations, are reassuring.

It is not fully clear whether recommending the stopping algorithm for ALT increases that was used in phase III would be associated with a positive or negative benefit-risk balance. On the one hand, serious DILI might theoretically be prevented, though given that only 2 patients stopped therapy due to ALT and that no definite cases of 3DAA associated, serious DILI with hepatic dysfunction have been documented, this potential benefit remains hypothetical. On the other hand, premature stopping of the antiviral regimen may result in rebound or

relapse with resistance to NS3/4A and NS5A inhibitors. For these reasons, routine transaminase monitoring is not recommended

While it is highly likely that concomitant ethinyl oestradiol potentiates the risk of treatment emergent hepatotoxicity, the mechanism of this finding is unclear; notably, it does not appear to be due to a (plasma) pharmacokinetic interaction. An interaction study with between ABT-450+ritonavir+dasabuvir on the one hand, and efavirenz on the other, was prematurely discontinued due to ALT increases. Available data are not supportive of a pharmacokinetic interaction in this case either. Therefore, there is some lack of clarity on the ability of co-medications to impact the potential hepatotoxicity of the DAA combination.

There are no safety data in patients with HCV and decompensated liver disease.

***Benefit-risk balance***

The overall benefit-risk of Exviera is considered positive by the CHMP.

***Discussion on the benefit-risk balance***

The general efficacy of the proposed regimens is excellent in genotypes 1b. It is also very good in genotype 1a, though RBV is needed and in cirrhotics a prolongation of therapy to 24 weeks is required for optimisation. Furthermore, these regimens are generally very well tolerated, with most symptomatic adverse events being due to RBV. The proposed regimens may cause transaminitis; treatment-induced transaminitis has, however, hitherto not been associated with serious DILI including hepatic failure. When used for the treatment of genotype 1 in patients with compensated liver disease as recommended in the product information, the benefit-risk balance is positive.

# 4. Recommendations

***Outcome***

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Exviera in combination with other medicinal products the treatment of chronic hepatitis C infection in adults is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

***Conditions or restrictions regarding supply and use***

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

***Conditions and requirements of the Marketing Authorisation***

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

***Conditions or restrictions with regard to the safe and effective use of the medicinal product***

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

***New Active Substance Status***

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that dasabuvir (sodium) is qualified as a new active substance.