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20 November 2014
EMA/768346/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Viekirax

International non-proprietary name: ombitasvir / paritaprevir / ritonavir

Procedure No. EMEA/H/C/003839/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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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

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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 Viekirax, 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: Viekirax 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 ombitasvir and paritaprevir were considered to be new active substances.

The INN paritaprevir is currently being reviewed and is subject to approval by WHO. The applicant will inform the EMA of the outcome of the INN approval; the appropriate procedure will be followed should there be a need to amend the INN of the 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/0315/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0315/2013 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.

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New active Substance status

The applicant requested the active substances ombitasvir and paritaprevir contained in the above medicinal product to be considered as new active substances in themselves, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advices from the CHMP from 24 June 2010 to 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 countries: United States of America.

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

1.2. Manufacturers

Manufacturer(s) responsible for batch release

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
GERMANY

1.3. 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. 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 2014 (PRAC RMP Advice and assessment overview, adopted

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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 Viekirax.

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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. The aforementioned approval of sofosbuvir was followed by the approval of other medicinal products for the hepatitis C virus infection. There are numerous further medicinal products 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. Despite the very rapid development of new therapies, including interferon-free regimens, CHMP considered at the time of this application that the unmet medical need for many European patients with hepatitis C infection still persisted.

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:

- paritaprevir (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,

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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.

Viekirax contains ombitasvir, paritaprevir and ritonavir.

2.2. Quality aspects

2.2.1. Introduction

The finished product is a fixed combination immediate release film-coated tablet containing 12.5 mg/75 mg/50 mg of ombitasvir/ paritaprevir/ ritonavir, as active substances respectively per tablet.

Other ingredients are: copovidone, vitamin E polyethylene glycol succinate, propylene glycol monolaurate, sorbitan monolaurate, colloidal anhydrous silica (E551), sodium stearyl fumarate, polyvinyl alcohol (E1203), polyethylene glycol 3350, talc (E553b), titanium dioxide (E171), iron oxide red (E172), as described in section 6.1 of the SmPC.

The product is available in 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

Ombitasvir

General information

The chemical name of the active substance ombitasvir is dimethyl([(2S,5S)-1-(4-tert-butylphenyl)pyrrolidone--2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]}) biscarbamate hydrate, corresponding to the molecular formula $C_{50}H_{67}N_7O_8$ • 4.5 H_2O and has a relative molecular mass 975.20 (hydrate) and 894.11 (anhydrate). It has the following structure:

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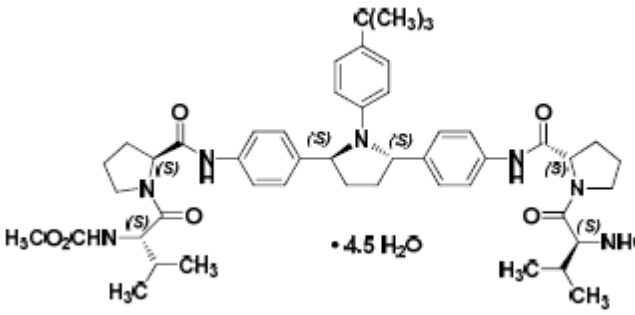

The structure of the active substance has been confirmed by mass spectrometry, infrared spectroscopy, ^{1}H- and ^{13}C-NMR spectroscopy and X-ray crystallography, UV as well as from solid form screening studies (X-ray powder diffraction, DSC, TGA, DVS, microscopy and laser diffraction all of which support the chemical structure.
It appears as a white to light yellow to light pink crystalline powder. It is practically insoluble in 0.1 N HCl pH 1, and sodium phosphate buffer pH 6.8, soluble in ethanol and freely soluble in VP-dimer: VA-dimer. The dissociation constant of ombitasvir was determined to be pKa = 2.5 and its distribution coefficient (n-octanol/pH 7.4) LogD was determined to be 7.4.

Ombitasvir has six chiral centres. Enantiomeric impurity is ensured through starting material specifications and in-process controls. Multiple crystal forms of ombitasvir have been discovered as a result of polymorphic screen studies. Four structurally distinct forms most relevant to ombitasvir development and manufacture have been reported. The active substance is consistently manufactured as Form I.

The active substance is packaged in double plastic bag which complies with the relevant EC regulations and Ph. Eur. requirements.

Manufacture, characterisation and process controls

Ombitasvir is manufactured by a seven-stage process followed by purification and drying. Reprocessing if needed, is foreseen and described. Intermediate products are defined. The proposed five starting materials are also well-defined and considering the overall control strategy over the synthetic process are considered acceptable.

The synthesis has been described in sufficient detail and critical process parameters (CPPs) and in-process controls (IPCs) have been reported and are considered satisfactory. Changes of the synthetic process during development have also been reported in sufficient detail.
The characterisation of the active substance and its impurities are 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. The different stereoisomeric impurities have been described and their origin and fate have been adequately discussed. The various controls either during manufacturing or in the final active substance are considered adequate.

An adequate control strategy for any potential genotoxic impurities and their precursors has been established based on control of material attributes (input materials and intermediates), or downstream process due to their reactivity, or testing at appropriate limits by release specification of ombitasvir active substance as per ICH M7.

Process validation and/or evaluation has been completed and showed that the process, operated within established parameters, can reproducibly produce the active substance meeting its predetermined specifications and quality attributes.

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Specification

The active substance specification includes appropriate tests and limits for: appearance and colour (visual), clarity and colour of solution (Ph. Eur.), identity (IR, HPLC), crystal form (XRPD), assay (HPLC), impurities (HPLC, GC), residual solvents (GC), sulphated ash (Ph. Eur.), water content (Ph. Eur.) and microbiological quality (Ph. Eur.). Impurities, including potential genotoxic ones, and heavy metals are sufficiently controlled either by suitable specification or they are adequately controlled upstream in the process, in which case they are not included in the active substance specification.

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

Batch analysis data for three full scale and six smaller scale batches of ombitasvir manufactured with the proposed process in two different sites and used in clinical, primary stability and process validation were provided. Additional data were provided for five batches manufactured with the slightly different processes used during development were also submitted.

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 three commercial size batches of active substance from a different manufacturer stored in the intended commercial package for up to 12 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, data on four full scale batches from the proposed manufacturer were also provided for under the same long term and accelerated conditions for three months (study ongoing). Stress studies have been performed on one batch at elevated temperature (50 °C/75 % RH and 80 °C, 80 °C/75 % RH respectively), light, UV radiation stress and solution stress (acid, base and peroxide).

The following parameters were tested: description, assay, identification, impurities, water content, crystal form and microbiological quality. The analytical procedures for assay and impurities have been validated and shown to be stability indicating. All results for all parameters at long term and accelerated storage conditions meet the proposed acceptance criteria. Ombitasvir was shown stable to ICH photostability conditions.

Impurities results for the stress stability samples indicated that ombitasvir is potentially susceptible to acid, base, oxidative and UV radiation degradation, but not to heat and/or moisture degradation. The assay results of the stress stability samples were determined for mass balance purposes and there are no significant unaccounted for degradation products.

Paritaprevir

General information

The chemical name of the active substance paritaprevir is (2R,6S,12Z,13aS,14aR,16aS)-N-(Cyclopropylsulfonyl)-6-{[(5-methylpyrazin-2-yl)carbonyl]amino}-5,16-dioxo-2-(phenanthridin-6-yloxy) 1,2,3,6,7,8,9,10,11,13a,14,15,16,-16atetradecahydrocyclopropa[e]pyrrolo[1,2-a][1,4] diazacyclopentadecine-14a(5H)-carboxamide dihydrate, corresponding to the molecular formula $C_{40}H_{43}N_7O_7S \bullet 2H_2O$ and has a relative molecular mass 801.91 (dihydrate) or 765.88 (anhydrous). It has the following structure:

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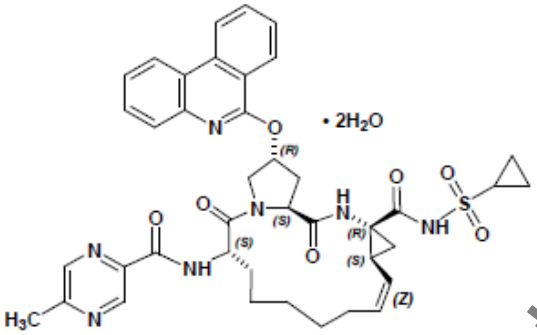

The structure of the active substance has been confirmed by mass spectrometry, infrared spectroscopy, 1H- and 13C-NMR spectroscopy and X-ray crystallography, all of which support the chemical structure.
It appears as a white to off-white crystalline powder. It is practically insoluble in 0.01 N HCl pH 2 and sodium phosphate buffer pH 6.8, slightly soluble in ethanol and freely soluble in VP-dimer: VA-dimer. The dissociation constant of paritaprevir was determined to be pKa = 4.6 and its distribution coefficient (n-octanol/pH 6.8) LogD was determined to be 3.1.
Paritaprevir has five chiral centres and one Z-double bond within the ring structure. Enantiomeric impurity is ensured through starting material specifications and appropriate in-process controls.
Multiple crystal forms of paritaprevir have been discovered. The three structurally distinct forms most relevant for the paritaprevir manufacture were identified. The drug substance is manufactured consistently as Form II.
The active substance is packaged in double polyethylene bags which comply with the relevant EC regulations and Ph. Eur. requirements.

Manufacture, characterisation and process controls

Paritaprevir is manufactured by a six-stage process consisting of nine chemical reactions. The proposed four starting materials also well defined and are considered acceptable taking into account the overall control strategy over the synthetic process. The 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 and in-process controls (IPCs) have been reported and are considered satisfactory.
The chirality of paritaprevir is established in the intermediates and the starting materials. The combination of starting material and intermediate specification, process controls, and the active substance specifications provide the necessary control for stereoisomerism in the paritaprevir active substance.
The characterisation of the active substance and its impurities are 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. There are multiple potential genotoxic impurities (GTIs) that could be formed in the paritaprevir active substance manufacturing process. These GTIs and their precursors are controlled through material attributes (input materials and intermediates), processing conditions, or are tested and controlled in the active substance at release.

Process validation and/or evaluation have been completed showing that the process, operated within established parameters, can produce reproducibly a drug substance meeting its predetermined specifications and quality attributes.

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Specification

The active substance specification includes appropriate tests and limits for: appearance and colour (visual), clarity and colour of solution (Ph. Eur.), identity (IR, HPLC), crystal form (XRPD), assay (HPLC), impurities (HPLC, GC), residual solvents (GC), particle size (laser diffraction), sulphated ash (Ph. Eur.), water content (Ph. Eur.) and microbiological quality (Ph. Eur.).
Impurities, including potential genotoxic ones, are sufficiently controlled either by suitable specification in line with ICH M7 guideline where appropriate.
The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.
Since the chirality of the active substance is controlled by appropriate material specifications, it is considered acceptable not to include a test for the undesired enantiomer in the paritaprevir specification.
Batch analysis results are provided for five full scale batches from the proposed manufacturer according to the commercial manufacturing process. Results for seven other development batches according to the commercial process but manufactured at a different site were also provided. In addition, five more development batches manufactured at the development site according to slightly different processes were provided as well.
All batch analysis results were presented and were compliant with the specifications valid at the time of testing, confirming that the manufacture is sufficiently robust and produces active substance of consistent quality.

Stability

Stability data on four primary stability batches (two commercial and two smaller scale) of active substance stored in the intended commercial package for twelve months under long term conditions at 25 °C/60 % RH and for 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 for a month. The primary stability batches, for which there are available long-term 12 months stability data, were manufactured by the same six-stage process with slight operating differences and slightly different specifications than the current commercial process. Nevertheless, the data from these batches are considered relevant for stability.
Data from another three commercial scale batches from the commercial site and process were also presented for three months under long term conditions at 25 °C/60 % RH and for three months under accelerated conditions at 40 °C/75 % RH.

No meaningful changes were observed on stability. The stability data from the commercial site and process are comparable to the stability data from the primary stability batches. The data generated at 50°C/75% RH support possible temperature excursions during shipping of up to 50°C for 1 month.

Photostability testing following the ICH guideline Q1B was performed on one batch. Paritaprevir was shown to be sensitive to ICH photostability conditions. Additionally, the active substance was exposed to acid, base, oxidation, heat, heat with moisture, metal stress and light (UV light) stress conditions. Paritaprevir was found sensitive to degradation by acid, base, oxidation, heat, and metals, but not to heat and moisture stress.

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

Ritonavir

General information

Ritonavir is a well-known active substance often formulated in combination with other antiretroviral agents for the treatment of HIV infection. Ritonavir is used into various authorised oral dosage forms. The chemical name of the active substance ritonavir is (Thiazol-5-ylmethyl [(1S,2S,4S)-1-benzyl-2-hydroxy

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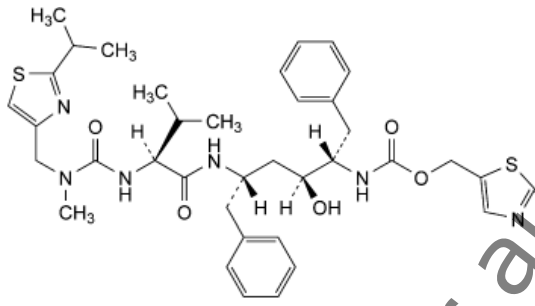
-4-[[(2S)-3-methyl-2-[[methyl[[2-(1-methylethyl)thiazol-4-yl]methyl]carbamoyl]-amino]-butanoyl]-amino]-5-phenylpentyl] carbamate, corresponding to the molecular formula $C_{37}H_{48}N_6O_5S_2$ and has a relative molecular mass 721. It has the following structure:



It appears as a white to almost white crystalline powder. Ritonavir's solubility is pH dependent, it is practically insoluble in water and freely soluble in methanol.

As there is a monograph of ritonavir in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for this active substance. The CEP has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The manufacture of ritonavir is covered by a CEP. Different suppliers are involved in the manufacture of intermediates and respective starting materials. The relevant information has been assessed by the EDQM before issuing the CEP.

Specification

The control tests comply with the specifications and test method of the Ph. Eur. monograph, as confirmed by the CEP. The CEP includes additional control of three additional residual solvents.

Batch analyses data for 27 batches ritonavir produced from different suppliers of the intermediates and respective starting materials and with fresh or recovered solvents. The results and consistent from batch to batch and comply with the specification in all cases.

Stability

The proposed re-test period and packaging material for ritonavir are covered by the CEP.

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2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The objective of the pharmaceutical development was to develop an immediate release film-coated tablet as a fixed combination containing 12.5 mg/ 75 mg /50 mg of ombitasvir, paritaprevir and ritonavir respectively per tablet. The physicochemical properties of the active substances, formulation screening, processing considerations, and the results of biostudies drove the selection of formulation and finished product manufacturing process. Considering that all three active substances are insoluble in aqueous media they are individually converted to amorphous materials in order to enhance their bioavailability via a specific manufacturing process. Each active substance is blended with extrusion excipients and extruded individually into three separate finished product intermediates. These extrudate intermediates (EI) are amorphous solid dispersions of each active substance in polymer/surfactant matrices manufactured by hot melt extrusion (HME). Amorphous solid dispersions are an effective method to improve the oral absorption of poorly soluble drugs. The basis of this improvement is the ability to form and sustain supersaturated solutions of the amorphous drug compared to the crystalline form. Pharmaceutical development was largely focused on the three EIs that comprise Viekirax tablets. The same key design requirements were identified for the three extrudates: bioavailability, manufacturability and storage stability.

Ombitasvir Extrudate Intermediate

An amorphous solid dispersion (SD) approach was employed to increase the low aqueous solubility and bioavailability of ombitasvir. In early development the amorphous solid dispersion formulation was manufactured using solvent based spray drying. However, a solvent free process was preferred for manufacturing amorphous SD and therefore a hot melt extrusion (HME) process was developed. The relative bioavailability of tablets containing ombitasvir SD manufactured by spray drying versus hot melt extrusion was investigated in an *in vivo* study. The results showed that both the C_{max} and AUC from the HME formulation were substantially higher compared to the spray drying formulation.

Ombitasvir undergoing the HME process is converted from Form I to amorphous. Ombitasvir EI has shown no re-crystallisation of during long-term storage, ensuring crystals will not form in the extrudate under normal storage conditions. Epimerisation of the ombitasvir active substance has not been observed on stability. The finished product manufacturing process involves operations that are not expected to induce epimerisation of any of the chiral centres in ombitasvir.

The choice of excipients has been sufficiently justified and their function has been explained.

Paritaprevir Extrudate Intermediate

Paritaprevir exhibits very poor aqueous solubility over the physiological pH range. Therefore a similar approach as for the ombitasvir extrudate was followed. The initial spray dried SD was soon replaced by HME. The relative bioavailability of tablets containing paritaprevir SD manufactured by spray drying versus HME was investigated with co-dosed ritonavir in an *in vivo* study. The results showed that both the C_{max} and AUC from the HME formulation were substantially higher compared to the spray drying formulation. During the extrudate manufacture paritaprevir Form II dehydrates to an amorphous form without residual crystallinity. Accelerated stability studies of the paritaprevir EI have shown no re-crystallisation during long-term storage, ensuring crystals will not form in the extrudate under normal storage conditions. Paritaprevir from two sources was evaluated during the extrudate process development. The particle size distribution (PSD) was found to affect the

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required energy to uniformly distribute the amorphous dehydrated material, therefore relevant PSD limit has been set for the active substance.

Ritonavir Extrudate Intermediate

Solubility studies for ritonavir demonstrated that amorphous ritonavir can form supersaturated solutions with peak solubility values as high as 10-fold greater than those from crystalline ritonavir. Hence this observation led similarly to the development of an SD manufactured by HME as with the other two substances. The same carrier (copovidone) but a different surfactant/plasticiser is employed. The ritonavir EI used in the Viekirax tablets is the same as the one used in commercial ritonavir tablets (Norvir).

The choice and functions of the excipients used in Viekirax tablets have been discussed and justified. All excipients are pharmacopoeial and safe in the proposed concentrations. The oral use of copovidone in the amount contained in the Viekirax tablets is considered safe considering the long-term use of Norvir film-coated tablets containing also the same copovidone-based extrudate with a maximum daily dosage of 12 tablets. The compositions of all the tablet formulations used during product development have been presented. All pivotal clinical studies have been performed with the commercial formulation.

Dissolution Method

The HME formulation releases the active substances through a surface erosion mechanism. The individual EIs gave similar *in vitro* drug release rates as the extrudate surfaces erode. Although the *in vitro* drug release profile of the tablets is slow due to the surface erosion mechanism, the tablets gave *in vivo* performance equivalent to that of known immediate release formulations. The dissolution methods used for single entity paritaprevir, ritonavir and ombitasvir formulations and paritaprevir/ritonavir tablet formulations used in the clinical trials were developed for each respective formulation and were presented. The proposed dissolution method was developed and optimised for the final Viekirax product. Sink conditions were achieved for ombitasvir and paritaprevir. For ritonavir only the maximum kinetic solubility was achieved. Although this value does not meet the compendial definition of sink conditions, it does provide sensitivity to crystalline active substance. No gastrointestinal pH was found where the concurrent solubility of all three substances was adequate in the absence of surfactant, therefore a surfactant, used in previous ritonavir-containing HME products, was added. The medium pH was selected based on the observed in vivo Tmax for each of the three substances. Considering the low solubility of the three substances, the test conditions are acceptable.
It has been demonstrated that the dissolution method is discriminative, vis-à-vis crystalline content in the extrudates and with respect to the surfactants in the extrudate formulations. In combination with controls for the CQAs of the individual extrudates, the proposed dissolution test is suitable as a quality control test for release and stability testing to ensure the *in vivo* performance of the Viekirax film-coated tablets.

A systematic approach was taken to develop the Viekirax tablets formulation and manufacturing process. The quality target product profile (QTPP) was defined as follows: an oral dosage form containing 12.5 mg/ 75 mg /50 mg of ombitasvir, paritaprevir and ritonavir in a fixed dose combination of acceptable appearance, meeting the relevant compendial requirements for this pharmaceutical form, comprised of known excipients and stable in different climatic zones. An initial list of product critical quality attributes (CQAs) was generated based on the QTPP. Subsequently, a systematic evaluation, understanding, and refinement of the manufacturing process were carried out using design of experiments, statistical analysis, simulations, and mathematical models were undertaken to define the relationship of the material attributes and process parameters to the product CQAs. After determining the CQAs, critical process parameters (CPPs), and in-process controls (IPCs), the control strategy was defined to ensure final product quality. A final risk assessment was then completed to demonstrate risks previously identified are mitigated using the proposed control strategy.
The proposed commercial formulation is the same as the one used in all Phase III clinical studies.

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The packaging material of Viekirax is PVC/PE/PCTFE –Alu blister which complies with the relevant EU regulations.

Manufacture of the product and process controls

Because Viekirax film-coated tablets include three different active substances, all of which are individually converted to amorphous via HME, the manufacturing process for the tablets is complex and consists of several unit operations. The individual extrudate intermediates (EI) are prepared separately but are milled and blended together. The manufacturing unit operations developed for Viekirax film-coated tablets are: blending I, extrusion, milling, blending II, tableting, and coating. The critical process parameters and in-process controls have been presented and are justified in relation to how the quality attributes are affected. The designed control strategy ensures that the manufacturing process consistently delivers a drug product that meets the defined criteria for all CQAs. Holding times for the three EI have been established based upon results from appropriately designed studies.

Process validation has been completed for the ombitasvir and paritaprevir EI as well as for the finished tablets film-coated tablets. The process validation for these three materials was completed at the largest claimed batch sizes. The ritonavir EI process has been validated before commercialisation of Norvir. Taking also into account the applicant's and the proposed manufacturer's extensive manufacturing experience with this type of formulations and processes which are also employed for other authorised products such as Kaletra and Norvir it is accepted that this complex process has been overall satisfactorily validated.

In conclusion it is considered that the manufacture is sufficiently robust to provide assurance that the process produces the finished product Viekirax 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 of ombitasvir (HPLC, TLC), identification of paritaprevir (HPLC, TLC), identification of ritonavir (HPLC, TLC), assay of ombitasvir, paritaprevir and ritonavir (HPLC), degradation products (HPLC), uniformity of dosage units (Ph. Eur.), water content (Ph. Eur.), dissolution for ombitasvir, paritaprevir and ritonavir (Ph. Eur.- HPLC) and microbial limits (Ph. Eur).

Genotoxic impurities are controlled via incoming active substances and compendial excipient controls and therefore it is acceptable that the tablets will not be tested for genotoxic impurities. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.

Batch analysis data for one development scale and seven commercial scale batches were presented. All batches are representative of the commercial formula and process. All batches meet the commercial specification limits.

Stability of the product

Primary stability batches of finished Viekirax tablets include three batches of the formulation proposed for marketing. Each of the primary stability batches was manufactured at the proposed site for commercial manufacture of the product, at approximately 30 to 50 % of the largest proposed commercial scale. In these primary stability studies the three used EI have been previously stored from 1-4 months. In further supportive

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stability studies for two batches (one pilot and one 50 % of full scale) of tablets, the three extrudates have been stored for up to 14 months before the tablets' manufacture.

The primary stability batches have been stored for twelve months at 30 °C/75 % RH; and for six months at 40 °C/75 % RH. The two supportive batches have been stored under the same conditions for six months. Parameters tested were description, assay, degradation products, dissolution and water content. At selected intervals the material is also tested for crystallinity and microbial quality. The analytical methods were shown to be stability indicating. No significant changes were observed for any of the tested parameters. In addition to the real time stability data, statistical evaluations (linear model) to predict the stability at the end of the proposed shelf life have been provided and accepted. Temperature excursion (at 5 °C, at 50 °C and -20 °C) and cycling stability (in conditions varying from -20 °C to 30 °C/75 % RH and 50 °C/75 % RH to 30 °C/75 % RH) studies were provided for the same primary stability batches. The samples were tested for description, assay, degradation products, dissolution and water content. The tablet temperature excursion stability data support total temperature excursions of up to 28 days at 40°C and/or up to 28 days at 50°C. The stability data also supports temperature excursions of up to 12 months at 2 to 8 °C and up to 14 days at −20 °C.
Additional stability data include ICH photostability, open dish stability study, and forced degradation stress testing by tablets to oxidation, hydrolytic, and in the solid state, heat, heat and moisture and UV light stress. Tablets are not sensitive to light.
In addition holding times for the three EI have been established based upon results from appropriately designed stability studies.

Based on the presented data and statistical evaluation, the shelf life as stated in the SmPC is acceptable.

Adventitious agents

Viekirax film coated tablets do not contain any excipient or any materials used in the manufacturing process that is of animal and/or human origin.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the three active substances has been presented in a satisfactory manner. The chirality and potential epimerisation of the new active substances ombitasvir and paritaprevir have been sufficiently investigated. Ritonavir complies with the Ph. Eur. specifications. An adequate control strategy in this respect has been set throughout both the active substances and the finished product manufacture. The finished product pharmaceutical development was focused on increasing the bioavailability of the active substances in view of their extremely low aqueous solubility. This was achieved by the choice of excipients in the formulation and via a specific complex manufacturing process which was based on the applicant's previous experience with other ritonavir containing marketed products. The function and choice of excipients in the formulation was sufficiently justified and the manufacturing process adequately validated. A systematic approach was followed to identify the QTPP and subsequently determining the CQAs, critical process parameters (CPPs), in-process controls, thus establishing a control strategy able to ensure final product quality. The development of the dissolution method, appropriate to test the three active substances simultaneously, has been clearly described and is considered suitable as a quality control test to ensure consistent batch to batch in vivo performance of the Viekirax film-coated tablets. 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

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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.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Pharmacology

Primary pharmacology

ABT-450 (paritaprevir) and ABT-267 (ombitasvir) have nanomolar to subnanomolar activity against genotypes 1 and 4) (see further below, section on pharmacodynamics). ABT-450 did not affect human proteases significantly. Low cytotoxicity and low activity against other virus also indicate high selectivity against HCV infected cells. The four most significant metabolites of ABT-267; M23, M29, M36 and M37 were at least 78000-fold less active than ABT-267 against the genotype 1a and 1b replicons in vitro and thus concluded not to be pharmacologically active.

Secondary pharmacology

Receptor screening: ABT-450 gave a weak to moderate effect on the A1, AT1, AT2, CCKB(CCK2), M1 and EP4 receptors and the Na^+ channel (site 2). These effects are not likely to be of clinical significance considering that the in vitro screening was performed at 10 µM and that the reported Cmax plasma level of for ABT-450 is 1.9 µM. The only significant effect (defined as an inhibition higher than 50%) was detected on the δ-opioid receptor δ2 (DOP), where a 77% inhibition was seen at 10 µM, indicating an IC50 < 10 µM. Opioid receptors are targets for both pain and alcohol abuse and are also reported to be involved in immune function and mood. The DOR2-selective antagonist NTB has e.g. been reported to be effective at reducing ethanol consumption in mice (Biol Psychiatry. Oct 15, 2009; 66(8): 777–784.) The possible significance of the effects seen on the δ2-oipioid receptor has not been discussed by the applicant. However, considering the low distribution to the brain and that ABT-450 is a substrate for both MDR-1 (PgP) and BCRP and also have a high plasma protein binding (>95%), an interaction with the δ-opioid receptor δ2 (DOP) is considered to be unlikely. This conclusion is also supported by the absence of any CNS effects in the safety pharmacology and repeat dose toxicology studies performed.

A possible interaction at high plasma levels of metabolites of ABT-267/ombitasvir with P2Y (IC50~10µM), the DA transporter (IC50=3.2 µM) and the Cl- channel (IC50=1.5 µM) was detected in the in vitro pharmacological screen performed, while no significant interactions between ABT-267 and the targets studied were detected. M23 also displaced binding at the A3 (51.9%); BZDperipheral (61.2%); CB1 (55%); D1 (46.3%); MT1 (49%); µ (44.1%); 5HT5a (62.2%); sigma (51.8%); GR (76.8%) receptors and Na^+-channel (53.4%) at 10 µM. However, none of these effects are considered to be clinically relevant based on the low plasma Cmax levels reported for ABT-267 (0.14 µM) and its metabolites. ABT-267, M23, M29, M36 and M37 are reported to be the

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main components in plasma after a single dose of ABT-267 alone, representing about 93% of total plasma radioactivity, 52% of which is contributed to ABT-267 and 33% to the two major metabolites M29 and M36.

The high human plasma protein binding of ABT-450 (97-98.5%) and ABT-267 and its major metabolites (>99% and 98.4-99.3%, respectively) further support the conclusion that the effects seen in the in vitro screens are not likely to be of clinical significance.

Safety pharmacology

CNS: ABT-450 in combination with Ritonavir (15mg/kg) did not give any CNS/neurobehavioral effects in rats at doses up to and including 30 mg/kg. No effects were seen on spontaneous locomotor activity (Activity Meter), Ethanol Interaction Test (sleep induction) or Pro-/Anticonvulsant Effects (Pentylenetetrazole (PTZ) Seizure Tests), while excitatory effects were seen in the Irwin Test at 100 and 300 mg/kg and induced stereotypies, salivation and mydriasis at 300 mg/kg. Neurobehavioral observation (functional observational battery; FOB) did not detect any effects of ABT-450 in combination with Ritonavir (15mg/kg) which did not give any effects in rats at doses up to and including 500 mg /kg, a dose associated with plasma levels of 2.60 ± 1.40 µg/mL ABT-450 at 3 hours and 4.92±2.38 µg/mL at 6 hours.

ABT-267 did not have an effect on locomotor activity in rats at oral doses ≤30mgkg and Neurobehavioral observation in mice (functional observational battery; FOB) did not detect any effects of ABT-267 at doses up to and including 120 mg/kg. (A dose of 120 mg/kg gave plasma Cmax levels of 5.42 µg/mL in another study in mice.)

Cardiovascular: No inhibition of hERG was seen at concentrations up to 7-20 µM (5-18% inhibition). Since Cmax plasma concentrations in the clinic of ABT-450 is reported to be 1.47 µg/mL (~2 µM) an effect on hERG is considered not likely to be of clinical significance, especially if the high protein binding (fu 1.5-3%) is also taken into account. A modest dose-dependent prolongation of the QT-interval was seen in Pentobarbital-anesthetized dogs given 30-minute intravenous infusions of ABT-450 and plasma levels of 2.6 ± 0.3 to 66 ± 4.1 µg/mL. A modest decrease in mean arterial pressure and tachycardia was also seen in a pilot study in anesthetized rats. No effects on blood pressure or any of the ECG parameters (HR, RR, PR, QRS, QT) measured were detected in conscious Beagle dogs at plasma exposures ≤ 96.9 ± 22.5 µg/mL (100 mg/kg).

ABT-267 did not have any effects on hERG in vitro and IC50 was indicated to be higher than 5µM (4.6 µg/mL). In a GLP study the only tested concentration 43 ng/mL was also negative. No cardiovascular effects were detected in anesthetized beagle dogs administrated ABT-267 via intravenous infusion at plasma levels ≤0.483 ± 0.034 µg/mL. In conscious dogs no effects on blood pressure, heart rate, or any of the ECG parameters were detected and there was no indication of QT or QTc prolongation at any of the doses tested with plasma levels up to 2.62 ± 0.351 µg/mL.

Taken together, obtained data thus suggest that neither ABT-450 nor ABT-267 have a potential for adverse QT-effects. This conclusion is also supported by the negative results obtained in a clinical thorough QT study performed using the combination of ABT-450, ritonavir, ABT-267, and ABT-333.

Respiratory: No systematic or substantial changes in the respiratory measures tested (respiratory rate, tidal volume, and minute volume) were detected in conscious Sprague Dawley rats exposed to ABT-450/ritonavir at the maximal plasma exposures achieved (0.7-1.0 µg/mL) which were below or similar to the reported human plasma Cmax level of 1.5 µg/mL.

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ABT-267 did not give any effects on respiratory rate, tidal volume, or minute volume at doses up to 120 mg/kg in mice. (A dose of 120 mg/kg gave plasma Cmax levels of 5.42 µg/mL in mice in another study.)

Gastrointestinal Tolerability: ABT-450 was non-emetic at 7.5 and 25 mg/kg and caused emesis in one in six ferrets at 75 mg/kg (8.15 ± 4.47 µg/mL; at 3h). No effects were seen in GI transit in rats at plasma exposures ≤ 8.15 ± 4.47 µg/mL; at 1.75h.

No GI-effects of ABT-267 were either detected (no dose dependent increased incidence of emesis or nausea in ferrets and no effect on Gi-transit in rats) at doses up to 15 mg/kg.

Ritonavir
Safety pharmacology studies performed with ritonavir in 1993 and 1997 were also included in this submission. These studies are considered to be of limited value and to be superseded by the long clinical experience with co-administration of ritonavir as a pharmacokinetic enhancer.

Pharmacodynamic drug interactions
Checkerboard assays were performed to investigate whether combinations of ABT-450 with IFN-α, ABT-333, ABT-267, ribavirin and ritonavir, or ABT-267 with ribavirin, IFN-α or ABT-333, were additive, synergistic or antagonistic. These combinations demonstrated mostly additive inhibition with occasional synergism or antagonism at low concentrations. Antagonism did not exceed ~15% from additivity. (For the combination of ABT-267 with ribavirin or IFN-α, the magnitude of the deviation was not given.)

Treatment of replicon cells with the combination of ABT-450 and IFN-α for three weeks resulted in greater HCV RNA decline than treatment with ABT-450 alone.

After treatment of replicon cells genotype 1a with the "three-drug combination" (ABT-450 + ABT-267 + ABT-333) for three weeks no colonies or only 1 colony survived. After treatment with two-drug combinations, still resistance associated variants could survive.

2.3.2. Pharmacokinetics

Introductory comment regarding data on ritonavir
ABT-450 is co-dosed with ritonavir, a potent CYP and efflux transport inhibitor in order to mitigate the high first-pass and hepatic elimination. The applicant has therefore included several previously performed pharmacokinetic studies on ritonavir in the dossier in support to the present application. However, the pharmacokinetics of ritonavir is considered to be well known and established knowledge and the pharmacokinetic data on ritonavir per se is therefore not included in the overall conclusions on pharmacokinetics presented below.

Species used
Mouse, rat, rabbit, monkey and dog have been used for pharmacokinetic investigations on ABT-450 (alone and in combination with ritonavir) and ABT-267. Due to low solubility and low bioavailability several studies on the effect of different formulations have been performed.

Absorption
ABT-450 has a moderate apparent permeability in vitro and is indicated to be a substrate for the efflux transporters P-gp (MDR-1) and BCRP. Oral absorption in rats is low, only 15% and increased to 51% when ABT-450 and ritonavir were co-dosed. The improved absorption is likely due to inhibition of both CYP mediated first-pass metabolism and intestinal efflux transporters by ritonavir.

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The ABT-450 pharmacokinetics is characterized by short plasma elimination half-lives after intravenous dosing, which ranged from 0.4 hr in rat and monkey to 1.2 hr in dog. Volumes of distribution were low to moderate in all species, with values ranging from 0.15 L/kg in dog to 0.98 L/kg in rat. Plasma clearance values were high in rat (3.0 L/hr•kg) and monkey (1.9 L/hr•kg), but lower in dog (0.11 L/hr•kg).

ABT-450 oral systemic bioavailability was non-detectable in rat and monkey, and averaged 41% in dog.

ABT-267 has a low to moderate apparent permeability in vitro and data from cells over-expressing MDR-1 or BCRP indicated no or low affinity for efflux transporters. Contrary to in vitro data, in vivo data obtained in Mdr1a/1b/Bcrp KO mice demonstrated an impact of efflux transporters on the overall absorption of ABT-267 in mice, which might indicate a possible species difference and/or an in vitro/in vivo difference in transporter activity. Oral absorption of ABT-267 in rat was low with only 9% of the dose indicated to be absorbed in bile duct cannulated rats.

Plasma clearance values were low in rat (0.46 L/hr•kg) and monkey (0.38 L/hr•kg), and even lower in dog (0.18 L/hr•kg) and mouse (0.11 L/hr•kg). The compound was characterized by moderate to high volumes of distribution (Vss) in all species, with values approximately 1.5 to 1.8 L/kg for mouse, dog and monkey and 4.8 L/kg in rat. The apparent elimination half-life ranged from 4.4 hr in monkey to approximately 11 hr in mouse and rat. Oral bioavailability from a PEG solution formulation ranged from 25% in rat to 57% in dog. ABT-267 plasma concentrations following oral co-dosing with ritonavir in rat, dog and monkey were comparable to those obtained from an equivalent dose of ABT-267 administered alone in each species.

The most favourable lipid/surfactant solution formulations provided AUCs in mice which were 5-10 fold higher than those in rat, leading to the selection of mouse as the preferred rodent species for multiple dose toxicity studies. The PEG-400: Tween 20: Poloxamer 124: Vitamin E TPGS (50:20:10:20, by weight) formulation was selected for repeat dose studies in mouse, rat and rabbit. An alternate formulation (Phosal 53 MCT: PEG-400: Poloxamer 124: Cremophor RH40; 40:20:20:20, by weight), which removed the Vitamin E TPGS while maintaining ABT-267 exposures, was selected for repeat dosing in the teratology and carcinogenicity studies.

Plasma protein binding and blood-plasma ratios

Plasma protein binding of ABT-450 was high at relevant plasma concentrations (0.1-10 µM; compared to the reported Cmax of ~2 µM) with no large species differences seen between mouse, rat, monkey and human (fu ~0.5-1.5 %) and a higher protein binding in dog plasma (fu <0.2 %). No partitioning into the cellular compartment was seen and blood-to-plasma concentration ratios averaged 0.58, 0.68, 0.85 and 1.0 in dog, human, monkey and rat, respectively at 1 µM (0.77 µg/mL).

ABT-267 was highly protein bound, with fraction unbound (fu) values in plasma <0.1 % in all species tested and independent of the 0.1-10 µM concentrations tested (Cmax ~130 ng/mL; ~0.15 µM). No partitioning into the cellular compartment was seen, and blood-to-plasma concentration ratios were between 0.44-0.79 in rat, dog, monkey and human, independent of the 8-400 ng/mL concentrations used.

For both major metabolites of ABT-267, protein binding was independent of concentration in mouse plasma (0.1 to 10 µM), with fu values ranging from 0.7-1 % and 2-3 % for M29 and M36, respectively. In human plasma data indicate a concentration dependent increase in protein binding at concentrations below 1 µM for both M29 and M36, with fu values ranging from 0.2-1.5 and 0.4-2 % for M29 and M36, respectively (with no further increase in fraction unbound in the concentrations ranging from 1-10 µM).

Tissue distribution

ABT-450: After a 30 mg [14C]ABT-450/kg and 15 mg ritonavir/kg oral dose (in oleic acid:PEG-400:Cremophor EL (80:10:10, w:w:w)) a limited distribution of radioactivity to tissues was seen in pigmented male Long-Evans

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rats analysed by Quantitative Whole-Body Autoradiography (QWBA). The liver contained the highest amount of radioactivity between 0.5 to 48 hr post-dose relative to other tissues. Cmax occurred at 4 hr post-dose in most tissues; tissue concentrations declined below quantifiable limits by 24 hr post-dose in all but urine and four tissues (cecum, liver, small intestine and urinary bladder). No preferential binding of radioactivity to eye(s) or non-pigmented skin was seen and only low amounts were detected in pigmented skin and only at 4 hr post-dose. No distribution to brain tissues was seen.

Small amounts of radioactivity were detected in foetal liver at 8 and 12 hr post-dose (600-900 ng-eq/g as compared to 156000 ng-eq/g in maternal liver at 8h and a Cmax in maternal whole blood of 10200 ng-eq/g at 2 hours).

14C-ABT-450-derived radioactivity was excreted in milk obtained from lactating rats for at least 24 hours post dose. Mean milk:plasma concentration ratios were less than one through 12 hours post dose, but steadily increased from 0.173 at 0.5 hours post dose to 0.788 at 12 hours post dose reaching ratios greater than one at 24 hours post dose (mean value of 1.86).

ABT-267: After a 5 mg/kg single oral dose of [14C]ABT-267 (in Phosal 53 MCT:PEG 400:Poloxamer 124:Cremophor RH40 (40:20:20:20 w:w:w:w)), drug derived radioactivity was slowly absorbed and distributed into tissues, with peak concentrations occurring 4-8 hours after dosing. Highest concentrations of radioactivity were found in adrenal gland, liver, pancreas, kidney cortex and stomach mucosa. Concentrations of radioactivity in tissues declined below the limits of quantitation by 168 hr post-dose. [14C]ABT-267-derived radioactivity did not preferentially bind to the melanin-containing tissues and did not distribute into the lens of the eye or CNS tissues. Only low amounts were detected in eye(s) (8 hr post-dose) and no differences between pigmented and non-pigmented skin was seen.

Minimal amounts of radioactivity were detected in the foetal liver tissues at 8 and 12 hrs. post-dose. All other foetal tissues, including foetal blood, and amniotic fluid were devoid of radioactivity throughout the course of this study.

Radioactivity was measurable in milk from lactating rats for at least 24 hours after a single oral gavage dose of 14C-ABT-267. Mean milk:plasma concentration ratios were less than one only at 1 hour post dose and were greater than one at all other collection times, with mean values ranging between 1.62 and 5.17 from 1 through 24 hours post dose.

Metabolism

Metabolic profiles have been investigated both in vitro and in vivo in rat and dog (ABT-450, ABT-267 and Ritonavir), mouse (ABT-450, ABT-267) and rabbit (ABT-267).

ABT-450: Microsomal intrinsic clearance of ABT-450 was relatively high in monkey (94 µL/min/mg) and human (88 µL/min/mg), followed by rat (50 µL/min/mg) and dog (31 µL/min/mg). Similar rank ordering was observed in hepatocytes, with intrinsic clearances of 22.1, 19.3, 8.2 and 3.2 µL/min/L x 10^6 cells in monkey, human, rat and dog, respectively. CYP3A4/5 is primarily responsible for the metabolism of ABT-450.

Metabolite identification showed that CYP-mediated oxidation of ABT-450 occurred on the phenanthridine group, the methylpyrazinyl group, the olefinic linker or combinations thereof. Unchanged parent drug was the major component in human plasma (90.1% of plasma radioactivity). Five minor metabolites were identified (metabolite M2, M3, M6, M13 and M29) and none of the metabolites were greater than 10% of the total radioactivity after administration of ABT-450 and ritonavir. M2 was the major circulating metabolite in human plasma (~23% of total drug) following 900 mg single oral dose of ABT-450, but the level was significantly

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reduced (to ~2.4% of total drug) when ABT-450 was co-dosed with ritonavir (ABT-450/r 300/100 mg). Unchanged parent accounted for the remaining drug-related material in plasma (97.6% of the total).

ABT-267 showed limited hepatic metabolism across species. Microsomal intrinsic clearance values were 1.9, 3.0, 18.4 and 3.4 µL/min/mg in rat, dog, monkey and human, respectively. Similar observations were found in hepatocytes, with intrinsic clearances of 0.11, 0.83, 1.16, and 0.47 µL/min/million cells in rat, dog, monkey and human, respectively. ABT-267 was metabolized to a low extent and at a slow rate by CYP3A4/5 and CYP2C8. In vivo metabolite identification in mouse, rat, rabbit, dog and human showed that ABT 267 is primarily metabolized through enzymatic amide hydrolysis at the aniline amide linker to generate metabolite M6 (monoaniline), M7 (A-1241411; pyrrolidine acid) and M23 (A 1242846; dianiline).

In humans, ABT-267, M23, M29, M36 and M37 are the main components in plasma after a single dose of ABT-267 alone, representing about 93% of total plasma radioactivity, with at least nine additional metabolites observed at either minor or trace levels. M23 is present in preclinical species at higher levels than in humans, providing safety coverage in all toxicology species. M29, M36 and M37 are downstream metabolites of M23, through t-butyl hydroxylation and demethylation, but they have not been observed in studies using animal and human-derived hepatic in vitro systems or in plasma or excreta of in vivo preclinical animals used in ADME or toxicology studies. M29 and M36 were defined as major disproportionate metabolites (i.e. greater than 10% of drug related AUC at steady state) and specific toxicological studies have been performed with these two metabolites. Metabolite M37 is reported to be present in human plasma at a level just below 10% (9.3%) and the possibility that this metabolite might be a major metabolite in some individuals has not been addressed by the applicant. However, based on the absence of pharmacological activity and the results from the toxicological studies with M29 and M36 together with the low levels found in plasma of humans (Cmax 9, 31, 23 and 16 ng/mL and AUC (ng•hr/mL) 194, 669, 442 and 312, for M23, M29, M36 and M37, respectively) and the similarity in structures, especially between M36 and M37 (a desmethyl keto-hydroxy dianiline as compared to a desmethyl di-hydroxy dianiline) any specific safety concerns due to the metabolite M37 as compared to the other major metabolites is considered to be unlikely.

Excretion

Excretion following oral administration of ABT-450/r, ritonavir or ABT-267 has been studied in rat, dog (ABT-450, Ritonavir and ABT-267) and mouse (ABT-267).

Following oral administration of ABT-450/r, ritonavir or ABT-267 to nonclinical species and humans, all compounds and their respective metabolites were mainly cleared via biliary excretion and fecal elimination, with minimal renal clearance. Bile duct cannulated rats treated intravenously with ABT-267 showed a mean recovery of 10.3% of the dose in faeces after 72 hours, indicating that a portion of the dose was secreted into the gut via a non-biliary route. No gender differences were seen in rats.

Following oral administration of [14C]ABT-450/r or [14C]ABT-267 to lactating Sprague Dawley rats, [14C]ABT-450- and [14C]ABT-267-derived radioactivity was excreted in milk. A majority of radioactivity excreted in milk was the ABT-450 hydrolysis product M13 (84.1% of milk radioactivity), followed by unchanged parent drug (15.9%) and the ABT-267-metabolite M19 (5.5%) together with one unidentified component (3.2% of milk radioactivity) and unchanged parent drug (91.2%), respectively.

Relevance of species used in toxicological studies

The choice of nonclinical species is considered acceptable. M29 and M36 were defined as major metabolites and have not been observed in studies using animal and human-derived hepatic in vitro systems or in plasma or excreta of in vivo preclinical animals used in ADME or toxicology studies. Separate toxicological studies have been performed with these two metabolites. Metabolite M37 is reported to be present in human plasma at a level

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just below 10% (9.3% in pooled plasma) and may also be considered to be a major disproportionate metabolite. However, as discussed above no safety concerns due to the metabolite M37 is expected and the lack of specific toxicological studies with this metabolite is considered acceptable.

2.3.3. Toxicology

The toxicological profiles of ABT-267 and ABT-450/r have been evaluated in a comprehensive set of non-clinical studies. Studies on ABT-267 comprise repeat-dose toxicity studies in mice, rats and dogs up to 3 months (rat) and 6 months (mouse, dog). Studies on ABT-450/r comprise repeat-dose toxicity studies in mice, rats and dogs up to 3 months (rat), 6 months (mouse) and 9 months (dog). Both compounds have been evaluated in genotoxicity, reproductive toxicity and carcinogenicity studies (Tg-rasH2 mice, Sprague-Dawley rats). The ABT-267 rat carcinogenicity study is still on-going. No combination genotoxicity, carcinogenicity or reproductive toxicity studies have been conducted. This is in agreement with ICH M3(R2), where it is stated that no such studies generally are recommended if the individual agents have been studied to current standards.

The choice of non-clinical species has been adequately justified. The non-clinical toxicology program has been performed according to relevant guidelines. All pivotal toxicology studies were performed in accordance with GLP.

Single dose toxicity

ABT-267

No single dose toxicity studies were conducted with ABT-267. In accordance with ICH M3 (R2) and EMA/CHMP/SWP/81714/2010, information on acute toxicity can be obtained from other types of studies (e.g. short duration dose ranging studies). A 5-day oral study in Tg-rasH2 non-transgenic mice with doses up to 300 mg/kg has been performed, which is considered sufficient to justify the lack of dedicated single dose studies with this compound. No toxicity was observed; however, the exposure was limited by the poor solubility of ABT-267 (AUC_{0-24} at 300 mg/kg was 43.5 µg·h/mL, corresponding to a 30x margin to human therapeutic exposure).

ABT-450

The acute toxicity of ABT-450 is considered to be low. Single oral doses of ≤600 mg/kg in rats and ≤100 mg/kg in dogs produced no mortality and were well tolerated. However, since ABT-450 was administered without ritonavir as a PK enhancer, the exposures were low, especially in male rats (rat 600 mg/kg, males: C_{max} 1.82 µg/mL, AUC_{0-24} 8.89 µg·h/mL; dog 100 mg/kg, mean: C_{max} 61.3 µg/mL, AUC_{0-24} 285 µg·h/mL).

Repeat dose toxicity

ABT-267

Maximum exposures in the repeat-dose toxicity studies with ABT-267 were limited by the low solubility of the compound in all species tested. This was particularly obvious in the rat, where AUCs at the end of the 3-month study were in the range of 20-35 µg·h/mL, with no differences between the 30 and 300 mg/kg/day treatment groups. In mice, maximum exposures were obtained at approximately 100 mg/kg, with comparable exposures at doses up to the limits of solubility (500 mg/kg). Highest exposure was achieved in Beagle dogs (mean AUC at the end of the 3- and 6-months studies: 83 µg·h/mL (margin to exposure at RHD: 58x).

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With the exception of adverse liver findings in a non-GLP 14-day mouse study, no dose-limiting toxicity was identified in the ABT-267 repeat-dose toxicity studies. A number of non-adverse findings were observed, as described below. No evaluation of recovery was performed in the 3- and 6-month dog studies. In view of the non-adverse nature of the findings this is considered acceptable.

Liver

Single cell hepatocellular necrosis and increased ALT, AST and GLDH were observed in a 14-day non-GLP study in mice. These effects on the liver were not observed in pivotal studies up to 6 months with higher doses; however, the exposure was not as high in the long-term studies. AUC_{0-24} on Day 1 in high-dose males in the 14-day study was 127.3 µg·h/mL, to be compared with the AUCs obtained at the high dose level in the 3- and 6-month studies (Day 1 values in males ranging from 28.4 to 69.7 µg·h/mL). The margin between predicted human exposure and the estimated exposure at NOAEL (3.8 µg·h/mL) in the 14-day study is 2.7x.

A few non-adverse liver findings related to treatment with ABT-267 were present in the dog studies. Increased liver weights were observed in females at 100 mg/kg (6-month study), and in one female in the 3-month study. In this dog, but not in the others, the liver weight change was associated with mild hepatocellular vacuolation. The margin to this latter finding, based on predicted human exposure (AUC) is at least 58x.

Increased ALT (1.3-4x) was observed in individual animals at 60 mg/kg (14-day non-GLP study), 2 mg/kg (3-month study) and 4 mg/kg (6 month study). Since there was no dose response correlation in the longer term studies, the relationship to treatment with ABT-267 is considered equivocal.

Intestine

Dogs administered 100 mg/kg showed dilatation of lymphoid vessels in the jejunum (3-month study) and vacuolation in the duodenum and jejunum (6-month study). Both changes were minimal to mild, and since there was no obvious effect on function they are not considered to be adverse.

Haematology and coagulation

Alterations of red blood cell parameters (decreased RBC, haemoglobin and haematocrit) were present in one female high dose dog (3-month study) and in females at > 20 mg/kg in the 6-month study. Decreased haemoglobin was also present in males at 100 mg/kg in the 6-month study. In addition, males at > 20 mg/kg showed increased platelets and at 100 mg/kg there was a decrease in APTT in males in the 6-month study. In the absence of other findings, none of the haematological changes are considered to be adverse.

Female reproductive system

Non-adverse effects on female reproductive organs (vaginal mucification, increased incidence of ovarian follicular cysts) were observed at the high dose level in the 3-month mouse study. The margin to predicted human exposure (AUC) is x26 (females). This effect was not reproducible in the 6-month study, despite similar exposure.

Body weight

Conflicting effects on body weight were noted in mice. While statistically significant body weight increase, associated with increased food consumption, was present in females at $\geq$ 40 mg/kg (3-month study), slightly lower body weight in females occurred at all dose levels in the 6 month study. None of the observed body weight changes are considered to be adverse.

In conclusion, oral administration of ABT-267 for up to 3 months in rats, and 6 months in mice and dogs, resulted in no dose-limiting effects, at saturating systemic exposures. The only toxicity observed was single cell hepatocellular necrosis and increased liver enzymes in a non-GLP 14-day mouse study (estimated margin to

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NOAEL: 2.7x). Non-adverse effects in the repeat dose toxicity studies comprised lymph vessel dilatation and vacuolation in the small intestine (dog), vaginal mucification and increased ovarian follicular cysts (mouse), increased liver weights with or without correlation to hepatocellular vacuolation (dog), changes in body weight (mouse) and alterations in red blood cell and coagulation parameters (dog). Overall, the margin to predicted human exposure associated with a 25 mg daily dose (1.42 µg·h/mL) and NOAELs in the ABT-267 repeat-dose toxicity studies are in the range of 20-50x.

ABT-450

All repeat dose toxicity studies with ABT-450 were conducted utilizing ritonavir as a pharmacokinetic enhancer. Different dosages of ritonavir were used for the various species, in order to achieve maximal feasible exposure of ABT-450. Effects attributable to ritonavir are described separately.

Gallbladder

Minimal to moderate focal erosion/ulceration, chronic active inflammation, epithelial hypertrophy/hyperplasia and diffuse acute inflammation were observed at ≥ 100/30 mg/kg in the 6-month mouse study. The gallbladder changes are considered to be the result of ABT-450 administration, as they have not been identified in previous studies with ritonavir and were not present at the low dose of 30/30 mg/kg, which had the highest ritonavir exposure. The finding of increased neutrophils in females at 300/30 mg/kg is probably linked to the gallbladder inflammation. The margin to predicted human exposure associated with a 150 mg daily dose (7 µg·h/mL) and the NOAEL is 3.7-5.8x (mean 4.8x). The gallbladder changes were partially resolved in mice after 1 month recovery.

In dogs, minimal to mild oedema, mononuclear/mixed cell infiltration, degeneration, necrosis and increased mitoses were observed to varying extent in the gallbladder in all repeat-dose toxicity studies > 1 month duration. Since degeneration and necrosis are considered to be adverse effects, even when present to minimal degree, the Applicant's proposed NOAELs for these findings are not agreed with. At a more appropriate lower NOAEL for these findings (10/5 mg/kg), the corresponding mean AUCs are in the range of 206-615 µg·h/mL (margin to RHD: 29-87x). The findings were fully reversible after 1 month recovery. Increased ALP in the 1-, 3- and 9-months studies is probably related to the gallbladder effects, since there was no increase in other liver enzymes and (apart from mild non-adverse findings in the 9-month study) no effects on liver morphology.

The mechanism behind the observed gallbladder findings is not known, but may conceivably be related to the high biliary excretion of ABT-450 with associated high local concentrations in the gallbladder. Review of the 3DAA Phase 2/3 data set revealed no evidence of treatment-related gallbladder disorders in humans. Thus, the non-clinical gallbladder findings appear not to be readily translatable to the clinical situation.

Intestine

Minimal to moderate vacuolation was observed in the lamina propria of the duodenum and jejunum of dogs treated at 20/10 or 80/20 mg/kg ABT-450/r for 9 months. The vacuoles were shown to contain fat, as demonstrated by positive Oil Red staining. There was no reversibility of this finding after 1 month recovery.

Liver and kidney

Mild diffuse intrasinusoidal vacuolation was observed in the liver in dogs at 80/20 mg/kg in the 9-month study. It is not clear which cell type was affected, and there was no attempt to determine the nature of the vacuoles. In the kidney, minimal to mild vacuolation of the tubular epithelium was observed at 80/20 mg/kg in the 9-month dog study. No special staining was performed to further characterize the vacuoles. Neither the liver nor kidney findings were reversible after 1 month recovery.

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Since the clinical exposure margins to the findings in the intestine, liver and kidney in the dog 9-month study are high (88-212x based on AUC), they are not considered to be of relevance in the clinical situation.

Food consumption
Increased food consumption, sometimes correlated with increased body weight, was observed in the 3- and 6-months mouse studies, as well as in the 1-month non-transgenic Tg-rasH2 study. The LOEL was 30/30 mg/kg, corresponding to an AUC (females) of 38.8 (5.5x margin to RHD). These effects are not considered adverse.

Findings of equivocal relationship to ABT-450
Changes in *coagulation parameters* were observed in dogs (decreased APTT in the 1-, 3- and 9-month studies, increased platelets and decreased mean platelet volume in the 9-month study). Although decreased APTT was observed in the original ritonavir 6-month dog study, this effect was not seen consistently in the ritonavir dog studies. Since decreased APTT showed a tendency toward dose response in the ABT-450/r dog studies, a relationship to treatment cannot be excluded. The margin at RHD to LOEL in the 3-month dog study is in the range of 6x. In the absence of other findings, these effects on coagulation parameters are considered non-adverse.

Increased bilirubin was observed in females at $\geq$ 30/30 mg/kg in the 3-month mouse study, and in females at 300/30 mg/kg in the 6-month mouse study. It is possible that this finding could be related to ritonavir; however, increases in bilirubin in the original 3-month ritonavir mouse study occurred at considerably higher exposure levels (16x based on AUC) as compared with the exposures in the ABT-450/r mouse studies. Since ABT-450 is a known inhibitor of OATP1B1 and OATP1B3 transporters, it cannot be excluded that the increased bilirubin in the ABT-450/r mouse studies is related to this mechanism. This effect is not considered adverse.

Alterations in *serum chemistry parameters* in CD-1mice (decreased total protein, albumin and globulin in females at 300/100 mg/kg and decreased globulin in males at 100/100 mg/kg) were observed in the 1-month study. Minimally decreased albumin and protein in males were observed in the 6-month mouse study, at $\geq$ 30/30 mg/kg and 300/30 mg/kg, respectively. There was also a slight increase in chloride in males at all dose levels in this study. Similar findings have not been reported for ritonavir in mice. However, since there was no clear dose response relationship, the relationship to treatment with ABT-450 is considered questionable. None of the observed serum chemistry changes is considered adverse.

Other findings
High pre-terminal mortality was noted in the ABT-450/r mouse studies. In general, this was associated with gavage error/aspiration. Although it was not possible to determine the cause of death in some cases, it is well known that mice are more sensitive than rats to handling, and there is usually higher mortality in mouse studies as compared with rat studies. There are no indications that the observed mortality was related to ABT-450/r treatment.

Decreased thymus and pituitary gland weights were observed in dogs in one of the 1-month studies. Since there was no correlation with microscopic findings and the organ weight changes were not present in the other 1-month study at comparable exposure levels, or in the 3- and 9-months studies, they are considered of no toxicological relevance.

Changes in serum phosphorus (increase or decrease) were seen in the 5-day and 9-month dog studies. Since these changes in general were of small magnitude and not correlated with any other findings, they are considered of no toxicological relevance.

In conclusion, oral administration of ABT-450 for up to 3 months in rats, 6 months in mice and 9 months in dogs, resulted in adverse effects on the gallbladder in mice and dogs. The clinical exposure margin to NOAEL for these

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effects is 4.8x in the mouse and 29.4x in the dog. Non-adverse effects in the repeat dose toxicity studies comprised diffuse intrasinusoidal vacuolation in the liver (dog), vacuolation in the small intestine and renal tubular epithelium (dog) and increased food consumption (mice). Non-adverse findings of equivocal relationship to treatment with ABT-450 included alterations in coagulation parameters (dog) and increased serum bilirubin (mice). Overall, the margins to predicted human exposure associated with a 150 mg daily dose (7.0 µg·h/mL) and NOAELs in the ABT-450 repeat-dose toxicity studies are in the range of 4.8-87.8x.

Ritonavir

Liver

Effects on the liver occurred in the majority of repeat-dose toxicity studies where ritonavir was dosed in combination with ABT-450. These liver effects are considered to be related to ritonavir and not to ABT-450 based on the known toxicological profile of ritonavir, the presence of similar incidence rates across dose groups, and a lack of increased incidence and/or severity with increased dose/exposure of ABT-450.

Increased liver weights were observed in repeat dose mouse studies from 7 days up to 6 months duration, with or without corresponding microscopic changes (hepatocellular hypertrophy, necrosis/inflammation), at $\geq$ 30 mg/kg. In rats, increased liver weights associated with hepatocellular hypertrophy, multinucleated hepatocytes and periportal/periductular mononuclear cell infiltration, occurred in one 1-month study and the 3-month study, at $\geq$ 15 mg/kg. Other liver effects related to ritonavir in rodent repeat dose toxicity studies comprised increases in ALT, AST, total protein, cholesterol and triglycerides. Most of the findings, including microscopic liver changes, were at least partially resolved after a 1 month recovery period. Exposure levels for liver effects in rodents in the original ritonavir repeat-dose toxicity studies are within the same range as those observed in the present application when ritonavir was administered in combination with ABT-450.

In dogs, ritonavir-related effects on the liver were less conspicuous than in rodents. Increased liver weight without any correlating microscopic findings was observed in one of the 1-month studies, and in the 9-month study. These liver weight changes were observed at exposures within the same range or higher as the original ritonavir dog studies.

The mean exposure (AUC_{0-24}) at the LOEL for liver weight changes in the long-term mouse and rat studies ranged from 15 µg·h/mL (rat 3-month study) to 24.4 µg·h/mL (mouse 3-month study). The margin to clinical exposure at RHD is < 2x for the effects in rats.

Thyroid gland

Minimal to mild follicular cell hypertrophy was observed in two rat studies (one of the 1-month studies, and the 3-month study). This effect was clearly related to ritonavir, since it occurred with highest severity in the 0/45 mg/kg dose group. In the 3-month study, the microscopic changes in the thyroid gland correlated with increased thyroid weight. There was a tendency towards decreased effects on the thyroid gland in females administered 450/45 mg/kg, associated with decreased ritonavir exposure when ABT-450 was coadministered at this dose level. The mechanism behind the thyroid findings is proposed to be an increased hepatic microsomal enzyme metabolism of thyroid hormone, leading to increased release of TSH and as a consequence of this thyroid gland hypertrophy. Rats are known to be much more sensitive to these effects compared with other species, including humans. Thus, the observed thyroid effects related to ritonavir administration are not considered adverse.

Erythroid parameters

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Effects on erythroid parameters (decreased RBC, haemoglobin and haematocrit; increased reticulocytes) were observed in several ABT-450/r repeat-dose toxicity studies in mice, rats and dogs. These shifts reflect a loss of red blood cell mass, with a compensatory regenerative response. Similar findings were seen in the original ritonavir toxicity studies.

Gastrointestinal effects in dogs
Vomiting/emesis and diarrhoea were observed in all ABT-450/r repeat-dose toxicity studies > 1 month duration in dogs. Decreased body weight (3- and 9 months studies) and decreased serum protein (9-month study) are considered to be consequences of these effects. Similar findings have been observed in the original ritonavir dog toxicity studies, at slightly (1.5-3.5x) higher exposure.

In conclusion, ritonavir added to ABT-450 as a pharmacokinetic enhancer caused a number of effects on the liver, thyroid gland, erythroid parameters, and (in dogs) gastrointestinal system. All of these effects have been observed in previous nonclinical toxicity studies with ritonavir and are mostly non-adverse. Considering that the majority of ritonavir-related findings in the ABT-450/r studies is of adaptive character and can be regarded as non-adverse, and that there is long clinical experience with ritonavir, the small exposure margin to RHD is considered acceptable.

Combination repeat-dose toxicity

In line with CHMP recommendations (EMEA/H/SA/1588/1/2010/III), no combination toxicity studies with ABT-267 and ABT-450/r were conducted. The exposure levels relative to RHD achieved in the single agent, repeat-dose toxicity studies with ABT-267 (35x in mice, 20x in rats, 58x in dogs) and ABT-450/r (59x in mice, 14x in rats, 212x in dogs) are considered sufficiently high to identify target organs of toxicity. The only potential overlapping toxicity concerns the ritonavir-related liver effects and the liver effects of ABT-267. Since the majority of ritonavir-related effects are considered non-adverse, and there is considerable clinical experience with this compound, a combination toxicity study is not considered to add any significant value to the safety evaluation of ABT-267 and ABT-450/r. Thus, it is agreed that no combination toxicity studies with these compounds are necessary.

The Applicant performed a 1-month *safety tolerability study* in mice, using a fixed dose combination of ABT/ritonavir/ABT-267 at 30/20/2 mg/kg/day, respectively. No adverse effects were observed. The margins to RHD, based on AUC, were for ABT-450 2.7x and for ABT-267 3.4x.

ABT-450/r in combination with ribavirin
In two rat studies (1- and 3-month duration) using ABT-450/r in combination with ribavirin several expected toxicological effects of ritonavir (increased liver and thyroid gland weights associated with hepatocellular hypertrophy and thyroid follicular hypertrophy) and ribavirin (decreased body weight and food consumption, alterations in erythroid parameters, decreased thymus weight correlated with decreased number of thymic lymphocytes) were observed. There were no findings directly related to ABT-450, and ABT-450 coadministration did not exacerbate the ritonavir- or ribavirin-related effects. Coadministration of ribavirin with ABT-450 and/or ritonavir did not significantly affect the compound-specific plasma exposures in the 1-month study. In the 3-month study, coadministration with ribavirin caused a slight decrease in exposure of ABT-450.

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Genotoxicity and carcinogenicity

ABT-267

ABT-267 tested negative in a complete package of genotoxicity studies, including tests for gene mutations and chromosomal aberrations in vitro and chromosomal aberrations in vivo. The carcinogenic potential of ABT-267 was evaluated in a 26-week study in Tg-rasH2 transgenic mice and a 2-year carcinogenicity study in Sprague Dawley rats. There were no significant increases in neoplastic changes due to ABT-267 treatment in the Tg-rasH2 mouse study at doses <150 mg/kg/day (26x clinical exposure based on AUC). Since the rat carcinogenicity study is still on-going it is not possible to conclude on the carcinogenic potential of ABT-267.

ABT-450

In the *in vitro* genotoxicity assays, ABT-450 tested negative for gene mutations but positive for chromosomal aberrations in human peripheral blood lymphocytes. The Applicant performed two *in vivo* genotoxicity studies (rat bone marrow micronucleus, Comet assay on rat liver). The results of both were negative up to 2000 mg/kg/day. Exposure (AUC) in the rat micronucleus study was 83.3 µg·h/mL at 2000 mg/kg, corresponding to a 12x margin to exposure at RHD. In the Comet assay, mean liver concentration at the high dose was 172 µg/g. The exposure in terms of microgram quantities in the liver was in the same range as the concentrations that produced positive chromosome aberration results *in vitro*. In conclusion, the weight of evidence indicates that ABT-450 does not carry a significant genotoxic risk.

The carcinogenic potential of ABT-450 was evaluated in a 26-week study in Tg-rasH2 transgenic mice and a 2-year carcinogenicity study in Sprague Dawley rats. There were no significant increases in neoplastic changes due to ABT-450 treatment in the Tg-rasH2 mouse study at doses $\leq$ 300 mg/kg/day (38x clinical exposure based on AUC). Non-neoplastic gallbladder effects similar to those in the 6-month repeat-dose toxicity study in CD-1 mice were observed at $\geq$ 60/30 mg/kg/day, without any signs of progression to neoplasia. In the 2-year rat carcinogenicity study, there were no statistically significant increases in neoplastic changes at doses $\leq$ 300 mg/kg/day, corresponding to 8.5-11.5x the exposure at RHD. However, there was an apparently increased incidence of hepatocellular carcinoma in males at the mid and high dose (1/160, 1/80, 6/160 in combined vehicle controls, low dose and similarly exposed combined mid/high dose groups, respectively). The mean historical control incidence of hepatocellular carcinoma at the test laboratory during the period 2009-2014 was 1.4-4.6%. In total, 26 control groups from 20 study occasions are included in the historical control data set. Of these, four groups had an incidence higher than (4.6%; two groups from the same occasion) or in the same range (2.9% and 3.3%) as the incidence in the mid/high dose males (3.7%), while most groups (22) had an incidence below or equal to 1.7%. The incidence of the combined mid and high dose group might thus be considered to be within or at least close to the historical control range. Based on these data, and the absence of hepatocellular carcinoma in female rats and TgHras mice and also considering the present indication and short duration of treatment, the apparently increased incidence of hepatocellular carcinoma in males is concluded to be without clinical relevance.

Ritonavir

Ritonavir was not mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays, including the Ames reverse mutation assay, the mouse lymphoma assay, the mouse micronucleus test, and chromosomal aberration assays in human lymphocytes. In the 2-year carcinogenicity study in Sprague Dawley rats, ritonavir at doses of 7, 15 and 30 mg/kg/day (mean combined-sex AUC at high dose: 6.39 µg·h/mL) did not cause any significant increase in neoplastic changes. However, in a 2-year carcinogenicity study in CD-1 mice, ritonavir at doses of 50, 100 and 200 mg/kg/day (mean AUC in males at high dose: 39.9 µg·h/mL) produced a significant increase in the incidence of hepatocellular adenomas and the combined incidence of hepatocellular adenomas and carcinomas at the high dose level in males. It is noted that liver tumours in CD-1 mice occurred at similar ritonavir exposure

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levels as were achieved in the ABT-450/r Tg-rasH2 mouse study, where no neoplastic changes in the liver were observed. This might indicate that the Tg-rasH2 model is less sensitive than the conventional 2-year mouse study for the detection of ritonavir-induced liver tumours.

Reproduction and developmental toxicity

ABT-267

Fertility and early embryonic development

The effects of ABT-267 on fertility and early embryonic development were evaluated in mice. There were no effects on male fertility and female reproductive parameters up to the highest dose tested (200 mg/kg/day). Toxicokinetics were not conducted in this study; however, it can be assumed that exposure was approximately within the same range as in the 6-months repeat-dose toxicity study, where the combined-sex exposure (AUC) at 200 mg/kg/day was 36.45 µg·h/mL (25.7x clinical exposure at RHD). In male mice, increased prostate/seminal vesicle weights and decreased testes weights were observed mainly at 200 mg/kg/day. In addition, one male at 5 mg/kg/day showed small testes and epididymides at necropsy. Since there were no similar organ weight changes and no microscopic findings in male reproductive organs in the repeat-dose toxicity studies in mice, and no effects were observed on mating performance, these observations in male mice are considered to be of equivocal relationship to ABT-267 and non-adverse. In conclusion, the NOAEL for both sexes in the ABT-267 fertility and early embryonic development study in mice was 200 mg/kg/day.

Embryo-foetal development

The effects of ABT-267 on embryo-foetal development were evaluated in mice and rabbits. In both species, the dose limit was determined by saturation of systemic exposure. In the *mouse* study, no maternal toxicity or embryotoxicity was observed. No statistically significant effects were observed on litter parameters. There was a slight non-significant increase in the incidence of foetuses with any alteration (malformation + variation) in the ABT-267-treated groups (22.6%, 24.8%, 26.1% and 27.3% in control, low, mid and high dose, respectively. Increased incidences as compared with the concurrent control group were noted for open eye lid and cleft palate in all ABT-267-treated groups. One foetus each at 15 and 150 mg/kg/day, respectively, displayed multiple craniofacial malformations. Furthermore, there was a foetus with craniofacial deformation in the dose range finding study.

Historical control data provided by the Applicant showed that the incidences of cleft palate were within the historical control range at the test laboratory. However, the foetal incidence (1.5%), as well as litter incidence (20%), for open eye lid at the low dose level was above the historical control range both for DRF and pivotal studies. There was no clear dose response; however, the exposure curve was rather flat and no difference in maternal or fetal exposure was present between the mid and high dose levels. There was only a 3-fold higher maternal exposure at the high dose level (GD 15 AUC 38 µg·hr/mL) as compared with the low dose level (GD15 AUC 13.6 µg·hr/mL). The highest AUC level was present at the mid dose (40.4 µg·h/mL, corresponding to 28.5x clinical exposure at RHD).

In the absence of a clear dose response for the observed malformations, the relationship to ABT-267 administration is considered uncertain. However, in view of the findings in the rabbit embryo-foetal development study, where craniofacial malformations were observed at the high dose level, it cannot be completely excluded that the increased incidences of open eye lid and cleft palate in the ABT-267 mouse embryo-foetal development study were related to treatment with ABT-267. The maternal NOAEL in the mouse EFD study was 150 mg/kg/day, the highest dose tested. This corresponds to an AUC_{0-24} level of 38 µg·h/mL (26.8x clinical exposure at RHD). For the foetal findings, there was no NOAEL.

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In the ABT-267 *rabbit* embryo-foetal development studies, very low exposures were achieved (AUC_{0-24} at 60 mg/kg/day in the pivotal study = 6.26 µg·h/mL, corresponding to 4.4x clinical exposure at RHD). Although a different vehicle was used in the pivotal study as compared with the dose range finding study, this did not result in any increased exposure. No maternal toxicity or embryotoxicity was observed in any of the studies. In the pivotal study, there was a non-significant increase in total external, visceral and skeletal malformations at 60 mg/kg/day. None of the malformations at the high dose level were above the upper end of the historical control incidence range, except for microphthalmia and absent incisors.

Microphthalmia was seen in 15% of the litters at 60 mg/kg/day versus 0% in the concurrent control group and 9.1% (upper end of range) in historical controls. The foetal incidence at 60 mg/kg/day (1.7%) was above the concurrent control group (0%) but within the range of historical controls (2.3%). Microphthalmia was seen in the dose range finding study as well, in 2/49 (4%) foetuses at 60 mg/kg/day (AUC_{0-24}:10 µg·h/mL on GD 19).

Absent incisors was seen in 10% of the litters at 60 mg/kg/day versus 0% in the control group and 5.3% (upper end of range) in historical controls. The foetal incidence at 60 mg/kg/day (1.2%) was also above historical controls (0.6%).

One foetus at 60 mg/kg was observed with microphthalmia, absent incisors, fused nares, and misshapen jaw. Another fetus at 60 mg/kg showed thoracogastroschisis, craniorachischisis, underdeveloped skin, ectrodactyly, abnormal flexure of the fore- and hind paw, microphthalmia, open eye, absent incisors, cleft palate, pinna smaller than normal, malrotated hind legs, and misshapen jaw. The third fetus at 60 mg/kg with microphthalmia showed a malpositioned kidney. In total across the two rabbit studies, 4/5 fetuses with microphthalmia showed additional malformations. Of special note is the fact that absent incisors and misshapen jaw occurred alongside microphthalmia in two fetuses from different litters, indicating a common pattern.

Based on the presence of microphthalmia and absent incisors at a higher incidence (both litter and foetal) in the high dose group versus concurrent and historical controls, the foetal NOAEL is considered to be 10 mg/kg/day (AUC_{0-24} = 3.44 µg·h/mL, corresponding to 2.4x clinical exposure at RHD). Based on the available data, a teratogenic effect in rabbits cannot be excluded.

The foetal effects in rabbits, which were observed in the absence of maternal toxicity at an exposure close to the intended therapeutic level, raise concern for use in pregnancy and in women of child-bearing potential. This concern is strengthened by the findings of increased incidences of foetal craniofacial malformations in mice treated with ABT-267. Accordingly, the SmPC text under sections 4.6 and 5.3 has been revised to the effect that Viekirax should not be used during pregnancy or in women of childbearing potential not using effective contraception. No additional risk minimization measures are considered necessary.

Prenatal and postnatal development

Effects of ABT-267 on prenatal and postnatal development were studied in mice. There were no adverse effects noted in the dams or in the F1 generation during the pre-and post-weaning periods, except for two mortalities at 200 mg/kg/day during the post-weaning period. Both of these animals had shown reduced body weights as compared with controls on the day after weaning. Since a relationship to treatment with ABT-267 cannot be excluded, the Applicant's proposed NOAEL for the F1 generation (200 mg/kg/day) is not agreed with. The maternal (F0) NOAEL is considered to be 200 mg/kg/day, and the F1 NOAEL for viability and growth in the offspring 40 mg/kg/day. Although a toxicokinetic analysis was performed, it only comprised average dam and pup concentrations (µg/mL) and no AUC values were measured. Therefore it is not possible to calculate a margin

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to human clinical exposure. As demonstrated by quantifiable levels of ABT-267 in pups at > 40 mg/kg/day, there was passage of ABT-267 across the placenta.

ABT-450

Fertility and early embryonic development

The effects of ABT-450/r on fertility and early embryonic development were evaluated in rats. There were no effects on male fertility and female reproductive parameters up to the highest dose tested (300/30 mg/kg/day), corresponding to ABT-450 AUC levels of 11.5 μg·h/mL (males) and 35.6 μg·h/mL (females). The margin to clinical exposure at RHD is low (1.6-5x). Small testes and epididymides were observed in one high dose males at necropsy. Since there were no similar gross findings and no microscopic findings in male reproductive organs in the repeat-dose toxicity studies in rats, and no effects were observed on mating performance, this observation is considered to be of equivocal relationship to ABT-450/r and non-adverse.

Embryo-foetal development

Due to vehicle-related maternal toxicity and the lack of appreciable exposures despite investigation of both oral and parenteral formulations, evaluation of embryo-foetal development effects in rabbits was not possible. Thus, the ABT-450/r embryo-foetal development studies were conducted in mice and rats. This is in line with CHMP scientific advice given to the Applicant, which recommended that various routes of administration as well as the feasibility of replacing the non-tolerated vehicle in rabbits should be explored. The choice of mice instead of rabbits is considered acceptable.

In the pivotal *mouse* embryo-foetal development study, no maternal toxicity or embryotoxicity was seen. There were no treatment-related effects on uterine or litter parameters. The Applicant considered that all observed malformations were unrelated to ABT-450/r based on absence of dose response, findings limited to the control group and/or incidences generally within historical control range at the test laboratory. However, increased incidences as compared with the concurrent control group were observed in ABT-450/r-treated groups for the craniofacial malformations exencephaly and open eye lids. The Applicant provided historical control data from the test laboratory, demonstrating that the incidences of exencephaly were within the historical control range. However, this was not the case for open eye lids, for which fetal and litter incidences at the low and mid dose levels were above the historical control range. Although there was no clear dose response, a relationship to treatment with ABT-450/r cannot be excluded. It is possible that the lack of dose response may be related to interactions between ritonavir and ABT-450.

In conclusion, the maternal NOAEL in the ABT-450/r mouse embryo-foetal development study was 300/30 mg/kg/day, corresponding to an AUC_{0-24} of 686 μg·h/mL (98x margin to clinical exposure at RHD). There was no NOAEL for the foetal effects. Thus, there is a concern for the use of ABT-450 in pregnancy and in women of child-bearing potential. The SmPC text under sections 4.6 and 5.3 has been revised accordingly. No additional risk minimization measures are considered necessary.

In the ABT-450/r pivotal *rat* study, no maternal toxicity or embryotoxicity was observed. There were no significant differences in number of litters or foetuses with malformations. Slightly increased, statistically non-significant incidences of total visceral ($\geq$100/15 mg/kg/day) and skeletal variations ($\geq$ 30/15 mg/kg/day) were observed. The increase in visceral variations was mainly due to higher incidence of dilated ureters and increased renal pelvic cavitation, within or slightly above the historical control range. Incidences of specific skeletal variations were within the historical control range, except for misaligned sternebrae, which were marginally above the historical control range for litter incidence. Due to the small magnitude of these effects, they are not considered adverse. In conclusion, the maternal and foetal NOAEL was 450/45 mg/kg/day, the highest dose tested. At this dose level, AUC_{0-24} was 58.6 μg·h/mL (8.4x margin to clinical exposure at RHD).

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Prenatal and postnatal development

The effects of ABT-450/r on prenatal and postnatal development were evaluated in *rats*. No adverse maternal F0 effects were observed. There were no effects on survival, growth, sexual maturation, motor activity, learning and memory, mating and fertility, male reproductive organ weights or ovarian and uterine parameters in the F1 generation rats. Accordingly, the maternal NOAEL as well as the F1 NOAEL for viability and growth in the offspring was 300/30 mg/kg/day, the highest dose tested. An unexpectedly high exposure for ABT-450 was achieved at this dose level: 116 μg·h/mL, corresponding to a 16.5x margin to clinical exposure at RHD. The presence of quantifiable concentrations of ABT-450 in pups at 300 mg/kg/day demonstrates passage of ABT-450 across the placenta. No quantifiable levels of ritonavir were present in the pups.

Ritonavir

No effects on male and female fertility, or embryonic development, were observed in rats at dosages up to 125 mg/kg/day in males and 75 mg/kg/day in females, corresponding to mean AUC levels of 61.0 and 90.5 μg·h/mL, respectively. In rabbit and rat embryo-foetal development studies, embryotoxicity occurred with maternally toxic high dose (75 mg/kg/day in the rat, 110 mg/kg/day in the rabbit). In the rat, a slight increase in cryptorchidism was seen at 35 mg/kg/day (mean AUC_{0-24} value 34.3 μg·h/mL). This finding, which may be regarded as a developmental retardation, did not lead to a contraindication of ritonavir in pregnant women. The peri/post natal toxicity study revealed no treatment-related effects.

Juvenile toxicity

No juvenile toxicity studies have been conducted. Since this application only concerns an indication in adults, this is considered acceptable.

Toxicokinetic data

Immunotoxicity

No dedicated immunotoxicology studies have been conducted with ABT-267 or ABT-450/r. Since the results of the repeat-dose toxicity studies do not indicate any significant effects on the immune system related to ABT-267 or ABT-450/r, this is considered acceptable.

Local Tolerance

No separate local tolerance studies were conducted with ABT-267, ABT-450 or ABT-450/r. Since the intended therapeutic route is oral, local tolerance can be evaluated within the frame of general toxicity studies. Accordingly, no separate local tolerance studies are required. In repeat dose toxicity studies with ABT-450/r, erosions/ulcerations and inflammation in the gallbladder occurred in mice and dogs, most likely reflecting high local concentrations of the test compound in bile with associated local irritative effects.

Other toxicity studies

Phototoxicity

ABT-267 and ABT-450 absorb light between 290 and 700 nm and have maximal molar extinction coefficients

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(MECs) that exceed the guideline threshold of 1000 mol^{-1} cm^{-1}. ABT-267 distributed to the skin and, at low concentrations, to the eyes. ABT-450/r distributed at low concentrations to pigmented skin, but not to the eyes. ABT-267 was not phototoxic in a 3-day *in vivo* study in hairless mice at doses $\leq$ 200 mg/kg/day (8x clinical exposure based on AUC). No *in vitro* or *in vivo* phototoxicity studies were performed with ABT-450. The Applicant refers to clinical data, demonstrating 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 it is concluded that there is no large concern regarding a risk for photosensitivity reactions associated with treatment using the 3DAA regimen. No additional phototoxicity testing is asked for.

Dependence

No drug dependence studies were submitted. Since ABT-450 as well as ABT-267 has no or very low distribution to the brain, and there was no evidence of effects on the central nervous system in pivotal toxicology studies, no drug dependence studies are considered necessary.

Metabolites

Two pharmacologically inactive, disproportionate human metabolites (M29 and M36) were evaluated in a combined toxicology and *in vivo* genotoxicity study in mice, as well as in *in vitro* genotoxicity tests and an embryo-foetal development study in mice. Both M29 and M36 were negative in GLP *in vitro* Ames tests and chromosomal aberration assays. M29 caused no adverse effects in any of the *in vivo* studies up to the highest tested exposures (15.8-18.1 µg·h/mL in the 1-month study, 17.4 µg·h/mL in the embryo-foetal development

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study), corresponding to RHD margins of 23.5-27x. In the 1-month study with M36, there were no adverse findings up to the highest exposure tested (16.8 µg·h/mL), corresponding to a margin of 38.2x.

In the mouse embryo-foetal development toxicity study with M36, there was a slightly higher incidence of a visceral variation (increased incidence of renal pelvic cavitation) at the mid and high dose levels (litter incidence: 5.9%, 9.5%, 15%, 21.1% in ctrl, low, mid and high dose groups, respectively). The Applicant provided historical control data, demonstrating that the foetal incidence of renal pelvic cavitation was within the historical control range. The litter incidence was above that seen historically (21.1% in the high dose group versus 12.5% upper end of control range). However, based on the presence of this variation in the concurrent controls as well as the rather high historical control incidence it is evident that renal pelvic cavitation occurs commonly in mice. Furthermore, this variation is considered to represent a delay in maturity that will eventually catch up and is not considered to be and adverse effect. Thus, the NOAEL (maternal and foetal) in study R&D/13/549 was 6 mg/kg/day, (margin to RHD 26.4x).

In conclusion, it is considered that the safety of the human metabolites M29 and M36 of ABT-267 has been adequately characterized. With the exception of M36 and its possible effects on foetal development, the totality of nonclinical data indicate that the metabolites are unlikely to pose a toxicity risk at the recommended ABT-267 daily dose of 25 mg for the 12- or 24-week treatment of chronic HCV infection.

Impurities

The toxicological qualifications of the specified ABT-450- and ABT-267-impurities as suggested by the applicant are endorsed. The previous qualification of the ritonavir impurities is considered also to be valid for the specified ritonavir impurities present in Viekirax as justified by the applicant.

2.3.4. Ecotoxicity / environmental risk assessment

Based on the previous environmental risk assessment performed for Kaletra film-coated tablets 200 mg lopinavir/50 mg ritonavir the presence of ritonavir in Viekirax is considered unlikely to represent a risk to the environment.

The Applicant has performed a screening tier (Phase I) and subsequent Phase II -Tier A and Tier B evaluations for both Ombitasvir (ABT-267) and Paritaprevir (ABT-450) according to the “Guideline on Environmental risk assessment of medicinal products for human use” (EMEA/CHMP/SWP/4447/00 corr 1*).

Paritaprevir

Paritaprevir (ABT-450) is not considered a PBT substance as Logkow is below 4.5. A potential for bioaccumulation can, however, not be excluded as the LogKow is 3.1 and the bioaccumulation potential needs to be determined either by the performing the OECD 305 study or by using a weight-of-evidence approach. A phase II Tier B assessment was triggered as the aerobic and anaerobic transformation in aquatic sediment systems study (OECD 308) showed that more than 10% of the substance was present in sediment. The sediment-water chironomid toxicity test using spiked sediment (OECD 218) is still ongoing.

Ombitasvir

A phase II Tier B terrestrial compartment assessment is required for Ombitasvir (ABT-267) as the adsorption-desorption study (OECD 106) yielded a Koc value (35413 L/Kg) that is above the threshold. The sediment-water chironomid toxicity test using spiked sediment (OECD 218) is ongoing and will been submitted as soon as finalized. An aerobic and anaerobic transformation in aquatic sediment systems (OECD 308) study

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has been performed, however the DT_{50} values have not been provided for the sediment and the applicant is requested to submit these values. The bioaccumulation study in fish (OECD 305) is currently ongoing and the final report will be submitted.

In conclusion an updated ERA will be submitted for both paritaprevir and ombitasvir as a post approval recommendation. The applicant has indicated that the final reports and the updated ERA will be provided in April 2015.

Substance (INN/Invented Name): ABT-450 (paritaprevir)					
CAS-number (if available): 1456607-71-8 (dehydrate) and 1216941-48-8 (anhydrate)					
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	logD pH 6.8	3.1			not B
Persistence	DT50 or ready biodegradability	7-15 days at 20 °C (freshwater) 42-81 days at 20 °C (whole system) $DT_{50,\ sediment}$ missing			P/not P
Toxicity	NOEC	0.54 mg/L			not T
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{\ surfacewater}$, default	0.75	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = 2423 mL/g and 7855 mL/g in soil; 10656 mL/g in sediment; 1068 mL/g and 664 mL/g in activated sludge			"slightly mobile" to "immobile" according to McCall classification scale
Biodegradability Test	OECD 314	$DT_{50\ biotic\ system}$ 2.7 days $DT_{50\ abiotic\ system}$ > 1 year			activated sludge
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = 7 and 15 days at 20 °C $DT_{50,\ sediment}$ = not calculated $DT_{50,\ whole\ system}$ = 81 and 42 days at 20 °C % shifting to sediment = >10% after 14 days			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	28	mg/L	*Pseudokirchneriella subcapitata*
Daphnia magna. Reproduction Test	OECD 211	NOEC	0.7	mg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	0.54	mg/L	*Pimephales promelas*
Activated Sludge, Respiration	OECD 209	EC_{15}	>1000	mg/L	

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Inhibition Test					
Phase IIb Studies					
Sediment dwelling organism	OECD 218	NOEC		mg/ kg	**ongoing** *Chironomus riparius*

Substance (INN/Invented Name): ABT-267 (ombitasvir)					
CAS-number (if available): 1456607-70-7 (hydrate); 1258226-87-7 (anhydrate)					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	5.74			Potential PBT (Y)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log D_{ow} pH 7.4	5.74			B
	BCF				**ongoing**
Persistence	DT50	7-15 days at 20 °C (freshwater) 42-81 days at 20 °C (whole system) $DT_{50,\ sediment}$ missing			P/not P
Toxicity	NOEC	47 µg/L			not T
PBT-statement :	No conclusion can be made at this stage				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.125	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					(Y/N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = 230808 mL/g and 5185 mL/g in soil; 24682 mL/g in sediment; 46788 mL/g and 24038 mL/g in activated sludge			Assessment of terrestrial compartment triggered
Biodegradability Test	OECD 314	$DT_{50\ biotic\ system}$ 45.9 days $DT_{50\ abiotic\ system}$ 121.2 days			activated sludge
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = 16.8 and 17.2 days at 20 °C $DT_{50,\ sediment}$ = not calculated $DT_{50,\ whole\ system}$ = 45.3 and 44.1 days at 20 °C % shifting to sediment = >10% after 14 days			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	47	µg/L	*Pseudokirchneriella subcapitatarate*
Daphnia magna Reproduction Test	OECD 211	NOEC	430	µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	92	µg/L	*Pimephales promelas*

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Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{15}	1000	mg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	**Ongoing**
Sediment dwelling organism	OECD 218	NOEC		mg/ kg	**Ongoing** *Chironomus riparius*

2.3.5. Discussion on non-clinical aspects

ABT-450 (ABT-450) and ABT-267 (ombitasvir) have nanomolar to subnanomolar activity against genotypes 1 and 4 and are indicated to be specific for viral targets. The four most significant metabolites of ABT-267 were concluded not to be pharmacologically active. No secondary pharmacological targets were identified in the in vitro screening performed, although a significant effect of ABT-450 was seen on the δ-opioid receptor δ2 (DOP). However, considering the low distribution to the brain and that ABT-450 is a substrate for both MDR-1 (PgP) and BCRP and also have a high plasma protein binding (>95%), an interaction with the δ-opioid receptor δ2 (DOP) is considered to be unlikely. This conclusion is also supported by the absence of any CNS effects in the safety pharmacology and repeat dose toxicology studies performed.

No safety issues were identified in the non-clinical safety pharmacology studies performed and no additional non-clinical investigations are considered to be needed.

Both ABT-450 and ABT-267 have low solubility and low bioavailability. ABT-450 is co-dosed with ritonavir, a potent CYP and efflux transport inhibitor in order to mitigate the high first-pass and hepatic elimination. The pharmacokinetics of ritonavir is considered to be known and have not been assessed in this application. Oral absorption of ABT-450 in rats is low but increases when ABT-450 and ritonavir is co-dosed. The improved absorption is likely due to inhibition of both CYP mediated first-pass metabolism and intestinal efflux transporters by ritonavir. ABT-450 oral systemic bioavailability was non-detectable in rat and monkey, and averaged 41% in dog while the oral bioavailability for ABT-267 ranged from 25% in rat to 57% in dog with a PEG solution formulation. ABT-267 plasma concentrations following oral co-dosing with ritonavir in rat, dog and monkey were comparable to those obtained from an equivalent dose of ABT-267 administered alone in each species. Although interactions between ABT-450 and ritonavir are expected this indicate that there are no large pharmacokinetic interactions between ABT-450/ritonavir and ABT-267.

Plasma protein binding is high for both compounds and no partioning to red blood cells were seen. A limited distribution of radioactivity to tissues was seen in pigmented male Long-Evans rats given ABT-450/ritonavir and the liver was shown to contain the highest amount of radioactivity relative to other tissues. No retention was seen and no preferential binding of radioactivity to eye(s) or non-pigmented skin (low amounts were detected in pigmented skin). No distribution to brain tissues was seen. Small amounts of radioactivity were detected in foetal liver and ABT-450-derived radioactivity was excreted in milk obtained from lactating rats. ABT-267 was more widely distributed. Highest concentrations of radioactivity were found in adrenal gland, liver, pancreas, kidney cortex and stomach mucosa. Concentrations of radioactivity in tissues declined below the limits of quantitation by 168 hr. post-dose. ABT-267-derived radioactivity did not preferentially bind to the melanin-containing tissues and did not distribute into the lens of the eye or CNS tissues. Low amounts were detected in eye(s) and no differences between pigmented and non-pigmented skin was seen. Radioactivity was detected in the foetal liver and in milk from lactating rats.

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A CYP-mediated oxidation of ABT-450 was seen and following a single oral dose of ABT-450 M2 was the major circulating metabolite in human plasma (~23% of total drug). The level was significantly reduced (to ~2.4% of total drug) when ABT-450 was co-dosed with ritonavir (ABT-450/r 300/100 mg) and unchanged parent accounted for the remaining drug-related material in plasma (97.6% of the total). No major metabolites were thus identified after administration of ABT-450/ritonavir. ABT-267 showed limited hepatic metabolism across species and was metabolized to a low extent and at a slow rate by CYP3A4/5 and CYP2C8. In humans, ABT-267, M23, M29, M36 and M37 are the main components in plasma after a single dose of ABT-267 alone, representing about 93% of total plasma radioactivity. M23 is present in preclinical species at higher levels than in humans, providing safety coverage in all toxicology species. M29, M36 and M37 are downstream metabolites of M23 but have not been observed in hepatic in vitro systems or in plasma or excreta of in vivo preclinical animals. M29 and M36 were defined as major disproportionate metabolites and specific toxicological studies have been performed with these two metabolites. Metabolite M37 is reported to be present in human plasma at a level just below 10% (9.3%) and the possibility that this metabolite might be a major metabolite in some individuals has not been addressed by the applicant. However, based on the absence of pharmacological activity and the results from the toxicological studies with M29 and M36 together with the low levels found in plasma of humans and the similarity in structures any specific safety concerns due to the metabolite M37 as compared to the other two major metabolites is considered to be unlikely.

Following oral administration of ABT-450/r, ritonavir or ABT-267 to nonclinical species and humans, all compounds and their respective metabolites were mainly cleared via biliary excretion and faecal elimination, with minimal renal clearance. Parent compounds as well as metabolites were detected in milk from lactating rats after oral administration of ABT-450/ritonavir and ABT-267, respectively.

The choice of nonclinical species is considered acceptable. In addition the performance of toxicological studies with the two major metabolites M29 and M36 present in human plasma at levels above 10%, but not with M37 which is reported to be present at a level of 9.3% in pooled plasma, is also considered acceptable since no specific safety concern regarding M37 is to be expected based on the low plasma concentrations and structural similarity.

In accordance with scientific advice received, ABT-267 and ABT-450 were evaluated separately in the toxicology studies. No combination repeat-dose toxicity study was conducted. Since no significant overlapping toxicity was identified in the single-agent studies, this is considered acceptable. ABT-267 administered orally up to 3 months in rats and 6 months in mice and dogs, respectively, did not cause any adverse effects at saturating systemic exposures. The only toxicity observed was single cell hepatocellular necrosis and increased liver enzymes in a non-GLP 14-day mouse study (estimated margin to NOAEL: 2.7x). Non-adverse effects in the repeat dose toxicity studies comprised lymph vessel dilatation and vacuolation in the small intestine (dog), vaginal mucification and increased ovarian follicular cysts (mouse), increased liver weights with or without correlation to hepatocellular vacuolation (dog), changes in body weight (mouse) and alterations in red blood cell and coagulation parameters (dog). Overall, the margin to predicted human exposure associated with a 25 mg daily dose (1.42 µg·h/mL) and NOAELs in the ABT-267 repeat-dose toxicity studies are in the range of 20-50x.

Oral administration of ABT-450/r for up to 3 months in rats, 6 months in mice and 9 months in dogs, resulted in adverse effects on the gallbladder (erosion/ulceration, inflammation, epithelial hyperplasia) in mice and dogs. The clinical exposure margin to NOAEL for these effects is 4.8x in the mouse and 29.4x in the dog. The mechanism behind the observed gallbladder findings is not known, but may conceivably be related to the high biliary excretion of ABT-450 with associated high local concentrations in the gallbladder. Review of the 3DAA Phase 2/3 data set revealed no evidence of treatment-related gallbladder disorders in humans. Thus, the non-clinical gallbladder findings appear not to be readily translatable to the clinical situation.

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Non-adverse effects in the repeat dose toxicity studies comprised diffuse intrasinusoidal vacuolation in the liver (dog), vacuolation in the small intestine and renal tubular epithelium (dog) and increased food consumption (mice). Non-adverse findings of equivocal relationship to treatment with ABT-450 included alterations in coagulation parameters (dog) and increased serum bilirubin (mice). Overall, the margins to predicted human exposure associated with a 150 mg daily dose (7.0 µg·h/mL) and NOAELs in the ABT-450 repeat-dose toxicity studies are in the range of 4.8-87.8x.

In all repeat-dose toxicity studies with ABT-450, ritonavir was co-administered as a pharmacokinetic enhancer. Effects related to ritonavir were observed in the liver (increased organ weight, hepatocellular hypertrophy, multinucleated hepatocytes, mononuclear cell infiltration, focal necrosis), and thyroid gland (follicular epithelial hypertrophy). There were also ritonavir-related effects on erythroid parameters and (in dogs) the gastrointestinal system. All of these effects have previously been observed in nonclinical toxicity studies with ritonavir. The margin to clinical exposure at RHD is < 2x for liver effects in rats. Considering that the majority of ritonavir-related findings in the ABT-450/r studies is of adaptive character and can be regarded as non-adverse, and also that there is long clinical experience with ritonavir, this small margin to RHD is considered acceptable.

ABT-267 tested negative in a complete package of genotoxicity studies, including tests for gene mutations and chromosomal aberrations *in vitro* and chromosomal aberrations *in vivo*. There were no significant increases in neoplastic changes due to ABT-267 treatment in a 6-month Tg-rasH2 mouse carcinogenicity study at doses ≤150 mg/kg/day (26x clinical exposure based on AUC). However, since the rat carcinogenicity study is still ongoing it is not possible to conclude on the carcinogenic potential of ABT-267 at the moment.

In the in vitro genotoxicity assays, ABT-450 tested negative for gene mutations but positive for chromosomal aberrations in human peripheral blood lymphocytes. Two follow-up in vivo genotoxicity studies (rat bone marrow micronucleus, Comet assay on rat liver) were negative. The weight of evidence indicates that ABT-450 does not carry a significant genotoxic risk. There were no significant increases in neoplastic changes due to ABT-450 treatment in a 6-month Tg-rasH2 mouse carcinogenicity study at doses < 300 mg/kg/day (38x the clinical exposure based on AUC). In the 2-year rat carcinogenicity study, there was an increased incidence of hepatocellular carcinoma in males at the mid and high dose as compared with the concurrent control group. The Applicant provided historical control data, demonstrating that the incidence of the combined mid and high dose groups might be considered to be within or at least close to the historical control range. Based on these data, and the absence of hepatocellular carcinoma in female rats and TgHras mice, and also considering the present indication and short duration of treatment, the apparently increased incidence of hepatocellular carcinoma in males is concluded to be without clinical relevance.

Complete packages of reproductive toxicology studies were conducted for both ABT-267 and ABT-450. None of the compounds caused any effects on fertility and early embryonic development in mice (ABT-267) or rats (ABT-450/r). In the embryo-foetal development studies, possible teratogenic effects were observed with both compounds. ABT-267 caused increased incidences of open eye lid in mice (no clear dose response), and microphthalmia and absent incisors in rabbits at the high dose level. There were also foetuses with multiple craniofacial malformations in both studies. It should be noted that these effects occurred in the absence of any maternal toxicity, and at low exposure margins (4x) relative to RHD in the rabbit. Thus, there is a concern for the use of ABT-267 in pregnancy and in women of child-bearing potential. The SmPC text under sections 4.6 and 5.3 has been revised accordingly. No additional risk minimization measures are considered necessary.

Embryo-foetal development studies with ABT-450/r were conducted in two rodent species, the mouse and the rat, due to vehicle-related intolerance and lack of appreciable exposure despite investigation of both oral and parenteral formulation in rabbits. This is considered acceptable. In the mouse study, increased incidences were

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observed in ABT-450/r-treated groups for the malformation open eye lids. Although there was no clear dose response, a relationship to treatment with ABT-450/r cannot be excluded. Thus, there is a concern for the use of ABT-450 in pregnancy and in women of child-bearing potential. The SmPC text under sections 4.6 and 5.3 has been revised accordingly. No additional risk minimization measures are considered necessary.

In the ABT-450/r rat embryo-foetal development study, the only findings were slightly increased, statistically non-significant incidences of total visceral ($\geq$100/15 mg/kg/day) and skeletal variations ($\geq$ 30/15 mg/kg/day). The increase in visceral variations was mainly due to higher incidence of dilated ureters and increased renal pelvic cavitation, within or slightly above the historical control range. Incidences of specific skeletal variations were within the historical control range, except for misaligned sternebrae, which were marginally above the historical control range for litter incidence. Due to the small magnitude of these effects, they are not considered adverse.

In the ABT-267 prenatal and postnatal development study in mice, there were no findings except for two F1 mortalities at 200 mg/kg/day during the post-weaning period. No effects related to ABT-450/r were observed in the prenatal and postnatal development study in rats.

No juvenile toxicity studies have been conducted. Since the indication applied for is in adults only, this is considered acceptable.

No separate local tolerance studies were conducted with ABT-267 or ABT-450/r. Since the intended therapeutic route is oral, local tolerance can be evaluated within the frame of general toxicity studies. Accordingly, no separate local tolerance studies are required. In repeat dose toxicity studies with ABT-450/r, erosions/ulcerations and inflammation in the gallbladder occurred in mice and dogs, most likely reflecting high local concentrations of the test compound in bile with associated local irritative effects.

ABT-267 and ABT-450 absorb light between 290 and 700 nm and have maximal molar extinction coefficients (MECs) that exceed the guideline threshold of 1000 mol^{-1} cm^{-1}. ABT-267 distributed to the skin and, at low concentrations, to the eyes. ABT-450/r distributed at low concentrations to pigmented skin, but not to the eyes. ABT-267 was not phototoxic in a 3-day *in vivo* study in hairless mice at doses $\leq$ 200 mg/kg/day (8x the clinical exposure based on AUC). No *in vitro* or *in vivo* phototoxicity studies were performed with ABT-450. The Applicant refers to clinical data, demonstrating 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 are warranted for the 3DAA or 2DAA combinations to prevent phototoxicity-related adverse events in humans.

The performed clinical trials included the summer months in the Northern Hemisphere and there were no restrictions on sun exposure or requirements for sun protection or use of sunscreen. Results obtained suggest that the higher frequency of rash-related events in the 3DAA + RBV treatment groups was primarily due to the presence of RBV. In addition, a low and comparable incidence of photosensitivity preferred terms (non-serious, mild in severity and not leading to study drug discontinuation) was identified for the 3DAA+RBV regimen and placebo.

Approximately 88% of the patients in the Phase 2/3 trials (2309 patients) were 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

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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 it is concluded that there is no large concern regarding a risk for photosensitivity reactions associated with treatment using the 3DAA regimen.

No dedicated immunotoxicology studies have been conducted with ABT-267 or ABT-450/r. Since the results of the repeat-dose toxicity studies do not indicate any significant effects on the immune system related to ABT-267 or ABT-450/r, this is considered acceptable.

No drug dependence studies were submitted. Since ABT-450 as well as ABT-267 has no or very low distribution to the brain, and there was no evidence of effects on the central nervous system in pivotal toxicology studies, no drug dependence studies are considered necessary.

Two pharmacologically inactive, disproportionate human metabolites (M29 and M36) were evaluated in a combined toxicology and *in vivo* genotoxicity study in mice, as well as in *in vitro* genotoxicity tests and an embryo-foetal development study in mice. Both M29 and M36 were negative in GLP *in vitro* Ames tests and chromosomal aberration assays. M29 caused no adverse effects in any of the *in vivo* studies up to the highest tested exposures (RHD margins of 23-38x). In the mouse embryo-foetal development toxicity study with M36, there was a slightly higher incidence of a visceral variation (increased incidence of renal pelvic cavitation) at the mid and high dose levels. The Applicant provided historical control data, demonstrating that the foetal incidence of renal pelvic cavitation was within the historical control range. The litter incidence was above that seen historically (21.1% in the high dose group versus 12.5% upper end of control range). However, based on the presence of this variation in the concurrent controls as well as the rather high historical control incidence it is evident that renal pelvic cavitation occurs commonly in mice. Furthermore, this variation is considered to represent a delay in maturity that will eventually catch up and is not considered to be and adverse effect.

In conclusion, it is considered that the safety of the human metabolites M29 and M36 of ABT-267 has been adequately characterized. With the exception of M36 and its possible effects on foetal development, the totality of nonclinical data indicate that the metabolites are unlikely to pose a toxicity risk at the recommended ABT-267 daily dose of 25 mg for the 12- or 24-week treatment of chronic HCV infection.

The toxicological qualifications of the specified ABT-450- and ABT-267-impurities as suggested by the applicant are endorsed. The previous qualification of the ritonavir impurities is considered also to be valid for the specified ritonavir impurities present in Viekirax as justified by the applicant.

2.3.6. 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. An updated ERA will be submitted for both paritaprevir and ombitasvir as a post approval recommendation. The applicant has indicated that the final reports and the updated ERA will be provided in April 2015.

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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

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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	M11-388	5.3.1.1	Dosage form and food effect on BA	Open-label, randomized, 3-period crossover	ABT-450/r tablet: 75/50 mg single dose; PO; ABT-450 HGC: 50 mg single dose; PO; Ritonavir SGC: 100 mg single dose; PO	21	Healthy subjects	Single dose per treatment period	Complete, Full
BA	M10-923	5.3.1.1	Food effect on BA	Open-label, randomized, 2-period crossover	ABT-450 HGC: 50 mg single dose; PO; Ritonavir SGC: 100 mg single dose; PO	8	Healthy subjects	Single dose per treatment period	Complete, Full
BA	M11-389	5.3.1.1	Food effect on BA	Open-label, randomized, 3-period crossover	ABT-450/r/ABT-267 tablet: 150/100/25 mg single dose; PO	21	Healthy subjects	Single dose per treatment period	Complete, Full
BA	M10-797	5.3.1.2	Dosage form effect on BA	Open-label, randomized, 2- and 3-period crossover	Part 1: ABT-450: 50 mg HGC or SDD tablet formulation 1 or 2; PO Ritonavir SGC: 100 mg; PO Part 2: ABT-450: 200 mg HGC or SDD tablet formulation 2; PO Ritonavir SGC: 100 mg; PO	30	Healthy subjects	Single dose per treatment period	Complete, Full
BA	M12-683	5.3.1.2	Dosage form effect on BA	Open-label, randomized, 4-period crossover	ABT-450/r: 75/100 mg or 100/100 mg, 150/100 mg, or 200/100 mg coformulated or SDD tablet; PO Ritonavir SGC: 100 mg; PO	40	Healthy subjects	Single dose per treatment period	Complete, Full
BA	M12-115	5.3.1.2	Dosage form effect on BA	Open-label, randomized, 2-period crossover	ABT-267 HME tablet: 25 mg single dose; PO; ABT-267 SDD tablet: 25 mg single dose; PO	12	Healthy subjects	Single dose per treatment period	Complete, Full

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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	M12-647	5.3.1.2	Dosage form effect on BA	Open-label, randomized, 2-period crossover	ABT-267 coated or uncoated HME tablet: 25 mg; PO	12	Healthy subjects	Single dose per treatment period	Complete, Full
BA	M13-387	5.3.1.2	Dosage form effect on BA	Open-label, randomized, 3-period crossover	ABT-267 HDL or LDL tablet: 25 mg; PO	12	Healthy subjects	Single dose per treatment period	Complete, Full
BA	M13-391	5.3.1.2	Dosage form effect on BA	Open-label, randomized, 3-period crossover	ABT-450/r/ABT-267 tablet: 150/100/25 mg or 200/100/25 mg single dose; PO ABT-450 SDD: 150 or 200 mg; PO Ritonavir SGC: 100 mg; PO ABT-267 HME tablet: 25 mg; PO ABT-450/r tablet: 150/100 mg or 200/100 mg; PO	42	Healthy subjects	Single dose per treatment period	Complete, Full
PK	M10-749	5.3.3.1	Safety, tolerability, PK	Double-blind, randomized, placebo-controlled	Substudy 1: ABT-450 HGC: 300, 600, or 900 mg or placebo; PO Substudy 2: ABT-450 HGC: 25-400 mg or placebo; PO Ritonavir SGC: 50-200 mg or placebo; PO	87	Healthy subjects	Single dose	Complete, Full
PK	M10-861	5.3.3.1	Safety, tolerability, PK	Blinded, randomized, placebo-controlled	ABT-450 HGC: 50 or 100 mg BID, or 200 or 300 mg QD, or placebo; PO Ritonavir SGC: 100 mg BID, or 100 mg QD, or placebo, PO	38	Healthy subjects	14 days	Complete, Full

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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	M12-351	5.3.3.1	PK	Open-label, randomized	ABT-450 SDD: 100, 250, or 300 mg; PO Ritonavir SGC: 100 mg, PO	18	Healthy subjects	Single dose	Complete, Full
ADME	M10-798	5.3.3.1	ADME	Open-label	[^{14}C]ABT-450 powder for liquid-filled capsule: 200 mg; PO Ritonavir SGC: 100 mg; PO	4	Healthy subjects	Single dose	Complete, Full
PK	M12-116	5.3.3.1	Safety, tolerability, antiviral activity, PK, resistance	Substudies 1, 2, and 4: double-blind, randomized, placebo-controlled Substudy 3: open-label, randomized, 2-period crossover Substudy 5: rollover from Substudy 4 to monitor resistance	Substudy 1: ABT-267 SDD tablet: 1.5 to 200 mg or placebo; PO HME tablet 200 or 350 mg or placebo; PO Substudy 2: ABT-267 SDD tablet: 5 to 100 mg or placebo (5 mg group also received ritonavir 100 mg); PO ABT-267 HME tablet: 200 mg or placebo; PO Ritonavir SGC: 100 mg; PO Substudy 3: ABT-267 SDD tablet: 25 mg; PO Substudy 4: ABT-267 SDD tablet: 5 to 50 mg or placebo; PO ABT-267 HME tablet: 200 mg or placebo; PO	137	Healthy and HCV GT1-infected subjects	Substudy 1: single dose Substudy 2: QD for 10 days Substudy 3: single dose per treatment period Substudy 4: QD for 3 days	Complete, Full
ADME	M12-186	5.3.3.1	ADME	Open-label	[^{14}C]ABT-267 powder for liquid-filled capsule: 25 mg capsule; PO	4	Healthy subjects	Single dose	Complete, Full

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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/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 Ritonavir SGC: 100 mg or placebo; PO ABT-267 tablet: 100 mg or placebo; PO 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 Ritonavir SGC: 100 mg; PO 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
PK	M12-187	5.3.3.1	PK, safety	Open-label, randomized	ABT-450 SDD tablet: 150 or 250 mg QD; PO ABT-267 SDD tablet: 25 mg QD; PO ABT-267 HME tablet: 200 mg QD; PO ABT-333 tablet: 400 mg BID; PO ABT-072 SDD tablet: 400 mg QD; PO Ritonavir SGC: 100 mg QD; PO	51	Healthy subjects	21 days	Complete, Full

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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	M11-602	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 ABT-072 tablet 100, 300, or 600 mg or placebo QD; PO ABT-333 tablet: 400 or 800 mg or placebo BID; PO pegIFN: 180 µg QW; SC RBV tablet: 500 to 600 mg BID; PO 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
PK	M12-688	5.3.3.3	Safety, tolerability, PK	Open-label	ABT-450 tablet: 250 mg; PO Ritonavir SGC: 100 mg; PO	30	Healthy subjects	Single dose	Complete, Full
PK	M11-384	5.3.3.3	Safety, tolerability, PK	Blinded, randomized	Part 1: ABT-450 HGC: 50-200 mg or placebo; PO Ritonavir SGC: 100 mg or placebo; PO Part 2: ABT-450 HGC: 50-200 mg or placebo; PO Ritonavir SGC: 100 mg or placebo; PO	54	Healthy subjects	Single dose or QD for 14 days	Complete, Full
PK	M11-385	5.3.3.3	Safety, tolerability, PK	Blinded, randomized, placebo-controlled	ABT-450 HGC: 50-200 mg or placebo; PO Ritonavir SGC: 100 mg or placebo; PO	52	Healthy subjects	Single dose or QD for 14 days	Complete, Full
PK	M12-181	5.3.3.3	Safety, tolerability, PK	Blinded, randomized, placebo-controlled	ABT-267 tablet: 25 or 200 mg or placebo; PO	48	Healthy subjects	7 days	Complete, Full

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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	M13-505	5.3.3.3	Dosage form effect on PK	Open-label, randomized, 2-period crossover	ABT-450/r/ABT-267 tablet: 100/100/25 mg or 150/100/25 mg; PO ABT-450 SDD tablet: 100 or 150 mg; PO ABT-267 HME tablet: 25 mg; PO Ritonavir SGC: 100 mg; PO	48	Healthy subjects	Single dose per treatment period	Complete; Full
PK	M12-221	5.3.3.3	Safety, PK	Open-label, randomized	ABT-450 tablet: 150, 200, or 250 mg QD; PO ABT-267 HME tablet: 25 mg QD; PO ABT-333 tablet: 400 mg BID; PO 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 ABT-267 HME tablet: 25 mg; PO ABT-333 tablet: 400 mg; PO 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 ABT-267 HME tablet: 25 mg; PO ABT-333 tablet: 400 mg; PO	24	Subjects with normal renal function or with mild to severe renal impairment	Single dose	Complete; Full

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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	M12-196	5.3.3.4	PK effect by gemfibrozil	Open-label	ABT-450 tablet: 150 mg QD; PO ABT-333 tablet: 400 mg QD; PO Ritonavir SGC: 100 mg QD; PO Gemfibrozil tablet: 600 mg QD; PO	12	Healthy subjects	ABT-450/r and ABT 333: 2 days; Gemfibrozil: 5 days	Complete, Full
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 ABT-267 tablet: 25 mg QD; PO ABT-333 tablet: 400 mg BID; PO Ritonavir SGC: 100 mg QD; PO Warfarin tablet: 5 mg; PO 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 ABT-333 tablet: 250 mg BID; PO 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 ABT-333 tablet: 250 mg QD; PO 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

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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	M14-027	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 ABT-333 tablet: 250 mg; PO 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
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 ABT-267 tablet: 25 mg QD; PO ABT-333 tablet: 400 mg BID; PO Ritonavir SGC: 100 mg QD; PO 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 ABT-267 tablet: 25 mg QD; PO ABT-333 tablet: 400 mg BID; PO Ritonavir SGC: 100 mg; PO Rosuvastatin tablet: 5 mg QD; PO 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

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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	M13-492	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 ABT-267 HME tablet: 25 mg QD; PO ABT-333 tablet: 400 mg QD; PO Ritonavir SGC: 100 mg QD; PO LPV/r tablet: 400/100 mg BID; PO	60	Healthy subjects	28 days	Complete, Full
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 ABT-267 tablet: 25 mg QD; PO ABT-333 tablet: 400 mg QD; PO 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 ABT-267 tablet: 25 mg QD; PO ABT-333 tablet: 400 mg BID; PO Ritonavir SGC: 100 mg QD; PO 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 ABT-333 tablet: 250 mg BID; PO Ritonavir SGC: 100 mg QD; PO Darunavir tablet: 800 mg QD; PO	24	Healthy subjects	28 days	Complete, Full

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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	M13-394	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 ABT-267 tablet: 25 mg QD; PO ABT-333 tablet: 400 mg BID; PO Ritonavir SGC: 100 mg QD; PO Atazanavir capsule: 300 mg QD; PO	72	Healthy subjects	28 days	Complete, Full
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 ABT-267 tablet: 25 mg QD; PO ABT-333 tablet: 400 mg BID; PO Ritonavir SGC: 100 mg QD; PO Emtricitabine capsule: 200 mg QD; PO 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 ABT-333: 400 mg BID; PO Ritonavir SGC: 100 mg; PO Efavirenz, emtricitabine, and tenofovir disoproxil fumarate tablet: 600/200/300 mg QD; PO	16	Healthy subjects	17 or 3 days	Complete, Full

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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	M13-782	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; ABT-267 tablet: 25 mg QD; PO; ABT-333 tablet: 400 mg BID; PO; Rilpivirine tablet: 25 mg QD; PO	60	Healthy subjects	28 days	Complete, Full
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 ABT-267 HME tablet: 25 mg QD; PO ABT-333 tablet: 400 mg BID; PO Ritonavir SGC: 100 mg QD; PO 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 ABT-267 HME tablet: 25 mg QD; PO ABT-333 tablet: 400 mg BID; PO Ritonavir SGC: 100 mg QD; PO 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

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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	M13-491	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; ABT-267 HME tablet: 25 mg QD; PO; ABT-333 tablet: 400 mg BID; PO; Ritonavir SGC: 100 mg QD; PO 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
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; ABT-267 HME tablet: 25 mg QD; PO; ABT-333 tablet: 400 mg BID; PO; ABT-450/r/ABT-267 tablet: 150/100/25 mg QD; PO; Ritonavir SGC: 100 mg QD; PO 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; 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; ABT-267 HME tablet: 25 mg QD; PO; ABT-333 tablet: 400 mg BID; PO; ABT-450/r/ABT-267 tablet: 75/50/12.5 mg QD; PO Ritonavir SGC: 100 mg QD; PO 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; Buprenorphine/ naloxone: 25 days	Complete, Full

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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	M12-205	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 ABT-333 tablet: 250 mg BID; PO EE/NGM tablet: 35/250 µg; PO NET tablet: 0.35 mg; PO EE/NET tablet: 35 µg/0.4 mg; PO	34	Healthy subjects	ABT-450/r/ ABT-267: 8, 19, or 21 days ABT-333: 19 or 21 days EE/NGM: 21 days NET: 17 days EE/NET: 15 days	Complete; Full
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 ABT-333 tablet: 250 mg BID; PO Escitalopram tablet: 10 mg; PO Duloxetine capsule: 60 mg; PO	48	Healthy subjects	ABT-450/r/ ABT-267: 16 or 20 days ABT-333: 16 or 20 days Escitalopram: single dose; 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 ABT-333 tablet: 250 mg BID; PO Alprazolam tablet: 0.5 mg; PO Zolpidem tartrate tablet: 5 mg; PO	24	Healthy subjects	ABT-450/r/ ABT-267 and ABT-333: 16 days Alprazolam and zolpidem tartrate: 2 days with washout	Complete, Full

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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	M14-325	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 ABT-333 tablet: 250 mg BID; PO Furosemide tablet: 20 mg with 20 mEq potassium bicarbonate tablet; PO Amlodipine besylate tablet: 5 mg; PO	26	Healthy subjects	ABT-450/r/ ABT-267 and ABT-333: 16 days or 24 days Furosemide or amlodipine besylate: 2 days with washout	Complete; Full
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 ABT-267 HME tablet: 25 or 50 mg or placebo; PO ABT-333 tablet: 250 or 500 mg or placebo; PO Ritonavir SGC: 150 mg or placebo; PO Moxifloxacin tablet: 400 mg; PO	60	Healthy subjects	Single dose per treatment period	Complete; Full
Efficacy and Safety	M12-114	5.3.5.1	Safety, PK, virologic response	Blinded, randomized, placebo-controlled	ABT-267 tablet: 5, 50, or 200 mg or placebo QD; PO pegIFN: 200 mg SC; RBV tablet: 1,000 to 1,200 mg QD (divided BID); PO	37	HCV GT1-infected treatment-naïve subjects	ABT-267: 12 weeks pegIFN and RBV: 48 weeks	Complete, Full

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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	M13-386	5.3.5.1	Safety, tolerability, antiviral activity, PK	Open-label	ABT-450 tablet: 150 mg QD; PO; ABT-267 tablet: 1.5 to 50 mg QD; PO; ABT-333 tablet: 400 mg BID; PO; Ritonavir SGC: 100 mg QD; PO 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	M13-393	5.3.5.1	Efficacy and safety with and without RBV	Open-label	ABT-450 tablet: 150 mg QD; PO; ABT-267 tablet: 25 mg QD; PO; Ritonavir SGC: 100 mg QD; PO RBV tablet: 1,000 or 1,200 mg QD (divided BID); PO	316	HCV GT1b and GT4-infected treatment-naïve and experienced adults	12 or 24 weeks	Ongoing; Interim
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; ABT-267 tablet: 25 mg QD; PO; ABT-333 tablet: 400 mg BID; PO Ritonavir SGC: 100 mg QD; PO 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

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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

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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	M13-961	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
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; ABT-333 tablet: 250 mg BID; PO; 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; ABT-333: 400 mg BID; PO; Ritonavir: 100 mg QD; PO 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	M12-998	5.3.5.2	Efficacy, safety, and PK with and without RBV	Open-label, randomized	ABT-450 tablet: ≤ 200/100 mg QD; PO; ABT-267 tablet: 25 mg QD; PO Ritonavir SGC: 100 mg QD; PO RBV tablet: 1,000 to 1,200 mg QD (divided BID); PO	61	Treatment-naïve, HCV-infected adults	12 weeks	Complete, Full

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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	M13-099	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 ABT-333 tablet: 250 mg BID; PO 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 ABT-333 tablet: 250 mg BID; PO; 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

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2.4.2. Pharmacokinetics

ABT-450

In the current application, ABT-450/r will be given in combination in a 3-DAA regimen with ombitasvir and dasabuvir or in a 2-DAA regimen with ombitasvir. Except for three single doses of ABT-450 (300, 600 and 900 mg) administered in the first-in-human study, ABT-450 has been administered with the pharmacokinetic enhancer ritonavir.

Absorption

The oral bioavailability of ABT-450 at 150 mg is approximately 50% (ranging from 35% to 71%). ABT-450 tmax occurred approximately 4 to 5 hours following single and multiple oral dosing with the co-formulated ABT-450/r/ombitasvir tablets at the 150/100/25 mg dose with and without dasabuvir in the non-fasting state. ABT-450 has low solubility.

Food increases the bioavailability of ABT-450 (up to 4 fold), which possibly could be explained by increased solubility. All Phase 1 to 3 studies have dosed ABT-450/r and ombitasvir with food and, hence, safety and efficacy data from these studies take into account the higher exposures observed when administered with food.

Different formulations of ABT-450 were used during development. The SDD formulation and the phase 3 formulations (co-formulated ABT-450/r/ombitasvir) differed with regards to the exposure of ABT-450. The co-formulated ABT-450/r/ombitasvir showed approx. 60% higher exposure of ABT-450 compared to the SDD formulation.

ABT-450 is a substrate of the transporter P-gp and BCRP.

Distribution

ABT-450 is approximately 97% to 98.6% bound to human plasma proteins showing no concentration dependency. The protein binding do not differ between subjects with normal renal and hepatic function, and subjects with renal and hepatic impairment.

The blood-to-plasma concentration ratio is approximately 0.7 in human blood, indicating that ABT-450 is preferentially distributed into the plasma compartment of whole blood.

Metabolism

ABT-450 was shown to be metabolised via CYP3A4/5 and possibly also extrahepatic CYP1A1 using cDNA expressed recombinant CYP enzymes. However, only disappearance of parent was investigated. Strong CYP3A inhibitors ritonavir and ketoconazole have confirmed that CYP3A is involved in vivo. An increase in the ABT-450 exposure was also seen after dosing with gemfibrozil (a strong CYP2C8 inhibitors as well as OATP1B inhibitor).

Unchanged parent drug was the major component (88.9%) of drug-related radioactivity in plasma. Five metabolites were identified in human plasma, including M2 (7.8% of total AUC), M29 (3.2% of total AUC), and trace levels of M3, M13 and M6.

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In urine, hydrolysis product M13 was the major component, accounting for 8.6% of the administrated radioactive dose. In faeces, hydrolysis product M29 was the most abundant radiochemical component, representing approximately 60% of the administered dose, followed by M2 and co-eluting metabolites M3/M18.

ABT-450 is a substrate of the liver uptake transporter OATP1B1 and OATP1B3. This was confirmed in vivo with the OATP1B1/OATP1B3 inhibitor cyclosporine, which increased the exposure to ABT-450 by 72%.

Elimination

Following dosing of ABT-450 with ritonavir mean plasma half-life of ABT-450 was approximately 5.5 hours. Following a single oral dose of [14C]ABT-450/r, the majority of the administered radioactive dose (87.8%) was recovered in faeces and only 8.76% was recovered in urine after a single dosing. Unchanged ABT-450 recovered in faeces and urine represented about 1.2% of the radiochemical dose. ABT-450 likely undergoes enterohepatic recirculation.

Dose proportionality and time dependency

ABT-450 has non-linear pharmacokinetics and shows greater than proportional increase in exposure with dose. At a ritonavir dose of 100 mg, increasing the ABT-450 dose from 25 mg to 400 mg increased the mean dose-normalized ABT-450 Cmax and AUC by approximately 60- and 50-fold, respectively. This non-linearity was observed across formulations and in the presence of ombitasvir.

The accumulation of ABT-450/r administered in combination with ombitasvir, with and without dasabuvir, was approximately 2-fold. Steady state was achieved within 7 to 11 days.

Special populations

The pharmacokinetics of ABT-450/r in special populations has only been investigated in the combination DAA regimens, as described below.

Interactions

P-gp and BCRP were inhibited by ABT-450 in vitro with IC50 of 29 µM and 0.6 µM, respectively. Based on the maximum expected concentration in the intestinal lumen (78 µM) there is a risk for clinically relevant drug-drug interactions of BCRP and P-gp in the gut. Based on systemic concentration *50 (1 µM) there is a risk for clinically relevant drug-drug interactions due to BCRP inhibition. In the P-gp digoxin study, 2-DAA gave rise to a higher effect (36%) than 3-DAA (16%) with dasabuvir. ABT-450 also inhibited OATP1B1 and OATP1B3 in vitro with IC50 values of 0.013 µM and 0.017 µM, respectively.

Interaction studies with pravastatin and rosuvastatin have confirmed that inhibition of OATP1B1 and BCRP is observed in vivo as well. Pravastatin (OATP1B1 substrate) exposures were increased by 36% and 82% by concomitant 2- and 3-DAA treatment, respectively. ABT-450, ritonavir, ombitasvir and dasabuvir (M1) are all inhibitors of OATP1B1 and could contribute to this inhibition. The exposure to rosuvastatin (substrate of OATP1B1 and BCRP) increased by 160% and by 30% when co-treated with the 3-DAA and 2-DAA regimen, respectively. These results show the in vivo BCRP inhibitory potential of ABT-450 and dasabuvir.

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The risk for clinically relevant drug-drug interactions due to ABT-450 inhibition of competitive CYP inhibition via CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4 is considered low. No metabolism-dependent inhibitors (MBI) for any CYP except a weak signal for CYP3A4 were observed.

ABT-450 is an inhibitor of UGT1A1 with an IC50 of 3.6 µM. This inhibitory effect was confirmed in an interaction study with ABT-450/r, ombitasvir and dasabuvir (the DAAs also being UGT1A1 inhibitors) and the UGT1A1 substrate raltegravir.

ABT-450 induced CYP2B6 and CYP3A4 mRNA in human hepatocytes, indicating that ABT-450 might affect PXR and CAR pathways. In combination with ritonavir, ombitasvir and dasabuvir induction was however only observed in vivo for CYP2C19.

In vivo interactions

Please see the section describing the *in vivo* interaction for the combination DAAs/r.

Ombitasvir

Ombitasvir will be administered in combination in a 3-DAA regimen with ABT-450/ritonavir and dasabuvir or in a 2-DAA regimen with ABT-450/ritonavir. The studies that have been performed with ombitasvir as a single DAA include an ADME studies, a single-ascending dose study, a multiple-ascending dose study and in vitro assays. All other studies were performed as combination DAA studies with ABT-450/ritonavir ± dasabuvir.

Absorption

Ombitasvir has an oral bioavailability of approximately 50%. The compound is absorbed with a tmax occurring approximately 5 h following single oral dosing of the co-formulated ABT-450/r/ombitasvir tablet (to-be marketed formulation) with food. There is no data on the absolute bioavailability of ombitasvir. Poor solubility and seemingly low in vitro permeability of the compound suggest that ombitasvir is not completely absorbed. Food increases the exposure to ombitasvir approximately 2-fold, which possibly could be explained by increased solubility. All Phase 1 to 3 studies have dosed ombitasvir with food and, hence, safety and efficacy data from these studies take into account the higher exposures observed when administered with food. These are also the recommendations given by the Applicant in the SmPC.

Distribution

The plasma protein binding, investigated over a concentration range covering the therapeutic concentrations of ombitasvir, is on average 99.9% and does not differ between subjects with different degree of renal function. In subjects with severe hepatic impairment, the unbound fraction of ombitasvir increased 2.24-fold.

Elimination

Ombitasvir was best described by a two-compartment model in the PPK model. It has a terminal $t_{½}$ ranging from approximately 18 h to 26 h.

Ombitasvir is mainly eliminated unchanged via the hepatobiliary route. Following an oral dose of [^{14}C] ombitasvir, ~90% of the dose was recovered in faeces (~88% as parent compound) and ~2% of the dose was recovered in urine (several minor unidentified metabolites). The specific transport pathways for hepatic uptake and biliary efflux of ombitasvir remain uncertain. The Applicant is encouraged to identify the transport mechanisms for hepatic uptake and efflux. This issue will however not be pursued since ombitasvir has been well

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tolerated at doses up to 200 mg for 12 weeks (refer to section 3.4.1. The dose selection of regimen components). In addition, co-administration with potent inhibitors such as cyclosporine, atazanavir/ritonavir and ketoconazole do not significantly affect the exposure to ombitasvir.

Ombitasvir was stable in both human liver microsomes and hepatocytes. Upon incubation with cDNA expressed recombinant enzymes some turnover of ombitasvir was observed with CYP3A4 and CYP2C8. In plasma, the major circulating components were unchanged ombitasvir and the metabolites M29, M36, M37 and M23. These four metabolites have negligible viral activity compared to ombitasvir.

Dose proportionality and time dependency

There was no statistically significant non-proportional effect when increasing the dose of ombitasvir from 1.5 mg to 200 mg. However, there seemed to be a tendency towards greater-than proportional increase at the doses up to 50 mg, which possibly could be caused by saturation of efflux transport proteins in the intestine and/or liver. Saturation of an uptake mechanism and/or elimination pathway may explain that the effect of ABT-450/r was greater on a 25 mg dose of ombitasvir compared to a 200 mg dose of ombitasvir.

Special populations

The pharmacokinetics of ombitasvir in special populations has only been investigated in the combination DAA regimens, as described below.

Interactions

The inhibition potential of ombitasvir was investigated for the most common CYP isoenzymes, UGT1A1 and several uptake and efflux transporters. Ombitasvir inhibited UGT1A1 with an IC50 of ~2 µM, suggesting an effect of intestinal UGT1A1. This inhibitory effect was confirmed in an interaction study with ABT-450/r and dasabuvir (the other DAAs also being UGT1A1 inhibitors) and the UGT1A1 substrate raltegravir. Ombitasvir also inhibited CYP2C8, but at the recommended dose of 25 mg ombitasvir is not expected to affect CYP2C8 in vivo (IC_{50} 7.4 µM). At a higher dose level (200 mg) ombitasvir seemed to increase the exposure to dasabuvir (cross-study comparison), which could be attributed to its inhibitory effect on CYP2C8. In vitro there was also a signal of induction of CYP2B6 mRNA levels, and at a high dose of ombitasvir (200 mg) the exposure to ABT-450 was reduced in vivo upon co-administration. The inducing effect of ombitasvir was, however, not observed at the clinically relevant dose.

In vivo interactions

See section describing the In vivo interaction for the DAA combination regimen.

Pharmacokinetic information of the DAA combination in the target population and special populations

Population pharmacokinetic analyses of Phase I/II and Phase III data suggested cirrhosis, sex, age, concomitant medication with opioids and anti-diabetics to be statistically significant predictors of ABT-450 CL. Significant covariates pertaining to ombitasvir CL were cirrhosis, sex, age and weight. Females had higher exposures ($AUC_{24,ss}$) to the DAAs compared to males: the highest increase of exposure was for ABT-450 (~100% higher), followed by ombitasvir (~55% higher), ribavirin (~30% higher), dasabuvir (≤ 30% higher), and ritonavir (~15% higher). There were no indications of an altered DAA exposure in Asians; Black and Hispanic/Latinos.

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The effects of the covariates were not considered clinically relevant and no dose adjustment based on gender, age, weight and race is warranted. ABT-450 and ombitasvir can be used irrespective of renal function but are contraindicated in patients with severe hepatic impairment.

Exposure associated with clinical response (efficacy and safety)
Phase II data suggest no impact on SVR rates when the ABT-450 exposure was reduced by 50%. Similarly ombitasvir monotherapy data suggest that Emax is reached at a dose of 25 mg without ritonavir, which is equivalent to an exposure 50% lower compared to the Phase 3 exposure.

Multivariate logistic regression of Phase III data did not identify a significant correlation between exposure and response for ABT-450 or dasabuvir, which implies that the dose of these two compounds corresponds to Emax. A correlation was identified for ombitasvir, however, the potential change in SVR associated with a 50% reduction is expected to be small. 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, ombitasvir and dasabuvir) were reduced by 50%.

Exposure-safety response modeling of phase II data was also conducted using multivariate logistic regression. ALT elevations and total bilirubin elevations were associated with increased ABT-450 and ribavirin exposures. However, based on the observed range of exposures a doubling of the predicted exposure appears acceptable.

In vivo interactions with the 3-DAA or the 2-DAA combination regimen

In the in vivo studies, all DAAs (2-DAA or 3-DAA combinations) are included and knowledge about the net effect of the two regimens is gained. This is satisfactory, but sometimes hinders mechanistic conclusions to be drawn for the individual compounds. Ritonavir affects a multitude of enzymes and transporters in a time dependent manner, and hence time dependent interactions are expected.

Ribavirin
The combination DAA regimen will be given together with ribavirin to a significant proportion of patients. Ribavirin is not hepatically eliminated and is not expected to interact with the DAAs or other hepatically eliminated compounds. Consequently, drug-interaction studies, thorough QT studies, and renal and hepatic impairment studies were conducted with the DAA combination without ribavirin. The influence of ribavirin on PK parameters was investigated in the PPK analysis, and the results did not show any relationship between use of ribavirin as covariate and CL/F of the DAAs.

Ritonavir
Ritonavir is primarily metabolized by CYP3A, with a minor contribution from CYP2D6. The compound is also a substrate of P-gp.

In vitro, ritonavir inhibited CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. No inhibitory effect was observed on CYP1A2. When the respective IC_{50} values were compared to the guideline cut off values, it was concluded that an in vivo effect of the in vitro inhibition could not be excluded for CYP2C9 and CYP3A4. The inhibition against CYP3A4 was shown to be time dependent. Ritonavir is also an inducer of several enzymes, and the net effect on the respective enzyme is dependent on which medicinal products ritonavir is administered together with. In combination with ABT-450, ombitasvir and dasabuvir induction was only observed for CYP2C19.

Ritonavir was not an in vitro inhibitor of OAT1, OAT3, OCT1, OCT2, MATE1, MATE2K and MRP2. In addition, it was concluded to be a negligible risk for systemic inhibition of BCRP by ritonavir, but potential inhibition at the intestinal level cannot be excluded. Ritonavir also inhibited P-gp, OATP1B1, OATP1B3 and OATP2B1 at clinically relevant concentrations. However, literature data suggest that ritonavir is not an in vivo inhibitor of OATP1B1.

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Use of different ABT-450 formulations in the DDI studies

Different ABT-450, ritonavir, ombitasvir and dasabuvir formulations have been used in DDI studies and Phase 3 studies. Exposures of ombitasvir, dasabuvir and ritonavir are comparable across these formulations. However, the exposure to ABT-450 following administration of the to-be-marketed formulation is ~60% higher bioavailability than the ABT-450 SDD tablet used in some of the DDI studies. Based on a mechanistic rational and regression analyses, the interaction studies performed with raltegravir, pravastatin, rosuvastatin, cyclosporine and tacrolimus may to some extent have underestimated the interaction magnitude. The recommendations for these interactions are adequately reflected in the SmPC.

Interaction between the individual components of the 3-DAA combination

ABT-450/r reduced dasabuvir exposures by ~50% and increased ombitasvir exposures by ~50%. Ombitasvir (at a therapeutic dose) did not affect the exposure to ABT-450, and based on cross-study comparison did not seem to affect dasabuvir pharmacokinetics to any clinically relevant degree. Dasabuvir increased ABT-450 exposures by ~50%, but did not affect ombitasvir exposures, the latter conclusion based on cross-study comparison.

Interaction studies providing a mechanistic understanding

Effects of other drugs on the pharmacokinetics of the DAAs

CYP3A4 and transporter inhibition (ketoconazole, cyclosporine and protease inhibitors)

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 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 to ketoconazole increased 2-fold. Given the time dependent effects of ritonavir, it cannot be excluded that the contribution of CYP3A4 mediated metabolism to the total elimination of ABT-450 may differ depending on whether ABT-450/rtv is dosed as a single dose or is at steady state. Hence, the effect of strong CYP3A4 inhibitors on ABT-450 at steady state remains uncertain. There are DDI studies with other strong CYP3A4 inhibitors that were co-administered at steady state and where the exposure to ABT-450 increased several-fold (e.g. see atazanavir/ritonavir below). As it cannot be excluded that the design of the ketoconazole study underestimated the effect of CYP3A4 inhibition on the exposure to ABT-450, a conservative approach with contraindication for concomitant use of strong CYP3A4 inhibitors is applied. To enable co-administration with an anti-fungal azole during treatment with Viekirax, the Applicant is encouraged to perform a DDI study with a suitable azole (of note, both victim and perpetrator drugs should be at steady state).

Cyclosporine: The combination of cyclosporine A (single dose; 10 mg or 30 mg) with the 3- and 2-DAA combinations (at steady state) was investigated. The exposure to ABT-450 was increased by approximately 72%, and there was an approximate 30% reduction in the exposure to dasabuvir (~20% reduction of its metabolite M1). Cyclosporine is classified as a moderate inhibitor of CYP3A4 and is also an inhibitor of OATP1B1/1B3, P-gp and BCRP. The increased exposure to ABT-450 may be explained by the inhibitory actions of cyclosporine A, and the reduced exposure to dasabuvir could potentially be caused by inhibited intestinal uptake transporters.

Protease inhibitors: Lopinavir/r and atazanavir increased the exposure to ABT-450 (by 2-to 6-fold), whereas darunavir both increased and decreased the exposure to ABT-450 depending on the combination of the DAAs as well the dosing regimen of the protease inhibitor (see section below “DDI studies with commonly co-administered HIV drugs”). In the cases where an increased exposure to ABT-450 was observed, the effect of

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the protease inhibitor is consistently higher for the 2-DAA regimen compared to the 3-DAA regimen. The greater effect on ABT-450 exposure may be caused by the combined effect of inhibited CYP3A4 and transporters (OATP1B1/3, BCRP and/or P-gp) by atazanavir and lopinavir.

CYP3A4 induction (carbamazepine)

Carbamazepine: In the presence of a strong CYP3A4 inducer, carbamazepine (200 mg BID), the concentrations of the DAAs were reduced: the decrease was 65% for ABT-450, 32% decrease for ombitasvir, 70% decrease for dasabuvir and 38% for dasabuvir M1. Further, ritonavir exposure was decreased with 83% to 87%. In this study, the 3-DAA combination was administered as a single dose in the form of co-formulated tablet. The carbamazepine study does not provide the worst case scenario, due to the use of single dosing of the DAA, which is not representative of the DAAs at steady state (as described above). The use of strong and moderate inducers is contraindicated in the SmPC.

CYP2C8 and OATP1B1 inhibition (gemfibrozil)

Gemfibrozil: In the presence of gemfibrozil (a mechanism based CYP2C8 inhibitor and OATP1B1 inhibitor) at steady state, the elimination of dasabuvir (given as a single dose in the 3-DAA regimen) was markedly reduced. The AUC of dasabuvir increased approx. 11-fold, and the metabolism to M1 was inhibited as evident from the 78% reduction of M1 AUC. There was a 38% and a 21% increase in the AUC and Cmax, respectively, of ABT-450. The pharmacokinetics of ritonavir was unaffected. Due to the effect on dasabuvir, concomitant use of strong CYP2C8 is contraindicated when Viekirax is administered with dasabuvir.

Other mechanism (tacrolimus)

Tacrolimus: A single dose of tacrolimus gave rise to a small to moderate reduction of the exposure of ABT-450, ritonavir, dasabuvir and dasabuvir M1. For ABT-450 the decrease was up to 40%, this effect is not considered clinically relevant.

Effects of the DAAs on the pharmacokinetics of other drugs

CYP3A substrates (alprazolam, amlodipine, cyclosporine, tacrolimus)

In Viekirax, ritonavir is included as a pharmacokinetic enhancer of ABT-450. Based on the inhibitory actions of ritonavir on CYP3A4, co-administration with compounds that are dependent on CYP3A4 for clearance and for which elevated plasma levels are associated with serious events is contraindicated.

Alprazolam: The 3-DAA combination at steady state and alprazolam were given alone and in combination. Alprazolam AUC was increased by 34%, the increased exposure to alprazolam is probably due to CYP3A4 inhibition by ritonavir and possibly also by ABT-450. 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 CYP3A4 substrate is likely higher. In the SmPC clinical monitoring of alprazolam is recommended. A decrease in alprazolam dose can be considered based on clinical response.

Amlodipine: When multiple doses of 3-DAAs were co-administered with a single oral dose of amlodipine besylate the amlodipine AUC increased 157%, while amlodipine harmonic mean $t_{1/2}$ increased from 42 hours to 104 hours. Cmax increased by 26% in amlodipine. No change in DAAs was observed.

Cyclosporine: Upon co-administration with the DAAs the dose normalised AUC of cyclosporine was increased 4.3-fold by 2-DAA and 5.8-fold by 3-DAA. The effect of C_{24} was 3-fold higher that the effect on AUC. The half-life was increased from 8.7 h to 9.8 h (2-DAA), indicating that the major part of the DDI occurred during absorption and/or first pass extraction. When the 3-DAA regimen was administered, the half-life was increased from 7.3 h

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to 24.5 h. A reduction of the initial cyclosporine dose to 1/5 of the normal daily dose is proposed in the SmPC with a dosing frequency of once daily instead of twice daily.

Tacrolimus: Dose normalised tacrolimus AUC was increased between 57- to 86-fold by the 3-DAA depending on the study design (tacrolimus given as single dose). Cmax and C_{24} of tacrolimus were decreased as well. The half-life increased up to 230 h. The 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. Administration of tacrolimus every week instead of BID is recommended. The resulting plasma concentration-time course of and the exposure to tacrolimus may differ from when a CYP3A4 inhibitor is not co-administered, however, there are clinical data on this combination.

CYP2C19 substrates (omeprazole and escitalopram)

Omeprazole: Co-administration of omeprazole with the DAAs regimen resulted in a 40-50 % decrease in omeprazole exposure. The omeprazole exposure decrease is likely a consequence of CYP2C19 induction mediated by ritonavir. Omeprazole is also metabolised by CYP3A, which is inhibited by ritonavir. Hence, the inducing effect on CYP2C19 may be more marked for those medicinal products where CYP3A4 mediated metabolism do not contribute to the elimination. The net induction effect by the 3-DAA and 2-DAA regimen on CYP2C19 is reflected in the SmPC.

Escitalopram: The exposure of a single dose of escitalopram was increased by 13% and 25% when co-dosed with the 2- and 3-DAA regimen, respectively, at steady state. Escitalopram is metabolized to S-desmethylcitalopram primarily by CYP2C19 and also by CYP3A and CYP1A2, and S-desmethylcitalopram is further metabolized by CYP2D6. Ritonavir can induce CYP2C19 and inhibit CYP2D6, while dasabuvir probably is a weak in vitro CYP2C19 inhibitor. The effect of the 2- and 3-DAA combination on escitalopram and S-desmethylcitalopram could be the effect of ritonavir and dasabuvir on these enzymes. As single dosing of escitalopram was used, the effect at steady state could be different due to the time-dependent effect seen by ritonavir.

CYP2C9 substrates (warfarin)

S-warfarin: The study aimed at evaluating the steady-state effect of the DAAs on a single dose warfarin and vice versa. The study results showed that both the 3-DAA and 2-DAA combination decreased the AUC of S- and R warfarin by 12-16 %. The half-life of warfarin was also reduced (mainly for S-warfarin). Warfarin is a NTI drug and even a small change may be clinically significant. Hence, it is recommended that INR should be monitored when warfarin is co-administered with 2-DAA and 3-DAA combinations. Clinically significant DDIs are not expected with other CYP2C9 substrates.

UGT1A1 substrates (raltegravir)

Raltegravir: Raltegravir was co-administered at steady state with the DAAs. The effect on raltegravir exposure was most marked with the 3-DAA combination, which increased the exposure to raltegravir approximately 2.5-fold. All DAAs are UGT1A1 inhibitors in vitro, therefore it is likely that several or all DAAs inhibits raltegravir's glucuronidation. The effects of the DAAs on drugs that are metabolised by glucuronidation are reflected in the Viekirax SmPC.

P-gp substrates (digoxin)

Digoxin: The potential for the 2-DAA or 3-DAA regimen (at steady state) to affect P-gp substrates was investigated with digoxin (single dose; 0.5 mg) as a P-gp probe. The exposure to digoxin was increased by 16% and 36% in the 3-DAA and 2-DAA regimen, respectively, whereas the terminal $t_{½}$ seemed to be unaffected. Digoxin is not considered to be a sensitive probe for P-gp interaction mediated in the intestine. Hence, even though the increase in digoxin was relatively small the SmPC needs to reflect that the DAAs may increase the

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plasma exposure to medicinal products that are sensitive for changed intestinal P-gp activity (such as dabigatran etexilate).

OATP1B1 and BCRP substrates (pravastatin and rosuvastatin)

Pravastatin: The effects of the 3-DAA and 2-DAA regimen (at steady state) on pravastatin (10 mg) (single dose) were investigated. The exposure to pravastatin was increased approx. 1.8 fold in both DAA regimens, and the terminal t½ of the compounds remained unchanged. The pharmacokinetics of pravastatin is known to be affected by changes in OATP1B1 and/or MRP2 activity. There were no in vitro inhibitory effects of any of the DAAs on MRP2, and the interaction is therefore hypothesized to be mediated via OATP1B1.

Rosuvastatin: The effects of the 3-DAA and 2-DAA regimen (at steady state) on rosuvastatin (5 mg) (single dose) were investigated. The exposure to rosuvastatin was dependent on whether dasabuvir was included in the DAA regimen. In the 3-DAA and 2-DAA regimen, the exposure to rosuvastatin was increased by 160% and 30%, respectively. The pharmacokinetics of rosuvastatin is mainly affected by inhibition of OATP1B1 and BCRP. The greater effect on rosuvastatin in the 3-DAA regimen suggests that dasabuvir contributes to the BCRP inhibitory effect.

Drug-drug interaction studies with commonly co-administered HIV drugs

Protease inhibitors (lopinavir/r, darunavir, atazanavir)

Lopinavir/ritonavir: Lopinavir/ritonavir (steady state 800/200 mg QD and 400/100 mg BID) was investigated with DAA regimens. The exposure to ABT-450 increased in all treatment groups with a fold increase that varied between 1.9 and 6.1, depending on both which DAA combination that was given and whether lopinavir/r was given BID or QD in the evening. The greatest effect on ABT-450 exposure (AUC increased 6-fold, Cmax increased 12-fold) was observed in the arm containing the 3-DAA regimen and lopinavir/r BID. Since increased exposure to ABT-450 is associated with a potential risk for ALT elevations, the combination of lopinavir/r and the DAA regimen is not recommended.

Darunavir: The effect of the DAAs on darunavir (800 mg QD morning and 600 mg BID) and vice versa was investigated. In an additional study, co-administration with darunavir/r (800/100 mg QD in the evening) was investigated. The mutual interactions were investigated when all study drugs were at steady state. The exposure to ombitasvir, dasabuvir and M1 were either comparably or decreased upon co-administration with darunavir. The greatest effects were observed on the exposure to ABT-450, but the results differed between the DAA combination as well as the PI regimen.

Due to the reduced darunavir concentrations, this combination will not be recommended in patients with extensive PI resistance (which excludes the darunavir BID dosing as a treatment option). Also, for simplicity, the combination with darunavir should only be allowed when darunavir without ritonavir is administered at the same time together with the DAAs.

Atazanavir: The effect of the DAAs 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 greatest magnitude of interaction was observed when atazanavir/r was added QD in the evening to the 3-DAA regimen and when atazanavir (without ritonavir) QD was added to the 2-DAA regimen (AUC increased ~3-fold). The increase in exposure to ABT-450 may be acceptable when the 3-DAA regimen is combined with atazanavir (QD in the morning). The combination carries an increased risk for hyperbilirubinemia (including ocular icterus), and this information is reflected in the SmPC.

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Other co-administered HIV drugs (emtricitabine, tenofovir disoproxil fumarate, efavirenz, rilpivirine, raltegravir)

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).

Efavirenz/emtricitabine/tenofovir disoproxil fumarate: The combination of ABT-450/r+dasabuvir and efavirenz/emtricitabine/tenofovir disoproxil fumarate (600/200/300 mg QD) was also investigated, but this study had to be terminated due to treatment emergent increases in ALT levels (see further the clinical safety summary and discussion).

Rilpivirine: The DAA combination regimen increased the exposure to rilpivirine (25 mg QD) approximately 2.5- to 3.2-fold (all study drugs administered to steady state). The effect of the DAAs on rilpivirine was more pronounced than what is reported for other strong CYP3A4 inhibitors, and based on the plasma concentration-time profile indicating enterohepatic recirculation of rilpivirine and the interaction profile of the DAAs, it can be hypothesized that other transporter pathways (potentially OATP inhibition) are involved in the interaction. Would an HIV protease inhibitor be added (atazanavir, darunavir) together with rilpivirine to the DAA regimen, rilpivirine exposure may increase even further (not recommended). Rilpivirine should be used cautiously, in the setting of repeated ECG monitoring.

Raltegravir: the study is described in section with UGT1A1 inhibition. The combination of raltegravir together with the DAA regimens was not linked to any particular safety issues in a limited set of patients treated for 12-24 weeks, and may therefore be recommended.

Drug-drug interaction studies with other commonly co-administered medicinal products

Methadone: A DDI study was conducted with subjects, who were on stable methadone therapy. The study showed a minimal effect on the methadone exposure, and compared to historical controls methadone seemed to have minimal impact on ritonavir, ombitasvir, dasabuvir and M1 exposures. However, data initially presented by the applicant suggested that the exposure to ABT-450 was significantly reduced. Methadone is an auto-inducer in vivo, but due to the difficulty in performing studies with methadone there are little in vivo DDI data on the compound.

More pharmacokinetic data with the final formulation used in the study have now been gained, and when comparing these data with historical controls there were no clear difference in ABT-450 exposures. There is a marked inter-study difference in ABT-450 exposure and using historical controls is not a satisfactory approach for this compound. However, it is difficult to study this interaction without making comparisons with historical controls. The efficacy of the combination of the 3-DAA regimen with methadone has been evaluated in GT1 HCV patients taking methadone (n=19), the majority of these patients were 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% (3-DAA) and

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by 111% (2-DAA). It is not understood why the absence of dasabuvir gives rise to these increases in exposure. This again indicates that there is induction when dasabuvir is present; either that dasabuvir is an inducer or that it increases the exposure of an inducer. Comparison of DAA exposure was made with historical controls. This approach is not adequate for this kind of high variability situation. No marked differences were observed.

Zolpidem: A single dose of zolpidem decreased ABT-450 exposure by up to 37%. The mechanism behind this interaction is not known, but there is data in the literature that shows that zolpidem is a PXR activator in vitro. The reduction in ABT-450 exposure is not considered clinically relevant.

Duloxetine: A single dose of duloxetine exposures were 17% to 25% lower when co-dosed with the 2-DAA or 3-DAA regimen 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 due to 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.

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 10th, 4 th and 8th 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. Based on this study and on clinical safety data analyses, use of EE is contraindicated. Based on available safety data, use of other estrogens is not restricted.

Ortho-Cyclen (EE/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 to 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 to 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 (EE) 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 POP. The pharmacokinetics of ritonavir, ombitasvir and dasabuvir was largely unaffected. The exposure to 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 exposure to ombitasvir seems to have been increased based on C24, but this could be due to accumulation during multiple-dosing. The sparse C24 data on dasabuvir and M1 did not indicate a marked increase in exposure.

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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 to norethindrone was increased (AUC at day 4 29% increased) but the full extent is unknown.

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) could explain both reduced DAA exposure and higher risk of hepatic safety issues. Other mechanisms such as BSEP inhibition/down-regulation are also possible.

Transaminases observed in DDI studies

Inhibitors of the bile salt export pump (BSEP), such as glybenclamide, troglitazone and oestrogen have been associated with liver cholestasis (Paulis Magnus et al 2010). Both ABT-450 and ritonavir have been shown to be inhibitors of BSEP *in vitro*. Dasabuvir and is also an inhibitor *in vitro* but at 30-fold higher than clinically relevant concentrations. Oestrogen and progesterone metabolites are also 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. There is a post approval measure (PAM) on a safety analysis of the risk of raised transaminases if the 3DAAS are combined with a BSEP inhibitor.

2.4.3. Pharmacodynamics

Mechanism of action

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.

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.

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

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.

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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 the 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.

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.

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.

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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.

Resistance in HCV Genotype 4a Chimeric Replicons

In a stable cell line replicon containing NS3 from HCV genotype 4a, variants at amino acid positions 155, 156 and 168 were observed subsequent to passaging in the presence of ABT-450. In transient assays, A156T and R155C conferred 40-fold and 59-fold resistance to ABT-450, respectively, relative to the wild-type HCV genotype 4a chimeric replicon; while A156V, D168H, and D168V conferred 155 to 323-fold resistance to ABT-450. Thus, resistance to ABT-450 in genotype 4a occurs through mutations at similar positions as in genotype 1

In a stable cell line replicon containing NS5A from HCV genotype 4a, L28V was the only variant selected subsequent to passaging in the presence of ABT-267. L28V conferred 30-fold resistance to ABT-267 relative to the wild-type HCV genotype 4a chimeric replicon in a transient assay. Like other NS5A inhibitor, the barrier to resistance of ABT-267 in genotype 4 may be more similar to genotype 1b than to -1a.

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ABT-333 has no activity against genotype 4.

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 1. 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			

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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.

Table 2.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

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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 and genotype 4, 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 3. Frequencies of RAVs in PVF population vs. in those achieving 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

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	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 4. Observed Data SVR24 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.

There were only 3 subjects with genotype 4 that experienced virological failure. Phylogenetic analysis indicated that all 3 were infected with subtype 4d. Prior to treatment, no variants were seen in samples from any of the 3 subjects at resistance-associated positions relative to the reference sequence in NS3, whereas 1 subject had T58P and 1 had T58T/S present in NS5A at baseline. It is not known whether T58P or T58S in subtype 4d confers resistance to ABT-267.

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,

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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 5. 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	-

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		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

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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.

As stated above, 3 patients with genotype 4 experienced virological failure. 2 subjects had D168V and 1 subject had Y56H + D168V present in NS3. In NS5A at the time of virologic failure, 1 subject had L28V, 1 subject had L28S and M31M/I in addition to the T58P which had pre-existed at baseline, and 1 subject had L28V in addition to the T58S which was present at baseline.

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 6. Persistence of Emerged RAVs over 48 weeks of follow-up (clonal sequencing)

Target	Emerged Variant[a]	Prior to PTW24[b] n/N, %[c]	PTW24	PTW48
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.

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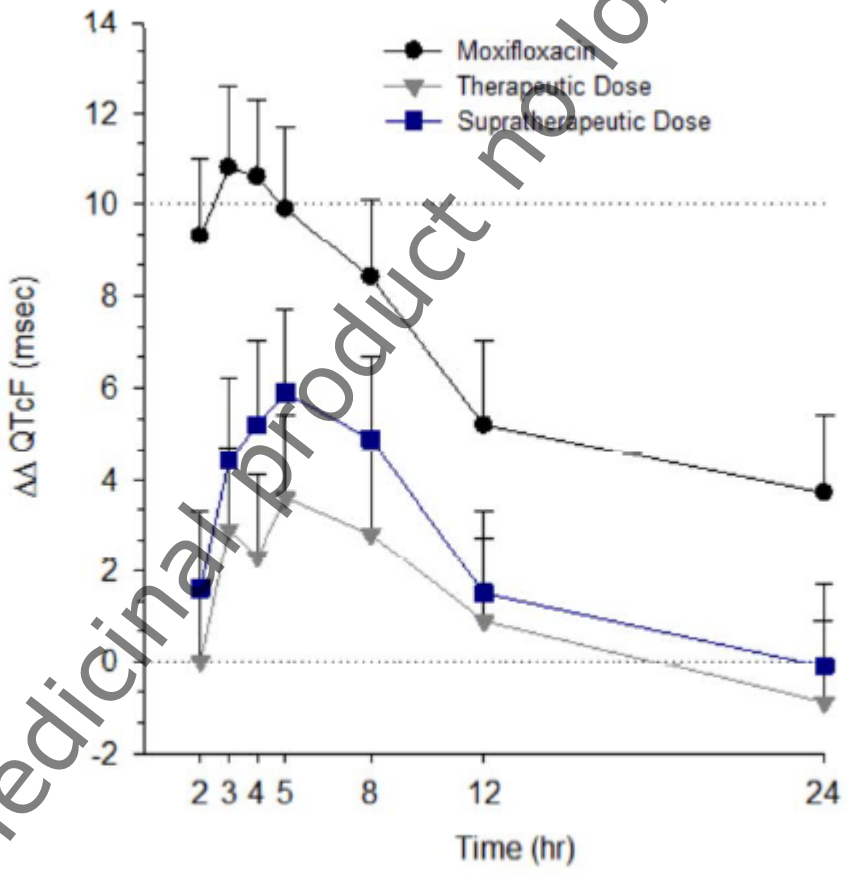
Thorough QT study

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.

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2.4.4. Discussion on clinical pharmacology

The relative contribution of CYP3A4 and other pathways to the total elimination of ABT-450 at steady state remains uncertain due to the time-dependent effects of ritonavir. This means that the elimination pathways and metabolite pattern of ABT-450 may be different following a single dose of ABT-450/ritonavir compared with multiple doses. For example, M2 represented 3-8% of parent AUC after a single dose, but only 0.6% of parent AUC at steady state. Hence, it is unfortunate that the ADME study was performed as a single dose study.

There are interaction studies that have been performed with the DAAs at steady state, but from these studies it is difficult to delineate the contribution of CYP-mediated metabolism and transporter-mediated hepatobiliary secretion, respectively.

Hence, CHMP decided to request that, in order to identify potential interactions that may not have been sufficiently addressed by the Applicant, further in vitro studies to characterise the enzyme(s) catalysing the formation of the main metabolites of ABT-450 found in urine and faeces are to be submitted as a post-authorisation measure. It is important that the design of such studies is optimized in order to enable extrapolation to the in vivo steady state situation, where the metabolism of ABT-450 is affected by ritonavir. Recognising that this is a challenging task, the Applicant should submit the study protocol to CHMP for agreement as a first step.

To understand the elimination of ABT-450 further, the formation of metabolite M29 (representing a large part of the total radioactive dose in the ADME study) needs to be clarified. It is agreed that data indicate that the formation of M29 occurs within the intestinal lumen, but this should be confirmed by stability data of ABT-450 in human intestinal fluid (eg., FaSSIF/FeSSIF) and faecal homogenates as a post-authorisation measure to be submitted by the Applicant by March 2015. If formation of M29 is not evident from such studies, further investigations may be warranted.

Co-administration of ABT-450 with BSEP inhibitors could in theory lead to a higher frequency of transaminases elevations or hepatotoxicity (both ABT-450 and ritonavir may be inhibitors of BSEP). The applicant has evaluated the potential association between co-administration of a BSEP inhibitor (Phase 2/3 data) and frequency of post baseline serum ALT elevations. However, the analysis should have been performed with potential BSEP inhibitors defined using the cut-offs provided in the EMA Guideline on the Investigation of Drug Interactions and the Applicant is requested to analyse the clinical safety data with respect to concomitant use of drugs that may inhibit BSEP based on the EU guideline criteria (50*Cmax,u/Ki≥1) and submit this analysis as a post-authorisation measure by March 2015.

Discussion on pharmacodynamics

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.

Similar to NS5A inhibitor daclatasvir, 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.

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.

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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

The Applicant has provided an extensive number of in vitro and in vivo studies, and the basic pharmacokinetic characteristics of ABT-450, ritonavir, ombitasvir and dasabuvir have been sufficiently well described. Three post-approval measures are suggested in order to improve the understanding of the elimination of ABT-450 and further investigate potential mechanism for the transaminases elevations, and the SmPC needs further amendments to adequately describe the interaction potential.

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 (the discussed further in the efficacy section).

2.5. Clinical efficacy

2.5.1. Dose response studies

The dose selection of regimen components

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.

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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 for ABT-450

M11-602 was a dose-ranging study for ABT-450/r was conducted using monotherapy and combination therapy with pegIFN and RBV in HCV genotype 1-infected treatment-naïve subjects.

While 3-day monotherapy with ABT-450/r doses of 50/100 mg to 200/100 mg with the capsule (HGC) formulation showed similar ~4.0 log10 viral load decline, a possible dose-response relationship was observed for virologic failure rates when these doses were administered for 12 weeks in combination with pegIFN and RBV followed by administration of pegIFN and RBV for a total duration of up to 48 weeks.

In treatment-naïve, GT1-infected subjects, ABT-450 doses ≥ 100 mg using the capsule formulation combined with pegIFN and RBV, showed a lower virologic failure rate compared to a lower ABT-450 dose of 50 mg – 0/15 (0%) subjects with virologic failure at ABT-450/r 100/100 mg and 200/100 mg compared to 3/8 (37.5%) at ABT-450/r 50/100 mg.

Resistant variants selected with ABT-450/r suggested a potential advantage of the higher ABT-450 doses as shown in the following table:

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Table 70. Selection of Protease Mutant R155K Following ABT-450/r Monotherapy and at the Time of Virologic Failure in DAA Combination Therapy

Treatment	Population	ABT-450/r Dose	R155K % (n/N)
Monotherapy (3 Day)	Naïve	50/100 mg HGC	100% (3/3)
		100/100 mg HGC	50% (1/2)
		200/100 mg HGC	0% (0/3)
DAA Combination	Naïve[a] and Treatment-experienced	100/100 mg SDD	20% (2/10)
		150/100 mg SDD	11.4% (4/35)[b]
		200/100 mg SDD	0% (0/11)

Table includes Studies M11-602, M12-746, M12-998, and M11-652.

N = number of subjects with HCV RNA > 500 IU/mL in Study M11-602 or with HCV RNA > 1000 IU/mL in Study M12-746 and Study M11-652.

a. Includes RBV-free regimens (ABT-450/r + ABT-267 in M12-998 and ABT-450/r + ABT-267 + ABT-333 in Study M11-652).

b. One subject took ABT-450 50 mg instead of ABT-450 150 mg for the first 3 weeks and has been excluded from the table.

Thus, in monotherapy, all tested doses yielded an approximate 4 log10 decline in plasma HCV-RNA. The antiviral potency of this NS3/4A inhibitor is similar to that seen, e.g., for telaprevir and simeprevir. This effect in a short term monotherapy study is exerted on the dominant viral population. The applicant points to indications that within the tested dose range, activity against the common R155K escape variant, conferring a 37-fold shift in EC50, was higher with higher doses within the tested interval. The notion that the selected dose, and subsequent exposure, should, if possible, also impact emerging resistant variants, is central to antiviral drug dose selection. This is anticipated to increase the barrier to resistance. The applicant applied principles entirely in line with the prevailing drug development paradigm.

While higher doses of ABT-450 provided better suppression of resistant variants in Phase 2 studies, higher doses have also been associated with a higher incidence of ALT elevations.

Table 71. ALT Elevations Across ABT-450/r Doses of 100/100 mg to 250/100 mg in Phase 2 Studies M12-746, M11-652, M12-998, and M13-386

	ABT-450/r Dose			
	100/100 mg	150/100 mg	200/100 mg	250/100 mg
N	164	365	105	19
Grade 1	29 (17.7%)	80 (21.9%)	35 (33.3%)	2 (10.5%)
Grade 2	2 (1.2%)	5 (1.4%)	1 (1.0%)	1 (5.3%)
Grade 3	1 (0.6%)	1 (0.3%)	4 (3.8%)	1 (5.3%)
Grade 4	0	0	1 (1.0%)	0

N indicates the number of subjects with post-baseline ALT value through the final treatment; only subjects with HCV GT1-infection are included from Study M12-998.

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For a further discussion of ABT-450-associated transaminitis and hepatic safety, see section on clinical safety.

A comparison of grade 3+ ALT elevations following DAA combination therapy and R155K selection following monotherapy and DAA combination therapy across different ABT-450/r doses from Phase 2 studies is shown below.

Figure 13. Comparison of Grade 3+ ALT Elevations Following Combination Therapy and R155K Selection Following Monotherapy and Combination Therapy in Phase 2 Studies

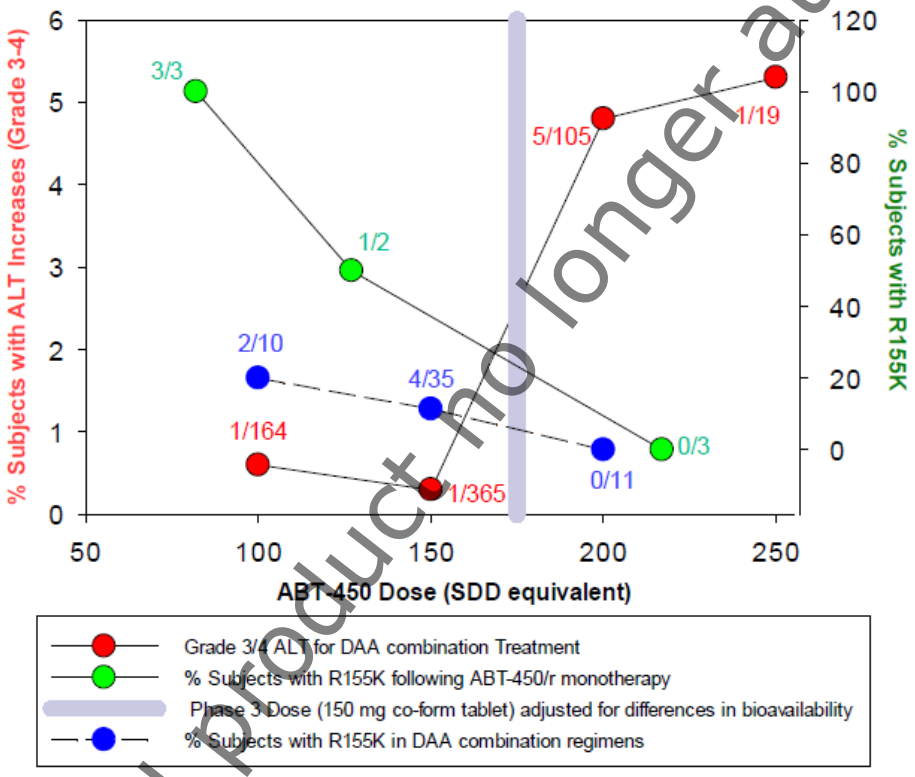

Figure includes Studies M11-602, M12-746, M12-998, M11-652, and M13-386.

Notes: One subject in the 150 mg dose group (who was misdosed) was excluded from the plot. The gray vertical bar reflects exposure with the Phase 3 formulation at the ABT-450/r 150/100 mg dose.

Thus, the selected dose of ABT-450 is a compromise to confer further benefit in providing antiviral efficacy, and therefore a greater barrier to resistance, given the certainly pre-existing resistant variants on the one hand, and the need to limit the incidence of transaminitis, which is an exposure dependent effect of ABT-450, on the other.

The dose selection of ABT-267

ABT-267 has been administered as monotherapy (Studies M12-116 and M13-386) at doses ranging from 1.5 mg QD to 200 mg QD for 2 to 3 days. The maximum change in viral load decline following monotherapy with ABT-267 doses in the range of 1.5 mg QD to 200 mg QD is shown below.

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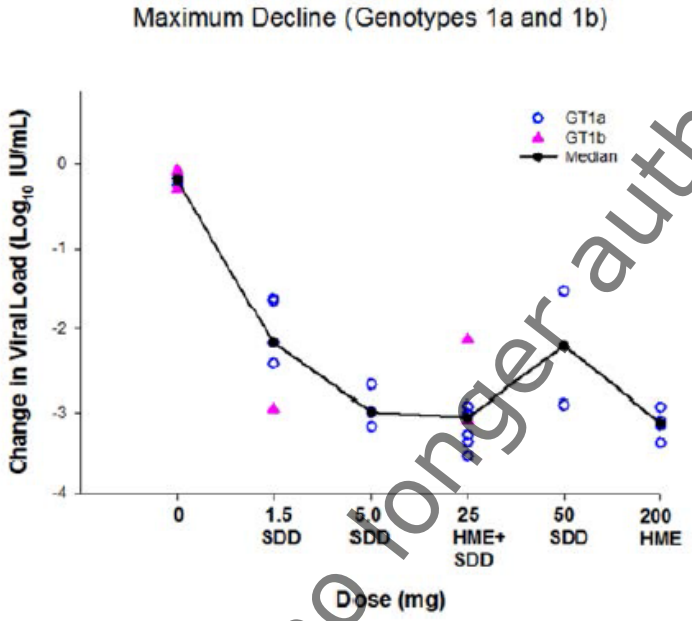
Figure 16. Maximum Change in Log_{10} Viral Load from Baseline Versus ABT-267 Dose Following ABT-267 Monotherapy for 2 Days in Studies M12-116 and M13-386 (GT1a and GT1b Combined)



ABT-267 at 5 mg QD (N = 9), 50 mg QD (N = 9) and 200 mg QD (N = 10) has also been administered for 12 weeks in combination with pegIFN/RBV, followed by administration of pegIFN/RBV for an additional 36 weeks in Study M12-114. Virologic failure rates were comparable across ABT-267 5 mg, 50 mg, and 200 mg doses. Two subjects in the 5 mg dose group who completed assigned treatment relapsed; 2 subjects and 1 subject rebounded in 50 mg and 200 mg dose groups, respectively.

Based on the protein-adjusted EC50 value in replicon and Ctrough concentration in HCV-infected subjects, ABT-267 doses ≥ 25 mg QD have the potential to suppress the GT 1a M28V variant which confers approximately 60-fold loss in susceptibility to ABT-267 compared to wild type. Other single mutants such as Y93H confer much higher fold-changes and could not reasonably be covered with a higher dose.

In Study M12-114, ABT-267 doses of 5 mg QD, 50 mg QD, and 200 mg QD for a duration of 12 weeks were well-tolerated by HCV-infected subjects in combination with pegIFN and RBV, with adverse events and laboratory abnormalities comparable to pegIFN/RBV alone.

ABT-267, when dosed with ABT-450/r, has been shown to decrease ABT-450 exposures. The effect of ABT-267 on ABT-450 exposures is shown in Figure 18.

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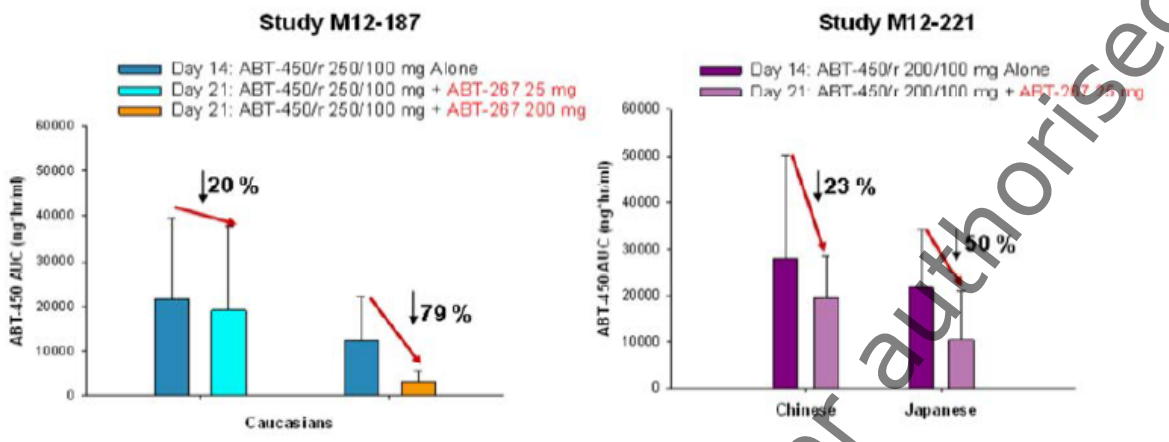
Figure 18. Effect of ABT-267 on ABT-450 Exposures



Note: Study M12-187: arms for which data are shown above had 70% Caucasians and no Asians. Study M12-221 was conducted in Chinese and Japanese subjects.

This suggests that increasing ABT-267 dose could have a detrimental effect on ABT-450 exposures. As ABT-450 is the most potent of the relevant DAAs, the increase in ABT-267 exposure at the expense of ABT-450 exposures is undesirable.

Based on these data, the ABT-267 25 mg QD dose was selected for Phase 3 studies.

The dose selection of ritonavir

The ritonavir dose selected for coadministration with ABT-450 is 100 mg. This is based on the pharmacokinetics of ABT-450 at different ritonavir doses and historic data with ritonavir 100 mg in HIV-1-infected subjects.

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.

The selection of treatment regimens for the phase 3 studies

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.

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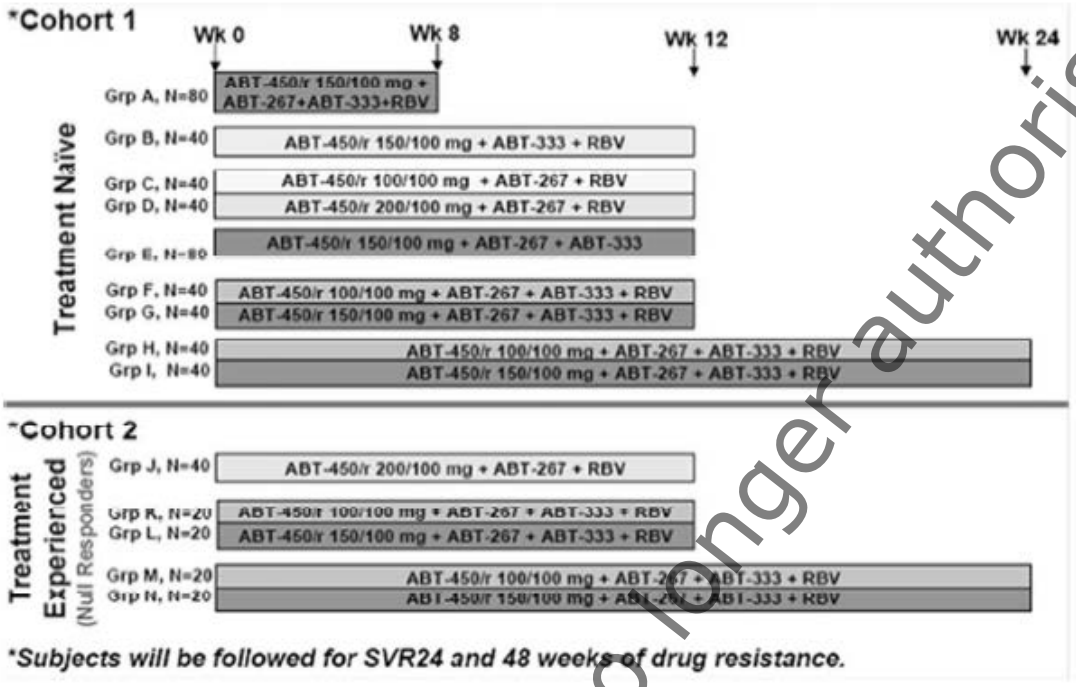
Figure 4. Study Schematic (Study M11-652)



For each arm, dosing was as follows:

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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.

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- 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 7. 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	450 267 333 RBV	450 - 333 RBV	450 267 - RBV	450 267 333 -	450 267 333 RBV	450 267 333 RBV	450 267 - RBV	450 267 333 RBV	450 267 333 RBV
SVR GT 1a n/N %	47/56 83.9	22/29 75.7	43/52 82.7	43/52 82.7	51/54 94.4	48/54 88.9	21/26 80.8	25/28 89.3	26/27 96.3
SVR GT 1b n/N %	23/24 95.8	12/12 100	27/27 100	25/25 100	25/25 100	24/25 96	19/19 100	17/17 100	15/16 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.

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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.

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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 8. 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). It is notable, however, that among the non-cirrhotic patients with genotype 1b infection in the AVIATOR study, 46/46 patients treated with 2DAA+RBV achieved SVR, indicating that this is a highly effective regimen in genotype 1b, as it has been shown to be in genotype 4 (see below).

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.

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2.5.2. 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 genotype 4 patients in patients with genotype 1 virus that are on opiate substitution, and in patients with genotype 1 infection that have HIV coinfection.

Table 9. 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
M13-393 (PEARL-1)	1b and 4	TN/TE	N+Y	ABT-450/r + ABT-267 +/- RBV for 12 or 24 weeks	316
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.

2.5.2.1. 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.

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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 the existing 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 10. Definitions of cirrhosis as inclusion/exclusion criterion in phase 3.

	Defining cirrhosis (inclusion criterion), - studyM13-099	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,

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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.

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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	Risperidone
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)	

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2.5.2.2. Results of the main studies

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

Table 11. Main demographics/characteristics in the phase 3 studies Numbers concern total number of patients randomized to active therapy

	SAPPHIRE-1 (GT-1) 3-DAA + RBV (N=473)	PEARL-4 (GT1a) 3-DAA +/- RBV (N=305)	PEARL-3 (GT1b) 3-DAA +/- RBV (N=419)	Sapphire-2 (GT1) 3-DAA + RBV (N=297)	PEARL-2 (GT1b) 3-DAA +/- RBV (N=186)	TURQUOISE-2 (GT1) 3-DAA + RBV (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

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

Study M11-646 (SAPPHIRE-1)

Title of the study:
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 12. 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]

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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)

Title of the study:

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 13. 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).

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Study M13-961 (PEARL-III)

Title of the study:

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 14. 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.

2.5.2.2.2. 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% relapsed after the end of treatment; 10-15% are partial responders and approximately 20% are null responders.

Study M13-098 (SAPPHIRE-II)

Title of the study:

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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 15. 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)

Title of the study:

A randomized, open-label, multicenter 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.

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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 16. 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

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

Study M13-099 (TURQUOISE-II)

Title of the study:

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 subgenotype; 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.

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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 17. SVR12 by duration and subtype, and treatment populations, TURQUOISE-2 (ITT)

	3DAAs + RBV 12 weeks (N=208)		3DAAs + RBV 24 weeks (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 18. 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)

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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 19. 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 20. 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.

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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

2.5.2.3. Efficacy in genotype 4

Study M13-393 (PEARL-1)

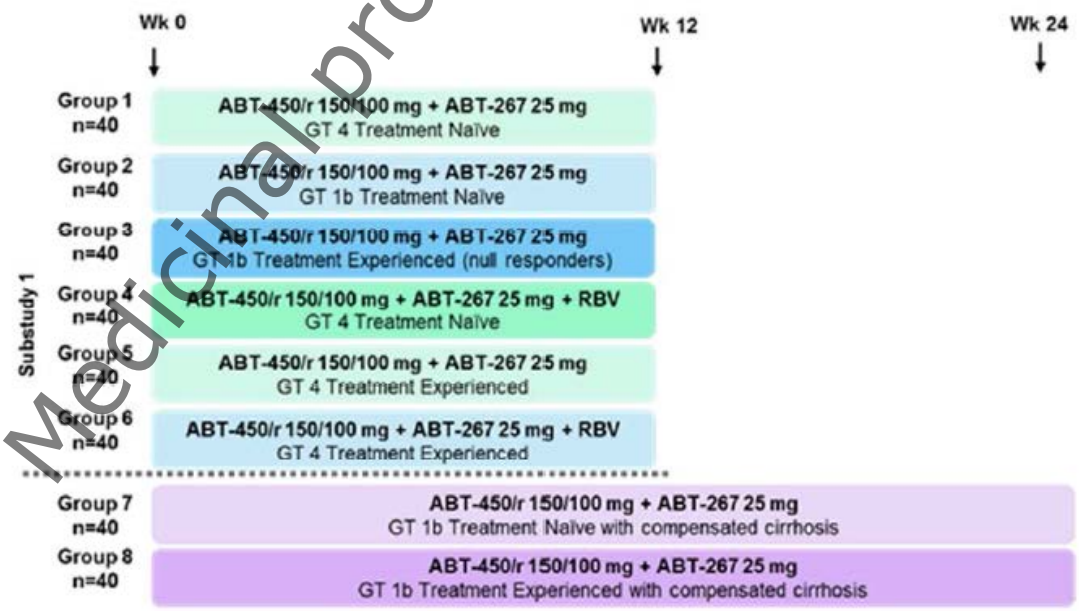
Title of the study:

A randomized, open-label study to evaluate the safety and efficacy of co-administration of ABT-450 with ritonavir (ABT-450/r) and ABT-267 in adults with chronic hepatitis C virus infection (PEARL-I)

This study comprises different study arms where patients have either genotype 4 or genotype 1b virus. In the present context, the focus is on genotype 4, and genotype 1b data are only discussed insofar as they are used for bridging assumptions. .

ABT-450 + ombitasvir (2DAA) was administered for 12 weeks, with or without RBV, in adult HCV genotype 4-, non-cirrhotic treatment-naïve subjects. This 2-DAA regimen was also administered with RBV in adult HCV genotype 4-infected, non-cirrhotic pegIFN/RBV treatment-experienced subjects. As previously stated, based on in vitro findings, ABT-333 in not anticipated to show any activity against genotype 4. In arms 7 and 8 (see below) 2-DAA alone were given for 24 weeks to treatment naïve and pegIFN/RBV treatment experienced patients with GT1b infection and compensated cirrhosis.

Figure 1. Study Schematic



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The study mainly comprised patients with viral subtypes 4a and 4d, which is typical of a European genotype 4 population. Among 1b cirrhotics, approximately 40% had platelets below 120 and 87% had IL28 non-CC genotype

Table 21.

Endpoint	Genotype 4 treatment naive		Genotype 4 treatment experienced	Genotype 1b cirrhotic, TN or TE
	Group 1 2 DAA for 12 weeks	Group 4 2 DAA + RBV for 12 weeks	Group 6 2 DAA + RBV for 12 weeks	Group 7+8 2 DAA for 24 weeks
SVR12	40/44 (90.9%)	42/42 (100%)	49/49 (100%)	96/99 (97%)
On treatment virological failure	1	0	0	0
Relapse	2	0	0	1
Premature study drug discontinuation	1	0	0	1

Thus the efficacy of 2 DAA+RBV was excellent, as would have been anticipated given that there may be similarities in response between genotype 4 and genotype 1b based on virological considerations. Notably, there were a few virological failures when RBV was excluded.

While there are presently no data available on the treatment of patients with genotype 4 and cirrhosis, it is notable that the in vitro EC50 for GT1b and GT4 is similar for both paritaprevir and ombitasvir. Furthermore, the barrier to resistance may be roughly similar for both drugs and (sub)genotypes (see pharmacodynamics section). As 2DAA were highly effective when given for 24 weeks to GT1b cirrhotics, it appears that an inference of likely similar efficacy of 2DAA+RBV if given for 24 weeks to GT4 cirrhotics can be made.

2.5.2.4. 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

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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%) 1b: 5 (14.7%)
IL28B C/C	8 (23.5%)
Baseline HCV-RNA	6.6 log10
Immunosuppressive medication	Cyclosporine: 5 (14.7%) Tacrolimus: 29 (85.3%)
Baseline fibrosis stage	F0-F1: 19 (55.9%) 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.

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2.5.2.5. 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 co-administered with ribavirin (RBV) in adults with genotype 1 hepatitis C Virus (HCV) infection taking methadone or buprenorphine.

From a regulatory perspective, patients with HCV infection taking opiate substitution therapy are 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. (also 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.

2.5.2.6. 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.

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2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Each of the medicines 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 ABT-450+ombitasvir +/- RBV in non-cirrhotic patients with genotype 4 infection and 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.

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

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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 12 weeks	3 DAAs + RBV 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 12 weeks	3DAAs + RBV 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.

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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	59/64 (92.2)	52/56 (92.9)
	Relapse	5/64	1/56
IL-28 CC	SVR12	19/19 (100)	15/16 (93.8)
	Relapse	0/19	0/16
IL-28 non-CC	SVR12	40/45 (88.9)	37/40 (92.5)
	Relapse	5/45	1/40
Rebound:		0/64	0/56
Treatment experienced			
ALL	SVR12	65/76 (85.5)	62/65 (95.4)
	Relapse	7/76	0/65
Prior NULL-response	SVR12	40/50 (80.0)	39/42 (92.9)
	Relapse	7/50	
Prior Partial response	SVR12	11/11 (100)	10/10 (100)
	Relapse	0/11	
Prior relapse	SVR12	14/15 (93.3)	13/13 (100)
	Relapse	0/15	
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

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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.

As anticipated based on virological findings, the efficacy of ABT-450+ombitasvir+ribavirin for 12 weeks is very high in non-cirrhotic patients with genotype 4, with 100% SVR among 91 patients presented in an interim analysis from the PEARL-1 study. This supports an indication in such patients, including those with prior exposure to peginterferon+ribavirin. Available in vitro and resistance selection data indicate the possibility of bridging efficacy from genotype 1b to 4 and vice versa. On the basis of the efficacy of 2DAA without RBV for 24 weeks in compensated cirrhotics with genotype 1b in the M13-393 study, the applicant proposes that 2DAA+RBV for 24 weeks may be inferred to show high efficacy in patients with GT4 infection and compensated cirrhosis. This is accepted.

These drugs in combination have not been thoroughly developed in other genotypes; notably, efficacy is anticipated to be genotype dependent for at least ABT-450 and dasabuvir.

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.

2.5.4. 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. ABT-450+ombitasvir+ RBV is highly effective in patients with genotype 4. Failure of

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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.

2.6. 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 the existing ICH recommendations.

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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.

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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.

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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:

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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.

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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.

- One subject 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.
- One subject 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.
- One subject 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.

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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 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.

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

Subject (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						
(63/M/W)/M13-098	3-DAA + RBV for 12 weeks	54	59	Cerebrovascular accident	Severe	HOS
(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
(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						
(48/F/W)/M13-961	3-DAA for 12 weeks	73	ongoing	Arthritis	Moderate	HOS
(19/M/W)/M14-002	3-DAA + RBV for 12 weeks	83	98	Pancreatitis[c]	Moderate	HOS

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Subject (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						
(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
(25/F/W)/M13-099	3-DAA + RBV for 12 weeks	8	29	Hepatitis acute[b]	Severe	IMP
(67/F/B)/M13-099	3-DAA + RBV for 24 weeks	152	156	Anaemia[b]	Severe	HOS, IMP
(61/F/W)/M13-099	3-DAA + RBV for 24 weeks	12	19	Chronic obstructive pulmonary disease[b]	Severe	HOS
(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
(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.

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Table 2. Definitions of CTCAE Grades for Selected Laboratory Parameters

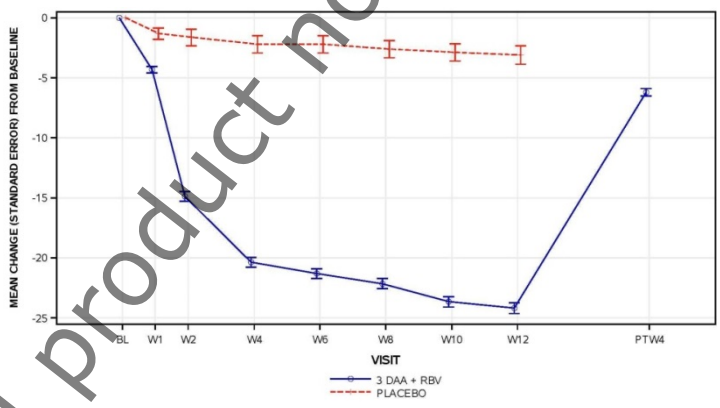
Test	Grade 1	Grade 2	Grade 3	Grade 4
ALT	> ULN – 3 × ULN	> 3 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN
AST	> ULN – 3 × ULN	> 3 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN
Alkaline phosphatase	> ULN – 2.5 × ULN	> 2.5 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN
Total bilirubin	> ULN – 1.5 × ULN	> 1.5 – 3 × ULN	> 3 – 10 × ULN	> 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.

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

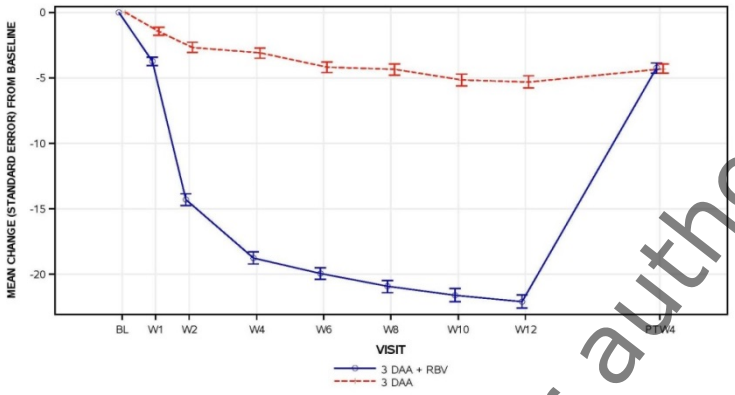

Table 31. Haemoglobin by Grade During the Treatment Period (Placebo-Controlled and Regimen-Controlled Analysis Sets)

	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.

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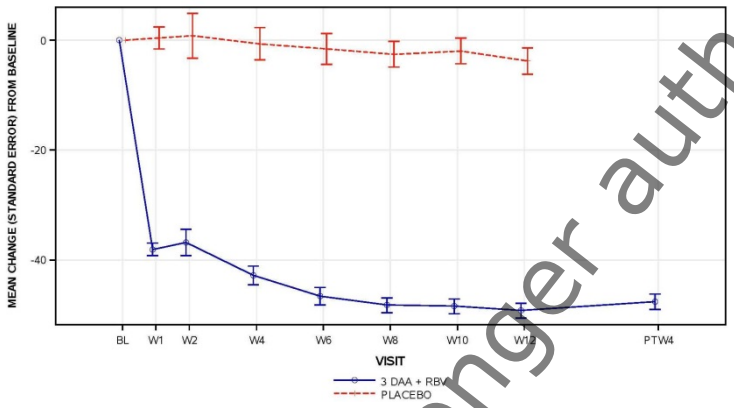
2.6.1. Hepatic safety

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.

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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 subanalysis, patients on ethinyl estradiol (rather than other oestrogens such as oestradiol, estriol and conjugated oestrogens) were the driver of the excess transaminitis 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.

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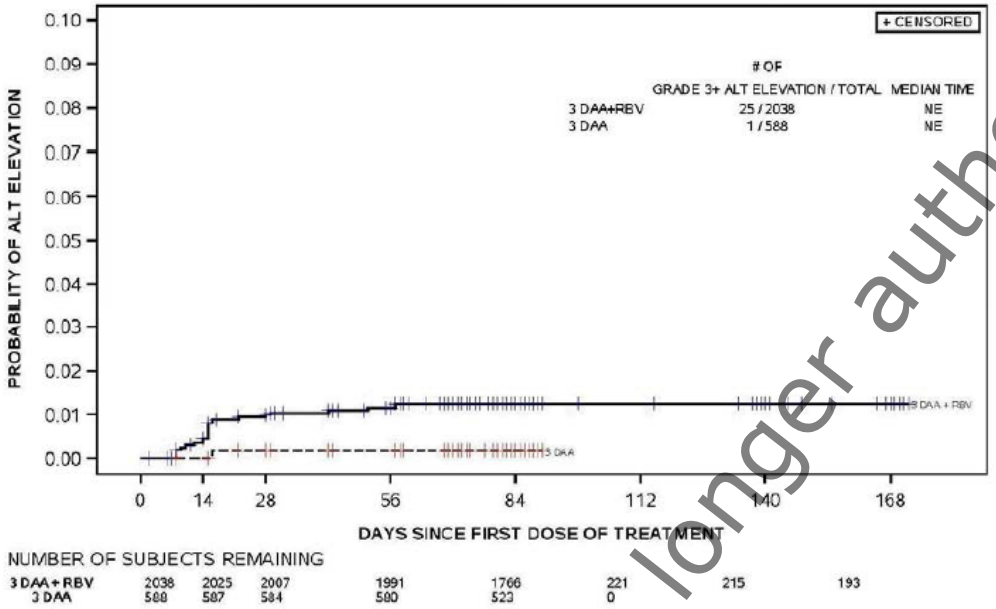
Figure 9. **Kaplan-Meier Curve of Time to Onset of Grade 3+ ALT Elevations (All Treated Analysis Set)**



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 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.

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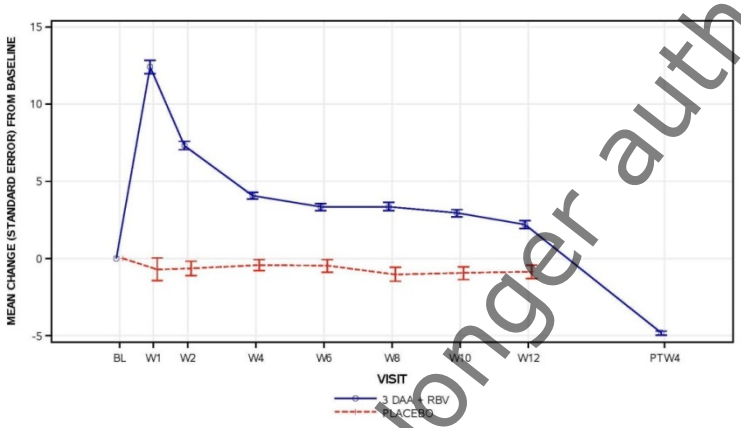
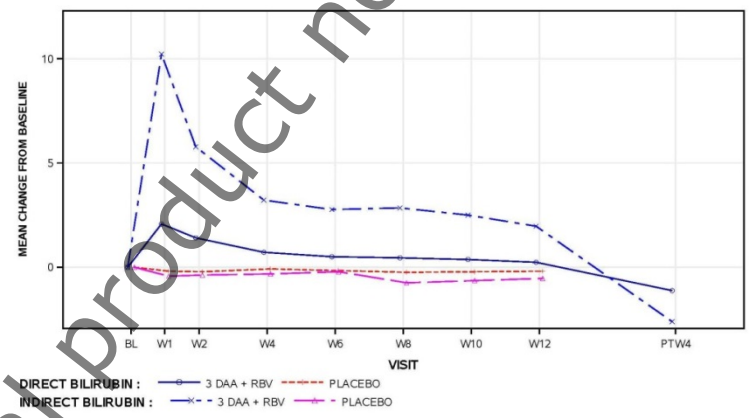
The number of patients discontinuing study therapy due to ALT or transaminase increases was very low – 2/2632 in the all treated analysis set.

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

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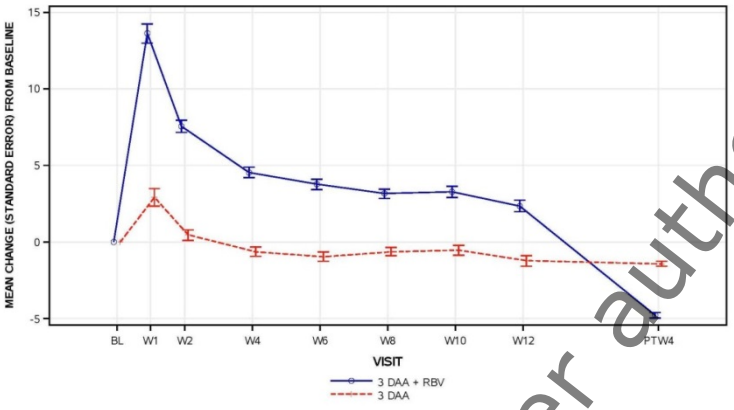
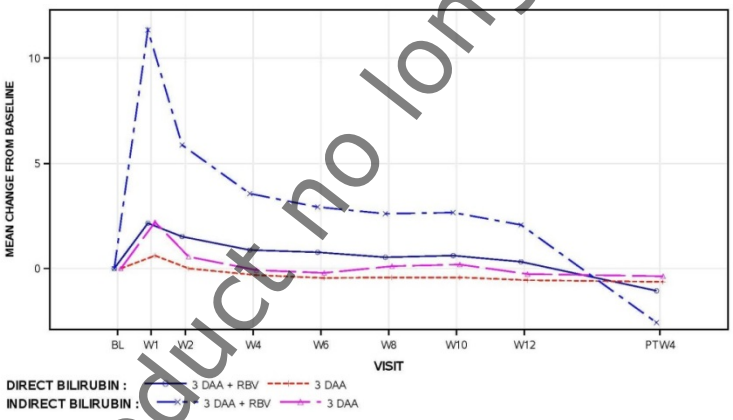
Figure 2. Mean Change from Baseline in Total, Direct, and Indirect Bilirubin (µmol/L) (Regimen-Controlled Analysis Set)



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.

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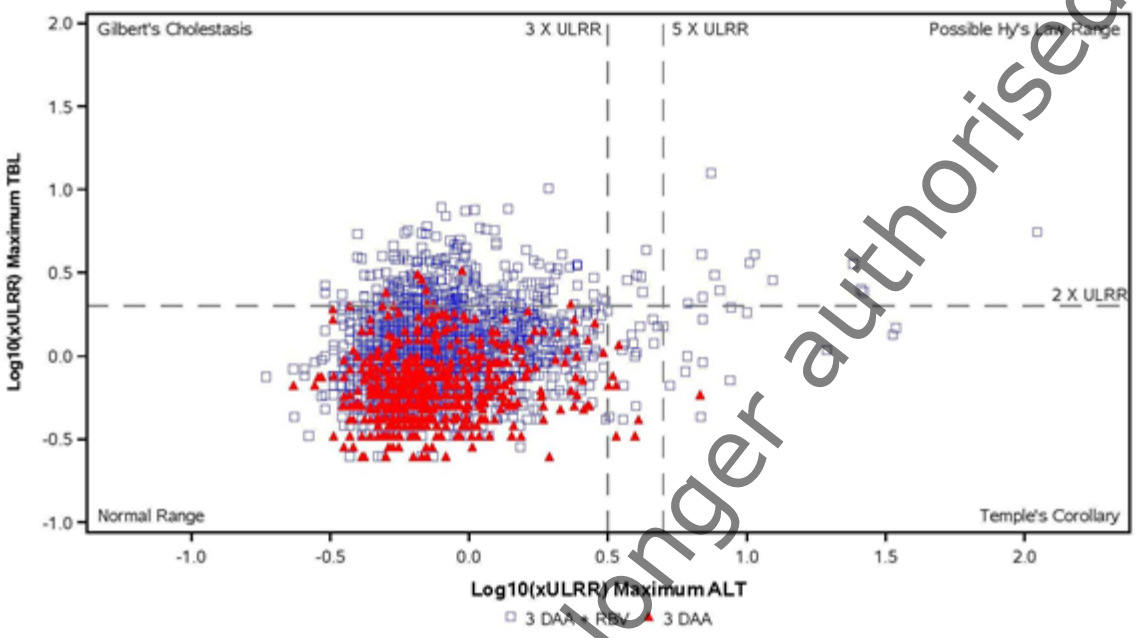
Figure 3. eDISH Plot (All Treated Analysis Set)



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.

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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 non-cirrhotic 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 does not have advanced fibrosis. Overall safety was as follows:

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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.

2.6.1.1. HCV/HIV coinfection

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 the applicant considers that this risk is not relevant. However, the possibility of bridging from in vitro to in vivo in this particular regard is unclear. In the absence of reassuring in vivo data, 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

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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) is expected. Dolutegravir is approved for 50 mg q.d. and b.i.d., and the lower dose is therefore considered a safe alternative.

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.

2.6.2. 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

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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.

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Paritaprevir as a component of these regimens is a cause of transaminitis, seen at grade 3 or more in approximatel 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 estradiol-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 estradiol 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 estrogens is considered sufficiently reassuring to support the limitation of the proposed contraindication to ethinyl estradiol.

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.

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2.6.3. 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.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

2.8. 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:

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Safety concerns

Summary of Safety Concerns	
Important identified risks	Drug-drug interactions: – Concomitant use with drugs that are moderate or strong inducers of CYP3A (e.g., carbamazepine, phenytoin, phenobarbital, efavirenz, rifampicin, and St. John's Wort) – Concomitant use with drugs that are moderate or strong inducers of CYP2C8 (e.g., rifampicin) when used as 3-DAA regimen. – Concomitant use with drugs that are sensitive CYP3A substrates (e.g., ergotamine, lovastatin, and salmeterol) – Concomitant use with drugs that are strong CYP3A4 inhibitors Concomitant use with drugs that are strong CYP2C8 inhibitors (e.g. gemfibrozil) when used as 3-DAA regimen.
	Hepatotoxicity when co-administered with ethinyl estradiol-containing medications
Important potential risks	Drug-drug interactions: – 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: – use of the DAA regimen in patients with genotypes other than HCV GT1 or GT4 – use in other DAA combinations – use in pediatric patients
	Medication errors
	Risk of resistance development
	Fetal development toxicity
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
	Safety in GT4-infected patients with cirrhosis

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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 Study M13-862 (Studies comparing 3-DAA + RBV to telaprevir + Peg-IFN and RBV) Category 3	Assess safety and efficacy of the 3-DAA regimen, comparing 3-DAA + RBV to telaprevir + Peg-IFN and RBV, in treatment-naïve and treatment-experienced genotype 1 subjects	Potential risk of hepatotoxicity	Ongoing	July 2016
Longitudinal cohort safety study in the TARGET registry Voluntary PASS 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; Protocol under development and planned for submission Jan 31, 2015	To be determined
Study M14-222 Study M14-423 (Long-term efficacy studies with 5-year follow-up) Category 3	To evaluate the effect of response to treatment (assessed by SVR12 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 Potential risk of resistance development	Ongoing	2021 for both studies Yearly interim reports provided in PSURs
Study M14-227 (Study in Child-Pugh B subjects) Category 3	Evaluate safety and efficacy (SVR_{12}) in subjects with Child-Pugh B	Missing information in patients with hepatic impairment	Planned; Protocol finalized	March 2017
Study M14-226 (Study in subjects with renal dysfunction) Category 3	Evaluate safety and efficacy (SVR12) in subjects with CrCl < 60 mL/min	Missing information in patients with renal impairment	Planned; Protocol finalized	March 2017
Study M12-999 (Study in liver transplant patients) Category 3	Evaluate safety in liver transplant patients	Missing information in post liver transplant patients	Ongoing	To be determined

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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 M14-004 (Study in patients co-infected with HIV-1) Category 3	Evaluate safety in patients coinfected with HIV-1	Missing information in patients co-infected with HIV-1	Ongoing	To be determined
Study M13-102 (Study to assess resistance and durability of response) 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 (Study to evaluate re-treatment of subjects who have failed the 3-DAA regimen) 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 -Potential risk of resistance development	Under development	To be determined
Study M13-101 (Study to evaluate re-treatment of subjects who experienced virologic failure) 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 -Potential risk of resistance development	Ongoing	June 2018
Study M11-665 (Study in GT4-infected subjects with cirrhosis) Category 3	Evaluate the safety and efficacy of 2-DAA regimen with RBV in adults with GT4 chronic HCV infection and cirrhosis	Missing information in GT4-infected patients with cirrhosis	Planned; protocol being amended	November 2016
PAM 1	To obtain in vitro data on the formation of the main metabolites of ABT-450 found in urine and faeces	Missing nonclinical information for ABT-450	Being planned	Due date March 2015
PAM 2	To obtain stability data of ABT-450 in human intestinal fluid (eg., FaSSIF/FeSSIF) and faecal homogenates	Missing nonclinical information for ABT-450	Being planned	Due date March 2015
PAM 3	Toinvestigate interactions with drugs that are BSEP inhibitors, which would be classified as such based on the EU; to investigate drug interactions	Missing nonclinical information for ABT-450	Being planned	Due date March 2015

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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)
	with combined BSEP and MRP inhibitors/relevant genotypes.			

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.

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Risk minimisation measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Identified risk – Drug-drug interactions – Concomitant use with drugs that are moderate or strong inducers of CYP3A (e.g., carbamazepine, phenytoin, phenobarbital, efavirenz, rifampicin, and St. John's Wort) – Concomitant use with drugs that are moderate or strong inducers of CYP2C8 (e.g., rifampicin) when used as 3-DAA regimen – Concomitant use with drugs that are sensitive CYP3A substrates (e.g., ergotamine, lovastatin, and salmeterol – Concomitant use with drugs that are strong CYP3A4 inhibitors _ -Concomitant use with drugs that are strong CYP2C8 inhibitors (e.g. gemfibrozil) when used as 3-DAA regimen.	Proposed text in product information: 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. Prescription only medicine	None
Identified risk – Hepatotoxicity when co-administered with ethinyl estradiol-containing medications	Proposed text in product information: Language concerning elevations in serum ALT and discontinuation of ethinyl estradiol-containing medications will be included in Section 4.3 and Section 4.4 of the SmPC. 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. Prescription only medicine	None

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Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Potential Risk – Drug-drug interactions – 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: 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. Prescription only medicine	None
Potential risk – Hepatotoxicity among non-users of ethinyl estradiol-containing medications	Proposed text in product information: Language concerning elevations in serum ALT and discontinuation of ethinyl estradiol-containing medications will be included in Section 4.4 of the SmPC. 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. Prescription only medicine	None
Potential risk – Potential for off-label use including: – use of the DAA regimen in patients with genotypes other than HCV GT1 or GT4 – use in other DAA combinations – use in pediatric patients	Proposed text in product information: Section 4.2 of the SmPC will provide guidance on method of administration. Prescription only medicine	None
Potential risk – Medication errors	Proposed text in product information: 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). Prescription only medicine	None

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Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Potential risk – Risk of resistance development	Proposed text in product information: Section 4.2 of the SmPC will advise on appropriate dosing and administration to achieve maximal efficacy. Prescription only medicine	None
Potential risk – Fetal development toxicity	Proposed text in product information: Section 4.6 of the SmPC will advise on this potential risk and that use in pregnancy or women of child bearing potential should not be done without effective contraception. Prescription only medicine	None
Missing information – Safety in patients with hepatic impairment (Child-Pugh B)	Proposed text in product information: Section 4.2 and Section 4.4 of the SmPC will advise that safety and efficacy have not yet been established in certain populations. Prescription only medicine	None
Missing information – Safety in patients with renal impairment (creatinine clearance < 60 mL/min)	Proposed text in product information: Section 4.2 and Section 4.4 of the SmPC will advise that safety and efficacy have not yet been established in certain populations. Prescription only medicine	None
Missing information - Safety in post liver transplant patients	Proposed text in product information: Sections 4.4, 4.8 and 5.1 of the SmPC will provide information on currently available data in this population. Prescription only medicine	None
Missing information - Safety in patients co-infected with HIV-1	Proposed text in product information: Sections 4.4, 4.8 and 5.1 of the SmPC will provide information on currently available data in this population. Prescription only medicine	None

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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: Section 4.6 of the SmPC will provide information with respect to reproductive studies performed in animals. Prescription only medicine	None
Missing information – Safety in patients co-infected with HBV	Proposed text in product information: Section 4.4 of the SmPC will advise that safety and efficacy have not yet been established in certain populations. Prescription only medicine	None
Missing information – Safety in elderly patients	Proposed text in product information: Section 4.4 of the SmPC will inform on the number of subjects ≥ 65 years of age that were included in clinical trials Prescription only medicine	None
Missing information – Safety in patients who have failed prior DAA treatments	Proposed text in product information: Product information will advise that safety and efficacy have not yet been established in certain populations. Section 4.4 of the SmPC under Retreatment: The efficacy of ABT-450/r/ABT-267 in patients previously exposed to ABT-450/r/ABT-267, or to medicinal products of the same classes as those of ABT-450/r/ABT-267 (NS3/4A- or NS5A inhibitors), has not been demonstrated Prescription only medicine	None
Safety Concern – Missing information – Safety in GT4 patients with cirrhosis	Proposed text in product information: Section 4.2 and Section 4.4 of the SmPC will advise that safety and efficacy have not yet been established in GT4-infected patients with compensated cirrhosis. 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.

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2.9. Product information

2.9.1. 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.*

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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)+RBV yielded an SVR (sustained virologic response) rate of 95.7% (404/422) across the SAPPHIRE-I and PEARL-IV studies. In non-cirrhotic pegIFN+RBV 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.

In non-cirrhotic treatment naïve patients with genotype 4 infection, the combination of ABT-450(r) + ombitasvir + RBV for 12 weeks yielded an SVR rate of 100% (42/42). In a similarly defined population, albeit with experience of non-curative treatment with pegIFN+RBV, the same regimen also yielded 100% (49/49) SVR. (PEARL-1)

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.

The efficacy of 2DAA+RBV for 24 weeks in genotype 4 cirrhotics has not been directly studied, but is based on bridging from genotype 1b.

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, 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 estradiol 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

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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 unclarity 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 Viekirax is considered positive.

Discussion on the benefit-risk balance

The general efficacy of the proposed regimens is excellent in genotypes 1b and 4. 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 genotypes 1 or-4 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 Viekirax in combination with other medicinal products the treatment of chronic hepatitis

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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 ombitasvir and paritaprevir are qualified as new active substances.

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