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Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Cokiera

International non-proprietary name: dasabuvir / ombitasvir / paritaprevir / ritonavir

Procedure No. EMEA/H/C/004235/0000

Note

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

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List of abbreviations

%CV	Coefficient of variation
2DAA	Co-administration of ABT-450, ABT-267 together with ritonavir in clinical trials
3DAA	Co-administration of ABT-450, ABT-267 and ABT-333 together with ritonavir in clinical trials
3QD	Extended-release dasabuvir with immediate-release ombitasvir, paritaprevir, and ritonavir fixed-dose combination tablets
5-HT2A	Serotonin receptor
ΔΔQTcF	Time-matched baseline-and placebo-adjusted QT interval corrected for heart rate using Fridericia's formula
A1, A2A, A3	Adenosine receptors
A1c	Glycated hemoglobin
Ab	Antibody
ABT-267	Ombitasvir (A-1233617) Inhibitor of NS5A protein
ABT-333	Dasabuvir. Non nucleoside inhibitor of NS5B polymerase
ABT-450	Paritaprevir (A-1043422) Inhibitor of NS3/4A protease
ABT-450/r	ABT-450 plus ritonavir
ABT-450/r/	
ABT-267	ABT-450 and ritonavir co-formulated with ABT-267
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
APRI	Aspartate aminotransferase to platelet ratio index
APTT	Activated partial thromboplastin time
AR	Assessment report
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AT1, AT2	Angiotensin receptors
AUC	Area under the plasma concentration-time curve
$AUC_{0-\infty}$	Area under the plasma concentration time curve from time 0 to infinity
BB	Bombesin receptor
BE	Bioequivalence
BID	Twice daily
BL	Baseline
BMI	Body mass index
BUN	Blood urea nitrogen
BZD	Benzodiazepine receptor
C_{24}	Concentration at 24 hours
CB1	Cannabinoid receptor 1
CCKB	Cholecystokinin receptor
CHC	Chronic Hepatitis C
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
CMQ	Company MedDRA query
CNS	Central nervous system
C_{trough}	Pre-dose trough plasma concentration
CHMP	Committee for Medicinal Products for Human Use
CTCAE	Common Terminology Criteria for Adverse Events

CYP	Cytochrome P450
CYP2C8	Cytochrome P450 2C8
CYP3A	Cytochrome P450 3A
D1, D3, D5	Dopamine receptors
D/C	Discontinuation
DAA	Direct-acting antiviral agent
DB	Double-blind
DDI	Drug-Drug Interaction
DILIN	Drug-induced liver injury network
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DOP	Delta opioid peptide receptor
EC_{50}	Half maximal effective concentration
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
eDISH	Evaluation of drug-induced serious hepatotoxicity
Emax	Maximum effect
EP4	Prostaglandin E receptor 4
ER	Extended release
EU	European Union
EVR	Early virologic response
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels Health State Instrument
FBS	Fetal bovine serum
FDA	United States Food and Drug Administration
FDC	Fixed dose combination
Fu	Fraction unbound
FSH	Follicle-stimulating hormone
GABA	Gamma aminobutyric acid
GCP	Good Clinical Practice
GeoMean	Geometric mean
GGT	Gamma glutamyl transferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
GR	Glucocorticoid receptor
eRVR	Extended rapid virologic response
FDA	United States Food and Drug Administration
GT	Genotype
GT1	Genotype 1
GT1a	Subgenotype 1a
GT1b	Subgenotype 1b
GT other 1	Genotype not 1a or 1b or unable to subtype
GT4	Genotype 4
H1	Histamine receptor
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HCVPRO	Hepatitis C virus patient-reported outcome
HCC	Hepatocellular carcinoma

hERG	Human Ether-à-go-go-Related Gene
HIV-1	Human immunodeficiency virus 1
HME	Hot-melt extrusion
HOMA-IR	Homeostasis model of assessment – insulin resistance
HPMC	Hydroxyl propyl methylcellulose
IC50	Concentration causing 50% inhibition
IFN-α	Interferon-alpha
IFN	Interferon
IL28B	Interleukin-28B genotype
INR	International normalized ratio
IP-10	Interferon gamma-induced protein 10
IR	Immediate release
IRT	Interactive response technology
ITT	Intent-to-treat
IU	international units
KOP	κ-opioid receptor
LCB	Lower confidence bound
LLOD	Lower limit of detection
LLN	Lower limit of normal
LLOQ	Lower limit of quantitation
M1	Muscarinic acetylcholine receptor 1
M29	(A-1538855) A major metabolite of ABT-267 in humans
M36	(A-1548255) A major metabolite of ABT-267 in humans
Max	Maximum
MC4	Melanocortin 4 receptor
MEMS	Medication event monitoring system
MID	Minimally important difference
Min	Minimum
MOP	μ-opioid receptor
mRNA	Messenger ribonucleic acid
MT	Monotherapy Treatment
MT1	Melatonin receptor 1
MTT	3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide
NA	Not applicable
NK2, NK3	Tachykinin receptors
NS	Non Structural Protein
NS3	Nonstructural protein 3
NS4A	Nonstructural protein 4A
NS5A	Nonstructural protein 5A
NS5B	Nonstructural protein 5B
OATP1B1	Organic anion transporting polypeptide 1B1
OL	Open-label
P2Y	Purinergic receptor
PBO	Placebo
Peg-IFN	Pegylated interferon
PI	Prediction interval
PK	Pharmacokinetic
PRO	Patient-reported outcome
PVF	Primary virologic failure

PT	Post Treatment
QD	Once daily
qPCR	Quantitative polymerase chain reaction
QTc	Corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBV	Ribavirin
$Relapse_{12}$	Confirmed HCV RNA $\geqslant$ LLOQ between end of treatment and 12 weeks after last actual dose of active study drug (up to and including the SVR12 assessment time point) for a subject with HCV RNA < LLOQ at Final Treatment Visit who completed treatment, among subjects with available post-treatment HCV RNA data
$Relapse_{24}$	Confirmed HCV RNA $\geqslant$ LLOQ during the SVR24 window among subjects who achieved SVR12 and had data available during the SVR24 window
$Relapse_{late}$	Confirmed HCV RNA $\geqslant$ LLOQ any time after the SVR24 assessment time point for a subject who achieved SVR24 and has post-SVR24 HCV RNA data available
$Relapse_{overall}$	Confirmed HCV RNA $\geqslant$ LLOQ between end of treatment and up to and including the last HCV RNA measurement collected in the PT Period for a subject with HCV RNA < LLOQ at Final Treatment Visit who completes treatment and had post-treatment HCV RNA data available
RNA	Ribonucleic acid
RT PCR	Real-time reverse transcriptase-polymerase chain reaction
RVR	Rapid virologic response
SE	Standard error
SD	Standard deviation
SDD	Spray dried dispersion
SGC	Soft gelatin capsule
SmPC	Summary of Product Characteristics
SOC	System organ class
SVR	Sustained virologic response
SVR12	Sustained virologic response at 12 weeks
SVR24	Sustained virologic response at 24 weeks
t1/2	Terminal phase elimination half-life
TC50	50% cytotoxic concentration
TVR	Telaprevir
ULN	Upper limit of normal
VL	Viral load
W, Wk	Week

1. Recommendation

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the application Cokiera

For the treatment of chronic hepatitis C (CHC) in adults,

is not approvable as a major objection has been identified.

Questions to be posed to additional experts

N/A

Inspection issues

None identified

New active Substance status

The active substances are present in marketed products and the applicant has made no claim for NAS.

2. Executive summary

2.1. Problem statement

Hepatitis C viral (HCV) infection is a global health problem, with 170 million individuals chronically infected worldwide and at risk of developing liver cirrhosis, hepatocellular carcinoma, or both. Cirrhosis develops after prolonged HCV infection. Complications of cirrhosis include hepatic decompensation (ascites, encephalopathy, variceal hemorrhage, hepatorenal syndrome, or hepatic synthetic dysfunction) and hepatocellular carcinoma.

Treatment of HCV-infected patients could reduce the risk of cirrhosis, decompensation, cancer, and liver-related deaths. Among HCV-infected patients in the care of the United States (US) Department of Veterans Affairs treated with pegylated interferon (pegIFN) and ribavirin (RBV) therapy, achieving a sustained virologic response (SVR) was associated with significant reduction in all-cause death compared to subjects who did not achieve SVR (5-year mortality rate in HCV genotype [GT] 1-infected patients: 6.7% versus 14.4%, respectively). In addition, the 5-year occurrence of the composite clinical events of death, liver failure, and hepatocellular carcinoma were significantly lower in HCV-infected patients with advanced fibrosis or cirrhosis who achieved SVR versus those without SVR (9.2% versus 28.2%, respectively). Patients with SVR following treatment with pegIFN with or without RBV have also shown improvement in liver histology and a reduction in liver-related mortality in several studies. Moreover, patients with compensated cirrhosis who achieve SVR essentially eliminate their subsequent risk of decompensation, may achieve histologic regression, and decrease their risk of hepatocellular carcinoma by two-thirds.

Hepatitis C virus can be classified into 6 major GTs based on sequence divergence of 30% or more. These GTs have evolved differently throughout the world and are divided into several subgenotypes. HCV GT1 is the most common worldwide; however, HCV GT1 subtypes vary by geographic region. HCV GT1 is the most common GT in North America and Europe. HCV GT1 accounts for 70% of chronically infected Europeans, with the GT1b subgenotype predominating over GT1a in the majority of European countries, including those with the highest prevalence.

Until recently, treatment for HCV infection included pegIFN and RBV coadministered with 1 of the direct-acting antivirals (DAAs) telaprevir, boceprevir, and sofosbuvir. While these therapies are more efficacious than pegIFN/RBV alone, they still have significant limitations including suboptimal response rates in key patient populations, significant side effects, and prolonged treatment durations (up to 48 weeks). New DAAs that can be used without interferon have recently been approved in the European Union (EU), US, and other countries transforming the treatment of chronic HCV into a relatively short, well-tolerated course of therapy.

AbbVie developed an IFN-free regimen containing 3 DAAs with distinct mechanisms of action and nonoverlapping resistance profiles for the treatment of chronic HCV infection. Paritaprevir (also known as ABT-450) is a nonstructural protein (NS) NS3/NS4A protease inhibitor of the HCV developed to be administered with other DAAs, including dasabuvir (also known as ABT-333), a non-nucleoside NS5B polymerase inhibitor, and ombitasvir (also known as ABT-267), an NS5A inhibitor, with or without RBV. Ritonavir has no activity against HCV and is employed as a pharmacokinetic enhancer (due to its potent cytochrome P450 3A4 [CYP3A4] inhibition) to increase paritaprevir bioavailability and terminal phase elimination half-life (t1/2) allowing for once daily (QD) dosing at lower paritaprevir doses.

The 3-DAA combination regimen for the treatment of GT1 chronic HCV infection includes Viekirax, which consists of ombitasvir/paritaprevir/ritonavir tablets (12.5/75/50 mg, 2 tablets QD), and Exviera, which consists of dasabuvir tablets (250 mg, 1 tablet twice daily [BID]). The 3-DAA regimen was approved in January 2015.

2.2. About the product

The present application concerns a fixed-dose combination (FDC) of the above active agents, the 3QD tablet (dasabuvir 200 mg/ombitasvir 8.33 mg/paritaprevir 50 mg/ritonavir 33.33 mg) to enable a QD dosing regimen (3 tablets) to replace Viekirax and Exviera (3-DAA regimen, EU/1/14/982/001 and EU/1/14/983/001) for the treatment of GT1 chronic HCV infection ('substitution indication' per the Committee for Medicinal Product for Human Use [CHMP] draft Guideline on clinical development of FDC medicinal products). The 3QD tablet would provide a simpler QD treatment regimen of the DAAs.

For those patients that require RBV, it is currently coadministered with the 3-DAA regimen as a BID weight-based regimen (1000 mg and 1200 mg daily dose for subjects with body weight < 75 kg and $\geqslant$ 75 kg, respectively). In addition to the 3QD tablet regimen, AbbVie also intends to propose a fixed lower-dose QD RBV regimen (600 mg daily dose) to replace the current 1000 mg or 1200 mg daily weight-based regimen, to be coadministered with the 3QD regimen. It is anticipated that this reduction in RBV exposures (steady-state trough plasma concentration [Ctrough] and area under the plasma concentration-time curve [AUC]) with the new QD 600 mg regimen (40% lower relative to the 1000 mg dose and 50% lower relative to the 1200 mg dose) will enhance the tolerability of this regimen and allow a fully QD dosing regimen with minimal impact on the rate of sustained virologic response at 12 weeks post-treatment (SVR12).

The evidence base to support this Marketing Authorisation Application (MAA) consists of data with the combined use of the specific components, as previously submitted for the Viekirax and Exviera MAAs, which is bridged to the 3QD FDC.

The pivotal aspects of the clinical development program to support the approval of the selected 3QD formulation include the following:

- Single-dose relative bioavailability study under nonfasting (fed) conditions comparing the approved immediate-release (IR) formulations (the 3-DAA reference formulations) with the 3QD formulation among 88 healthy volunteers (Part 1 of Study M14-566).

- Steady-state relative bioavailability study under nonfasting conditions comparing the approved IR formulations with the 3QD formulation among 66 healthy volunteers (Part 2 of Study M14-566).

Exposure-response analyses and simulations have been completed to show the similarity of the safety and efficacy profiles between the 3QD and reference 3-DAA formulations.

2.3. The development programme/compliance with CHMP guidance/scientific advice

Scientific advice from CHMP/Scientific Advice Working Party (SAWP) was sought in May 2014 with final advice received in September 2014. In summary, the CHMP advised that standard bioequivalence criteria should be used for the planned bioavailability studies in accordance with the Guideline on the Investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1). In addition it was anticipated clinical data would be required if the FDC was not bioequivalent to the approved formulations in accordance with the draft Guideline on clinical development of FDC medicinal products (CHMP/EWP/240/95/ Rev. X). The CHMP also provided advice on a potential focused clinical study in 'difficult to treat' patients should clinical data be required.

Following SAWP advice and availability of the final bioavailability data, AbbVie met with the Medical Products Agency (MPA), Sweden in March 2015 to discuss the HCV 3QD program. As noted above, during the previous CHMP advice meeting at which significant differences in bioavailability were assumed for 3QD, a clinical study was discussed to establish efficacy of 3QD. However, based on the final bioavailability results, the MPA agreed it was reasonable to propose that modelling could achieve the same objective to quantify the risk of loss in SVR and how this risk can be anticipated. The Applicant was advised to focus on patients where dasabuvir is likely to have the largest impact on SVR rates. From a pharmacokinetic perspective, a key question will be how the differences in exposures observed with 3QD versus the 3-DAA regimen will affect SVR rates in various subpopulations. The MPA suggested the use of simulations to predict SVR in different populations (similar to the original proposed clinical study) and in different subgroups. Clinically relevant subgroups (e.g., patients with cirrhosis) should be retained in the model and can be used for simulations even if they are not statistically significant. Additionally, the differences in variability for the 3QD versus the 3-DAA regimen should be taken into considerations in the simulations. In addition the MPA agreed that a modelling approach could in principle be applied to qualify low-dose RBV as well.

2.4. General comments on compliance with GMP, GLP, GCP

The Applicant confirms that all clinical studies were conducted in accordance with the International Conference on Harmonisation (ICH) and Good Clinical Practice guidelines and relevant regulatory requirements. Subjects were accorded all rights granted by the Declaration of Helsinki.

2.5. Type of application and other comments on the submitted dossier

- Legal basis: This application concerns a centralised procedure application submitted under Article 10b of Directive 2001/83/EC, fixed combination.
- Accelerated procedure: NA
- Conditional approval: NA
- Exceptional circumstances: NA

- Biosimilar application: NA
- 1 year data exclusivity: NA
- Significance of paediatric studies: Product-Specific Waiver Decision Number P/0228/2015 (EMA/617396/2015)

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Active Substance

The drug product contains four active substances. These active substances are the same as used in the recently approved medicinal products Viekirax and Exviera. The changes made to the documentation have been summarised by the applicant and can be accepted. No additional information for the drug substances has thus been made to this application. The documentation for ritonavir is based on a CEP. Full information has been presented for the other three active substances.

The characteristics of the drug substances are summarised below.

Dasabuvir:

General Information

Dasabuvir is a weak acid. The free acid solubility is relatively low at biorelevant pH values; therefore a crystalline sodium salt in the form of a monohydrate was used for development. Development studies demonstrated that a wide range particle sizes are acceptable and yield drug product that meet the proposed specification. The range of particle sizes evaluated during development does not have an effect on dissolution or drug product processability. It does not show stereoisomerism. As a result of polymorphic screen studies several crystal forms have been identified; five of them are most relevant to the proposed manufacture. The active substance is consistently manufactured as monosodium salt monohydrate (Form I), which is also the thermodynamically stable form.

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

Manufacture, characterisation and process controls

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

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

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

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

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

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

Specification

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

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

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

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

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

Stability

Stability data on four commercial size batches of active substance stored in the intended commercial package for up to nine months under long term conditions at 25 °C/60% RH and for up to six months under accelerated conditions at 40 °C/75% RH according to the ICH guidelines were provided. In addition, one full scale batch was stored at 50 °C/75% RH. In addition, data from another three smaller than commercial scale batches from a different site used in development were also presented for up to 12 months under long term conditions at 25 °C/60% RH a and for up to six months under accelerated conditions at 40 °C/75% RH. The batches were stored in the packaging configuration intended for marketing. The stability parameters tested were appearance, identification, assay, related substances and microbial controls. Crystal form and water content were monitored on the three smaller scale batches. The methods used were the same as those used for release and are considered stability indicating.

No significant changes were observed in any of the monitored parameters through the stability study period, compared to the initial values, for any of the tested storage conditions. The commercial site batches were found comparable to the smaller batches from the different site.

Photostability testing following the ICH guideline Q1B was performed on one batch. Furthermore, the active substance was exposed to acid, base, oxidation, heat, heat with moisture and light (exposure to high intensity UV light) stress conditions. Results for the stress stability samples indicated that dasabuvir sodium is potentially susceptible to base and oxidative degradation, and to a much lesser extent, acid and ultraviolet radiation degradation whereas it appears stable to heat, heat with moisture and light stress conditions.

Finally, the data generated at 50 °C/75% RH support temperature excursions during shipping of up to 50 °C for 1 month.

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

Ombitasvir:

General Information

Ombitasvir is a weak base. Ombitasvir has very low aqueous solubility over the physiological pH range. An amorphous solid dispersion approach manufactured via hot melt extrusion is employed to increase the apparent aqueous solubility and bioavailability of ombitasvir. 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 ombitasvir drug substance is manufactured as Form I. Several particle size ranges of ombitasvir drug substance, were evaluated. Development activities demonstrated that over the particle size ranges studied, there was no impact on any of the extrudate quality attributes.

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 starting materials are also well-defined and considering the overall control strategy over the synthetic proposed 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 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. 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.

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.

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

Paritaprevir:

General Information

Paritaprevir is a weak acid. Paritaprevir exhibits very poor aqueous solubility over the physiological pH range. Therefore, an amorphous solid dispersion manufactured by hot melt extrusion is employed to increase the apparent aqueous solubility and bioavailability of paritaprevir. During the discovery stage, paritaprevir was found to be highly susceptible to first pass elimination and required co-administration of ritonavir to boost plasma exposures after oral administration. 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. The drug substance is manufactured as Form II.

The particle size distribution (PSD) ranges of paritaprevir batches from the proposed manufacturing site were larger than the PSD ranges from batches manufactured during development at a different site. The defined extrusion operating range was able to successfully manufacture the entire particle size range evaluated. Batches with larger PSD ranges were found to require more energy to uniformly distribute the amorphous dehydrated material; therefore, an upper limit has been designated as critical for the paritaprevir drug substance manufacturing process.

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

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 are acceptable.

Ritonavir:

General Information

There is a monograph of ritonavir in the European Pharmacopoeia and 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.

Ritonavir is a weak base with a pH-dependent solubility. Solubility studies have demonstrated that amorphous ritonavir forms supersaturated solutions with peak solubility values as high as 10-fold greater than those from crystalline ritonavir. This observation led to the development of an amorphous solid dispersion manufactured by hot melt extrusion for the Ritonavir Extrudate Intermediate.

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.

3.1.2. Finished Medicinal Product

The drug product is a bilayer film-coated tablet, where dasabuvir is formulated in the extended release (ER) layer and the other three active substances on the immediate release (IR) layer. The ER layer contains 200 mg dasabuvir. The IR layer contains 8.3 mg ombitasvir, 50 mg paritaprevir and 33.3 mg ritonavir. The excipients are commonly used in medicinal preparations.

Drug development

The hot-melt extrudates of ombitasvir, paritaprevir and ritonavir are stated to be the same as used in the marketed products Viekirax and Exviera and have not been assessed further for this application. The IR layer blend of the three active substances and the ER layer blend of dasabuvir are manufactured separately. The ER layer and IR layer blends are compressed into a bilayer tablet and a non-functional film coating is applied. An acceptable risk assessment taking into account the Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQA) is presented.

A formulation development is presented, where three targets were specified. 1. Maintain comparable pharmacokinetic (PK) profile with the currently approved Dasabuvir Tablet and Ombitasvir/Paritaprevir/ Ritonavir tablet formulations to ensure equivalent performance with once daily dosing. 2. Ensure manufacturability. The physicochemical properties of the active substances and the bilayer tableting process required formulation optimization to ensure a robust manufacturing process. 3. Stability. The final drug product must be chemically and physically stable during bulk storage, distribution and the duration of the product's shelf life.

Dissolution studies were conducted using an apparatus 3 (reciprocating cylinder) with cetyltrimethyl-ammonium bromide (CTAB) and sodium phosphate buffer, pH 6.8.

The applicant describes attempts to establish an IVIV correlation. However, these attempts were not fruitful and had to be abandoned. Dose-dumping studies with up to 40% ethanol have been conducted and a somewhat slower release from the ER layer was seen. To ensure optimal dasabuvir exposure, comments on the effects of alcohol intake in combination with the medicine are included in the SPC.

The manufacturing process has been adequately described. The control of critical steps and intermediates can be accepted. The applicant has provided acceptable process validation information.

The drug product specification, its analytical methods, the batch analyses, characterisation of impurities and the justification of specification are adequate. The reference standards and container closures system can be accepted.

The drug product stability section is well presented. The proposed shelf-life of two years can be accepted.

3.1.3. Discussion on chemical, pharmaceutical and biological aspects

Drug substances

The active substances are the same as used in the previously marketed products Viekirax and Exviera. The very low solubilities of the crystalline drug substances are overcome by the formation of melt extrusions to form amorphous substances with substantially increased apparent solubility to allow for an oral dosage form. Particle size distribution is of some importance to allow complete transformation of the originally crystalline substances into their amorphous forms in the extrusion processes.

Drug product

The drug product is a bilayer film-coated tablet, where dasabuvir is formulated in the extended release (ER) layer and the other three active substances on the immediate release (IR) layer. The hot-melt extrudates of ombitasvir, paritaprevir and ritonavir are stated to be the same as used in the marketed products Viekirax and Exviera. The formation of an oxidative degradation product of ombitasvir has been suitably reduced by the choice of formulation. The release of dasabuvir has been fine-tuned in the formulation development. The drug product specification and stability studies of the drug product are acceptable after the second round of questions.

3.1.4. Conclusions on the chemical, pharmaceutical and biological aspects

All questions on the Quality part of the documentation have been resolved and the application is acceptable from a Quality point of view.

3.2. Non clinical aspects

The non-clinical documentation in support of this application is entirely based on the non-clinical studies submitted for registration of the individual components and previously assessed in the procedures for Viekirax and Exviera. No new non-clinical studies have been conducted to support the 3QD formulation. This is acceptable. A brief summary of non-clinical pharmacology, pharmacokinetics and toxicology of the individual components is given below.

3.2.1. Pharmacology

Primary pharmacology

Dasabuvir is a non-nucleoside inhibitor of the HCV RNA-dependent RNA polymerase encoded by the NS5B gene. Paritaprevir is a non-structural protein (NS) 3/4A protease inhibitor, which is necessary for the proteolytic cleavage of the HCV encoded polyprotein and is essential for viral replication. In order to achieve efficacious exposure, **paritaprevir** is dosed with ritonavir, a potent CYP3A4 inhibitor used as a pharmacokinetic (PK) enhancer. **Ombitasvir** is an inhibitor of HCV non-structural protein 5A (NS5A), which is essential for viral replication.

Secondary pharmacodynamics

The individual components of the 3DAA were tested in *in vitro* assays covering a broad range of receptors, ion channels and transporters. With the exception of the peripheral benzodiazepine receptor, showing binding both by the ombitasvir metabolite M23 and dasabuvir, no common targets were identified in *in vitro* screens. Target interactions between paritaprevir, ombitasvir and dasabuvir are thus not expected.

Safety pharmacology

No inhibition of hERG was seen with **paritaprevir** at concentrations up to 7-20 µM (5-18% inhibition). Since Cmax plasma concentrations in the clinic of paritaprevir is reported to be 1.47 µg/mL (~2 µM) an effect on hERG is unlikely 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 anesthetized dogs given 30-min intravenous (iv) infusions of paritaprevir (plasma levels of 2.6 to 66 µg/mL). A modest decrease in mean arterial pressure, and tachycardia, were also seen in a pilot study in anesthetized rats. No effects on blood pressure or any of the ECG parameters were detected in conscious Beagle dogs at plasma exposures ≤ 96.9 µg/mL (100 mg/kg).

Ombitasvir did not have any effects on hERG and IC50 was indicated to be higher than 5µM (4.6 µg/mL). No cardiovascular effects were detected in anesthetized beagle dogs administered ombitasvir via iv infusion at plasma levels ≤0.483 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 plasma levels up to 2.62 µg/mL.

IC50 of **dasabuvir** in the hERG assay was 0.3 µg/mL, to be compared with the clinical plasma concentration at the maximum recommended human dose, 1.03 µg/mL. This indicates a possible effect of dasabuvir on hERG. No prolongation of dog Purkinje fiber action potential duration was seen up to and including the highest concentration tested, 14.9 µg/mL. In anesthetized dogs, dasabuvir produced a modest increase in mean arterial blood pressure and a shortening of the QT interval at plasma concentrations of 0.23 and 1.84 µg/mL, respectively. In conscious dogs, 10 mg/kg dasabuvir (exposure = 6 µg/mL) produced a slight decrease in blood pressure.

3.2.2. Pharmacokinetics

Absorption

Paritaprevir is a high molecular weight, lipophilic compound, with minimal aqueous solubility. Paritaprevir oral systemic bioavailability was non-detectable in rat and monkey, and averaged 41% in dog, consistent with the low aqueous solubility, moderate apparent intestinal permeability and moderate to high rates of metabolism. To mitigate the high first-pass and hepatic elimination, paritaprevir is co-dosed with ritonavir (paritaprevir/r), a potent CYP and efflux transport inhibitor,

resulting in substantial increases in systemic bioavailability in both nonclinical species and humans. There were no apparent gender differences in mice, rats or dogs, nor any apparent accumulation with multiple daily dosing in all three species. Following iv dosing, the plasma elimination half-lives of paritaprevir were short, ranging from 0.4 hr in rat and monkey to 1.2 hr in dog.

Ombitasvir is a high molecular weight, lipophilic compound, with minimal solubility in aqueous solutions. Passive permeability was low to moderate, with oral systemic bioavailability from low doses of a PEG solution formulation ranging from 24.8% in rat to 57.3% in dog. There were no apparent gender differences in rats or dogs, with exposures in male mice ~2-fold higher than in females. No accumulation was noted following multiple dosing in mice; an accumulation of ~2- fold in rats and dogs was in line with the pharmacokinetic profile defined in single dose studies.The apparent elimination half-life ranged from 4.4 hr in monkey to approximately 11 hr in mouse and rat.

Dasabuvir was rapidly absorbed with Tmax values being around 2 hr in rats, dogs and rabbits and around 1 hr in mice and somewhat higher in monkey. The oral bioavailability values from studies using the solution formulation of free acid in 10% DMSO in PEG-400 were wide-ranging, with values high in dog (96%), moderate in rat (21%) and very low in monkey (4.5%). There were no apparent gender differences in monkeys or dogs, with exposures in female rats and mice higher than in males. No accumulation was noted following multiple dosing in mice or rats; accumulations ranging from ~2-fold in monkey, ~3-fold in rabbit and ~6.6-fold in dogs were in line with the PK profiles defined in single dose studies.

Distribution

Paritaprevir/r, ombitasvir and dasabuvir are all highly bound to plasma proteins and preferentially distribute into the plasma compartment of whole blood. **[14C]paritaprevir/r** was primarily distributed to the liver and poorly to most other tissues following a single oral dose in Long Evans rats. There was no selective association with melanin-containing tissues and no distribution to tissues protected by the blood-brain barrier. In pregnant rats, small amounts of radioactivity were detected in fetal liver. [14C]paritaprevir/r was excreted in milk obtained from lactating rats for at least 24 hr post dose.

[14C]ombitasvir was primarily distributed to the adrenal gland, liver, pancreas, renal cortex and stomach mucosa of rats. There was no selective association with melanin-containing tissues and no distribution to tissues protected by the blood-brain barrier. Minimal amounts of radioactivity were detected in fetal liver after administration to pregnant rats. [14C]ombitasvir was excreted in milk obtained from lactating rats for at least 24 hr post dose.

[14C]dasabuvir showed a similar distribution pattern as [14C]paritaprevir/r, with highest concentrations in the liver and no distribution to tissues protected by the blood brain barrier or the lens of the eye. [14C]dasabuvir-derived radioactivity did not selectively associate with tissues containing melanin. Following oral administration of [14C]dasabuvir to pregnant Sprague-Dawley rats, there was a lack of drug-derived radioactivity in the amniotic fluid and detectable foetal levels only in the liver. Radioactivity was detected in milk from lactating rats for at least 24 hr post dose.

Metabolism

Biotransformation of **paritaprevir** in the toxicology species mouse, rat and dog as well as in human involves amide hydrolysis at the acyl cyclopropane-sulfonamide moiety and the pyrazine-2-carboxyamide moiety, with CYP-mediated oxidation on the olefinic linker, the phenanthridine group, the methylpyrazinyl group, or combinations thereof. When co-dosed with ritonavir, [14C]paritaprevir was the major component in human plasma, with five minor metabolites, including M2 (A-1231059,

monohydroxy), M3 (dihydroxy), M6 (monohydroxy), M29 (an acyl cyclopropane-sulfonamide hydrolysis product) and M13 (methylpyrazine-2-carboxylic acid); none of the metabolites in human plasma were greater than 10% of the total drug related material.

Ombitasvir shows limited hepatic metabolism across species. Biotransformation in all nonclinical species (mouse, rat, rabbit, dog) and human involves enzymatic amide hydrolysis to form M23 (dianiline, A-1242846), M6 (monoaniline) and M7 (pyrrolidine acid, A-1241411). In rat, M23 and M26 are further metabolized via acetylation, oxidation and glucuronidation. In human, the product of amide hydrolysis, M23, is further metabolized through CYP-mediated oxidative metabolism primarily by CYP2C8. M29 and M36 were identified as major disproportionate metabolites at steady state in human plasma, representing approximately 19.9% and 13.1% of the total drug related material, and specific toxicological studies were performed with these two metabolites.

Biotransformation of **dasabuvir** in mouse, rat and human primarily involves CYP-mediated hydroxylation at the *t*-butyl group to form the active metabolite M1 (A-1041392). M1 has similar activity against genotype 1 HCV infection as dasabuvir. M1 is further oxidized to M4 (*t*-butyl aldehyde) and M5 (A-1039710, *t*-butyl acid). Subsequent glucuronidation of M1 and M5 produces metabolite M3 (*t*-butyl etherglucuronide) and M6 (*t*-butyl acid glucuronide), respectively; M2 is derived from the sulfation of M1. M1 was characterized as a major human metabolite (21.4% of total plasma radioactivity), and was covered in the pivotal toxicity studies in rats and mice.

Excretion

Following oral administration of paritaprevir/r, ombitasvir or dasabuvir to non-clinical species and humans, all compounds and their respective metabolites are mainly cleared via biliary excretion and fecal elimination, with minimal renal clearance.

Pharmacokinetic drug interactions

See the Clinical Pharmacokinetics section.

3.2.3. Toxicology

Single dose toxicity

The acute toxicity of **paritaprevir** 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 paritaprevir was administered without ritonavir as a PK enhancer, the exposures were low, especially in male rats. No single dose studies were conducted with ombitasvir or dasabuvir.

Repeat-dose toxicity

Paritaprevir/r

Studies were conducted in mice, rats and dogs up to 3 months (rat), 6 months (mouse) and 9 months (dog) duration. The *gallbladder* was identified as target organ of toxicity. In the 6-month mouse study, focal erosion/ulceration, chronic active inflammation, epithelial hypertrophy/hyperplasia and diffuse inflammation were observed at > 100/30 mg/kg. In dogs, edema, mononuclear/mixed cell infiltration, degeneration, necrosis and increased mitoses were observed in the gallbladder in all repeat-dose toxicity studies > 1 month duration. The gallbladder changes were partially resolved in mice, and fully reversible in dogs, after 1 month recovery. Margins between predicted human exposure and NOAEL were 3.7-5.8x (mouse) and 29-87x (dog), based on AUC.

The mechanism behind the observed gallbladder findings is not known, but may be related to the high biliary excretion of paritaprevir/r 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.

Vacuolation in the lamina propria of the intestine, in the hepatic sinusoids and renal tubular epithelium, presumably due to fat deposition, was observed in the 9-month dog study. There was no reversibility of these findings after 1 month recovery. Since the clinical exposure margins are high (88-212x based on AUC), they are not considered to be of relevance in the clinical situation.

Ritonavir
Ritonavir added to paritaprevir as a PK enhancer caused a number of effects on the *liver*, *thyroid gland,* erythroid parameters, and (in dogs) gastrointestinal (GI) system. Most of these findings were of an adaptive character and thus regarded as non-adverse. The exposure margins to recommended human dose (RHD) were small, which was considered acceptable in light of the long clinical experience with ritonavir and the non-adverse nature of the findings.

Ombitasvir

Repeat-dose toxicity studies were conducted in mice, rats and dogs up to 3 months (rat) and 6 months (mouse, dog) duration. Maximum exposures were limited by the low solubility of the compound in all species tested. The only adverse effect 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 ombitasvir repeat-dose toxicity studies were in the range of 20-50x.

Dasabuvir
Dasabuvir was evaluated in repeat-dose toxicity studies in mice (up to 3 months), rats (up to 6 months) and dogs (up to 9 months). No dose-limiting effects were noted in the chronic rat and dog studies up to 18-/47x (males/females) exposure margins (6-month rat), and 120x exposure margin (9-month dog). Adverse effects including mortality and *GI tract effects* were observed in mice. Microscopic findings included hyperplasia of the gastric mucosal epithelium, mucus metaplasia of gastric glands, increased inflammation in the glandular stomach and hyperkeratosis and squamous metaplasia in the non-glandular stomach. The deaths and GI tract effects were attributed to the administration of large amounts of dasabuvir locally, rather than a systemic effect. This was supported by the lack of similar GI tract findings in the dog at equivalent exposures. The findings in mice are not anticipated in humans. Findings in rat (lung and small intestine) and dogs (liver, adrenal gland and lymphoid tissue) were not considered adverse.

Genotoxicity

Ombitasvir, **ritonavir** and **dasabuvir** tested negative in a complete package of genotoxicity studies, including test for gene mutations and chromosomal aberrations *in vitro* and chromosomal aberrations *in vivo*. **Paritaprevir** 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 paritaprevir does not carry a significant genotoxic risk.

Carcinogenicity

Paritaprevir

There was no significant increase in neoplastic changes due to paritaprevir/r treatment in a 6-month Tg-rasH2 mouse study at doses < 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 > 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 < 300 mg/kg/day, corresponding to 8.5-11.5x the exposure at RHD. A slightly increased incidence of hepatocellular carcinoma in males at the mid and high dose was concluded to be without clinical relevance.

Ritonavir

Findings from previous carcinogenicity studies conducted with ritonavir as a single agent were limited to an increased incidence of hepatocellular adenomas in male mice administered ritonavir at the high dose (200 mg/kg/day). Hepatocellular adenomas associated with nongenotoxic compounds such as ritonavir are considered to have little relevance to the response of the human liver when limited to mice (particularly when present only in males).

Ombitasvir

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). Similarly, ombitasvir was not carcinogenic in the 2-year rat study up to the highest dose tested (30 mg per kg per day), resulting in ombitasvir exposures approximately 16x higher than those in humans at 25 mg.

Dasabuvir

The carcinogenic potential of dasabuvir was evaluated in a 26-week study in TgHras transgenic mice with no statistically significant increases in neoplastic changes up to the highest dosage tested (2 g/kg/day), corresponding to 39x clinical exposure based on AUC. Dasabuvir was not carcinogenic in a 2-year Sprague Dawley rat study up to the highest dose tested (800 mg/kg/day), resulting in dasabuvir exposures approximately 19x higher than those in humans at 500 mg. Adenoma of the prostate gland in males was statistically significantly increased at the high dose, but based on a weight of evidence approach this finding was not considered to be clinically relevant.

Reproductive and developmental toxicity

Fertility and early embryonic development

Paritaprevir

The effects of paritaprevir/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 paritaprevir AUC levels of 11.5 µg·h/mL (males) and 35.6 µg·h/mL (females). The margin to clinical exposure at RHD was low (1.6-5x).

Ritonavir

No effects on male and female fertility, or early 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.

Ombitasvir

There were no effects on male fertility and female reproductive parameters in mice up to the highest dose tested (200 mg/kg/day, approximately 25x the clinical AUC exposure at RHD).

Dasabuvir

In the fertility and early embryonic development study in rats, there were no significant effects on male or female fertility parameters when tested up to doses of 800 mg/kg/day (400 mg/kg BID) corresponding to 29- and 36x the expected clinical AUC in males and females, respectively.

Embryo-foetal development

Paritaprevir

Due to vehicle-related maternal toxicity and the lack of appreciable exposures, evaluation of embryofoetal development (EFD) effects in rabbits was not possible. Thus, the paritaprevir/r EFD studies were conducted in mice and rats. In the pivotal mouse EFD study, increased incidences as compared with the concurrent control group were observed in paritaprevir/r-treated groups for the malformation open eye lids, at exposures 32x higher than the exposure in humans at the RHD. In the pivotal *rat* EFD study, the only notable treatment-related finding was a marginal increase in the incidence of a skeletal variation (misaligned sternebrae), which was considered non-adverse.

Ritonavir

In rabbit and rat EFD 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 AUC0-24 value 34.3 µg·h/mL). This finding, which may be regarded as developmental retardation, did not lead to a contraindication of ritonavir in pregnant women.

Ombitasvir

Ombitasvir EFD studies were conducted in mice and rabbits. Ombitasvir caused malformations at low incidence in the eyes (microphthalmia) and teeth (absent incisors) of rabbits at maximal feasible exposures 4x higher than the AUC exposure at RHD. In mice, an increased incidence of open eye lid was present in foetuses of dams administered ombitasvir; however, the relationship to treatment with ombitasvir was considered uncertain.

Dasabuvir

EFD studies were performed in rats and rabbits. There were no dasabuvir-related changes in maternal or foetal parameters in either of the species. In rats, the NOAEL for maternal and foetal toxicity was 800 mg/kg/day (400 mg/kg BID) corresponding to 48x clinical exposure based on AUC and in rabbits, the NOAEL for maternal and foetal toxicity was 400 mg/kg/day corresponding to 12x clinical exposure based on AUC.

Prenatal and postnatal development

Paritaprevir

No effects of paritaprevir/r on prenatal and postnatal development in rats were observed up to the highest dose tested (300/30 mg/kg/day), corresponding to a 16.5x AUC exposure margin to RHD. The presence of quantifiable concentrations of paritaprevir in pups at 300 mg/kg/day demonstrates passage of paritaprevir across the placenta. No quantifiable levels of ritonavir were present in the pups.

Ombitasvir

No adverse effects of ombitasvir on prenatal and postnatal development in mice were noted, except for two mortalities at 200 mg/kg/day during the post-weaning period. The maternal (F0) NOAEL was considered to be 200 mg/kg/day, and the F1 NOAEL for viability and growth in the offspring 40 mg/kg/day. As demonstrated by quantifiable levels of ombitasvir in pups at > 40 mg/kg/day, there was passage of ombitasvir across the placenta.

Dasabuvir

There were no adverse effects of dasabuvir on prenatal and postnatal development in rats up to the highest dose tested (800 mg/kg/day), corresponding to 44x clinical exposure based on AUC.

Juvenile toxicity

No studies have been conducted. This is acceptable.

Local tolerance

No separate local tolerance studies were conducted on the individual DAAs or the combination. In repeat dose toxicity studies with paritaprevir/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. Local irritating properties of dasabuvir in the GI tract have been observed in mice after administration of ≥6000 mg/kg/day (110x above the clinical AUC exposure). This is not considered a concern in the clinical situation.

Immunotoxicity

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

Dependence

No studies have been conducted. This is acceptable.

Metabolites

Ombitasvir

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 EFD 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, corresponding to 23.5-27x margins to RHD. In the 1-month study with M36, there were no adverse findings up to the highest exposure tested, corresponding to a 38.2x margin to RHD. In the mouse EFD 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, which was considered to be non-adverse. In conclusion, it is considered that the safety of the human metabolites M29 and M36 of ombitasvir has been adequately characterized.

Impurities

The drug product impurity profiles for the 3QD and 3DAA formulations are stated to be similar. No additional studies are considered necessary.

Ecotoxicity/environmental risk assessment

The Applicant has submitted an environmental risk assessment (ERA) for the individual drug substances dasabuvir, ombitasvir, paritaprevir and ritonavir, including the results of phase II studies that were still ongoing at the time of approval of Exviera and Viekirax. The Applicant was asked to submit some missing study reports, and to address a number of issues. It can now be concluded that dasabuvir, ombitasvir and paritaprevir are not PBT or vPvB substances. While dasabuvir can be considered very persistent in fresh water sediment and ombitasvir is transformed to at least one persistent metabolite in soil, none seem to pose any risk for the environment. However, there are some inconsistencies and factual errors in the ERA document plus some missing study reports that should be amended **(LoQ**).

3.2.4. Discussion on non-clinical aspects

The non-clinical documentation in support of the present application is the same as submitted for registration of Exviera and Viekirax, with the post-approval addition of the dasabuvir and ombitasvir rat carcinogenicity data. The safety pharmacology studies with the individual substances identified a potential QT signal, which was further evaluated in a clinical thorough QT study using the 3DAA regimen. There was no QTc prolongation in humans in this study. In line with current recommendations and guidelines, combination safety pharmacology studies are not considered necessary.

Since the 3QD formulation is clinically equivalent to the Exviera and Viekirax formulations when used as the 3-DAA regimen, no combination non-clinical toxicity study is considered necessary.

Individually, neither substance was shown to be genotoxic or carcinogenic; therefore no combination

genotoxicity or carcinogenicity studies are considered necessary.

Due to findings of malformations in the paritaprevir/r and ombitasvir embryo-foetal development studies, there is a concern for the use of the 3QD formulation in pregnancy and in women of childbearing potential (WOCBP). The proposed SmPC text under section 4.6 concerning paritaprevir/r and ombitasvir is identical to that of the SmPC for Viekirax, and recommends that the product should not be used during pregnancy or in WOCBP not using effective contraception. This is endorsed.

3.2.5. Conclusion on non-clinical aspects

There is no objection to an approval of Dasabuvir/ombitasvir/paritaprevir/ritonavir AbbVie from a non-clinical point of view. In order to finalize the environmental risk assessment, the Applicant is asked to submit a revised ERA document (**LoQ**).

3.3. Clinical aspects

3.3.1. Pharmacokinetics

The application concerns a new fixed dose combination of dasabuvir, ombitasvir, paritaprevir and ritonavir as well as a new dosage form for dasabuvir (prolonged release). The pharmacokinetics of the 3QD formulation has been characterized in several bioavailability studies in healthy volunteers; the bioavailability of the 3QD formulation has been compared to the 3-DAA regimen and the effect of food on the new formulation has been investigated. No new data regarding pharmacokinetics in special populations or drug-drug interactions have been provided and none are considered necessary.

There is no new clinical efficacy or safety data with the 3QD regimen. Instead, pharmacokinetic data are used to bridge to efficacy and safety results from previous studies with the 3-DAA regimen. Study M14-566 in which the bioavailability of the 3QD formulation was compared to the 3-DAA regimen together with exposure-response analyses and simulations are pivotal in the application.

Absorption

Comparative bioavailability

The pivotal study M14-566 was a two-part comparative bioavailability study comparing the bioavailability of dasabuvir, ombitasvir, paritaprevir and ritonavir from the 3QD regimen (FDC) compared to the 3-DAA regimen after single-dose administration (part 1) and at steady-state (part 2) under fed conditions in healthy volunteers. The 3-DAA regimen with ritonavir has time-dependent pharmacokinetics and the results at steady-state are thus considered to be more relevant for the clinical evaluation than the single-dose results.

A prolonged release profile for dasabuvir from the 3QD regimen was observed with a median Tmax of 8 h compared to 4 h with the conventional IR tablet included in the 3-DAA regimen.

After single-dose administration with a standardised breakfast (medium to high fat meal), comparative bioavailability of the 3QD formulation and the 3-DAA regimen was demonstrated except for *paritaprevir* Cmax which was 31% lower for the 3QD regimen.

After multiple-dose administration with a standardised breakfast (medium to high fat meal), comparative bioavailability of the 3QD formulation and the 3-DAA regimen was demonstrated except for a lower *dasabuvir* C24 (29%), lower *paritaprevir* Cmax (28%), and lower *ritonavir* Cmax (21%). The point estimates and the 90% confidence intervals of Cmax, AUC24 and C24 in Part 2 are shown in Table 1.

Table 1. Cmax, AUC and C24 Ratios of Central Values and 90% Confidence Intervals for Dasabuvir, Dasabuvir M1, Ombitasvir, Paritaprevir and Ritonavir in Part 2 of Study M14-566

	Central Value[a]		Relative Bioavailability	
Pharmacokinetic Parameter (units)	**Test (Regimen A)**	**Reference (Regimen B)**	**Point Estimate[b]**	**90% Confidence Interval[c]**
		Dasabuvir		
C_{max} (ng/mL)[d]	797	880	0.905	0.823 – 0.995
AUC_{24} (ng•h/mL)	8767	9823	0.892	0.809 – 0.985
C_{24} (ng/mL)	116	163	0.710	0.622 – 0.812
		Dasabuvir M1		
C_{max} (ng/mL)[d]	448	565	0.793	0.714 – 0.880
AUC_{24} (ng•h/mL)	4595	5294	0.868	0.782 – 0.963
C_{24} (ng/mL)	48.1	72.1	0.666	0.577 - 0.769
		Ombitasvir		
C_{max} (ng/mL)	127	122	1.040	1.005 – 1.077
AUC_{24} (ng•h/mL)	1367	1254	1.090	1.063 – 1.117
C_{24} (ng/mL)	29.5	26.9	1.098	1.064 – 1.132
		Paritaprevir		
C_{max} (ng/mL)	1452	2011	0.722	0.638 – 0.818
AUC_{24} (ng•h/mL)	8645	9608	0.900	0.814 – 0.994
C_{24} (ng/mL)	33.7	31.9	1.055	0.970 – 1.147
		Ritonavir		
C_{max} (ng/mL)	1328	1676	0.793	0.746 – 0.842
AUC_{24} (ng•h/mL)	8604	9630	0.893	0.846 – 0.943
C_{24} (ng/mL)	36.1	35.8	1.009	0.946 – 1.075

Regimen A = Three Film-Coated ER-12 bilayer tablets (total dose of dasabuvir/ombitasvir/paritaprevir/ritonavir is 600/25/150/100 mg) administered in the morning under non-fasting conditions on Days 1 through 14 of each corresponding period (Test Regimen).

Regimen B = Two ombitasvir/paritaprevir/ritonavir co-formulated tablets (total dose of 25/150/100 mg) with one dasabuvir IR tablet (250 mg) administered under non-fasting conditions in the morning and one dasabuvir IR tablet (250 mg) administered under non-fasting conditions in the evening on Days 1 through 14 of each corresponding period (Reference Regimen).

a. Exponentiation of the least squares means for logarithms.
b. Exponentiation of the difference (test minus reference) of the least squares means for logarithms.
c. Exponentiation of the endpoints of confidence intervals for the difference in the least squares means between the test and reference regimens for logarithms.
d. For dasabuvir and dasabuvir M1 from Regimen B, Cmax comparisons shown are for Cmax over 0 to 72 hours

Peak-to trough ratio was somewhat higher (approx. 30%) for the 3QD regimen compared to the 3-DAA regimen. Also, between-subject variability in dasabuvir PK-parameters was somewhat larger (20-37%) for the 3QD formulation.

To summarize; comparative bioavailability of the 3QD formulation and the 3-DAA regimen was demonstrated except for a lower dasabuvir C24, lower paritaprevir Cmax, and lower ritonavir Cmax. A justification for the lack of clinical relevance of the lower Cmax for paritaprevir and ritonavir was included in the dossier. Exposure-response analyses were conducted to estimate the impact of the

lower dasabuvir C24. These aspects are further described under Section Relationship between concentration and effect.

Influence of food

The exposure of all active substances was increased by concomitant food-intake. Dasabuvir AUC and Cmax was 5.9-fold and 6.6-fold higher, dasabuvir M1 AUC and Cmax 6.6-fold and 6.5-fold higher, paritaprevir AUC and Cmax 4.6-fold and 6-fold higher, ombitasvir and ritonavir exposures 2-fold higher after administration of a high-fat meal compared to in the fasted state (see table 2).

Table 2 Relative Bioavailability and 90% Confidence Intervals for Dasabuvir, Dasabuvir M1, Ombitasvir, Paritaprevir and Ritonavir in Study M14-240

Regimens Test vs. Reference	Pharmacokinetic Parameter (units)	Central Value[a]		Relative Bioavailability	
		Test	Reference	Point Estimate[b]	90% Confidence Interval[c]
A vs. B Food Effect		**Dasabuvir**			
	C_{max} (ng/mL)	1377	208	6.625	5.547 – 7.911
	AUC_t (ng•h/mL)	19624	3083	6.366	5.419 – 7.478
	AUC_{inf} (ng•h/mL)	19798	3347	5.915	5.059 – 6.916
B vs. C Relative Bioavailability in Fasted Condition	C_{max} (ng/mL)[d]	208	800	0.260	0.218 – 0.309
	AUC_t (ng•h/mL)	3083	10394	0.297	0.253 – 0.348
	AUC_{inf} (ng•h/mL)	3347	10551	0.317	0.272 – 0.370
A vs. B Food Effect		**Dasabuvir M1**			
	C_{max} (ng/mL)	621	95.1	6.529	5.398 – 7.896
	AUC_t (ng•h/mL)	8272	1111	7.445	6.201 – 8.938
	AUC_{inf} (ng•h/mL)	8407	1277	6.585	5.552 – 7.809
B vs. C Relative Bioavailability in Fasted Condition	C_{max} (ng/mL)[d]	95.1	315	0.302	0.250 – 0.363
	AUC_t (ng•h/mL)	1111	4206	0.264	0.220 – 0.317
	AUC_{inf} (ng•h/mL)	1277	4303	0.297	0.250 – 0.352
A vs. B Food Effect		**Ombitasvir**			
	C_{max} (ng/mL)	104	50.9	2.055	1.828 – 2.310
	AUC_t (ng•h/mL)	1430	716	1.997	1.841 – 2.167
	AUC_{inf} (ng•h/mL)	1558	785	1.985	1.829 – 2.154
B vs. C Relative Bioavailability in Fasted Condition	C_{max} (ng/mL)	50.9	53.6	0.948	0.844 – 1.066
	AUC_t (ng•h/mL)	716	720	0.994	0.901 – 1.096
	AUC_{inf} (ng•h/mL)	785	790	0.994	0.903 – 1.094
		Paritaprevir			
A vs. B Food Effect	C_{max} (ng/mL)	481	80.5	5.967	4.623 – 7.702
	AUC_t (ng•h/mL)	3918	835	4.693	3.862 – 5.704
	AUC_{inf} (ng•h/mL)	3944	857	4.600	3.800 – 5.569
B vs. C Relative Bioavailability in Fasted Condition	C_{max} (ng/mL)	80.5	115	0.701	0.543 – 0.904
	AUC_t (ng•h/mL)	835	1060	0.787	0.648 – 0.957
	AUC_{inf} (ng•h/mL)	857	1083	0.792	0.654 – 0.958
		Ritonavir			
A vs. B Food Effect	C_{max} (ng/mL)	837	401	2.088	1.754 – 2.486
	AUC_t (ng•h/mL)	6545	3022	2.166	1.885 – 2.488
	AUC_{inf} (ng•h/mL)	6702	3150	2.128	1.862 – 2.432
B vs. C Relative Bioavailability in Fasted Condition	C_{max} (ng/mL)	401	445	0.901	0.735 – 1.103
	AUC_t (ng•h/mL)	3022	3312	0.913	0.781 – 1.066
	AUC_{inf} (ng•h/mL)	3150	3433	0.917	0.790 – 1.066

Regimen A = 3QD Regimen: three ER-12 bi-layer tablets (total dose of dasabuvir/ombitasvir/paritaprevir/ritonavir was 600/25/150/100 mg) administered in the morning under non-fasted conditions (high-fat breakfast).

Regimen B = 3QD Regimen: three ER-12 bi-layer tablets (total dose of dasabuvir/ombitasvir/paritaprevir/ritonavir was 600/25/150/100 mg) administered in the morning under fasted conditions.

Regimen C = 3-DAA Regimen: two ombitasvir/paritaprevir/ritonavir co-formulated tablets (total dose of 25/150/100 mg) QD with one dasabuvir IR tablet (250 mg) administered under fasted conditions in the morning and one dasabuvir IR tablet (250 mg) administered under fasted conditions in the evening.

a. Exponentiation of the least squares means for logarithms.
b. Exponentiation of the difference (test minus reference) in the least squares means between the test and reference regimens for logarithms.
c. Exponentiation of the endpoints of confidence intervals for the difference in the least squares means between the test and reference regimens for logarithms.
d. C_{max} was calculated from 0 to 72 hours post-morning dose for Regimen C.

For dasabuvir and paritaprevir, the effect of a high-fat meal was larger with the 3QD regimen compared to previous studies with the 3-DAA regimen. In previous studies with the 3-DAA regimen dasabuvir AUC and Cmax were 1.3- and 1.4-fold higher and paritaprevir AUC and Cmax were 2.8- and 4-fold higher after a high fat meal compared to fasting conditions.

The larger effect of food on dasabuvir and paritaprevir is mainly explained by a lower bioavailability from the 3QD tablet after administration under fasting conditions, in particular for dasabuvir. After single-dose administration in the fasted state the dasabuvir exposure was 70% lower from the 3QD regimen than from the 3-DAA regimen. Also for paritaprevir the exposure was lower (approx. 20%) for the 3QD formulation compared to 3-DAA under fasting condition.

Influence of alcohol

The effect of alcohol on the 3QD formulation has been evaluated in vitro. No dose dumping effect was observed. The release of dasabuvir from the extended release layer was however decreased and delayed in the presence of alcohol.

Distribution

The data on distribution derive from studies with Viekirax and Exviera.

Ombitasvir, paritaprevir and ritonavir are highly bound to plasma proteins. Plasma protein binding is not meaningfully altered in subjects with renal or hepatic impairment. The blood to plasma concentration ratios in humans ranged from 0.6 to 0.8 indicating that ABT-267 and ABT-450 were preferentially distributed in the plasma compartment of whole blood. ABT-267 was approximately 99.9% bound to human plasma proteins. ABT-450 was approximately 97-98.6% bound to human plasma proteins. Ritonavir was greater than 99% bound to human plasma proteins.

In vitro data indicate that ABT-450 is a substrate for the human hepatic uptake transporters, OATP1B1 and OATP1B3.

Dasabuvir is highly bound to plasma proteins. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment. The blood to plasma concentration ratios in human ranged from 0.5 to 0.7 indicating that ABT-333 was preferentially distributed in the plasma compartment of whole blood. ABT-333 was greater than 99.5%, and M1 major metabolite of ABT-333 was 94.5% bound to human plasma proteins over a concentration range of 0.05 to 5 µg/ml. At steady-state the exposures ratio of M1 to ABT-333 is approximately 0.6. Taking into account the protein binding and in vitro activity of M1 against HCV genotype 1, its contribution to efficacy is expected to be similar to that of ABT-333. In addition, M1 is a substrate of the hepatic uptake transporters OATP family and OCT1

and thus, the hepatocyte concentration and thereby contribution to efficacy, may be larger than ABT-333.

Elimination

The data on elimination derive from studies with Viekirax and Exviera.

- **Excretion**

Ombitasvir: Following dosing of ABT-267/ABT-450/rtv with or without ABT-333, mean plasma half-life of ABT-267 was approximately 21 to 25 hours. Following a single 25 mg dose of ^{14}C-ABT-267 approximately 90% of the radioactivity was recovered in faeces and 2% in urine. Unchanged parent drug accounted for 88% of total radioactivity recovered in faeces, indicating that biliary excretion is a major elimination pathway for ABT-267.

Paritaprevir: Following dosing of ABT-267/ABT-450/rtv with or without ABT-333, mean plasma half-life of ABT-450 was approximately 5.5 hours. Following a 200 mg ^{14}C-ABT-450 dose with 100 mg ritonavir, approximately 88% of the radioactivity was recovered in faeces with limited radioactivity (8.8%) in urine. Metabolism as well as biliary excretion of parent drug contribute to the elimination of ABT-450.

Dasabuvir: Following dosing of ABT-333 with ABT-267/ABT-450/rtv, mean plasma half-life of ABT-333 was approximately 6 hours. Following a 400 mg ^{14}C-ABT-333 dose, approximately 94% of the radioactivity was recovered in faeces with limited radioactivity (approximately 2%) in urine. Unchanged ABT-333 accounted for 26.2% and ABT-333 M1 for 31.5% of the total dose in faeces. ABT-333 M1 is mainly cleared through direct biliary excretion with the contribution of UGT-mediated glucuronidation and, to a small extent, oxidative metabolism.

Ritonavir: Following dosing of ABT-267/ABT-450/rtv, mean plasma half-life of ritonavir was approximately 4 hours. Following a 600 mg dose of ^{14}C-ritonavir oral solution, 86.4% of the radioactivity was recovered in the faeces and 11.3% of the dose was excreted in the urine.

- **Metabolism**

Ombitasvir is metabolised via amide hydrolysis followed by oxidative metabolism. Following a 25 mg single dose of ^{14}C-ABT-267 given alone, unchanged parent drug accounted for 8.9% of total radioactivity in human plasma; a total of 13 metabolites were identified in human plasma. These metabolites are not expected to have antiviral activity or off-target pharmacologic activity.

Paritaprevir is metabolised predominantly by CYP3A4 and to a lesser extent CYP3A5. Following administration of a single 200 mg/100 mg oral dose of ^{14}C-ABT-450 /ritonavir to humans, the parent drug was the major circulating component, accounting for approximately 90% of the plasma radioactivity. At least 5 minor metabolites of ABT-450 have been identified in circulation that accounted for approximately 10% of plasma radioactivity. These metabolites are not expected to have antiviral activity.

Dasabuvir is predominantly metabolised by CYP2C8 and to a lesser extent by CYP3A. Following a 400 mg ^{14}C-ABT-333 dose in humans, unchanged ABT-333 was the major component (approximately 60%) of drug related radioactivity in plasma. Seven metabolites were identified in plasma. The most abundant plasma metabolite was M1, which represented 21% of drug-related radioactivity (AUC) in circulation following single dose. M1 is formed via oxidative metabolism predominantly by CYP2C8.

Ritonavir is predominantly metabolised by CYP3A and to a lesser extent, by CYP2D6. Nearly the entire plasma radioactivity after a single 600 mg dose of ^{14}C-ritonavir oral solution in humans was attributed to unchanged ritonavir.

Inter-conversion

Ombitasvir is produced as a single isomer. Metabolism does not occur at the chiral centers of the molecule. Therefore, it is unlikely that interconversion plays a role.

Paritaprevir is produced as a single isomer. Metabolism does not occur at the chiral centers of the molecule. Therefore, it is unlikely that interconversion plays a role.

Dasabuvir does not contain any chiral centers.

- **Pharmacokinetics of metabolites**

Ombitasvir: M29 and M36 are considered to be major plasma metabolites with 31.2 and 21.4% drug-related radioactivity in plasma and having a plasma AUC0-24h at steady state of about 38 and 25% of that of parent compound. After a single oral radio labelled dose of 25 mg ABT-267, M29 and M36 tmax were observed at about 48 h after administration with Cmax values of 38 and 23 ng.q/g, respectively. None of the metabolites is expected to have any antiviral activity.

Paritaprevir: Five (major) metabolites were identified in human plasma after administration of ABT-450 with ritonavir, including M2 (7.8% of total drug related material AUCt), M29 (3.2% of total AUCt), and trace levels of M3, M13 and M6. None of the metabolites had exposure greater than 10% of the total radioactivity. None of the metabolites is expected to have any antiviral activity.

Dasabuvir: The main metabolite of ABT-333 is the M1 metabolite (t-butyl hydroxyl-ABT-333). This metabolite follows the pharmacokinetic profile of the parent. The elimination half-life is comparable to the parent. Moreover, the M1 concentrations are highly correlated with the parent concentrations, with a mean ratio of about 0.35.

Dose proportionality and time dependency

The data on dose-proportionality and time dependency derive from studies with Viekirax and Exviera.

Paritaprevir has non-linear pharmacokinetics and shows greater than proportional increase in exposure with dose. At a ritonavir dose of 100 mg, increasing the paritaprevir dose from 25 mg to 400 mg increased the mean dose-normalized paritaprevir 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 paritaprevir/ritonavir administered in combination with ombitasvir, with and without dasabuvir, was approximately 2-fold. Steady state was achieved within 7 to 11 days.

Ombitasvir: 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.

Dasabuvir: Single dose pharmacokinetics using early formulations is linear up to doses of 800-1200 mg, where absorption starts to decrease, possibly due to solubility. There is no single-dose vs. multiple-dose comparison, thus, it cannot be properly assessed whether there is any change over time

in clearance. There is an *in vitro* induction signal and in some of the DDI studies, the results could be interpreted as dasabuvir mediating a small induction. There is also a signal of CYP3A4 TDI *in vitro*. The accumulation ratio of dasabuvir and M1 are about 2 and 1.5, respectively. Based on the short half-life of dasabuvir (ca. 6 hrs), a somewhat smaller accumulation would be expected. In conclusion, there seems to be no marked time-dependency. Steady state for both substances was reached approximately on the third day of treatment.

Intra- and inter-individual variability

For dasabuvir, the between-subject variability was somewhat larger for the 3QD formulation compared to the 3-DAA regimen; at steady-state, the AUC, Cmax and C24 %CV was approximately 24%, 20% and 37% higher for the 3QD formulation.

Special populations

The data on special populations derive from studies with Viekirax and Exviera.

- **Impaired renal function**

Ombitasvir, paritaprevir and ritonavir: Pharmacokinetics of the combination of ABT-267/ABT45-/rtv 25/150/100 mg, with or without ABT-333 400 mg were evaluated in subjects with mild (CrCl: 60 to 89 ml/min), moderate (CrCl: 30 to 59 ml/min) and severe (CrCl: 15 to 29 ml/min) renal impairment. Compared to the subjects with normal renal function, ABT-267 exposures were comparable in subjects with mild, moderate and severe renal impairment. Compared to the subjects with normal renal function, ABT-450 Cmax values were comparable, but AUC values were 19%, 33% and 45% higher in mild, moderate and severe renal impairment, respectively. Ritonavir plasma concentrations increased when renal function was reduced: Cmax and AUC values were 26% to 42% higher, 48% to 80% higher and 66% to 114% higher in subjects with mild, moderate and severe renal impairment, respectively.

The changes in ABT-267, ABT-450 and ritonavir exposures in subjects with mild, moderate and severe renal impairment are not considered to be clinically significant. No dose adjustment for ABT-267, ABT-450 and ritonavir (Viekirax) with and without ABT-333 is recommended in HCV-infected patients with mild, moderate or severe renal impairment. ABT-267/ABT-450/ritonavir (Viekirax) has not been studied in HCV-infected patients on dialysis.

Dasabuvir: Pharmacokinetics of the combination of ABT-267/ABT-450/rtv 25/150/100 mg, with ABT-333 400 mg were evaluated in subjects with mild (CrCl: 60 to 89 ml/min), moderate (CrCl: 30 to 59 ml/min) and severe (CrCl: 15 to 29 ml/min) renal impairment, relative to subjects with normal renal function. In subjects with mild, moderate and severe renal impairment, ABT-333 mean AUC values were 21% higher, 37% higher and 50% higher, respectively. ABT-333 M1 AUC values were 6% lower, 10% lower, and 13% lower, respectively. The changes in ABT-333 exposures in subjects with mild, moderate and severe renal impairment are not considered to be clinically significant. ABT-333 (Exviera) has not been studied in patients on dialysis.

- **Impaired hepatic function**

Ombitasvir, paritaprevir and ritonavir: Following administration of ABT-267/ABT-450/ritonavir (Viekirax) and ABT-333 the pharmacokinetics of the combination (25 mg/200 mg/100 mg + ABT-333 400 mg) were evaluated in subjects with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment.

In subjects with mild hepatic impairment, ABT-450, ritonavir and ABT-267 mean Cmax and AUC values decreased by 29% to 48%, 34% to 38% and up to 8%, respectively, compared to subjects with normal hepatic function.

In subjects with moderate hepatic impairment, ABT-267 and ritonavir mean Cmax and AUC values decreased by 29% to 30% and 30 to 33%, respectively, while ABT-450 mean Cmax and AUC values increased by 26% to 62% compared to subjects with normal hepatic function.

In subjects with severe hepatic impairment, ABT-450 mean Cmax and AUC values increased by 3.2-to 9.5-fold; ritonavir mean Cmax values were 35% lower and AUC values were 13% higher and ABT-267 mean Cmax and AUC values decreased by 68% and 54%, respectively, compared to subjects with normal hepatic function.

The changes in ABT-267, ABT-450 and ritonavir exposures in subjects with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment are not considered clinically significant. As indicated in the EPAR of Viekirax, no dose adjustment for Viekirax or ABT-333 is recommended in HCV-infected patients with mild and moderate hepatic impairment. Viekirax must not be used in patients with severe hepatic impairment.

Dasabuvir: Pharmacokinetics of the combination of ABT-333 400 mg, with ABT-267 25 mg, ABT-450 200 mg, and ritonavir 100 mg were evaluated in subjects with mild (Child-Pugh A), moderate (Child Pugh B) and severe (Child-Pugh C) hepatic impairment, relative to subjects with normal hepatic function. In subjects with mild, moderate and severe hepatic impairment, ABT-333 AUC values were 17% higher, 16% lower and 325% higher, respectively. The AUC values of ABT-333 M1 metabolite were unchanged, 57% lower, and 77% higher, respectively. Plasma protein binding of ABT-333 and its M1 metabolite were not meaningfully different in subjects with hepatic impairment compared to normal control subjects.

The changes in ABT-333 exposures in subjects with mild and moderate hepatic impairment are not considered clinically significant. As indicated in the EPAR of Exviera, the safety and efficacy of ABT-333 and ABT-267/ABT-450/ritonavir have not been established in HCV-infected patients with moderate hepatic impairment (Child-Pugh B).

- **Gender**

Ombitasvir, paritaprevir and ritonavir: Based on population pharmacokinetic analysis of data from Phase 3 clinical studies, female subjects would have approximately 55% higher, 100% higher and 15% higher ABT-267, ABT-450 and ritonavir exposures than male subjects. However, no dose-adjustment based on gender is warranted.

Dasabuvir: Based on population pharmacokinetic analysis of data from Phase 3 clinical studies, female subjects would have approximately 14 to 30% higher ABT-333 exposures than male subjects.

- **Race**

Ombitasvir, paritaprevir and ritonavir: Based on population pharmacokinetic analysis of data from Phase 3 clinical studies, Asian subjects had 18% to 21% higher ABT-267 exposures, and 37% to 39% higher ABT-450 exposures than non-Asian subjects. The ritonavir exposures were comparable between Asians and non-Asians.

Dasabuvir: Based on population pharmacokinetic analysis of data from Phase 3 clinical studies, Asian subjects had 29% to 39% higher ABT-333 exposures than non-Asian subjects.

- **Weight**

Ombitasvir, paritaprevir and ritonavir: A 10 kg change in body weight from 76 kg (median weight in the Phase 3 studies) would results in <10% change in ABT-267 exposures, and no change in ABT-450 exposures. Body weight is not a significant predictor of ritonavir exposures.

Dasabuvir: A 10 kg change in body weight from 76 kg (median weight in the Phase 3 studies) would result in <10% change in ABT-333 exposures.

- **Elderly**

Ombitasvir and paritaprevir: Based on population pharmacokinetic analysis of data from Phase 3 clinical studies, a 10 year increase or decrease in age from 54 years (median age in the Phase 3 studies) would result in approximately 10% change in ABT-267 exposures, and ≤20% change in ABT-450 exposures. There is no pharmacokinetic information in patients >75 years.

Dasabuvir: Based on population pharmacokinetic analysis of data from Phase 3 clinical studies, a 10 year increase or decrease in age from 54 years (median age in the Phase 3 studies) would results in <10% change in ABT-333 exposures. There is no pharmacokinetic information in patients >75 years.

- **Children**

The pharmacokinetics of dasabuvir with ombitasvir/paritaprevir/ritonavir in paediatric patients has not been investigated.

Interactions

The data on interactions derive from studies with Viekirax and Exviera and consists of an extensive DDI data package with *in vitro* and *in vivo* studies. The potential for systemic drug-drug interactions is expected to be similar for the 3QD- and the 3-DAA regimens.

Potential for ombitasvir/paritaprevir/ritonavir/dasabuvir to affect the pharmacokinetics of other medicinal products

In vivo drug interaction studies evaluated the net effect of the combination treatment, including ritonavir.

Medicinal products metabolised by CYP3A4

Ritonavir is a strong inhibitor of CYP3A. Co-administration of 3QD with medicinal products primarily metabolized by CYP3A may result in increased plasma concentrations of these medicinal products.

Medicinal products transported by the OATP family and OCT1

Paritaprevir is an inhibitor of the hepatic uptake transporters OATP1B1 and OATP1B3, and paritaprevir and ritonavir are inhibitors of OATP2B1. Ritonavir is an *in vitro* inhibitor of OCT1, but the clinical relevance is unknown. Co-administration of 3QD with or without dasabuvir with medicinal products that are substrates of OATP1B1, OATP1B3, OATP2B1 or OCT1 may increase plasma concentrations of these transporter substrates, potentially requiring dose adjustment/clinical monitoring.

Medicinal products transported by BCRP

Paritaprevir, ritonavir and dasabuvir are inhibitors of BCRP *in vivo*. Co-administration of 3QD together with medicinal products that are substrates of BCRP may increase plasma concentrations of these transporter substrates.

Medicinal products transported by P-gp in the intestine

While paritaprevir, ritonavir and dasabuvir are *in vitro* inhibitors of P-gp, no significant change was observed in the exposure of the P-gp substrate digoxin when administered with Viekirax and dasabuvir. However, co-administration of digoxin with Viekirax without dasabuvir may result in increased plasma concentrations. Viekirax may increase the plasma exposure to medicinal products that are sensitive for changed intestinal P-gp activity.

Medicinal products metabolised by glucuronidation (UGT1A1)

Paritaprevir, ombitasvir and dasabuvir are inhibitors of UGT1A1. Co-administration of 3QD with medicinal products that are primarily metabolized by UGT1A1 result in increased plasma concentrations of such medicinal products.

Medicinal products metabolised by CYP2C19

Co-administration of 3QD can decrease exposures of medicinal products that are metabolized by CYP2C19.

Medicinal products metabolised by CYP2C9

Viekirax administered with or without dasabuvir did not affect the exposures of the CYP2C9 substrate, warfarin.

Medicinal products metabolised by CYP2D6 or CYP1A2

Viekirax administered with or without dasabuvir did not affect the exposures of the CYP2D6/CYP1A2 substrate, duloxetine.

Medicinal products renally excreted via transport proteins

Ombitasvir, paritaprevir, and ritonavir do not inhibit organic anion transporter (OAT1) *in vivo* as shown by the lack of interaction with tenofovir (OAT1 substrate). *In vitro* studies show that ombitasvir, paritaprevir, and ritonavir are not inhibitors of organic cation transporters (OCT2), organic anion transporters (OAT3), or multidrug and toxin extrusion proteins (MATE1 and MATE2K) at clinically relevant concentrations. *In vitro* studies show that dasabuvir is not an inhibitor of organic cation transporters (OCT2), organic anion transporters (OAT3), or multidrug and toxin extrusion proteins (MATE1 and MATE2K) at clinically relevant concentrations.

Potential for other medicinal products to affect the pharmacokinetics of ombitasvir, paritaprevir, and dasabuvir

Medicinal products that inhibit CYP3A4

Co-administration of 3QD with strong inhibitors of CYP3A may increase paritaprevir concentrations.

Medicinal products that inhibit CYP2C8

Co-administration of dasabuvir with medicinal products that inhibit CYP2C8x) may increase dasabuvir plasma concentrations.

Enzyme inducers

Co-administration of 3QD with medicinal products that are moderate or strong enzyme inducers is expected to decrease ombitasvir, paritaprevir, ritonavir and dasabuvir plasma concentrations and reduce their therapeutic effect.

Dasabuvir is a substrate of P-gp and BCRP and its major metabolite M1 is a substrate of OCT1 *in vitro*. Dasabuvir M1 metabolite was quantified in all the drug interaction studies. Changes in exposures of the metabolite were generally consistent with that observed with dasabuvir except for studies with CYP2C8 inhibitor, gemfibrozil, where the metabolite exposures decreased by up to 95% and CYP3A inducer, carbamazepine, where the metabolite exposures decreased by only up to 39%.

Medicinal products that inhibit CYP3A4 and transport proteins

Paritaprevir is eliminated via CYP3A4 mediated and biliary excretion (substrate of the hepatic transporters OATP1B1, P-gp and BCRP).

Medicinal products that inhibit transport proteins

Potent inhibitors of P-gp, BCRP, OATP1B1 and/or OATP1B3 have the potential to increase the exposure to paritaprevir.

3.3.2. Pharmacodynamics

Comparative bioavailability was demonstrated following single and multiple doses of the 3QD and 3-DAA regimens (study M14-566) except for a lower paritaprevir C_{max} 28%, lower Ritonavir C_{max} 21%, and lower dasabuvir C_{trough} 29%, for the 3QD regimen compared to the 3-DAA regimen.

- **Paritaprevir**

The lower plasma Cmax of paritaprevir following treatment with the 3QD-tablet compared to the 3-DAA reference is considered to be of limited clinical relevance since it is believed that AUC or C_{trough} are better correlated to efficacy than plasma C_{max} in the treatment with anti-viral/anti-infective drugs.

- **Ritonavir**

Ritonavir has no activity against HCV and therefore, the lower ritonavir C_{max} with the 3QD formulation compared to the 3-DAA reference formulation will not affect the efficacy of the 3QD formulation.

- **Dasabuvir**

Exposure-response analyses were conducted to estimate the impact of the lower dasabuvir C_{trough} obtained with the 3QD formulation compared with the 3-DAA reference regimen. Two different approaches were evaluated using data from all pivotal Phase 3 studies and one Phase 2 study. Approach #1 was considered the primary analysis and was based on correlating exposures to SVR_{12} by logistic regression. A secondary supporting analysis (Approach #2) included development of a viral load model to correlate DAA concentrations to HCV ribonucleic acid (RNA) and predict SVR_{12}.

Only exposure and SVR_{12} data from GT1a-infected subjects were included in the analyses as > 99% of GT1b-infected subjects who completed assigned treatment achieved SVR_{12}. The evaluation of the effect of a lower dasabuvir exposure in HCV GT1a subjects represents the worst case scenario since HCV GT1b subjects achieve SVR_{12} to a greater extent, consequent on the higher activity of all DAAs in the combo against this subgenotype.

Approach #1: Logistic regression model for exposure vs. SVR_{12}

The **objectives** of the analysis were:

- To develop relationships between DAA and ribavirin steady-state C_{trough} or AUC and SVR_{12} following administration of the 3-DAA regimen with and without ribavirin in GT1a-infected subjects

- To predict the impact on SVR_{12} of a 29-38% lower dasabuvir C_{trough} with 32% higher between-subject variability with the 3QD regimen relative to the 3-DAA regimen in GT1a-infected subjects, under non-fasting conditions.

Data:

The analysis included data following treatment under non-fasting conditions with the 3-DAA regimen or 2-DAA regimen (in the absence of either dasabuvir or ombitasvir) with and without ribavirin in four Phase 3 studies and two Phase 2 studies.

Individual steady state DAA and ribavirin exposure variables (Ctrough or AUC) were derived by empirical Bayes post-hoc estimates from population PK models for each of the DAA and ribavirin. The population PK models are used to predict DAAs and ribavirin exposure measures to be used in the logistic regression model. In the original MAA for Exviera and Viekirax, the population PK models were considered adequate to describe the general trend and to evaluate covariate effects. However, based on the comparison of observed and model predicted Cmax, AUC and Ctrough values, dasabuvir Ctrough values appear to be under predicted (approximately 40% lower). The visual predictive check indicates over prediction of the variability for Ctrough but does not reveal any clear indication of structural model misspecification or under prediction for Ctrough.

Model development:

Data analysis was performed using multiple linear logistic regression procedure using SAS version 9.2 with SVR_{12}, a binary response (Yes or No) as the dependent variable and DAA and ribavirin steady state C_{trough} or AUC (log transformed) as predictor and subject or study specific variables as covariates. C_{trough} was considered the primary exposure variable. The logistic regression model was developed under the assumption that there are no correlations between the included predictors.

Predictions and Simulations:

The impact on efficacy of the lower dasabuvir C_{trough} (28-38%) obtained with the 3QD formulation was determined for various GT1a-infected populations based on statistically significant covariates and clinical relevance. The four subpopulations non-cirrhotic 1) females, 2) males with IL28B CC genotype and cirrhotic 3) females, 4) males with IL28B non-CC genotype were considered.

The SVR_{12} predictions were carried out using the geometric means of steady-state DAAs and ribavirin C_{trough} along with arithmetic means of baseline viral load and age for the specific populations.

The following scenarios for each sub-population were predicted:

a) Geometric mean of dasabuvir C_{trough} (representing the 3-DAA regimen as reference)

b) 29% reduction in dasabuvir C_{trough} (representing a point estimate of 0.71 for the 3QD regimen as Test)

c) 38% reduction in dasabuvir C_{trough} (representing the lower bound of the 90% CI of 0.62 for the 3QD regimen as Test)

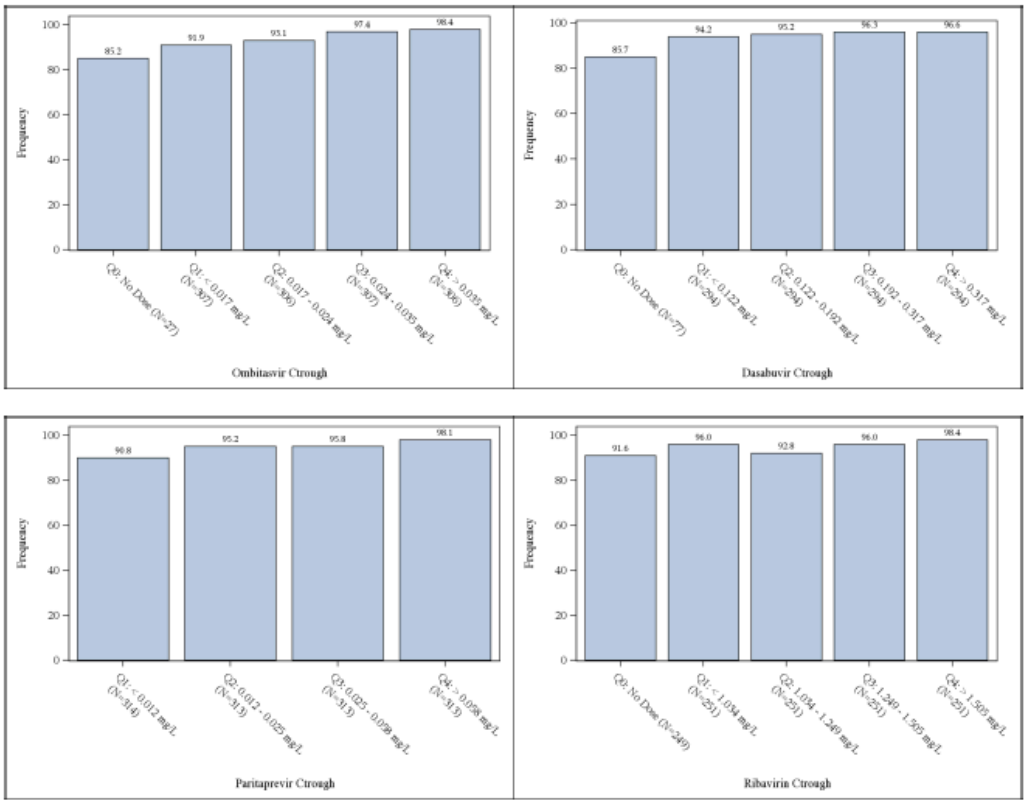
Pharmacodynamic equivalence ratio (ratio of predicted SVR_{12} from the 3QD regimen relative to the 3-DAA regimen) with 90% CI and ΔSVR_{12} (differences in SVR_{12} rate) with 95% CI between the 2 regimens were estimated.

Results:

The results from the initial graphical analysis of the relationship between observed $\%SVR_{12}$ vs C_{trough} quartiles at steady state of the DAAs and ribavirin are presented in the below figure. For dasabuvir,

change in C_{trough} values from 0 mg/mL to 0.47 mg/L (median of 4th quartile) showed a 10.9% change in SVR_{12} rate.

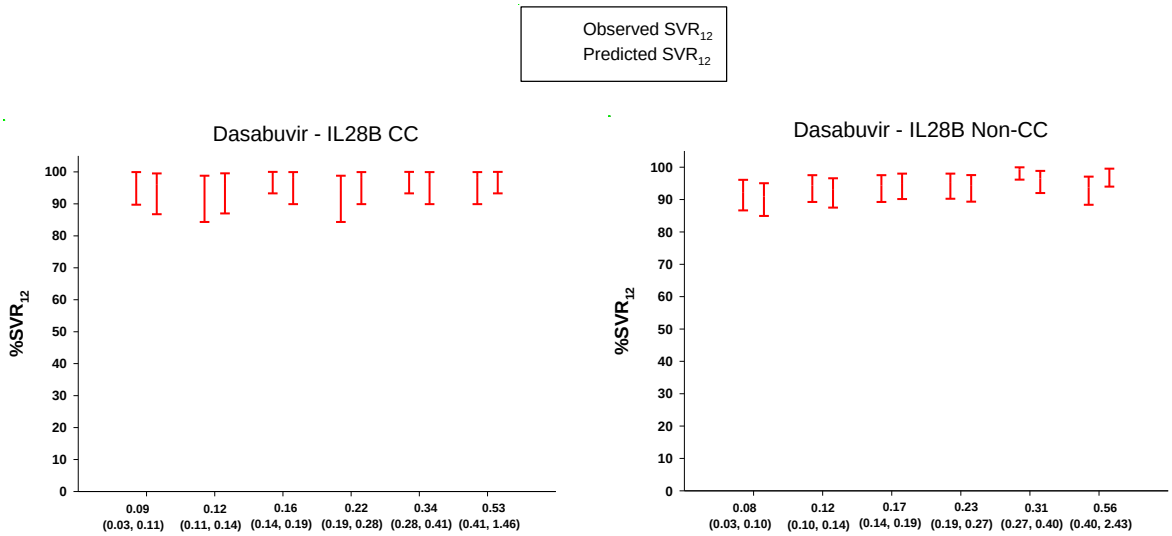
Figure 1. Quartile Plots paritaprevir, ombitasvir, dasabuvir and ribavirin C_{trough} vs % SVR_{12}.



Frequency represents % SVR_{12}
Median Ombitasvir $C_{troughs}$ (mg/L): Q1 – 0.0136, Q2 – 0.0201, Q3 – 0.0283, Q4 – 0.0453
Median Dasabuvir $C_{troughs}$ (mg/L): Q1 – 0.0925, Q2 – 0.154, Q3 – 0.243, Q4 – 0.467
Median Paritaprevir $C_{troughs}$ (mg/L): Q1 – 0.00690, Q2 – 0.0171, Q3 – 0.0360, Q4 – 0.115
Median Ribavirin $C_{troughs}$ (mg/L): Q1 – 0.922, Q2 – 1.14, Q3 – 1.36, Q4 – 1.76

The relationship between observed and predicted %SVR_{12} and dasabuvir C_{trough} for all GT1a subjects stratified by IL28B genotype (CC versus non-CC), is shown in the following figure:

Figure 2. Observed and Predicted Relationship Between Proportion of Subjects with SVR12 and Dasabuvir Following Administration of the 2-DAA and 3-DAA ± Ribavirin Regimen in IL28B CC (Left Panel) and IL28B Non-CC (Right Panel) HCV GT1a-Infected Subjects



SVR_{12} predictions were performed using each subject's dasabuvir, ombitasvir, paritaprevir and ribavirin (C_{trough} or AUC as appropriate), and other categorical and continuous covariates.

Light green color and the error bars represent the mean of the individual predicted SVR_{12} and 95% exact binomial CI. Dark green color and the error bars represent the observed proportion of subjects that achieved SVR_{12} and the corresponding 95% exact binomial CI plotted at the midpoint (8.33%, 25%, 41.67%, 58.33%, 75% and 91.67%) of each dasabuvir (C_{trough} or AUC), ribavirin (C_{trough} or AUC) and paritaprevir AUC sextile respectively.

Predictions: A 29% lower dasabuvir C_{trough} for the 3QD regimen (scenario 'b') and a 38% lower mean C_{trough} (scenario 'c') is predicted to have a low impact on SVR_{12} rates (0.02% - 0.54% and 0.04%-0.77% lower SVR_{12}. respectively) compared to the current 3-DAA regimen as the reference (scenario 'a' (table 3).

Table 3. The predicted effect of lower dasabuvir C_{trough} on SVR_{12} in HCV GT1a-infected subjects.

Population	Observed SVR_{12} %	Predicted SVR_{12} % (95% CI)		Decrease in SVR_{12} for 3QD vs. 3-DAA (Delta SVR_{12} %) (95% CI)	Pharmacodynamic Equivalence (Ratio and 90% CI)
		3 DAA (Reference)	3QD		
Effect of 29% Lower Dasabuvir C_{trough}[a]					
Noncirrhotic, female, IL28B CC	100	99.80 (99.56 to 100.03)	99.77 (99.52 to 100.03)	0.02 (0.00 to 0.05)	1.00 (1.00 to 1.00)
Noncirrhotic, male, IL28B CC	96.6	99.0 (98.1 to 99.9)	98.9 (97.9 to 99.8)	0.13 (0.02 to 0.23)	0.999 (0.998 to 1.00)
Cirrhotic, female, IL28B non-CC	100	99.1 (98.1 to 100)	99.0 (97.9 to 100)	0.11 (−0.01 to 0.24)	0.999 (0.998 to 1.00)
Cirrhotic, male, IL28B non-CC	92.4	95.4 (92.2 to 98.6)	94.9 (91.3 to 98.4)	0.54 (0.10 to 0.97)	0.994 (0.990 to 0.998)
Effect of 38% Lower Dasabuvir C_{trough}[b]					
Noncirrhotic, female, IL28B CC	100	99.80 (99.56 to 100.03)	99.76 (99.49 to 100.03)	0.04 (0.00 to 0.07)	1.00 (0.999 to 1.00)
Noncirrhotic, male, IL28B CC	96.6	99.0 (98.1 to 99.9)	98.8 (97.8 to 99.8)	0.18 (0.03 to 0.33)	0.998 (0.997 to 1.00)
Cirrhotic, female, IL28B non-CC	100	99.1 (98.1 to 100)	98.9 (97.8 to 100)	0.16 (−0.02 to 0.34)	0.998 (0.997 to 1.00)
Cirrhotic, male, IL28B non-CC	92.4	95.4 (92.2 to 98.6)	94.6 (90.9 to 98.4)	0.77 (0.14 to 1.39)	0.992 (0.986 to 0.998)

CI = confidence interval; C_{trough} = trough plasma concentration; SVR_{12} = sustained virology response at 12 weeks post-treatment

a Based on the geometric mean ratio of 0.710 (0.622 – 0.812) for dasabuvir C_{trough} at steady state (Part 2 of Study M14-566).

b Based on the lower bound of the 90% confidence interval of the geometric mean ratio of 0.622 for dasabuvir C_{trough} at steady state (Part 2 of Study M14-566).

Note: SVR_{12} predictions were performed at mean baseline viral load, age and geometric mean for DAAs and RBV steady state C_{trough} of each subpopulation.

Simulations with a 29% lower dasabuvir C_{trough} (scenario 'b') incorporating a 32% higher between subject variability for the 3QD regimen and corresponding between-subject variability for the predictor variables suggest comparable SVR_{12} rates (0.03% to 0.35% lower SVR_{12}) to the current 3-DAA regimen. Scenario 'c' with a maximum of 38% lower mean dasabuvir C_{trough} levels and 32% higher between subject variability indicated a 0.04% to 0.64% lower SVR_{12} (table 4).

Table 4. Simulated effect of lower dasabuvir C_{trough} with higher between subject variability on SVR_{12}.

Population	Predicted SVR_{12} % (95% PI)		Decrease in SVR_{12} for 3QD vs. 3-DAA (Delta SVR_{12} %) (95% PI)	Pharmacodynamic Equivalence (Ratio and 90% PI)
	3-DAA (Reference)	3QD		
Effect of 29% Lower Dasabuvir C_{trough}[a]				
Noncirrhotic, female, IL28B CC	99.66 (98.91 to 99.90)	99.63 (98.82 to 99.89)	0.03 (−0.01 to 0.14)	1.00 (0.999 to 1.00)
Noncirrhotic, male, IL28B CC	98.3 (96.2 to 99.3)	98.2 (96.0 to 99.2)	0.10 (−0.08 to 0.43)	0.999 (0.997 to 1.00)
Cirrhotic, female, IL28B non-CC	98.44 (96.13 to 99.47)	98.34 (95.92 to 99.43)	0.08 (−0.08 to 0.42)	0.999 (0.997 to 1.00)
Cirrhotic, male, IL28B non-CC	93.3 (87.3 to 96.5)	92.9 (86.4 to 96.3)	0.35 (−0.15 to 1.27)	0.997 (0.989 to 1.00)
Effect of 38% Lower Dasabuvir C_{trough}[b]				
Noncirrhotic, female, IL28B CC	99.66 (98.91 to 99.90)	99.61 (98.77 to 99.88)	0.04 (0.00 to 0.19)	1.00 (0.999 to 1.00)
Noncirrhotic, male, IL28B CC	98.3 (96.2 to 99.3)	98.1 (95.8 to 99.2)	0.18 (0.00 to 0.57)	0.998 (0.995 to 1.00)
Cirrhotic, female, IL28B non-CC	98.4 (96.1 to 99.5)	98.3 (95.7 to 99.4)	0.15 (−0.01 to 0.59)	0.999 (0.995 to 1.00)
Cirrhotic, male, IL28B non-CC	93.3 (87.3 to 96.5)	92.6 (85.9 to 96.1)	0.64 (0.10 to 1.79)	0.994 (0.983 to 0.999)

C_{trough} = trough plasma concentration; PI = prediction interval; RBV = ribavirin; SVR_{12} = sustained virology response at 12 weeks post-treatment

c Based on the geometric mean ratio of 0.710 (0.622 – 0.812) for dasabuvir C_{trough} at steady state (Part 2 of Study M14-566) and 32% higher between subject variability.

d Based on the lower bound of the 90% CI of the geometric mean ratio of 0.622 for dasabuvir C_{trough} at steady state (Part 2 of Study M14-566) and 32% higher between subject variability.

SVR_{12} simulations were performed at mean baseline viral load, age, and geometric mean for DAAs and RBV steady-state C_{trough} of each subpopulation and corresponding between subject variability.

Each trial consisted of 100 subjects in each subpopulation. The mean SVR_{12} was obtained for each trial.

Results are summarized as median and 95% (2.5^{th} and 97.5^{th} percentile) or 90% PI (5^{th} and 95^{th} percentile) from 1000 trials.

The model prediction and simulations indicate a minor effect on SVR_{12} of a reduced dasabuvir C_{trough}.

Approach #2- Viral dynamic model (R&D/15/0187)

The viral dynamic semi-mechanistic exposure response model previously developed for the currently marketed 3-DAA regimen was updated and applied to conduct simulations to determine the effect of the change in the absorption profiles of dasabuvir and paritaprevir from the 3QD formulation on SVR_{12}

rates. Based on the presented data, model performance is not considered robust and the model is not qualified to perform simulations illustrating the effect of different absorption profiles.

- **Impact on efficacy of lower ribavirin dose (600 mg QD) with the 3QD formulation**

Exposure-response analyses were conducted to estimate the impact of the lower dasabuvir C_{trough} obtained with the 3QD formulation and a concurrent reduction in Ribavarin $C_{through.}$ The logistic regression model predictions and simulations of the 600 mg QD dose regimen indicate a minor effect on SVR_{12} of the reduced ribavirin dose. However, the simulated geometric mean Ribavarin C_{trough} was 0.72 mg/L and observations for only 19 subjects supported the logistic regression model in that range as described in table 5.

Table 5. Observed and Predicted SVR_{12} Rates for Subjects in Observed Data with Ribavirin C_{trough} Within the Predicted Range for 600 mg QD

	N	Observed SVR_{12} Rates	Predicted SVR_{12} Rates
Number of Subjects ≤ 0.72 mg/L	19	18/19 (94.7%)	96.4%
Number of Subjects > 0.72 mg/L	985	944/985 (95.8%)	95.8%
Number of Subjects within one standard deviation of geometric mean of 0.72 mg/L (0.49 to 0.94 mg/L)	148	142/148 (95.9%)	95.6%
Number of Subjects > 0.94 mg/L	856	820/856 (95.8%)	95.9%

Simulations based on *post hoc* estimates from R&D/14/0047.

Table 5: Simulation Results; Effect of Lower Dasabuvir C_{trough} and Higher Between Subject Variability for the 3QD Regimen and 50% Lower Ribavirin C_{trough} for the 600 mg QD Dosing on SVR_{12}

Population	Predicted SVR_{12} % (95% PI)		Decrease in SVR_{12} for 3QD vs. 3-DAA (Delta SVR_{12} %) (95% PI)	Pharmacodynamic Equivalence (Ratio and 90% PI)
	3-DAA (Reference)	3QD		
Effect of 50% Lower RBV and 29% Lower Dasabuvir C_{trough}[a]				
Noncirrhotic, female, IL28B CC	99.66 (98.91 to 99.90)	99.58 (98.68 to 99.87)	0.09 (0.03 to 0.27)	0.999 (0.998 to 1.00)
Noncirrhotic, male, IL28B CC	98.3 (96.2 to 99.3)	97.9 (95.5 to 99.1)	0.37 (0.14 to 0.86)	0.996 (0.992 to 0.998)
Cirrhotic, female, IL28B non-CC	98.4 (96.1 to 99.5)	98.1 (95.4 to 99.3)	0.33 (0.09 to 0.96)	0.997 (0.992 to 0.999)
Cirrhotic, male, IL28B non-CC	93.3 (87.3 to 96.5)	92.0 (84.8 to 95.7)	1.33 (0.51 to 2.86)	0.986 (0.971 to 0.994)
Effect of 50% Lower RBV and 38% Lower Dasabuvir C_{trough}[b]				
Noncirrhotic, female, IL28B CC	99.7 (98.9 to 99.9)	99.6 (98.6 to 99.9)	0.10 (0.03 to 0.32)	0.999 (0.997 to 1.00)
Noncirrhotic, male, IL28B CC	98.3 (96.2 to 99.3)	97.8 (95.4 to 99.0)	0.46 (0.18 to 1.06)	0.995 (0.990 to 0.998)
Cirrhotic, female, IL28B non-CC	98.4 (96.1 to 99.5)	98.0 (95.2 to 99.3)	0.42 (0.12 to 1.15)	0.996 (0.990 to 0.999)
Cirrhotic, male, IL28B non-CC	93.3 (87.3 to 96.5)	91.6 (84.3 to 95.6)	1.65 (0.69 to 3.54)	0.982 (0.965 to 0.992)

C_{trough} = trough plasma concentration; PI = prediction interval; RBV = ribavirin; SVR_{12} = sustained virology response at 12 weeks post-treatment

e Based on the geometric mean ratio of 0.710 (0.622 – 0.812) for dasabuvir C_{trough} at steady state (Part 2 of Study M14-566) and 32% higher between subject variability.

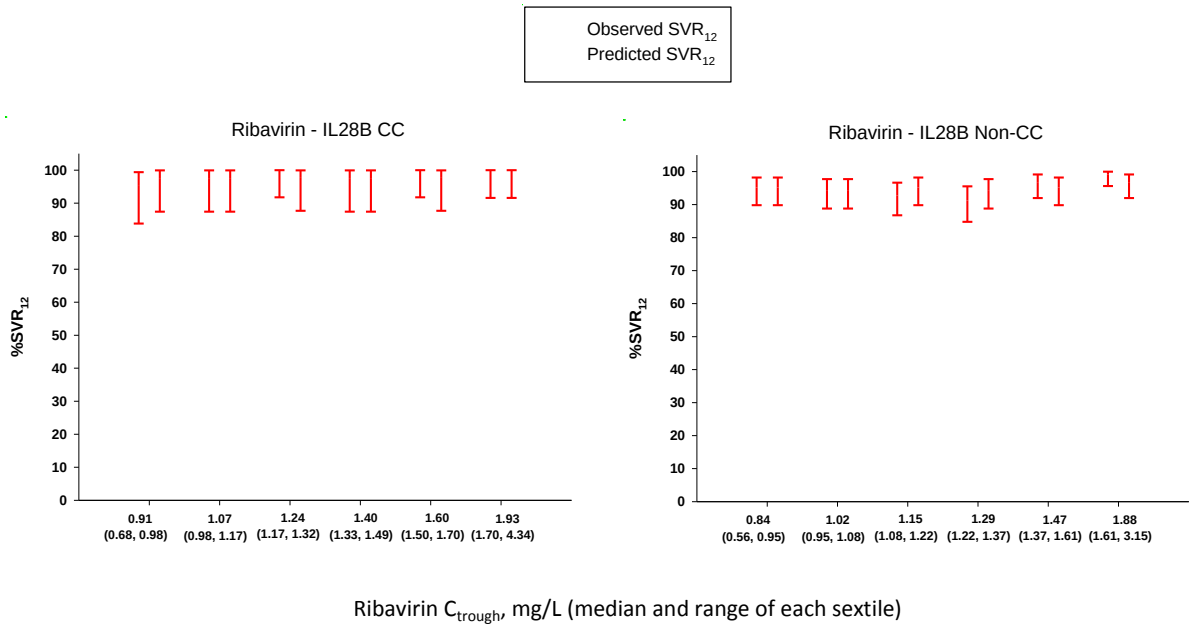
f Based on the lower bound of the 90% CI of the geometric mean ratio of 0.622 for dasabuvir C_{trough} at steady state (Part 2 of Study M14-566) and 32% higher between subject variability.

SVR_{12} simulations were performed at mean baseline viral load, age, and geometric mean for DAAs and RBV steady-state C_{trough} of each subpopulation and corresponding between subject variability.

Each trial consisted of 100 subjects in each subpopulation. The mean SVR_{12} was obtained for each trial.

Results are summarized as median and 95% (2.5^{th} and 97.5^{th} percentile) or 90% PI (5^{th} and 95^{th} percentile) from 1000 trials. Figure 3 show that the Ribavirin C_{trough} observations and predictions are in good agreement.

Figure 3. Observed and Predicted Relationship Between Proportion of Subjects with SVR_{12} and Dasabuvir, Paritaprevir or Ribavirin Following Administration of the 2-DAA and 3-DAA ± Ribavirin Regimen in IL28B CC (Left Panel) and IL28B Non-CC (Right Panel) HCV GT1a-Infected Subjects



SVR_{12} predictions were performed using each subject's dasabuvir, ombitasvir, paritaprevir and ribavirin (C_{trough} or AUC as appropriate), and other categorical and continuous covariates.

Light green color and the error bars represent the mean of the individual predicted SVR_{12} and 95% exact binomial CI. Dark green color and the error bars represent the observed proportion of subjects that achieved SVR_{12} and the corresponding 95% exact binomial CI plotted at the midpoint (8.33%, 25%, 41.67%, 58.33%, 75% and 91.67%) of each dasabuvir (C_{trough} or AUC), ribavirin (C_{trough} or AUC) and paritaprevir AUC sextile respectively.

3.3.3. Discussion on clinical pharmacology

Pharmacokinetics

The application concerns a new fixed dose combination of dasabuvir, ombitasvir, paritaprevir and ritonavir as well as a new dosage form for dasabuvir (prolonged release). The comparative bioavailability studies together with the food-effect study are considered sufficient to characterise the pharmacokinetics of the new formulation. The dossier also includes an extensive number of pharmacokinetic studies mainly conducted with Viekirax and Exviera, including studies in special populations and interaction studies. Overall, the pharmacokinetics of all active substances has been satisfactorily characterised.

Pharmacokinetic data are used to bridge to efficacy and safety results from previous studies with the 3-DAA regimen (Viekirax+Exviera). Study M14-566 in which the bioavailability of the 3QD formulation was compared to the 3-DAA regimen (after single-dose and multiple-dose administration) together with exposure-response analyses and simulations are pivotal in the application.

The pivotal Study M14-566 was well-designed and the overall conductance adequate. The 3-DAA regimen with ritonavir has time-dependent pharmacokinetics and the results at steady-state (part 2) are thus considered to be more relevant for the clinical evaluation than the single-dose results. After multiple-dose administration with a standardised breakfast (a medium to high fat meal) bioequivalence

between the 3QD tablet and the 3-DAA regimen was demonstrated for all parameters except for a lower dasabuvir C24 (29%), lower paritaprevir Cmax (28%), and lower ritonavir Cmax (21%). The impact of the lower plasma concentrations on efficacy is further discussed in the Clinical Efficacy section. Considering that study M14-566 is a cross over bioequivalence study and 5 subjects did not completed both periods/treatments, the number of subjects to be included should be 61 and not 63. The applicant should provide statistical data excluding 5 subjects.The exposure of all active substances was increased by concomitant food-intake. For ombitasvir, ritonavir and paritaprevir the food effect was similar or marginally larger compared to the 3-DAA regimen. The effect of food on dasabuvir exposure was however markedly more pronounced with the dasabuvir ER-component included in the 3QD formulation compared the conventional IR-formulation (Exviera). This is mainly explained with a lower bioavailability of dasabuvir from the 3QD tablet after administration under fasting conditions. Under fasting conditions the relative bioavailability of dasabuvir in the 3QD tablet, compared to with Exviera/Viekirax, was low, with a GMR of 0.3 and 90% confidence limits from 0.25-0.35.

In the food-effect study the influence of a high-fat, high-calorie meal was investigated. The conditions under which equivalence with the 3-DAA regimen was evaluated also involved administration with a rather high-fat meal. The effect of smaller meals on dasabuvir bioavailability is not known. Neither are the clinical consequences of a dasabuvir exposure lower to the extent seen when the tablet is taken in the fasted state. This was considered as a major objection in the primary round. The Applicant suggests that the lower exposure of dasabuvir from the 3QD regimen under fasted conditions are likely due to faster gastric emptying combined with slower release from the ER layer for the 3QD tablets and reduced absorption of dasabuvir in the lower GI tract, rather than an effect of increased solubility of dasabuvir in the presence of food. This may be a possible explanation considering the relatively low effect of a high-fat meal on dasabuvir from the IR tablet. If this hypothesis is correct it would thus be of importance to administer the 3QD tablet with a sufficiently large meal to delay the gastric emptying and gastro-intestinal transit in order to maximise the absorption of dasabuvir. It is however uncertain how large such a meal needs to be. Only when taken under the conditions of the bioavailability studies performed with a meal, can the therapeutic equivalence of Cokiera to the reference formulations of the relevant drugs be reasonably certainThe Applicant proposes to revise the SmPC recommendation from "*To maximise absorption, Cokiera tablets should be taken <u>with food</u>*" to "*To maximise absorption, Cokiera tablets should be taken <u>with a full meal</u>*". This, however, is not considered to give sufficient assurance of clinical equivalence, in the absence of a bioequivalence study when Cokiera is taken with a low fat meal (e.g., a continental breakfast).

The release of dasabuvir from the 3QD formulation was delayed in the presence of alcohol in vitro. The clinical implications are unknown, but an interaction in the GI-tract during concomitant intake of 3QD and alcohol cannot be excluded. The Applicant has suggested a very careful approach recommending an alcohol free interval 4 h before and 4 h after administration of 3QD. It is agreed that an alcohol free interval after administration of the 3QD tablet may be a relevant precautionary measure. If the interval needs to be as long as 4 h is uncertain; however, the proposal is not unreasonable given the delayed gastric emptying and slow absorption of dasabuvir. Given that alcohol is rapidly absorbed from the gastro-intestinal tract, the recommended drug free interval after alcohol consumption may be overcautiously long. Since there are no data to support a shorter interval, the proposed recommendation is however acceptable.

<u>Relationship between plasma concentration and effect</u>

Paritaprevir: The lower plasma C_{max} of paritaprevir following treatment with the 3QD-tablet compared to the 3-DAA reference is considered to be of limited clinical relevance since it is believed that AUC or C_{trough} are better correlated to efficacy plasma C_{max} in the treatment with anti-viral/anti-infective drugs.

Ritonavir: Ritonavir has no activity against HCV and therefore, the lower ritonavir C_{max} with the 3QD formulation compared to the 3-DAA reference formulation will not affect the efficacy of the 3QD formulation.

Dasabuvir: Exposure-response analyses were conducted to estimate the impact of the lower dasabuvir C_{trough} obtained with the 3QD formulation compared with the 3-DAA reference regimen. The logistic regression model predictions and simulations indicate a minor effect on SVR_{12} of a reduced dasabuvir C_{trough} as seen in the bioequivalence study. It was indicated that the model captured the trend in observed SVR_{12} versus dasabuvir C_{trough} well, in both IL28B CC and non-CC populations with GT1a infection. The models predict observed data well, also for the lower 25th percentile of observed DAA and Ribavirin exposures.

Reduction of the ribavirin dose

The MAH proposes a fixed dose 600 mg once daily ribavirin (RBV) regimen to replace the current weight based, twice daily regimen (1000 mg and 1200 mg total daily dose for subjects with body weight < 75 kg and ≥ 75 kg, respectively). The main support for this proposal is the SVR_{12} logistic regression model in combination with the predicted exposure of the 600 mg once daily dose (no empirical exposure data for 600 mg ribavirin q.d. have been provided). The logistic regression model makes use of RBV C_{trough} values which in turn are obtained from a population PK model of RBV. The proposed RBV dose reduction is expected to result in approximately 40% to 50% lower RBV exposure. For the purpose of performing simulations, the MAH has assumed a 50% reduction. The MAH has reported that only 19 subjects had clinical C_{trough} observations below the simulated geometric mean (0.72 mg/L). This means that lower 50% of the simulated RBV exposure range has very limited support of clinical data and that the simulated SVR_{12} responses are very uncertain. This uncertainty is compounded by the fact that the ribavirin dose reduction would be made on top of the reduction in dasabuvir C_{trough} seen with Cokiera relative to Exviera. Further aspects of the proposed reduction of the RBV dose are addressed in the section Clinical Efficacy.

3.3.4. Conclusions on clinical pharmacology

The pharmacokinetics of the 3QD formulation has been characterised in fasting and with a full meal. . The lack of information regarding how lighter meals, such as a continental breakfast, affects the exposure to the dasabuvir and paritaprevir is, however, considered crucial in terms of the ability to ascertain the clinical equivalence of 3QD with the 3DAA regimen from which efficacy and safety are bridged.

Exposure-response analyses were conducted to estimate the impact of the lower dasabuvir C_{trough} obtained with the 3QD formulation compared with the 3-DAA reference regimen. The logistic regression model predictions and simulations indicate a minor effect on SVR_{12} of a reduced dasabuvir $C_{trough.}$

The main support for the lowering of the ribavirin dose is the SVR_{12} logistic regression model in combination with the predicted exposure of the 600 mg once daily dose. As there are very limited clinical data to support the simulated SVR_{12} response at a concentration range <0.72 mg/L, the proposed ribavirin dose reduction is not supported.

3.3.5. Clinical efficacy

Dose-response studies and main clinical studies

No clinical studies have been submitted for the 3QD product. The application bridges to the efficacy data for Viekirax and Exviera in the treatment of HCV genotype 1 infection, including the data provided within the approval dossier for these medicinal products, as well as the Study M14-490 – An Open-Label, Single-Arm Study to Evaluate the Safety and Efficacy of Ombitasvir/ABT-450/Ritonavir and Dasabuvir in Adults with Genotype 1b Chronic Hepatitis C Virus (HCV) Infection and Cirrhosis (TURQUOISE-III). This latter study is presently under regulatory assessment within the Exviera/Viekirax WS-878-G procedure.

A summary of the efficacy of Viekirax/Exviera in different populations is shown in table 6:

Table 6. Pooled SVR_{12} Rates (Intent-To-Treat, Missing = Failure) from Phase 3 Studies by Subpopulation of Subtype, Prior Treatment History, and Presence or Absence of Cirrhosis

Subpopulation	3-DAA 12 Weeks SVR_{12} (%)	3-DAA + RBV 12 Weeks SVR_{12} (%)	3-DAA + RBV 24 Weeks SVR_{12} (%)
Genotype 1b Noncirrhotic			
Naïve	99.0	98.9	--
Null	100	94.4	--
Partial	100	98.1	--
Relapser	100	98.5	--
Genotype 1a Noncirrhotic			
Naïve	90.2	95.7	--
Null	--	95.4	--
Partial	--	100	--
Relapser	--	94.0	--
Genotype 1b Cirrhotic			
Naïve	--	100	100
Null	--	100	100
Partial	--	85.7[a]	100
Relapser	--	100	100
Genotype 1a Cirrhotic			
Naïve	--	92.4	92.9
Null	--	80.0	92.9
Partial	--	100	100
Relapser	--	93.3	100

RBV = ribavirin; SVR = sustained virologic response; SVR_{12} = sustained virology response at 12 weeks post-treatment

g Based on N = 7; 6/7 achieved SVR.

3.3.6. Discussion on clinical efficacy

General considerations on available exposure data

The proposed efficacy of the Cokiera formulation is based on bridging to the efficacy of Exviera in combination with Viekirax, with or without ribavirin, for HCV genotype 1 infection. The advantage of Cokiera would be once daily administration of all the DAAs (Exviera is administered twice daily). Furthermore, the applicant proposes that a once daily RBV regimen of 600 mg qd may be used instead of the weight based posology of 1000/1200 mg divided into two daily doses, which was used in the study program for Viekirax/Exviera, with the exception of the M12-999 study in post-transplant subjects, where the starting dose was 600-800 mg. The applicant proposes 600 mg as an "alternative posology" to the 1000/1200 dose, per the SmPc.

A comparative bioavailability trial was performed under fed conditions with a meal consisting of nearly 700 kcal, with dosing to steady state. This demonstrated formal bioequivalence (80-125%) for paritaprevir and ombitasvir AUC and C24. Cmax for paritaprevir was somewhat lower than with Viekirax. For dasabuvir, bioequivalence was shown for AUC, but not for C24, where the point estimate for relative bioavailability was 0.71 with a 90% CI ranging for 0.62-0.81. Ritonavir is a PK booster without activity against HCV.

The relative bioavailability of dasabuvir in the Cokiera tablet, compared to with Exviera/Viekirax, when taken in the fasting condition, was low, with a GMR of 0.3 and 90% confidence limits from 0.25-0.35. Furthermore, paritaprevir exposure in the Cokiera formulation compared to Viekirax/Exviera is, contrary to the case when taken with a meal, no longer bioequivalent, with a GMR point estimate of 0.79 and 90% confidence limits stretching from 0.65-0.96.

No comparative PK study on the proposed 600 mg dose of ribavirin has been submitted. Simulations of ribavirin pharmacokinetic parameters indicated approximately 40% and 50% reduction in ribavirin Ctrough values for subjects who switch from 1000 mg and 1200 mg weight-based ribavirin dosing to 600 mg QD dosing, respectively.

Concerning the PK parameters, Cmax in plasma is not considered of interest as a correlative of efficacy. Whether AUC or Ctrough is the most important PK parameter for efficacy is unclear, and may depend on qualities of the drug in question. For ribavirin it is by no means clear which parameter to primarily consider, as the active moiety may be a phosphorylated species of the drug. For most nucleoside analogues, AUC is more predictive than Cmin, and the intracellular half-life of phosphorylated species substantially longer than that in plasma. The relation between ribavirin AUC and Ctrough is, however, based on modelling, assumed to be roughly proportional over the relevant exposure range. Therefore both AUC and Ctrough are considered of equal importance in terms of bridging efficacy data. Thus, in order for the applicant's bridging exercise to be acceptable, it must be reasonably demonstrated that the lower Ctrough of dasabuvir, and the lower AUC as well as Ctrough for ribavirin with the 600 mg qd dose does not result in an unacceptable loss of efficacy.

The combination of Exviera/Viekirax, to which the efficacy bridge is built, is only recommended for use against genotype 1 virus. The applicant has provided exposure-response analyses in genotype 1a. The reason for specific focus on 1a is that > 99% of GT1b-infected subjects who completed assigned treatment achieved SVR12. It is anticipated that the impact of an exposure reduction to dasabuvir will be greater in GT1a than -1b, and likely greatest in those patients that require the highest drug pressure to achieve high cure rates. These include patients with genotype 1a that have the host interferon response genotype IL28 non C/C patients, and who have compensated cirrhosis. Regarding ribavirin, this is only used when treating genotype 1a.

Evaluation of the impact of the exposure reduction for dasabuvir

The contribution of dasabuvir to the activity of the full regimen was evaluated in non-cirrhotic patients in the M11-652 study of Exviera/Viekirax development program. In genotype 1a, when given with ribavirin, the SVR rate increased from 82% (64/78) to 93% (76/82) when dasabuvir was added to the background. In genotype 1b, where Exviera/Viekirax is given without ribavirin, the additive effect of dasabuvir against the background is less clear. Whereas near 100% SVR rates have repeatedly been seen with the when the three DAAs are used, summary data from phase IIa in non-cirrhotic patients indicate that the background of only paritaprevir and ombitasvir yields >90% SVR.

The M1 metabolite of dasabuvir is presumed to contribute significantly to efficacy; changes in M1 exposure with the Cokiera formulation mimic those of dasabuvir.

The applicant has provided simulations of the likely impact of a 38% lower Ctrough for dasabuvir (lower bound of the 90% CI for this parameter). In the worst case scenario of a cirrhotic, male IL28B non C/C patient, the estimate is a loss in the SVR rate of 1.79% percentage units. If reasonably reliably inferred, this loss in SVR would be within the bounds of any practical clinical non-inferiorty demonstration and would be considered compatible with clinical equivalence.

The exposure of all active substances was increased by concomitant food-intake. Dasabuvir AUC and Cmax was 5.9-fold and 6.6-fold higher, dasabuvir M1 AUC and Cmax 6.6-fold and 6.5-fold higher, paritaprevir AUC and Cmax 4.6-fold and 6-fold higher, ombitasvir and ritonavir exposures 2-fold higher after the administration of 3QD with a high-fat meal compared to the fasted state.

The relative bioavailability of dasabuvir in the 3QD tablet, compared to with Exviera/Viekirax, when taken in the fasting condition, was low, with a GMR of 0.3 and 90% confidence limits from 0.25-0.35. Furthermore, paritaprevir exposure in the 3QD formulation compared to Viekirax/Exviera is, contrary to the case when taken with a meal, no longer bioequivalent, with a GMR point estimate of 0.79 and 90% confidence limits stretching from 0.65-0.96.

The applicant has provided a modelling and simulation exercise to demonstrate the potential impact of consistently taking the 3QD formulation in the fasting state, contrary to the instructions in the product information. This exercise, however, seeks to define exposure/response for dasabuvir in a region of exposures which is quite far from that seen with Exviera in the clinical trials to which efficacy is bridged, and where there are most likely few empirical observations. Furthermore, even if taken at face value, this exercise indicates the possibility of losing 8% units of SVR in patients with cirrhosis, which would not be acceptable.

For these reasons, it is be crucial to take 3QD with an appropriate meal for the inference of therapeutic equivalence with Viekirax/Exviera to be valid, and it is notable that there are no data on the relative bioavailability of 3QD compared to 3DAA when taken with a low fat meal. Therefore, assumptions on clinical equivalence rests either on a belief that this is likely to be similar to the situation with a moderate to high fat meal, or on faith in the ability of the target population to follow the instruction to take the product with "a full meal" rather at the occasion of any food intake

Evaluation of the additional impact of the exposure reduction for ribavirin

In the phase III M14-002 study in non-cirrhotic patients with genotype 1a infection, the addition of weight based ribavirin 1000/1200 mg divided into 2 daily doses, to the background of Viekirax/Exviera increased SVR rates from 90% (185/205) to 97% (97/100). In the abovementioned M11-652 study, the addition of ribavirin to Exviera/Viekirax increased SVR rates from 83% (43/52) to 94% (51/54).

Ribavirin doses lower than the weight-based 1000 mg – 1200 mg daily doses were evaluated in a study in the post-transplant setting (Study M12-999). Arm A of the study enrolled 34 HCV treatment-naïve post-liver transplant subjects who were treated with ombitasvir/paritaprevir/ritonavir plus dasabuvir with RBV for 24 weeks. Nineteen (19; 17 GT1a and 2 GT1b) of the 34 subjects started treatment with the 600 mg (N = 12) or 800 mg (N = 7) ribavirin daily dose and 18 subjects (16 GT1a and 2 GT1b, 95%) achieved SVR12. It is notable that despite being post-transplant, these patients had minimal fibrosis. Therefore, it is not clear whether the high efficacy seen is representative of more advanced liver disease.

The reason for giving lower ribavirin doses in the post-transplant treatment scenario is the lower ribavirin tolerability in post-transplant patients. This is due both due to lower bone marrow reserve, as well as to a tendency for lower renal function and subsequently higher ribavirin exposure at a given dose. Indeed, the applicant estimates that the geometric mean RBV Ctrough values in subjects who received the 600 mg total daily dose in Arm A of Study M12-999 were 30% – 39% lower than those observed in subjects who received weight-based dosing in Phase 3 studies. This should be compared to the 40-50% reduction of ribavirin exposure assumed in the case of normal renal function.

As stated above, no directly comparative bioavailability data for the different ribavirin doses have been submitted, nor has the applicant considered the relation between AUC and Ctrough with regards to their correlation and relative importance. For SVR12 predictions and simulations, however, a 50% lower ribavirin Ctrough was assumed for all subjects. In the Viekirax/Exviera program, 6% of patients had ribavirin dose modifications. The applicant states that lower exposures due to ribavirin dose reductions were not included in the model, i.e., ribavirin exposure values assuming full doses of ribavirin were used, which would be a conservative approach.

The company has provided exposure response modelling to define the likely impact of the proposed ribavirin dose reduction on SVR, in addition to the modelled impact of the dasabuvir exposure reduction.

According to the company predictions, the lower bound of the 95% prediction interval given a 50% reduction of the ribavirin Ctrough along with a 38% reduction of dasabuvir Ctrough would yield a 1% decrease in SVR rates in non-cirrhotic, non-IL28B C/C male patients, and a 3.5% decrease in similar patients with cirrhosis.

Whether the estimated SVR loss in cirrhotics would be acceptable, given the need to stop disease progression, and the fact that there may be delays in the availability of a likely effective retreatment regimen, is a matter of subjective judgment. It is notable, however, that the range of empirical observations within the range of the exposures with the proposed dose is lower with ribavirin compared to dasabuvir. The applicant has calculated a coefficient of variation around the geometric mean of ribavirin Ctrough which is below 30%. Thus, the number of actual observation within the predicted range of exposures with the lower ribavirin dose is small. Therefore, it seems that the assumed exposure-response relation for ribavirin within the predicted range would be more uncertain than that of dasabuvir. Furthermore, this model-based dose reduction would be done on top of the model-based exposure reduction to dasabuvir, increasing uncertainties.

To contextualise these uncertainties, it is notable that the CHMP did not accept a recommendation for ribavirin-free treatment of GT1a, based on a point estimate of 6.8% difference in SVR, with a lower 95% confidence limit of -12% when Viekirax/Exviera was given without ribavirin in GT1a non-cirrhotics. An important driver of this decision is the fact that selection of drug resistance on virological failure may limit retreatment options. This argument is stronger in cirrhotic patients, where clinically

significant disease progression may occur, e.g, prior to reversion of NS3/4A resistance and the availability of an effective treatment option may thus be delayed.

Based on these considerations, the uncertainties concerning the impact of the proposed ribavirin dose reductions make the applicant's proposal not acceptable.

3.3.7. Conclusions on clinical efficacy

The impact of lower dasabuvir Ctrough when using the 3QD regimen instead of 3DAA is likely to be low, also taking uncertainties into account. However, this presumes that 3QD is administered with meal that is comparable to that used in the bioequivalence studies in the fed state. The additional impact of halving the ribavirin dose compared to that studied in the program to which the efficacy bridge of the application is built, seems less certain due to a greater range of extrapolation compared to what has been clinically studied. These uncertainties are of a greater magnitude and added to the residual uncertainties concerning dasabuvir exposure. It is unclear what proportion of ribavirin effect would remain. This uncertainty is not acceptable, and primarily so in the subgroup of patients with cirrhosis, where the urgency of SVR is highest, and where effective retreatment options may not be immediately available in case of relapse with dual- or triple class resistant virus.

3.3.8. Clinical safety

The safety of the 3QD tablet in HCV GT1-infected subjects has not been evaluated in clinical studies; however, the safety profile of the 3QD tablet is expected to be similar to that of the reference Exviera/Viekirax regimen, given the similar exposures of the components.

A summary of treatment-emergent adverse events from the pooled analyses of data from the 3-DAA Phase 3 studies is presented in the table below. A majority of subjects experienced at least 1 event, but most subjects experienced events that were mild in severity. Rates of severe adverse events and adverse events leading to discontinuation were low across studies but numerically higher in the study of subjects with cirrhosis.

Overview of Treatment-Emergent Adverse Events

	Placebo-Controlled		**Regimen-Controlled**		**Cirrhotics**	
	12-Wk 3-DAA + RBV	**12-Wk Placebo**	**12-Wk 3-DAA + RBV**	**12-Wk 3-DAA**	**12-Wk 3-DAA + RBV**	**24-Wk 3-DAA + RBV**
Events (%)	N = 770	N= 255	N = 401	N = 509	N = 208	N = 172
Subjects ≥ 1 AE	89.0	76.9	82.8	75.0	91.8	90.7
Severe AE	3.5	0.4	1.0	1.2	6.7	7.6
Grade 3 or 4 AE	3.9	0.8	3.0	2.0	7.7	8.1
Serious AE	2.1	0.4	2.2	1.4	6.3	4.7
AE leading to discontinuation	0.8	0.4	0.5	0.4	1.9	2.3
Deaths	0.1[a]	0	0	0	0	0

AE = adverse event; RBV = ribavirin; Wk = week

h Lung cancer.

Adverse events that occurred at an incidence at least 5% greater with the 3-DAA + RBV regimen versus placebo were considered to be adverse drug reactions related to the study treatment. These include fatigue, nausea, pruritus, insomnia, asthenia, and anemia. The frequency of these events was generally lower in the subjects treated without RBV.

Transient elevations in total (predominantly indirect) bilirubin may occur due to ABT-450 inhibition of the bilirubin transporters OATP1B1 and OATP1B3, and RBV-induced hemolysis. The elevations generally peaked by Weeks 1 – 2, declined through the end of treatment, and returned to within the normal range by 4 weeks post-treatment. Rates of hyperbilirubinemia were lower in subjects treated with the 3-DAA regimen without RBV compared to the 3-DAA regimen with RBV. The frequency and degree of hyperbilirubinemia were higher in patients with cirrhosis, but the temporal pattern of elevation followed by resolution was similar and few were symptomatic (jaundice). Rates of ≥ Grade 2 hemoglobin reductions were 6% among subjects without cirrhosis who received the 3-DAA + weight-based RBV regimen for 12 weeks and 7% and 11% among subjects with cirrhosis who received the 3-DAA + weight-based RBV regimen for 12 weeks and 24 weeks, respectively. Grade 3 hemoglobin reductions were rare. The decline in hemoglobin was largely managed with RBV dose reductions; use of hematologic growth factor and blood transfusion were rare. Anemia was primarily reported in the clinical trials when the 3-DAA regimen was administered with RBV.

Transient asymptomatic postbaseline serum alanine aminotransferase (ALT) elevations of > 5 × the upper limit of normal (ULN) occurred at a frequency of 1% across active treatment arms and were evaluated by an external panel of expert hepatologists. The ALT elevations were asymptomatic, usually occurred within the first 4 weeks of treatment, and typically declined with ongoing treatment. A disproportionate number of the cases were in women on concurrent systemic estrogen-containing therapy (i.e., contraceptives or hormone replacement), and discontinuation of the hormonal therapy with continuation or brief interruption of the DAA regimen led to resolution in serum ALT elevation. Concomitant use of systemic estrogen-containing medications, therefore, appears to be a risk factor for post-baseline elevations in serum ALT. No ALT elevations > 5 × ULN were observed in subjects receiving progestins only or in subjects receiving topical vaginal estrogen preparations. Among the cases of serum ALT elevation thought to be related to the DAA regimen, none resulted in hepatic dysfunction and they generally resolved or improved with ongoing treatment. All cases had resolved in the post-treatment follow-up.

Available clinical trial experience in general, as well as the exposure-safety analyses for the low-dose RBV (600 mg QD) indicate that there will be reduction in adverse events and laboratory abnormalities, such as elevation in total bilirubin and lower rates of reductions in hemoglobin.

3.3.9. Discussion and conclusion on clinical safety

No clinical safety data outside bioequivalence studies in healthy volunteers have been provided for this application, which bridges to the clinical safety database for Viekirax/Exviera, including variation WS-873, which was not finalised at the time of the submission of the present dossier. The slightly lower Ctrough of dasabuvir is not anticipated to impact clinical safety. The proposed lower ribavirin dose would result in somewhat lower rates/levels of haemolytic anemia and hyperbilirubinemia; in general, however, ribavirin is reasonably well tolerated within the 3DAA regimen, and does not cause significant treatment discontinuation. Therefore, this safety advantage is not considered to balance any loss in efficacy.

3.4. Risk management plan

Safety Specification

The applicant identified the following safety concerns in the RMP:

Summary of Safety Concerns	
Important identified risks	Hepatic decompensation and hepatic failure in patients with cirrhosis.
	Drug-drug interactions: – Concomitant use with drugs that are moderate or strong inducers of CYP3A and/or strong inducers of CYP2C8. Examples include carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine, etravirine, enzalutamid, mitotane, rifampicin, and St. John's Wort (*Hypericum perforatum*). – 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)
	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 those specified in applicable product labeling – use in other DAA combinations – use in pediatric patients
	Medication errors
	Risk of resistance development
	Fetal development toxicity

Summary of Safety Concerns	
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 patients using Cokiera without RBV
	Safety in patients co-infected with HBV
	Safety in elderly patients
	Safety in patients who have failed prior DAA treatments

"Hepatic decompensation and hepatic failure in patients with cirrhosis" was added as an important identified risk in the current RMP (version 2.0) for Cokiera (Dasabuvir, Ombitasvir, Paritaprevir, and Ritonavir Fixed-Dose Combination Tablets) in line with changes made to the RMPs for Viekirax and Exviera, as requested.

Pharmacovigilance Plan

The proposed additional PhV activities (below) are endorsed and considered comprehensive and in line with the observed safety profile of the medicinal product.

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 M12-999 (Study includes liver transplant patients) Category 3	Evaluate safety in liver transplant patients	Missing information in post-liver transplant patients	Ongoing	February 2018
Study M13-101 (Study to evaluate re-treatment of subjects who experienced virologic failure) Category 3	To re-treat patients who have failed a prior AbbVie DAA combination 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	November 2017
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	May 2017
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	April 2017

Study/Activity Type, Title and Category (1 – 3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
Study M14-222 Study M14-423 (Long-term efficacy studies with 5-year follow-up) Category 3	To evaluate the effect of response to treatment (assessed by SVR_{12} status) on the long-term progression of liver disease in adults with chronic HCV GT1 infection who received treatment with ombitasvir/paritaprevir/ritonavir and dasabuvir with or without RBV, as measured by all-cause death, liver-related death, liver decompensation, liver transplantation, and HCC	Potential risk of hepatotoxicity among non-users of ethinyl estradiol-containing medications Potential risk of resistance development	Ongoing	2021 for both studies Yearly interim reports provided in PSURs
Study M14-224 (Study to evaluate re-treatment of subjects who have failed a DAA-containing regimen) Category 3	Evaluate safety and efficacy of 3-DAA + sofosbuvir in subjects who have failed treatment with a DAA-containing regimen	– Missing information in patients who have failed prior DAA treatments – Potential risk of resistance development	Ongoing	January 2018
Study M14-226 (Study in GT1-infected subjects with renal dysfunction) Category 3	Evaluate safety and efficacy (SVR_{12}) in subjects with eGFR < 30 mL/min/1.73 m^2	Missing information in patients with renal impairment	Ongoing	June 2017
Study M14-227 (Study in Child-Pugh B subjects) Category 3	Evaluate safety and efficacy (SVR_{12}) in subjects with Child-Pugh B	Identified risk of hepatic decompensation and hepatic failure in patients with cirrhosis; missing information in patients with hepatic impairment	New enrollment has been stopped; dosing is ongoing	August 2017

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 M14-567 (Study to evaluate 2-DAA + SOF in non-cirrhotic and cirrhotic subjects) Category 3	Assess safety and efficacy of 2-DAA + SOF with or without RBV in treatment-naïve or prior pegIFN, RBV, and/or SOF treatment-experienced adults with GT 2 and 3 HCV	Missing information in patients who have failed prior DAA treatments Potential risk of resistance development	Ongoing	November 2017
Study M15-461 (Study in GT1a and GT4 infected subjects with renal dysfunction) Category 3	Evaluate safey and efficacy (SVR_{12}) of 3-DAA regimen in GT1a and 2-DAA regimen in GT4 subjects with eGFR < 30 mL/min/1.73 m^2	Missing information in patients with renal impairment	Ongoing	June 2017
Study P15-421 Longitudinal cohort safety study in the HCV – TARGET registry PASS Category 3	Evaluation of ALT elevations and hepatic outcomes in patients using the AbbVie DAA regimens in real world settings; use of AbbVie DAA regimens in populations with limited data available will also be evaluated.	Identified risk of hepatic decompensation and hepatic failure in patients with cirrhosis, potential risks of hepatotoxicity among non-users of ethinyl estradiol-containing medications, off-label use, safety in post-liver transplant patients, HIV-1 co-infection, HBV co-infection, elderly patients	Approved by EMA on 01 April 2016	March 2018 (interim) and September 2020 (final)

*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)

A targeted follow-up questionnaire for post marketing serious hepatic events, including hepatic events which resulted in interruption or discontinuation of the DAA regimens, is currently in use for the purpose of obtaining additional information on events of hepatic decompensation and hepatic failure and is provided in Annex 7 of the RMP for Cokiera, which is endorsed by the PRAC rapporteur.

Risk minimisation measures for Cokiera

Risk minimization of safety concerns only pertains to routine measures, table below.
The proposed measures were endorsed by the PRAC rapporteur.

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Identified risk – Hepatic decompensation and hepatic failure in patients with cirrhosis	2-DAA and 3-DAA (including Cokiera) are not recommended in patients with moderate hepatic impairment (Child-Pugh B) and should not be used in patients with severe hepatic impairment (Child-Pugh C) and monitoring (baseline testing and during treatment) should be performed in patients with cirrhosis, per section 4.4 of SmPC. The Product Information Leaflet (PIL) educates patients using Cokiera 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. For the purpose of obtaining additional information on hepatic decompensation and ALT elevations, a targeted follow-up questionnaire for postmarketing serious hepatic events, including hepatic events which resulted in interruption or discontinuation of Cokiera is utilized (see Annex 7). Other routine risk minimization measures: Prescription only medicine.	None

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 and/or strong inducers of CYP2C8. Examples include carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine, etravirine, enzalutamid, mitotane, rifampicin, and St. John's Wort (*Hypericum perforatum*). – 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)	Contraindicated medications and DDIs which require dose adjustments or monitoring is listed in section 4.3, section 4.4, and section 4.5 of the SmPC. Other routine risk minimization measures: Prescription only medicine.	None
Identified risk – Hepatotoxicity when co-administered with ethinyl estradiol-containing medications	Language concerning elevations in serum ALT and discontinuation of ethinyl estradiol-containing medications is included in section 4.3 and section 4.4 of the SmPC. The Product Information Leaflet (PIL) educates patients using Cokiera 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. Other routine risk minimization measures: Prescription only medicine.	None

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	Contraindicated medications and DDIs which require dose adjustments or monitoring is listed in section 4.3, section 4.4, and section 4.5 of the SmPC. Other routine risk minimization measures: Prescription only medicine.	None
Potential risk – Hepatotoxicity among non-users of ethinyl estradiol-containing medications	Language concerning elevations in serum ALT is included in section 4.4 of the SmPC. The Product Information Leaflet (PIL) educates patients using Cokiera 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. Other routine risk minimization measures: Prescription only medicine.	None
Potential risk – Potential for off-label use of Cokiera including: – use in patients with genotypes other than those specified in applicable product labeling – use in other DAA combinations – use in pediatric patients	Section 4.2 of the SmPC provides guidance on method of administration. Other routine risk minimization measures: Prescription only medicine.	None Not applicable to Cokiera

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Potential risk – Medication errors	Section 4.2 of the SmPC provides guidance on method of administration. Labeling (immediate and outer packaging) is designed to minimize medication errors (Module SVI.4.2). Other routine risk minimization measures: Prescription only medicine.	None
Potential risk – Risk of resistance development	Section 4.2 of the SmPC advises on appropriate dosing and administration to achieve maximal efficacy. Other routine risk minimization measures: Prescription only medicine.	None
Potential risk – Fetal development toxicity	Section 4.6 of the SmPC advises on this potential risk and that use in pregnancy or women of childbearing potential should not be done without effective contraception. Other routine risk minimization measures: Prescription only medicine.	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Missing information – Safety in patients with hepatic impairment (Child-Pugh B)	2-DAA and 3-DAA (including Cokiera) regimens are not recommended in patients with moderate hepatic impairment (Child-Pugh B) and should not be used in patients with severe hepatic impairment (Child-Pugh C) and monitoring (baseline testing and during treatment) should be performed in patients with cirrhosis, per section 4.4 of SmPC. The Product Information Leaflet (PIL) educates patients using Cokiera 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. For the purpose of obtaining additional information on hepatic decompensation and ALT elevations, a targeted follow-up questionnaire for postmarketing serious hepatic events, including hepatic events which resulted in interruption or discontinuation of Cokiera is utilized (see Annex 7). Other routine risk minimization measures: Prescription only medicine.	None
Missing information – Safety in patients with renal impairment (creatinine clearance < 60 mL/min)	Section 4.2 and section 4.4 of the SmPC that no dose adjustment of Cokiera is required for patients with mild, moderate, or severe renal impairment (sections 4.2 and 4.4) and concomitant use of Cokiera and colchicine in patients with renal impairment is contraindicated (section 4.5). Other routine risk minimization measures: Prescription only medicine.	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Missing information – Safety in post liver transplant patients	Sections 4.8 and 5.1 of the SmPC provide information on currently available data in this population, including treatment duration. Sections 4.2 and 4.4 include dosing instructions including treatment duration, dose of RBV, and concomitant use of calcinuerin inhibitors/immunosuppressants. Other routine risk minimization measures: Prescription only medicine.	None
Missing information – Safety in patients co-infected with HIV-1	Section 4.2 of the SmPC provides guidance on method of administration; section 4.4 and 4.5 include information regarding concomitant use of HIV antiviral agents; and section 5.1 provide information on currently available data in this population. Other routine risk minimization measures: Prescription only medicine.	None
Missing information – Safety in pregnancy for patients using Cokiera without RBV	Section 4.6 indicates that limited data are available and section 5.3 of the SmPC provides information with respect to reproductive studies performed in animals. Other routine risk minimization measures: Prescription only medicine.	None
Missing information – Safety in patients co-infected with HBV	Section 4.4 of the SmPC advises that safety and efficacy have not yet been established in HCV/HBV co-infection. Other routine risk minimization measures: Prescription only medicine.	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Missing information – Safety in elderly patients	Section 4.4 specifies that no dose adjustment is warranted in elderly patients. Section 5.2 describes pharmacokinetic data Prescription only medicine.	None
Missing information – Safety in patients who have failed prior DAA treatments	Section 4.4 of the SmPC under 'Retreatment' states that the efficacy of Cokiera in patients previously exposed to AbbVie 's DAAs, or to medicinal products of the same classes as those of dasabuvir and ombitasvir/paritaprevir/ritonavir (NS5B, NS3/4A or NS5A inhibitors), has not been demonstrated. Other routine risk minimization measures: Prescription only medicine.	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 2.0 is acceptable.

Public summary of the RMP

The public summary of the RMP does not require revision.

PRAC Outcome

The PRAC endorsed the assessment. The RMP V2 is endorsed.

3.5. Pharmacovigilance system

The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

4. Orphan medicinal products

N/A

5. Benefit risk assessment

Benefits

The present application concerns a FDC, the Cokiera tablet (dasabuvir 200 mg/ombitasvir 8.33 mg/paritaprevir 50 mg/ritonavir 33.33 mg) to enable a QD dosing regimen to replace Viekirax and Exviera (3-DAA regimen for the treatment of genotype 1 chronic HCV infection) The application is for a

'substitution indication'. Cokiera would provide a simpler QD treatment regimen of the DAAs. The company proposes to a pharmacokinetic bridge to the efficacy database for Exviera/Viekirax. Bioequivalence has been demonstrated for the paritaprevir and ombitasvir components under conditions of intake with a full meal. AUC for the dasabuvir component is bioequivalent on AUC, but demonstrates a 29% lower point estimate for Ctrough, with a 90% CI extending to 38%. Ritonavir is a PK enhancer which does not exert antiviral activity. The company has provided a modelling and simulation exercise to justify that this does not prompt an unacceptable loss of efficacy.

The company has further provided modelling data to support a dose reduction of ribavirin (used in combination when treating GT1a) from a weight-based dose of 1000/1200 mg divided in two daily doses, to a flat dose of 600 mg q.d.

Beneficial effects

The beneficial effects of Viekirax and Exviera, the reference medicinal products for this bridging application, are discussed above, in the section on clinical efficacy.

The applicant has investigated relative exposure to the individual components when Cokiera and Exviera/Viekirax is dosed to steady state in the fed condition, and has demonstrated bioequivalent AUC and Ctrough for paritaprevir and ombitasvir. Exposure to dasabuvir is lower (see above). Based on an exposure response model, the absolute loss in SVR rates with a 38% lower Ctrough would not exceed 0.6% in non-cirrhotic patients with genotype 1a infections, and 1.8% in cirrhotic patients (lower bound of 95% predicition interval). Due to the near 100% efficacy of Viekirax+Exviera in GT1b, an estimate has not been calculated for this subgenotype. However, the likely impact of any given reduction in exposure is anticipated to be lower than in genotype1a.

Concerning the suggested dose reduction of ribavirin, the company proposes that, under the assumption of a 50% reduction of Ctrough, in combination with the abovementioned reduction of dasabuvir Ctrough, would lead to an absolute loss of up to 1.1% in non-cirrhotic patients with genotype 1a, and up to 3.5% in cirrhotic patients with the same viral subgenotype. Ribavirin is not used when treating viral subgenotype 1b.

Uncertainty in the knowledge about the beneficial effects

The near-bioequivalence of the 3QD formulation, to Exviera/Viekirax, has been shown in the fed condition. However, the relative bioavailability of dasabuvir in the 3QD tablet, compared to with Exviera/Viekirax, when taken in the fasting condition, was low, with a GMR of 0.3 and 90% confidence limits from 0.25-0.35. Furthermore, paritaprevir exposure in the 3QD formulation compared to Viekirax/Exviera is, contrary to the case when taken with a meal, no longer bioequivalent, with a GMR point estimate of 0.79 and 90% confidence limits stretching from 0.65-0.96. For these reasons, it is only with an appropriately sized meal for the inference of therapeutic equivalence with Viekirax/Exviera is considered valid. Furthermore, it is unclear what precise concomitant food is necessary for therapeutic equivalence – e.g., if a continental breakfast would provide sufficient boost of bioavailablity. Therefore, equivalence assumptions rest either on reliance that the target population will follow a proposed SmPc statement that 3QD should be taken "with a full meal", or that concomitant administration with any food intake is sufficient.

The applicant has provided a modelling and simulation exercise to demonstrate the potential impact of consistently taking the 3QD formulation in the fasting state, contrary to the instructions in the product information. This exercise, however, seeks to define exposure/response for dasabuvir in a region of exposures which is quite far from that seen with Exviera in the clinical trials to which efficacy is bridged,

and where there are most likely few empirical observations. Furthermore, even if taken at face value, this exercise indicates the possibility of losing 8% units of SVR in patients with cirrhosis, which would not be acceptable.. Therefore, Cokiera should be taken with "a full meal". The possibility of non-compliance with this instruction poses an uncertainty regarding efficacy.

Apart from this, there is an intrinsic uncertainty as to the precise SVR rates that would be reached, as bioequivalence was not shown for dasabuvir Ctrough, and the efficacy estimate is based on modelling and simulation. There is formal bioequivalence for the AUC of dasabuvir in the fed state, and the range of empirically observed Ctroughs for dasabuvir in the Viekirax/Exviera program would to a considerable extent overlap that which will be observed with the 3QD. Estimated geometric mean Ctrough will be 30% lower with the 3QD, while the CV for this parameter in the dataset used for prediction was 65%.

For ribavirin, the anticipated Ctrough and AUC for ribavirin would be 50% lower than that studied with Viekirax/Exviera; further, the estimated CV for ribavirin Ctrough is less than 30%. Therefore, the range of overlap of empirical data and the prediction range is considerably smaller for the ribavirin assessment. It is unclear whether the exposure response curve has been adequately characterised in the crucial range; therefore, the predictions of the impact of the proposed ribavirin dose reductions are considered less reliable than those for dasabuvir. Furthermore, the adjusted ribavirin dose would be given on top of the less than bioequivalent exposure to dasabuvir.

Risks

Unfavourable effects

There are no clinical safety data for the 3DAA combination. The applicant proposes to bridge to the safety of Exviera/Viekirax, with or without ribavirin. This is considered acceptable, as exposure to any component will not be significantly higher than with Exviera/Viekirax, and therefore the safety profile will be no worse.

These drug combinations have a benign side effects profile, with a frequency of AEs leading to discontinuation around 1%. Most AEs were consistent with the previously described side effects profile of RBV (anaemia, hyperbilirubinemia, pruritus, rash, insomnia, asthenia). Paritaprevir causes an exposure-dependent risk of transaminitis of grade 3 (≥5xULN) and above, seen in less than 1% of patients at the therapeutic dose. Transaminitis has not been clearly associated with serious drug induced liver injury. Due to increased exposure to paritaprevir in decompensated liver disease, use is not recommended in CPT-B and contraindicated in CPT-C.

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 patients with advanced liver disease, a likely effective retreatment option may not be immediately available.

Uncertainty in the knowledge about the unfavourable effects

The company proposes that the 3QD may be given with a lower dose of ribavirin (see above). This is anticipated to reduce the incidence and severity of exposure dependent side effects such as haemolytic anemia and hyperbilirubinemia. The precise magnitude of this effect has not been described.

The impact of drug resistance acquired in case of virological failure, on the possibility to achieve SVR in a subsequent treatment attempt (with another regimen) cannot be fully ascertained.

Balance

Importance of favourable and unfavourable effects

SVR only rarely occurs spontaneously in chronic hepatitis C. This marks the clearance of HCV infection, and has been associated with a decreased risk of cirrhosis, decompensation, cancer, and liver-related deaths. The side effects of Exviera/Viekirax, with or without ribavirin, are generally mild and manageable.

When using Viekirax and Exviera SVR rates are >90% in all studied populations, including those with compensated cirrhosis, when used in combination with ribavirin, generally at a weight-based dose of 1000/1200 mg per day, for patients with GT1a. For patients with GT1b, SVR rates are near 100% in non-cirrhotic and compensated cirrhotic patients, when using Exviera and Viekirax without ribavirin. The general tolerability is good, with mainly ribavirin-associated side effects.

The applicant proposes to extrapolate the efficacy and safety profile of Viekirax/Exviera to the Cokiera formulation, based on pharmacokinetics supported by modelling and simulation.

Discussion on the benefit-risk assessment

The bridging of efficacy to Viekirax/Exviera is acceptable under the ideal condition that most or all doses are taken with a meal of sufficient character to replicate the conditions of the pivotal bioequivalence study. However, this cannot be ascertained if Cokiera is taken with a smaller meal, and will most likely not be the case if taken in fasting. Therefore, it is crucial that Cokiera be taken with "a full meal", as described in the product information.

The CHMP considered whether this approach would provide sufficient reassurance, given the risk of therapeutic failure with drug resistance that impacts retreatment options. The use of the term "a full meal" rather than intake with food in general, is not usual in SmPcs. A particular objection to the use of the "full meal" formula this context, is that, since the efficacy of 3QD is based not on a direct demonstration indicating the ability of the target population to follow the advice sufficiently to maintain efficacy, but rather on pharmacokinetic bridging to a formulation where the quantitative impact of fasting/food differs. The applicant claims, based on a theoretical argument, that the composition of a meal is unlikely to matter, as it is the physiological consequences of food intake that impact bioavailability. This may be correct, but evidence for the assertion is lacking. The relevant uncertainties would be alleviated if there was a demonstration of relative bioavailability versus 3DAA when 3QD is taken with a light, low fat meal (e.g. a continental breakfast). The proposal to recommend dosing with 600 mg ribavirin qd rather than 1000/1200 mg is not considered acceptable. The range of extrapolation of exposure from that which has been observed is larger for ribavirin than for dasabuvir, and the relation between exposure and response is not considered sufficiently well characterised given the low number of observations. Any assumption of the equivalence of the lower ribavirin dose would rely on data generated with other DAA regimens than the present 3DAA regimen, and it is uncertain whether this would be scientifically appropriate. Notably, extrapolation of dasabuvir efficacy through modelling is already fraught with some uncertainty, and the proposal on ribavirin adds further to that uncertainty. Therefore, this is not accepted based on available data, and it is anticipated that a clinical trial with SVR as outcome measure would be needed to support the new ribavirin posology.

5.1. Conclusions

The overall B/R of Cokiera is negative, as a major objection has been identified.