Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Paritaprevir / Ritonavir / Ombitasvir and Dasabuvir (as Sodium Salt)

Proprietary Product Name: Viekira Pak

Sponsor: AbbVie Pty Ltd

March 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au> .

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ABT-267	ombitasvir
ABT-333	dasabuvir
ABT-450	paritaprevir (also previously named veruprevir)
ACSOM	Advisory Committee for the Safety of Medicines
ADME	absorption, distribution, metabolism and excretion
ADRs	Adverse drug reactions
AE	adverse event
ALT	alanine aminotransferase
ASA	Australian Specific Annexe (to the RMP)
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{12}	area under the concentration-time curve (plasma concentration) 12 hours after dosing
AUC_{24}	area under the concentration-time curve (plasma concentration) 24 hours after dosing
AUC_{inf}	AUC extrapolated to time infinity
BA	bioavailability
BCRP	Breast cancer resistance protein
BD	twice daily
BMI	body mass index
BSA	body surface area
BSEP	bile salt export pump
CI	confidence interval
CL/F	apparent clearance
C_{24h}	plasma concentration after 24 hours
C_{max}	maximum plasma concentration

Abbreviation	Meaning
$C_{max,ss}$	maximum plasma concentration at steady-state
CNS	central nervous system
COC	combined oral contraceptive
CsA	cyclosporine
CV	coefficient of variation
CYP	cytochrome P450
CYP3A4	CYP isozyme 3A4
CYP3A5	CYP isozyme 3A5
CYPxxx	CYP isozyme xxx (where xxx letters describe the specific CYP isozyme)
$C_{\tau,ss}$, C_{trough}	trough plasma concentration
DAA	direct acting antiviral agent
DDI	drug-drug interaction
DMBA	7,12-dimethylbenz(a)anthracene
DNA	deoxyribonucleic acid
EC_{50}	50% effective concentration (the concentration required to obtain 50% of the maximum effect)
ECG	electrocardiogram
EE	ethinyl estradiol
ERAUC	Exposure ratio based on AUC
ERC_{max}	exposure ratio based on C_{max}
EVR	early virologic response; partial = HCV RNA decrease of > 2 $\log_{10}$ IU/mL at Study Week 12, complete = HCV RNA < 25 IU/mL at Study Week 12
FDC	fixed dose combination
fu	unbound fraction
GABA	gamma aminobutyric acid
GCP	Good Clinical Practice

Abbreviation	Meaning
GLDH	glutamate dehydrogenase
GLP	Good Laboratory Practice
GT1a	genotype 1a (HCV)
GT1b	genotype 1b (HCV)
h	hour/s
HBV	hepatitis B virus
HCV	hepatitis C virus
hERG	Human ether-a-go-go-related gene
HGC	hard gelatin capsule
HIV	human immunodeficiency virus
HME	hot melt extrusion
IC_{50}	half maximal inhibitory concentration
ICH	International Conference on Harmonisation
IFN-γ	Gamma interferon
IL28B	interleukin 28B
IP-10	interferon gamma-induced protein 10
ISS	integrated summary of safety
IU	international units
IV	intravenous
JTK-853	A nonnucleoside inhibitor (not yet registered)
LCB	lower bound of the 95% confidence interval
LFTs	Liver function tests
LOEL	lowest observed effect level
LPV	lopinavir
MD	maximum dose
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Meaning
MedDRA SMQ	Standardised MedDRA Queries
MRP2	multidrug resistance-associated protein 2
N	number
NET	norethindrone
NG	norgestrel
NGMN	norelgestromin
NK_2	neurokinin2
NMU	N-nitroso-N-methylurea
NOEL	no observable adverse effect level
NS	non-structural
NS3	non-structural protein 3
NS3/NS4A	NS protein 3/NS protein 4A
NS4A	non-structural protein 4A
NS5A	non-structural protein 5A
NS5B	non-structural protein 5B
OAT	organic anion transporters
OATP	organic anion transporting polypeptide
OATP1B1	organic ion transporting polypeptide
PASS	post authorisation safety studies
PD	pharmacodynamics
PegIFN	pegylated interferon
PegIFN/RBV	pegylated interferon plus ribavirin
P-gp	P-glycoprotein
PK	pharmacokinetics
pKa	acid dissolution constant

Abbreviation	Meaning
PO	per oral
PT	post-treatment
PVF	primary virologic failure
PY	patient-years
QD	once daily
QT	time between the start of the Q wave and the end of the T wave
QTc	QT interval duration corrected for heart rate
r	ritonavir
RBV	ribavirin
RNA	ribonucleic acid
RPE	retinal pigment epithelial
RSE	relative standard error
RUV	residual unexplained variability
RVR	rapid virologic response, HCV RNA level < 25 IU/mL at Study Week 4
RVR	rapid virologic response
SAE	serious adverse event
SD	standard deviation
SDD	spray dried dispersion
SGC	soft gel capsule
SNP	single nucleotide polymorphism
SVR	sustained virologic response
SVR_{12}	sustained virologic response 12 weeks post-dosing
SVR_{24}	sustained virologic response 24 weeks post-dosing
t½	Half life
TD_{50}	the median toxic dose

Abbreviation	Meaning
TEAE	treatment emergent adverse event
TGA	Therapeutic Goods Administration
TID	three times a day
TPA	12-o-tetradecanolyphorbol-13-acetate
UCB	upper bound of the 95% confidence interval
UGT1A1	UDP-glucuronosyltransferase family member A1
ULN	upper limit of normal
Vc/F	apparent volume of central compartment
Vd/F	volume of distribution
Vp/F	apparent volume of peripheral compartment
Vss/F	apparent steady-state volume of distribution
WT	body weight

I. Introduction to product submission

Submission details

Type of submission:	New chemical entities/ in a fixed dose combination
Decision:	Approved
Date of decision:	1 July 2015
Date of entry onto ARTG	10 July 2015
Active ingredients:	paritaprevir / ritonavir / ombitasvir and dasabuvir (as sodium salt)
Product names:	Viekira Pak
Sponsor's name and address:	AbbVie Pty Ltd Locked Bag 5029, BOTANY NSW 1455
Dose form:	Tablet, film coated
Strength:	Paritaprevir 75 mg / Ritonavir 50 mg/ Ombitasvir 12.5 mg and Dasabuvir (as Sodium Salt) 250 mg
Container:	blister pack
Pack size:	Composite Pack; 112 tablets (56 x paritaprevir / ritonavir / ombitasvir and 56 x dasabuvir (as sodium salt))
Approved therapeutic use:	*Viekira Pak is indicated for the treatment of genotype I chronic hepatitis C infection, including patients with compensated cirrhosis. Duration of therapy and addition of ribavirin are dependent on patient population (see DOSAGE AND ADMINISTRATION, PRECAUTIONS, CLINICAL TRIALS).*
Route of administration:	oral
Dosage:	The recommended oral dose of Viekira Pak is two paritaprevir/ritonavir/ombitasvir 75/50/12.5 mg tablets once daily (in the morning) and one dasabuvir 250 mg tablet twice daily (morning and evening). For further details please see the Product Information.
ARTG number:	224612

Product background

This AusPAR describes the application by the AbbVie Pty Ltd (the sponsor) to register Viekira Pak for the following indication:

> *Viekira Pak is indicated for the treatment of genotype 1 chronic Hepatitis C infection, including patients with cirrhosis. Duration of therapy and addition of ribavirin are*

dependent on patient population (see DOSAGE AND ADMINISTRATION, PRECAUTIONS, CLINICAL TRIALS)

This application seeks to register three new active substances; co-formulated with ritonavir which together target multiple stages of the hepatitis C virus life cycle.

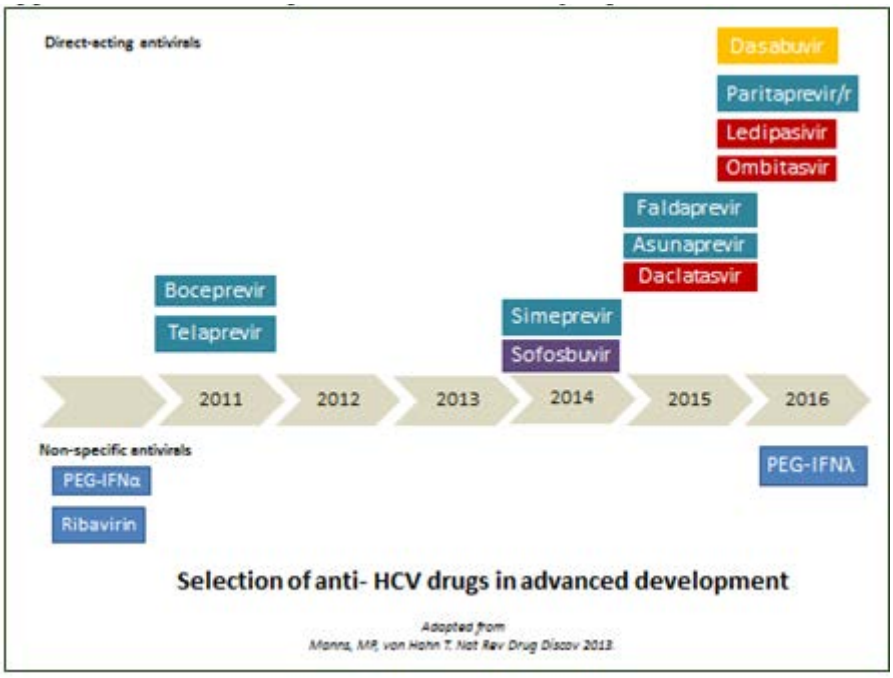
- Paritaprevir (ABT-450) is a non-structural NS3/4A protease inhibitor of hepatitis C virus (HCV) genotype 1. Other NS3/4A protease inhibitors currently registered include boceprevir, telaprevir and simeprevir.
- Ombitasvir (ABT-267) is a non-structural protein 5A (NS5A) inhibitor with activity against HCV genotype 1a and 1b.
- Dasabuvir (ABT-333) is a non-nucleoside NS5B polymerase inhibitor of HCV genotypes 1a and 1b. There are no other non-nucleoside NS5B inhibitors currently approved.
- Ritonavir, a potent inhibitor of cytochrome P450(CYP) CYP3A4 is not active against Hepatitis C, but acts as a pharmacokinetic enhancer to increase exposure to paritaprevir, which is primarily metabolised by CYP3A.[1]

NOTE: This submission was considered at the same time as the submission to register Viekira Pak RBV which contains applications for the Viekira Pak product presented as combination packs with different strengths of ribavirin (Submission number PM-2014-01438-1-2). The data in these submissions overlap and was considered concurrently and therefore the AusPARs are mostly the same except for the administrative information, detailed description of the ribavirin component and the risk management plan section of the report. Use of ribavirin with Viekira Pak is dependent on the patient population, including presence of cirrhosis and genotype subtype.

Paritaprevir (ABT-450) was initially known as veruprevir; however veruprevir was rejected by the INN (International Non-proprietary Name) on the basis of similarity to other generic names. The Australian Approved Name (ANN) was therefore amended from 'veruprevir' to 'paritaprevir'. A summary of anti-HCV drugs in advanced development (including those currently approved and those expected to be launched) is presented in Figure 1.

[1] Centre for Drug Evaluation and Research. Application number:206619Orig1s000 http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/206619Orig1s000MedR.pdf

Figure 1: Anti HCV drugs in advanced development including those currently approved and those expected to be launched



Dasabuvir(ABT-333): Non-Nucleoside NS5B inhibitor Sofosbuvir: Nucleoside NS5B inhibitor Boceprevir, telaprevir, simeprevir, paritaprevir(ABT-450), asunaprevir, faldaprevir: NS3/4A protease inhibitors. Dacalatasvir, ledipasivir, ombitasvir(ABT-267): NS5A inhibitors r: ritonavir, PEG-IFN: pegylated-interferon

The recommended dose of Viekira Pak is two paritaprevir /ritonavir/ombitasvir 75/50/12.5 mg tablets once daily (in the morning) and one dasabuvir 250 mg tablet twice daily (morning and evening).

Regulatory status

At the time the TGA considered this application; a similar application had been approved /rejected in (country, date) was under consideration in (country date) as shown in Table 1.

Table 1: Overseas regulatory status

Country	Submission date	Status
EU (Centralised Procedure)	06 May 2014	Approved: 15 January 2015 Indication: Exviera/Viekirax is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults.
USA	21 April 2014	Approved: 19 December 2014 Indication: Viekira Pak with or without ribavirin is indicated for the treatment of patients with genotype 1 chronic hepatitis C virus (HCV) infection including

Country	Submission date	Status
		those with compensated cirrhosis.
Canada	13 May 2014	Approved: 22 December 2014 Indication: HOLKIRA™ Pak (ombitasvir/paritaprevir/ritonavir and dasabuvir) is indicated for the treatment of adults with genotype 1 chronic hepatitis C (CHC) infection, including those with compensated cirrhosis: with ribavirin in non-cirrhotic patients with genotype 1a infection; without ribavirin in non-cirrhotic patients with genotype 1b infection; with ribavirin in patients with compensated cirrhosis.
Switzerland	07May 2014	Approved: 25 November 2014 Indication: Viekirax is indicated in combination with Exviera or Exviera with ribavirin for the treatment of adults with genotype 1 chronic hepatitis c (CHC) infections
New Zealand	15 July 2014	Approved: Under evaluation Indication: (Identical to Australia)
Brazil	21 Aug 2014	Approved: 22 April 2015 Indication: Viekira Pak is indicated for the treatment of patients with genotype 1 chronic hepatitis C virus (HCV) infection.
Russia	14 August 2014	Approved: 29 April 2015 Indication: The approved indication is for the treatment (with and without ribavirin) of genotype 1 chronic hepatitis C infection, including patients with compensated cirrhosis.
Israel	7 July 2014	Approved: 30 March 2015 Indication: The approved labels for genotype 1 indication are aligned with the EU labels.

Country	Submission date	Status
		Exviera/Viekirax is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults.

Approvals were also obtained in Turkey, Chile, Qatar, Saudi Arabia, Kuwait, Puerto Rico, Uruguay, and Macau. Additional submissions in other global markets are planned.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at < https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Introduction

Viekira Pak is a new antiviral combination therapy composite pack consisting of the following components:

- a new fixed-dose combination film coated tablet comprising of 75 mg paritaprevir, 50 mg ritonavir and 12.5 mg ombitasvir, and
- dasabuvir (as sodium salt) 250 mg film coated tablets.

The drug substances paritaprevir, ombitasvir and dasabuvir are direct acting antiviral agents (DAAs) which are new chemical entities (NCEs). Ritonavir is an established drug substance used in several registered products.

The combination therapy regimen includes three DAAs stated to have distinct mechanisms of action and non-overlapping resistance profiles to target HCV at multiple steps in the viral lifecycle. Paritaprevir, ombitasvir and dasabuvir inhibit non-structural (NS) proteins 3, 5A and 5B (NS3, NS5A and NS5B), respectively, which play a key roles in RNA replication in genotypes 1a and 1b of HCV. Paritaprevir is susceptible to first pass metabolism, so ritonavir (a potent CYP3A inhibitor), is included to increase exposure of paritaprevir.

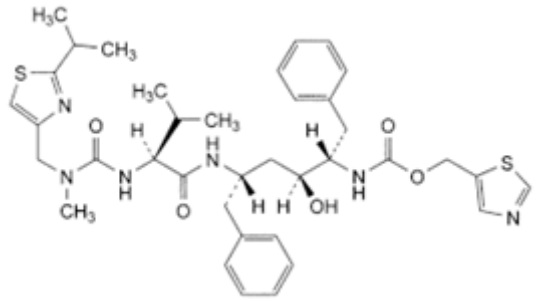
The intended commercial presentation provides a 28 day supply which will include daily blister wallets, each with a 1 day supply of each of the two tablet types co-packaged within a blister card [two paritaprevir/ritonavir/ombitasvir 75/50/12.5 tablets and two dasabuvir (as sodium salt) 250 mg tablets] with an outer cardboard cover. The wallets are packaged into weekly boxes (7 wallets per box). Four weekly boxes are supplied in an outer carton providing a total of 112 tablets [56 paritaprevir/ritonavir/ombitasvir 75/50/12.5 tablets and 56 dasabuvir (as sodium salt) 250 mg tablets].

[There is also a current parallel submission (PM-2014-01438-1-2) for another related composite pack 'Viekira Pak-RBV', consisting of the above described components in addition to ribavirin tablets (200mg, 400 mg or 600mg)].

Drug substances (active ingredients)

Ritonavir

Figure 2: Ritonavir structure



Ritonavir is a potent CYP3A inhibitor which is included as a component of the paritaprevir /ritonavir /ombitasvir 75/50/12.5 mg film coated fixed combination tablets to increase the exposure of paritaprevir, since that antiviral agent is susceptible to first pass metabolism.

Ritonavir is used in several registered products (Norvir tablets, AUST R 158301 and Kaletra lopinavir and ritonavir combination tablets, AUST R 121055 and 140509). There is a BP/EP monograph for the drug substance.

Ritonavir is a white or almost white powder exhibiting pH-dependent solubility ranging from 'very slightly soluble' in 0.1 N HCl (510 µg/mL) to 'practically insoluble' at pH ≥ 4 (2 µg/mL). Ritonavir is considered to be a BCS Class IV compound (low solubility, low permeability).

The company has not provided any details of manufacture or quality control with this submission but provided an assurance that all aspects are identical to those approved for the above Norvir tablets.

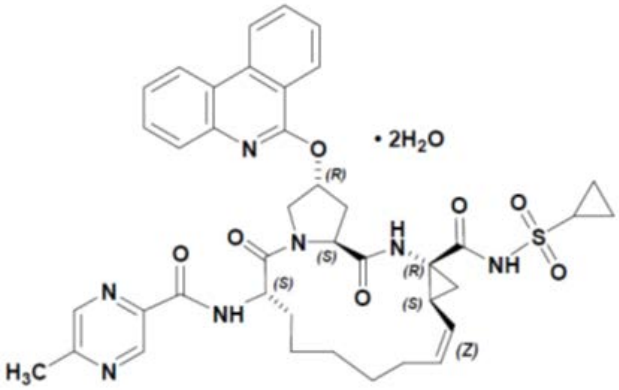
Ritonavir has four chiral centres, and is chirally pure.

The proposed drug substance specifications include all of the requirements of the BP/EP monograph with additional tests and limits for solution clarity, colour, identity and residual solvents. These are considered adequate to ensure the quality and consistency of manufacture of the finished product.

Paritaprevir

Paritaprevir is a direct acting antiviral agent that inhibits NS3/4A protease which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication. Paritaprevir is susceptible to first pass metabolism, so ritonavir (a potent CYP3A inhibitor), is included to increase exposure of paritaprevir.

Figure 3: Paritaprevir. dihydrate form



Paritaprevir dihydrate is a white to off-white powder which is practically insoluble in water (< 0.09 µg/mL). It exhibits moderate membrane permeability and is likely to be a BCS[2] Class IV compound (low solubility, low permeability).

It is consistently manufactured in 'Form II', a variable stoichiometry hydrate, nominally designated as a dihydrate, which undergoes dehydration (desolvation) followed by conversion to amorphous state at about 140°C. During manufacture of the finished product, paritaprevir is converted to a glassy amorphous state whereby it is dispersed into a polymer/surfactant matrix by 'hot melt extrusion' to form a transparent extrudate which enhances its solubility and hence bioavailability.

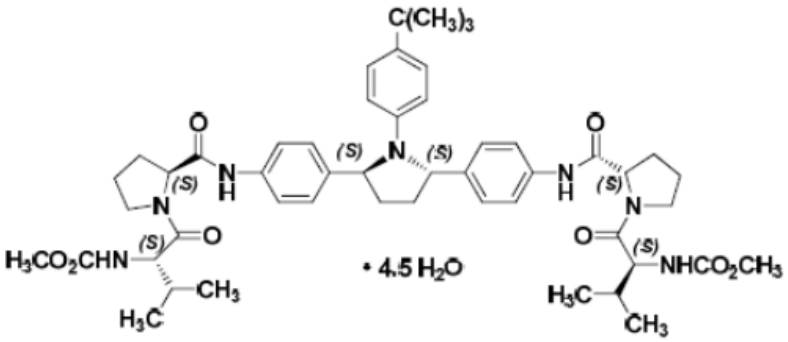
The drug substance is converted to an amorphous solid dispersion during finished product manufacture. Paritaprevir has five chiral centres, and is chirally pure.

The proposed drug substance specifications comply with TGA requirements and are considered adequate to ensure the quality and consistency of manufacture of the finished product.

Ombitasvir (NCE)

Ombitasvir is a direct acting antiviral agent which inhibits nonstructural protein HCV NS5A which plays a key role in RNA replication in HCV.

Figure 4: Ombitasvir (hydrate form)



Ombitasvir hydrate is a white to off-white powder which is practically insoluble in water (0.01 to 0.5 µg/mL; over the physiological pH range). It exhibits low/moderate membrane permeability and is likely to be a BCS Class IV compound (low solubility, low permeability).

[2] The Biopharmaceutical Classification System (BCS) drug substances are classified to four classes upon their solubility and permeability.

It is consistently manufactured in 'Form I', a variable stoichiometry hydrate, nominally designated as a 4.5 hydrate, which undergoes dehydration followed by conversion to amorphous state (Form II) prior to melting at about 157° C. During manufacture of the finished product, ombitasvir is converted to a glassy amorphous state whereby it is dispersed into a polymer/surfactant matrix by 'hot melt extrusion' to form a transparent extrudate which enhances its solubility and hence bioavailability.

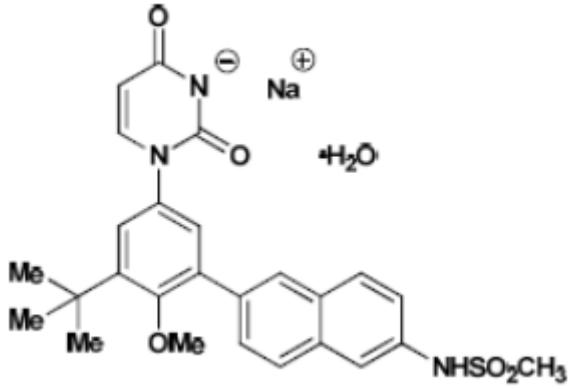
Since the drug substance is converted to an amorphous solid dispersion during finished product manufacture, particle size is not critical and is not routinely tested. Ombitasvir has six chiral centres, and is chirally pure.

The proposed drug substance specifications comply with TGA requirements and are considered adequate to ensure the quality and consistency of manufacture of the finished product.

Dasabuvir sodium

Dasabuvir is a direct acting antiviral agent which is a non-nucleoside inhibitor of the HCV RNA-dependent RNA polymerase encoded by the NS5B gene.

Figure 5: Dasabuvir sodium (monohydrate)



Dasabuvir sodium monohydrate is a non-hygroscopic white to off-white or pinkish powder which is slightly soluble in water, with pH dependent solubility over the pH range 1 to 11 (0.0001 to 1 mg/mL). It exhibits high membrane permeability and is likely to be a BCS Class II compound (low solubility, high permeability).

It is consistently manufactured in the monohydrate form of the sodium salt 'Form I'. Dasabuvir is achiral and has pKa's of 8.2 and 9.2.

The proposed drug substance specifications comply with TGA requirements and are considered adequate to ensure the quality and consistency of manufacture of the finished product. The specifications include adequate control on particle size distribution and crystal form.

Drug product

Drug Product 1; paritaprevir/ ritonavir/ ombitasvir 75/50/12.5 mg film coated fixed combination tablets

The first component of proposed Viekira Pak combination therapy is a fixed dosed combination film coated tablet comprising of 75 mg paritaprevir, 50 mg ritonavir and 12.5 mg ombitasvir. The proposed tablets are pink-coloured, film-coated, oblong, biconvex shaped, debossed with "AV1" on one side.

The tablet is comprised of three 'extrudate' intermediates which are milled, blended, and compressed to form the final tablet. These 'extrudate' intermediates are amorphous solid dispersions of each drug substance in polymer/surfactant matrices, manufactured by hot-melt extrusion (HME). Amorphous solid dispersions are stated to be an effective method to improve the oral absorption of poorly soluble drugs. This improvement is apparently based on the ability to form and sustain supersaturated solutions of the amorphous drug compared to the crystalline counterpart.

The three amorphous drug substances are incorporated into solid dispersions composed of a polymer/surfactant matrix using some or all of the following excipients:

- copovidone (polymer; used in all extrudate intermediates)
- Vitamin E polyethylene glycol succinate (surfactant/ plasticiser/antioxidant; used in paritaprevir and ombitasvir extrudate intermediates)
- propylene glycol monolaurate (plasticiser/surfactant; used in paritaprevir extrudate intermediate only)
- sorbitan monolaurate (plasticiser/surfactant; used in ritonavir extrudate intermediate only) and
- colloidal anhydrous silica (glidant; used in all extrudate intermediates).

Since residual crystallinity of the drug substances could potentially affect bioavailability, the amorphous nature of the intermediate extrudates has been verified by 'clarity of the solid' tests, X-ray diffraction and/or NIR. Routine in-process testing for 'clarity of the solid' is proposed for each extrudate intermediate to verify that drug substances are in their amorphous states. Separate specifications are applied to each extrudate intermediate and a shelf life for each of 12 months stored between 15 and 25° C is supported by stability studies.

All excipients, except propylene glycol monolaurate are conventional ingredients used in numerous registered oral dosage forms. Propylene glycol monolaurate is not a common excipient as it is present in only one registered oral dosage form. However propylene glycol and numerous other laurate esters are common excipients, food components (for example in coconut oil) and metabolites. Hence the excipient is considered unlikely to have safety concerns.

In the tablet manufacturing process, the solid dispersions of each drug substance (extrudate intermediates) are milled, blended together, combined with tabletting aids, compressed into tablets and film coated. Controls applied to the process are considered adequate.

Product performance was tested during development and for routine QC testing using a dissolution test whose parameters have been adequately justified and shown to be acceptably discriminating. Monitoring of each of the drug substances by gradient HPLC method shows a similar release profile for each, such that release is essentially complete after 180 minutes for each drug substance. A single point acceptance criterion of '(Q) = 80% in 180 minutes' for each drug substance, was adequately justified.

The tablets are to be co-packaged with dasabuvir 250 mg tablets (Drug product 2, see below) in blisters, each with a 1 day supply of each of the two tablet types, comprising two paritaprevir/ritonavir/ombitasvir 75/50/12.5 tablets and two dasabuvir (as sodium salt) 250 mg tablets with an outer cardboard cover ('daily wallets'). The wallets are packaged into weekly boxes (7 wallets per box). Four weekly boxes are supplied in an outer carton providing a total of 112 tablets.

The drug substance specifications include identification, assay and control of specified and unspecified degradants for each drug substance. In the related substances HPLC test

method, impurities are assigned to their respective drug substances based on their responses at 4 detections wavelengths. Individual unspecified degradants are controlled to NMT 0.2% which is within the applicable International Conference on Harmonisation (ICH) qualification threshold.

The proposed finished product specifications have been adequately justified and comply with TGA requirements. They are considered adequate to ensure the quality of the finished product at release and throughout the shelf-life.

The tablets show good stability and a shelf life of 24 months stored below 30°C, stored in original container and in a dry place, is considered justified. However, for consistency with the shelf-life applicable to the related combination pack 'Viekira Pak-RBV' (the subject of a parallel submission) which includes Viekira Pak as a component, the company has chosen to apply a shelf-life of 24 months stored below 25°C, stored in original container and in a dry place.

The company has sought to define the start of the shelf-life period as the start of the manufacturing step where the extrudate intermediates beads are milled. This was sought to support variability in the manufacturing dates for the extrudate intermediates and the potential use of multiple extrudate batches for a given tablet production batch. Although this is not the usual definition of the start of shelf-life, as per EMA guidance, it has is adequately supported by 'worst case' stability data and is considered acceptable in this case.

Formulation development

As shown below, the development history of the combination tablet involved seven different types of drug products used in support of clinical development from early Phase I to Phase III. Initial formulations, used in Phase I and II trials, utilised spray-dried dispersion (SDD) tablets and/or capsules of each drug substance, before the development of the proposed co-formulated HME.

There are no significant differences between the formulation and manufacturing processes used to produce the pivotal bioequivalence batch (Batch 12-006414) and the proposed commercial tablets.

Drug product 2 (dasabuvir (as sodium salt) 250 mg film coated tablets)

The first component of proposed Viekira Pak combination therapy is dasabuvir (as sodium salt) 250 mg film coated tablets which are to be co-packaged with the above combination tablets.

The proposed tablets are immediate release unscored film coated tablets containing dasabuvir sodium (270.26 mg), which is equivalent to 250 mg of dasabuvir free acid.

Dasabuvir 250 mg tablets are 'beige coloured, film coated, oval shaped, debossed with "AV2" on one side'. The tablets are co-packaged in blisters, along with the above fixed dose combination film coated tablets.

The excipients used in the drug products are all substances with well-known properties and functions and which are used in many registered tablet formulation. The manufacturing method is a conventional dry granulation process and has been logically developed and is adequately controlled.

Dissolution performance of the proposed tablets during development and for quality control purposes was monitored by a dissolution test method whose development and justification is described in detail. Each aspect of the dissolution testing conditions was adequately justified and the method was shown to be acceptably discriminating. The tablets dissolved rapidly with 82 to 100% of the drug substance being release in 15 minutes and with little or no change being observed on storage.

As described above, the product is to be co-packaged with the combination tablets, in blisters, each with a 1 day supply of each of the two tablet types (two combination tablets and two dasabuvir (as sodium salt) 250 mg tablets] with an outer cardboard cover ('daily wallets').

A limit at release and expiry limit for individual unspecified degradants of NMT 0.2% is proposed, which is within the applicable International Conference on Harmonisation qualification threshold. Batches of tablets typically have very low levels of total impurities at release (< 0.05%) and no significant increase was observed on storage.

The proposed finished product specifications have been adequately justified and comply with TGA requirements. They are considered adequate to ensure the quality of the finished product at release and throughout the shelf-life.

The tablets show good stability and a shelf life of 24 months when stored below 30°C, stored in original container and in a dry place, is considered justified. However, as described above, the company has chosen to apply a shelf-life of 24 months stored below 25°C, stored in original container and in a dry place to the Viekira Pak combination therapy pack.

Formulation development

Phase I and initial Phase II studies utilized 5 and 50 mg capsules. Through Phase I and initial Phase II clinical studies, it became clear that dosage strength higher than 50 mg would be required and a 400 mg tablet was developed. The Phase II formulation was subsequently optimized (with 300 and 400 mg dasabuvir). The optimised 300 mg tablet has approximately 25% higher bioavailability than the un-optimised Phase II tablet. This improvement in bioavailability led to a dose reduction to 250 mg for the Phase III formulation.

There are no significant differences between the formulation or manufacturing processes used to produce the pivotal bioequivalence batch and the proposed commercial manufacturing process although a different site and some different equipment was used. A bioequivalence study was conducted which confirmed the bioequivalence of these tablets.

Biopharmaceutics: Both component tablets

Summary of human pharmacokinetics

Rate and extent of absorption

Paritaprevir/ritonavir/ombitasvir and dasabuvir were absorbed after oral administration with mean T_{max} of approximately 4 to 5 hours.

Metabolism and distribution

Paritaprevir

Paritaprevir is metabolised predominantly by CYP isozyme 3A4 (CYP3A4) and to a lesser extent CYP isozyme 3A5 (CYP3A5). Following administration of a single 200/100 mg oral dose of ^{14}C paritaprevir/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 paritaprevir have been identified in circulation that accounted for approximately 10% of plasma radioactivity. These metabolites are not expected to have antiviral activity.

Ombitasvir

Ombitasvir is metabolised via amide hydrolysis followed by oxidative metabolism. Following a 25 mg single dose of ^{14}C ombitasvir 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.

Dasabuvir

Dasabuvir is predominantly metabolised by CYP2C8 and to a lesser extent by CYP3A. Following a 400 mg ^{14}C dasabuvir dose in humans, unchanged dasabuvir 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 area under the concentration-time curve (AUC) in circulation and has similar activity as the parent drug against genotype 1 in vitro.

Ritonavir

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.

Distribution

Paritaprevir, ombitasvir, ritonavir and dasabuvir are 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 humans ranged from 0.6 to 0.8, indicating that paritaprevir, ombitasvir, and dasabuvir were preferentially distributed in the plasma compartment of whole blood. Paritaprevir was approximately 97 to 98.6% bound to human plasma proteins over a concentration range of 0.08 to 8 µg/mL. Ritonavir was greater than 99% bound to human plasma proteins over a concentration range of 0.007 to 22 µg/mL. Ombitasvir was approximately 99.9% bound to human plasma proteins over a concentration range of 0.09 to 9 µg/mL. Dasabuvir was > 99.9% bound to human plasma proteins over a concentration range of 0.05 to 5 µg/mL.

Mode, route and rate of elimination

Paritaprevir

Following dosing of paritaprevir/ritonavir/ombitasvir with or without dasabuvir, mean plasma half-life of paritaprevir was approximately 5.5 hours. Following a 200 mg ^{14}C paritaprevir dose with 100 mg ritonavir, approximately 88% of the radioactivity was recovered in faeces with limited radioactivity (8.8%) in urine.

Ombitasvir

Following dosing of paritaprevir/ritonavir/ombitasvir with or without dasabuvir, mean plasma half-life of ombitasvir was approximately 21 to 25 hours. Following a 25 mg ^{14}C ombitasvir dose, approximately 90.2% of the radioactivity was recovered in faeces with limited radioactivity (1.91%) in urine.

Dasabuvir

Following dosing of dasabuvir with paritaprevir/ritonavir/ombitasvir, mean plasma half-life of dasabuvir was approximately 5.5 to 6 hours. Following a 400 mg ^{14}C dasabuvir dose, approximately 94.4% of the radioactivity was recovered in faeces with limited radioactivity (approximately 2%) in urine.

Ritonavir

Following dosing of paritaprevir/ritonavir/ombitasvir, 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.

Active entities

Paritaprevir, ritonavir, ombitasvir drug substance are the active entities. The most abundant plasma metabolite of dasabuvir was 'M1', which represented 21% of drug related radioactivity (AUC) in circulation, and this has similar activity as the parent drug.

Dose response proportionality

While ombitasvir and dasabuvir exposures increased in a dose proportional manner, paritaprevir and ritonavir exposures increased in a more than dose proportional manner. Accumulation is minimal for ombitasvir and dasabuvir and approximately 1.5 to 2 fold for ritonavir and paritaprevir. Pharmacokinetic steady state for the combination is achieved after approximately 12 days of dosing.

Effects of food

Paritaprevir, ritonavir, ombitasvir and dasabuvir should be administered with food and instructions to this effect are included in the PI. All clinical trials with paritaprevir, ritonavir, ombitasvir and dasabuvir have been conducted following administration with food.

Food increased the exposure (AUC) of paritaprevir, ombitasvir, ritonavir, and dasabuvir by up to 211%, 82%, 49%, and 30% respectively relative to the fasting state. The increase in exposure was similar regardless of meal type (for example, high fat versus moderate fat) or calorie content (approximately 600 Kcal versus approximately 1000 Kcal). To maximise absorption, Viekira Pak/Viekira Pak-RBV should be taken with food without regard to fat or calorie content.

Bioequivalence and food effect

Paritaprevir/ritonavir/ombitasvir 75/50/12.5 mg tablets

Comparative bioavailability study M11-389 compares the bioavailability of the pivotal bioavailability batch of paritaprevir/ritonavir/ombitasvir 75/50/12.5 mg tablets, dosed under fasted conditions, with the same tablet after a moderate fat meal or a high fat meal.

The following was concluded:

- Administration of two paritaprevir/ritonavir/ombitasvir 75/50/12.5 combination tablets with a moderate fat (Treatment B) or high fat (Treatment C) meal resulted in greater AUC and maximum plasma concentration (C_{max}) of all three active components in the formulation (paritaprevir, ritonavir and ombitasvir) compared to administration under fasting conditions (Treatment A).
- The extent of the food effect was greater for paritaprevir compared to ritonavir or ombitasvir.
- Following administration of the combination tablets with a high fat (Treatment C) meal, the exposures to each drug substance (AUC_{0-t}) increased by approximately 230%, 140% and 170%, respectively, whereas, following a moderate fat (Treatment B) meal, AUC increased by approximately 255%, 150% and 170%.
- The results indicate that increase in exposure was similar regardless of meal type.

Dasabuvir (as sodium) 250 mg tablets

Comparative bioavailability study M13-330 compares the bioavailability of a primary stability batch (batch 12-003123) of Dasabuvir (as sodium) 250 mg tablets dosed under fasted conditions or with a moderate fat meal or a high fat meal.

The following was noted regarding the study:

- Administration of the dasabuvir (as sodium) 250 mg optimized tablet with a moderate fat breakfast resulted in approximately 35% and 25% increase in dasabuvir exposures

(C_{max} and AUC, respectively) relative to the same tablet administered under fasting conditions.

- Administration of the dasabuvir (as sodium) 250 mg optimized tablet with a high fat breakfast resulted in approximately 30% and 20% increase in dasabuvir exposure (C_{max} and AUC, respectively) relative to the same tablet administered under fasting conditions.
- Food had a moderate effect on the bioavailability of the dasabuvir (as sodium) 250 mg Phase III optimized tablet in healthy adults, and the fat content of a meal did not affect dasabuvir exposures.

From a chemistry manufacturing and controls perspective, the conclusions from the above studies are considered to adequately support the proposed PI statement "To maximise absorption, Viekira Pak should be taken with food without regard to fat or calorie content."

Absolute bioavailability

Justification for waiving the requirement of absolute bioavailability studies' has been provided. The Justifications concludes:

"As part of the development program, the absolute bioavailability for dasabuvir has been determined (Study M11-030; dasabuvir absolute bioavailability estimate 46%); however, studies to evaluate the absolute bioavailability of the two active substances of the fixed dose combination tablet, namely paritaprevir and ombitasvir, have not been conducted.

The absolute bioavailability study for dasabuvir was conducted early in the program to aid in formulation development. For paritaprevir and ombitasvir, as Phase I and Phase II formulations were adequate to achieve therapeutic and supratherapeutic exposures, absolute bioavailability studies were not needed to aid formulation or clinical development. AbbVie has now conducted over 60 Phase I studies that characterize the pharmacokinetics of the active substances, and based upon the available data does not believe that absolute bioavailability studies for paritaprevir and ombitasvir would provide additional valuable information to characterize the pharmacokinetics of the product."

Quality summary and conclusions

Registration of the proposed Viekira Pak combination therapy composite pack, consisting of the following components:

A new fixed dose combination film coated tablet comprising of 75 mg paritaprevir, 50 mg ritonavir and 12.5 mg ombitasvir, and dasabuvir (as sodium salt) 250 mg film coated tablets, co-packaged within blisters [28 day supply pack; total 112 tablets; 56 paritaprevir/ritonavir/ombitasvir 75/50/12.5 tablets and 56 dasabuvir (as sodium salt) 250 mg tablets] is recommended with respect to quality and biopharmaceutic aspects. All issues raised during the initial evaluation of this application have been satisfactorily resolved apart from some minor PI revisions.

As no significant pharmaceutical chemistry issues were identified, the chemistry manufacturing and controls aspects of the submission were not referred to the Pharmaceutical Subcommittee of the ACPM, in keeping with recent branch policy.

III. Nonclinical findings

Introduction

The nonclinical evaluation of this submission has been performed in four parts the first three for each of the new chemical entities and the third for the combination product;

- Paritaprevir
- Ombitasvir
- Dasabuvir
- Fixed dose combination

Each of these will be presented separately below.

Paritaprevir

Pharmacology - paritaprevir

Primary pharmacology

Paritaprevir was developed as an inhibitor of HCV NS3/4A protease, the enzyme that catalyses HCV polyprotein cleavage into mature forms of the NS3, NS4A, NS4B, NS5A and NS5B proteins, which are essential for viral replication.[3] In addition to its role in replication, HCV protease also plays a key role in the inhibition of cellular targets involved in the induction of type-I interferon mediated responses, and thus the innate immunity of the host cell.[4] The efficacy studies submitted assessed the inhibitory activity of paritaprevir in in vitro enzyme assays and standard subgenomic HCV replicon assays. No proof-of-concept studies were conducted in animal models of HCV. This is not considered a major deficiency.[5]

Paritaprevir inhibited genotype 1 HCV NS3/4A protease in vitro, with half maximal inhibitory concentration (IC_{50}) values against genotypes 1a and 1b between 0.043 nM and 0.43 nM, compared with the clinical free C_{min} of 0.36 nM (0.27 ng/mL).[6] [7]In cell culture using subgenomic HCV replicon assays the 50% effective concentration (EC_{50}) values against standard laboratory genotype 1a and 1b strains (H77 and Con1, respectively) in subgenomic HCV replicon assays were 0.94 to 1.0 nM and 0.21 to 0.32 nM, respectively, and potency was reduced 24 to 27 fold in the presence of 40% human plasma (to 23 nM and 8.7 nM, respectively). Paritaprevir had similar efficacy against a panel of genotype 1a and 1b clinical isolates in the HCV subgenomic replicon assay; EC_{50} 0.86 nM (range 0.43 to 1.87 nM; n = 11) and 0.058 nM (range 0.033 to 0.087 nM; n = 9), respectively.

Paritaprevir also showed some activity against genotype 4a, with IC_{50} for NS3/4A protease determined at 0.1 to 0.16 nM, and the EC_{50} against cell culture replicons containing genotype 4a determined to be 0.09 nM. Efficacy against genotype 6a was also sub-nanomolar (EC_{50} = 0.68 nM).

[3] Lin, C. (2006). HCV NS3-4A Serine Protease. In: Hepatitis C Viruses: Genomes and Molecular Biology. Ed. S.L. Tan. Horizon Bioscience, Norfolk, UK.
[4] Hiscott J et al. MasterCARD: a priceless link to innate immunity. *Trends in Molecular Medicine* 2006; 12:53-56.
[5] FDA Draft Guidance for Industry: Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment. October 2013, Revision 1.
[6] Based on a C_{trough} of 20 ng/mL (2.6 nM) and assuming a free fraction of 1.37%
[7] Clarification. Liver levels are not known and may be higher than plasma levels

Investigation of HCV NS3/4A protease inhibition for genotypes 2a and 2b yielded IC_{50} values of 2.3 to 2.4 nM and 6.3 nM, respectively, while protease inhibition for the 3a strain was an order of magnitude higher again (IC_{50} = 14.5 to 20.5 nM). In stable cell culture replicons containing type 2a JFH-1 genotype the EC_{50} value for paritaprevir was 5.3 nM. The corresponding value for genotype 3a was 19 nM.

The protease inhibition and antiviral efficacy of paritaprevir was highly specific for HCV NS3/4A. Inhibition of a panel of representative human proteases was observed only at concentrations 4 x 10^6 times higher than those required to inhibit genotype 1 HCV NS3/4A protease, while the therapeutic index for its antiviral efficacy against genotypes 1a and 1b replicons was 58,000 fold.

Resistance and cross-resistance

Table 2: Mutations in NS3/4A that conferred resistance to paritaprevir in HCV replicon assays

Mutation	EC_{50} (nM)	Fold loss of activity	Replication Efficiency (%)
Wild type 1a	1.4	-	100
≤ 3 fold resistance			
V23A (NS4A)	2.6	2	70
V36A/L/M	2.5 to 4.4	2 to 3	81 to 130
T54S	0.54	0.4	6.2
V55I	1.4	1	81
Y56H	4.1	3	3.5
Q80K/L/R	2.2 to 3.9	2 to 3	38 to 91
R155M	1.2	1	5.6
E357K	2.4	2	131
> 3 fold resistance			
F43L	27	20	17
R155K	51	37	31
R155G	19	14	2.0
R155S	10	7	2.1
R155T	10	7	5.1
R155V	6.3	4	20
R155W	16	11	5.3

Mutation	EC_{50} (nM)	Fold loss of activity	Replication Efficiency (%)
A156T	24	17	5.2
D168A	70	50	35
D168E	20	14	34
D168F	289	206	4
D168H	87	62	24
D168N	19	13	28
D168V	135	96	1.5
D168Y	307	219	3.5
Wild type 1b	0.11	-	100
≤ 3 fold resistance			
T54A	0.09	0.8	59
T54S	-	-	< 0.5
V55A	0.07	0.6	14
A156S	0.06	0.5	61
V170A	0.09	1	64
> 3 fold resistance			
R155K	4.4	40	73
R155Q	-	-	< 0.5
A156T	0.81	7	19
D168A	3.0	27	69
D168E	0.48	4	80
D168H	8.3	76	108
D168K	96	882	50
D168T	5.4	49	129
D168V	17	159	157
D168Y	37	337	70

Mutations in NS3/4A that conferred some resistance to paritaprevir were identified from in vitro studies (treatment emergent mutations in HCV replicon assays) and early clinical studies. For genotype 1a, variants at amino acid positions 43, 155, 156 and 168 generally conferred 7 to 219 fold resistance to paritaprevir, while substitutions at 36, 54 and 80 were only associated with small (≤ 3 fold) increases in resistance. However, resistance mutations V36M, F43L, Y56H or E357K in combination with R155K or D168 increased the fold-resistance of the latter mutation a further 2 to 7 fold. In most cases the replication efficiency of the resistant 1a mutations was lower than that of the wild type virus (see Table 2). NS3 variants V36L, T54S, Q80L/R and R155T/V/W were not observed as treatment emergent variants either in vitro or in clinical studies.[8]

The mutations of the genotype 1b strain associated with markedly increased resistance to paritaprevir were those having substitutions at amino acid positions 156 and 168, with substitutions A156T and D168A/H/V/Y reducing antiviral activity by 7 and 27 to 337 fold respectively (NS3 variants R155K and D168E/K/T were not observed as treatment emergent variants either in vitro or in clinical studies5). The combination of Y56H with D168A/V/Y reduced the activity of paritaprevir by an additional 12 to 26 fold compared with the D168 substitution alone. Substitutions at amino acid positions 54, 55 and 170 were not notably more resistant to paritaprevir, while some substitutions at position 156 were associated with modestly increased resistance. The replication efficiency of the mutations conferring resistance to paritaprevir was ≥ 50% that of the wild type virus for variants R155K and D168V/H/K/T/Y.

Mutations at amino acid position 155 and 156 that are likely to confer resistance to paritaprevir based on the in vitro studies are also associated with resistance to most other NS3 protease inhibitors,[9] and hence patients that have failed therapy with other NS3/4A inhibitors may not be susceptible to paritaprevir (and vice versa). However, certain variants associated with resistance to telaprevir, boceprevir and a number of other NS3 inhibitors currently under development or more recently introduced to the market (V36A/M, T54A, V55A, Q80R/K, A156S, and V170A) may be susceptible to paritaprevir based on the results of the in vitro virology data. Mutations at position 168 are common to most macrocyclic NS3 inhibitors including paritaprevir, but these variants are susceptible to NS3 inhibitors having a linear chemical scaffold, such as telaprevir and boceprevir.

Ritonavir did not exhibit activity against HCV, and did not affect the antiviral efficacy of paritaprevir in a standard HCV replicon assay.

Secondary pharmacodynamics and safety pharmacology

Paritaprevir showed no relevant antiviral activity evident against human immunodeficiency virus 1 (HIV-1) and hepatitis B virus (HBV). In a screen for secondary activity at 75 receptors, ion channels and transporters, paritaprevir displaced ligand binding to human recombinant δ-opioid receptors expressed in CHO cells by 77%. This occurred at a concentration of 10 μM, which is approximately 380 times the clinical C_{max} (for unbound paritaprevir[10]) of 26.3 nM. No off target activities are predicted during clinical use.

Specialised safety pharmacology studies covered the central nervous system (CNS), cardiovascular, respiratory and gastrointestinal systems. Mild excitatory effects were seen in a non-good laboratory practice (GLP) study in male rats dosed with paritaprevir (≥ 100 mg/kg, in combination with 15 mg/kg ritonavir), but not in a GLP study in which exposures were 3.4 times the clinical C_{max} for paritaprevir, nor the repeat dose toxicity studies at exposures approximately 11 times the clinical C_{max}. Inhibition of human ether-a-go-go-related gene

[8] Sponsor's response to TGA, dated 27 February 2015.
[9] Halfon, P. and Locarnini, S. Hepatitis C virus resistance to protease inhibitors. *Journal of Hepatology* 2011; 55: 192-206.
[10] Assuming an unbound fraction of 0.0137

(potassium channel) (hERG) tail currents was only seen at very high concentrations (estimated IC_{50} corresponding to greater than 3,000 times the clinical C_{max} for unbound paritaprevir). A small, apparently dose dependent increase in QT interval duration corrected for heart rate (QTc) in anaesthetised dogs is considered unlikely to be related to treatment, as the increase continued during the washout period, and no effect was seen in a subsequent GLP study in conscious dogs at exposures 66 times the clinical C_{max}, nor in the 9 month repeat dose toxicity study at exposure levels 76 times the clinical C_{max}.

There were no significant effects on respiratory function in conscious rats dosed with paritaprevir/ritonavir up to 500/15 mg/kg, at maximum exposure levels (associated with the maximum dose (MD) group dosed at 150/15 mg/kg) approximately equal to the clinical C_{max}.

Potential effects on gastrointestinal motility were not adequately investigated as the exposure associated with an oral paritaprevir dose of 300 mg/kg (without ritonavir) was only 0.15 times the clinical C_{max} and the study did not include a positive control. Emesis was observed in one of six ferrets dosed orally with 75 mg/kg paritaprevir (5.5 times the clinical C_{max}), and there was a dose related increase in emesis in repeat dose studies in dogs. This effect appeared to be mild, with no adverse consequences on food intake or body weight gain. It is a frequently observed response to test article administration in this species. Overall, a markedly adverse effect on the gastrointestinal tract is considered to be unlikely based on the results of repeat dose toxicity studies in mice, rats and dogs co-dosed with paritaprevir and ritonavir, in which the treatment was well tolerated.

Paritaprevir is not expected to have any notable adverse effects on CNS, respiratory, gastrointestinal or cardiovascular function during clinical use.

Pharmacokinetics - paritaprevir

Paritaprevir is a high molecular weight, lipophilic compound with a moderate apparent intestinal permeability (based on in vitro data). It is subject to active efflux, and to moderate to high rates of metabolism by CYP3A4, resulting in high first pass hepatic metabolism. Markedly increased levels of systemic exposure were achieved in animal studies by using non-aqueous formulations, and by co-dosing with ritonavir to minimise the effects of first pass metabolism and active efflux. The non-aqueous formulations selected for paritaprevir were also appropriate for ritonavir, which is also a high molecular weight, lipophilic compound.

The plasma kinetics of paritaprevir (alone or when co-administered with ritonavir) were examined after single per oral (PO) doses in mice, rats, rabbits, dogs and monkeys, and after single intravenous (IV) doses in rats, rabbits, dogs and monkeys. Oral absorption in bile duct cannulated rats was low (15.3%). Bioavailability estimates are generally unreliable, since in most cases the co-administration of ritonavir was not consistent between oral and intravenous dosing, but the value of 41% in the dog is not subject to this limitation. In most species, paritaprevir kinetics were characterised by a high plasma clearance (≥ 1.9 L/kg/h), moderate volume of distribution (≥ 0.52 L/kg) and an apparent elimination half-life after IV dosing of approximately 0.4 hours. Clearance values were somewhat lower in the dog (0.1 L/h/kg), and elimination half-life was 1.2 h. A pronounced food effect was evident in this species, with plasma exposures being six fold higher in fasted dogs. Only very low systemic exposures could be achieved in the rabbit, even following parenteral administration. Plasma kinetics in mice, rats and dogs showed no consistent gender difference, and no evidence of accumulation with multiple dosing. Exposures increased with dose, but showed saturation at higher doses.

In all species paritaprevir was highly bound to plasma proteins in vitro over the concentration range 0.1 to 10 μM. The mean value in humans from two independent

experiments was 98.63% (mean unbound fraction = 0.0137), and was similar in animals. In one study the mean fraction unbound was slightly lower in dogs than in the other species, but this was not confirmed in a second experiment. There were no meaningful differences in protein binding in the plasma from human subjects with varying degrees of renal or hepatic impairment. Paritaprevir preferentially distributed to the plasma compartment in humans and animals (blood to plasma concentration ratio 0.58 to 1.0; human value = 0.68. Tissue distribution of radioactivity in pigmented rats following oral administration of radiolabelled paritaprevir was mainly limited to the gastrointestinal tract and excretory organs, with no penetration of the blood brain barrier, lens of the eye and uveal tract or testes, and no evidence of accumulation or retention. Exposure levels in the liver were higher than in plasma for mice, rats and dogs, with liver: plasma ratios following its oral co-administration with ritonavir in rats and dogs being approximately 2800 to 5400 and 6 to 14, respectively, and approximately 350 following IV administration to FVB mice.

The main metabolic pathways for paritaprevir biotransformation were CYP mediated oxidation of the olefinic linker or the phenanthridine or methylpyrazinyl groups, and amide hydrolysis at the acyl cyclopropane-sulfonamide and pyrazine-2-carboxyamide moieties. Unchanged paritaprevir was by far the dominant circulating species in humans and laboratory animals, and none of the metabolites circulating in plasma exceeded 10% of total drug related material. With the exception of the acyl cyclopropane-sulfonamide hydrolysis product M29, all circulating human metabolites were also seen in the plasma of at least one animal species. In vitro studies indicated a major role for CYP3A4 in the oxidative metabolism of paritaprevir. Following oral dosing, paritaprevir was predominantly excreted in the bile and eliminated via the faeces in mice, rats, dogs and human subjects. The predominant faecal metabolite in humans as well as in rats and dogs was the amide hydrolysis product M29, which was probably formed as a result of intestinal metabolism. Urinary excretion was 0.8% in mice, 2.1% in rats, 3.8% in dogs and 8.8% in humans, predominantly in the form of M13, the methylpyrazine-2-carboxylic acid. Overall, the pharmacokinetic profile of paritaprevir in mice, rats and dogs is considered adequately comparable for these animal species to serve as models for toxicity.

Pharmacokinetic drug interactions

Effects of other drugs on paritaprevir

Paritaprevir is metabolised by CYP3A4 and is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Therefore inhibitors/inducers of these CYP enzymes and transporters may affect paritaprevir exposure levels. The CYP3A4 inhibitor ritonavir was included in the Viekira Pak formulation to increase systemic exposure to paritaprevir, but this was further increased by co-administration with the CYP3A4/P-gp inhibitor ketoconazole. In addition, co-administration with the CYP3A4 inducer carbamazepine markedly reduced plasma concentrations of paritaprevir (AUC decreased by 71%). Based on this effect strong inducers of CYP3A4 are contraindicated during treatment with paritaprevir.

Paritaprevir is also a substrate for the hepatic organic anion transporting polypeptides (OATP) OATP1B1 and OATP1B3 (but not OCT1), and studies in gene knockout mice indicated a combined contribution from multiple efflux transporters to the elimination of paritaprevir in this species. This was confirmed in clinical studies, which reported that paritaprevir concentrations were increased by co-administration of atazanavir and cyclosporin. Overall, the results of the in vitro studies are in agreement with the clinical findings.

Effects of paritaprevir on other drugs

Paritaprevir was a weak competitive inhibitor of CYP2C8 and UDP-glucuronosyltransferase family member A1 (UGT1A1), but neither effect is anticipated to be clinically relevant. Co-administration of the UGT1A1 substrate raltegravir with the 3DAA agents in combination increased plasma exposures by approximately one third, but this effect is most likely to be due to the dasabuvir component, with a possible contribution by ombitasvir. The potential for CYP3A4 induction is negated by the strong inhibitory action of ritonavir, as shown in clinical studies, where the exposure of the sensitive CYP3A4 substrate tacrolimus was markedly increased when administered in combination with the 3DAA regimen (Study M13491).

Paritaprevir was an inhibitor of P-gp, BCRP and multidrug resistance associated protein 2 (MRP2). As the IC_{50} values (38.1, 0.59, 12 μM, respectively) were < 0.1 times the intestinal concentration, paritaprevir has the potential to affect the oral absorption of co-administered drugs that are substrates for these transporters.[11] However, co-administration of paritaprevir (as part of the 3DAA regimen) with the P-gp substrate, digoxin, was not associated with clinically relevant increases in the plasma concentration of this P-gp substrate.

Paritaprevir also inhibited the hepatic anion transporters OATP1B1, OATP1B3 and OATP2B1 (IC_{50} values 0.031, 0.017 and 0.2 μM, respectively). As the IC_{50} values for paritaprevir against these transporters are < 25 fold the unbound hepatic inlet concentration,[12] paritaprevir has the potential to alter the disposition of co-administered drugs that are substrates for these hepatic transporters. The AUCs of pravastatin (an OATP1B1 substrate) and rosuvastatin (an OATP1B1/B3 and BCRP substrate) were increased (by 82% and 159%, respectively) when these compounds were co-administered with paritaprevir (in combination with ombitasvir, dasabuvir and ritonavir) in human subjects. It is not possible to determine the relative contributions of each individual 3DAA agent to this effect, as dasabuvir and ritonavir were also likely to contribute to this effect.

Toxicology - paritaprevir

Acute toxicity

Paritaprevir had a very low oral toxicity in single dose toxicity studies in rats and dogs (oral doses of up to 600 mg/kg and 100 mg/kg, respectively). There were no remarkable findings associated with plasma exposures up to 9 and 41 times the clinical exposure (based on AUC). In the rat study, the liver to plasma concentration ratio for paritaprevir was up to 900.

Repeat-dose toxicity

Pivotal repeat-dose toxicity studies were of up to six months duration in mice, three months duration in rats and 9 months duration in dogs, and were conducted under GLP conditions. The duration of the pivotal studies, the species used group sizes and the use of both sexes was consistent with ICH guidelines.[13] The clinical route (PO) and dosing frequency was used in all studies, except that in the nine month dog study the highest dosage group received two divided doses rather than a single daily dose. This is not expected to significantly affect the validity of the toxicity studies. Paritaprevir was co-

[11] EMA guideline: CPMP/EWP/560/95/Rev. 1 Corr.* Guideline on the Investigation of Drug Interactions
[12] Assuming an absorption rate constant (ka) of 0.1 min-1 and a fraction absorbed from the gut to the portal vein (Fa) of 1 according to the EMA guideline above.
[13] ICH M3(R2): Note for guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals

administered with the CYP3A4 inhibitor ritonavir as a pharmacokinetic booster. The doses of ritonavir in the repeat dose toxicity studies were selected to optimise exposure to paritaprevir for each nonclinical species, and were capped at this level to enable paritaprevir toxicity to be explored without being confounded by ritonavir toxicity. Doses of paritaprevir were generally acceptable, achieving high relative exposures to paritaprevir (see Table 3 and Figure 6). In the earlier studies in rats, saturation of plasma exposure to paritaprevir was identified as limiting the usefulness of this species, and so the CD-1 mouse was chosen to be the rodent species for the remainder of the toxicology programme.

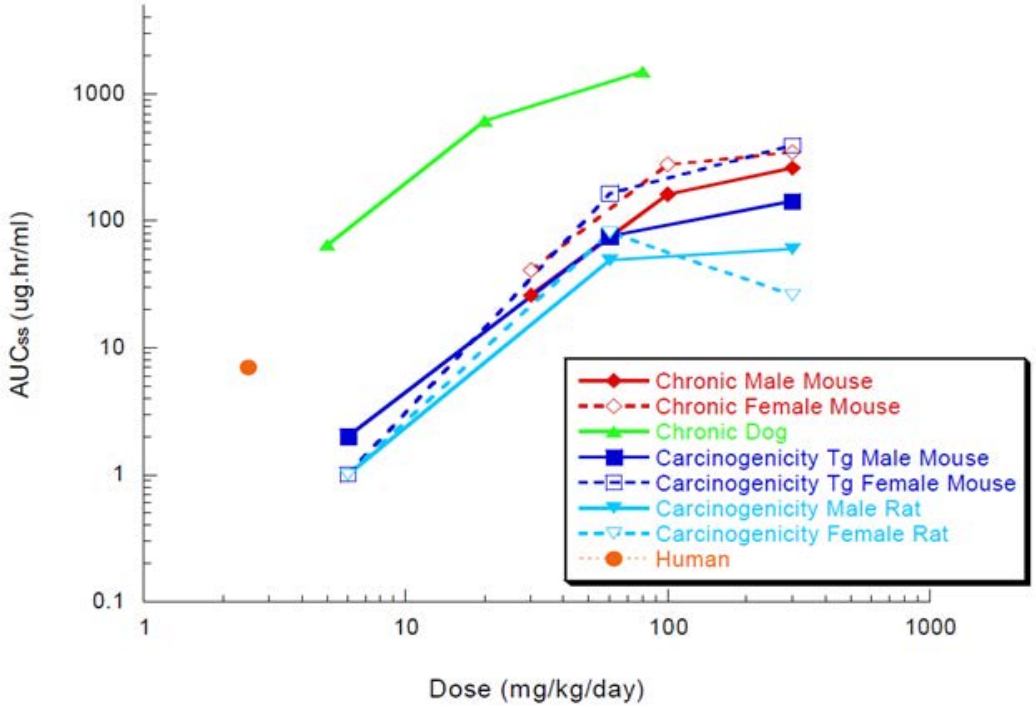
Table 3: Relative exposure

Species	Study duration	Analyte	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (µg·h/mL)	Exposure ratio#
Mouse (Transgenic)	4 weeks (Day 28)	paritaprevir	30	51	7.3
			100	131	19
			300	344	49
			450	421	60
		Ritonavir	30	49.5	5.2
	6 months [carcinogenicity] (Day 87)	paritaprevir	6	1.56	0.22
			60	121	17
			300	269	38
		Ritonavir	30	44.5	4.7
Mouse (CD-1)	6 months (Day 182)	paritaprevir	30	33.5	4.8
			100	220	32
			300	305	44
		Ritonavir	30	30.4	3.2
Rat (SD)	1 day (Micronucleus)	paritaprevir	500	33.1	4.7
			1000	87.1	12
			2000	83.3	12
	13 weeks (Day 87)	paritaprevir	100	73.9	11
			300	104.4	15
			450	91.4	13
		Ritonavir	15	15	1.5

Species	Study duration	Analyte	Dose (mg/kg/day)	$AUC_{0-24\ h}$ (µg·h/mL)	Exposure ratio#
			30	43.8	4.6
			45	58	6.1
	2 years [carcinogenicity] (day 182)	paritaprevir	6	0.66	0.094
			60	65	9
			300	53	8
		Ritonavir	30	43	4.6
Dog (Beagle)	9 months (Week 39)	paritaprevir	5	66	9
			20	616	88
			80	1495	214
		Ritonavir	5	10.6	1.1
			10	43	4.6
			20	38	4.0
Human (healthy volunteers)	steady state		PAR 150 mg	6.99	–
			RTV 100	9.47	

= animal:human plasma $AUC_{0-24\ h}$; a = 2 X AUC0-12 h (model predicted steady state exposure for 600 mg twice daily (BD) ribavirin, taken from Module 5.3.3.5; RD131098;Table 64);plasma kinetic data from males and females were similar, so the mean AUC data have been combined

Figure 6: paritaprevir toxicokinetic data



Major toxicities

The major target organ for paritaprevir was the gall bladder. Most other toxicities observed in the repeat dose studies could be attributed to ritonavir.

Ritonavir

Repeat dose toxicity studies with ritonavir were previously evaluated by the TGA. Toxicological findings which are relevant to the doses of ritonavir co-administered with paritaprevir were hepatotoxicity in the rat, including multinucleated hepatocytes, hepatocytomegaly and single cell necrosis, and thyroid follicular cell hypertrophy, associated with elevated thyroid stimulating hormone concentrations. Biliary hyperplasia and chronic pericholangitis were seen at higher doses. Hepatic pathology was associated with increased serum enzyme activities. Ocular changes were seen in rodents at doses higher than those administered in the current application. Effects included retinal degeneration and hypertrophy of the retinal pigment epithelial (RPE) cells, and electroretinography carried out in one study showed changes indicative of compromised retinal function. Retinal lesions were thought to be manifestations of phospholipidosis, and there was a widespread occurrence of microgranulomas in the 3 and 6 month rat studies, primarily in the liver, lungs and lymphoid tissues. In the dog, hepatotoxicity was manifest mainly as increased serum enzyme activities (for example, γ glutamyltransferase) and hepatocytic hydropic degeneration, although pericholangitis was seen in one study. Low incidences of testicular and prostatic degeneration/atrophy were also seen in this species, but there were no thyroid or ocular changes.

Paritaprevir

The main target organ for paritaprevir associated toxicity was the gallbladder. In the six month repeat dose study in CD-1 mice, focal erosion or ulceration of the gall bladder epithelium was characterised by focal necrosis and loss of mucosal epithelial cells, transmural fibrosis and inflammation, extending into the lamina propria, tunica muscularis and serosa. Hypertrophic or hyperplastic tissue was often found adjacent to the areas of mucosal erosion. The effect showed only partial recovery. The effect was clearly associated with paritaprevir treatment, as it was not observed in the previously

evaluated repeat dose studies with ritonavir, and showed a clearly dose dependent effect. The no observable adverse effect level (NOEL) for paritaprevir was 30 mg/kg/day, which corresponds to systemic exposure (based on AUC) 4.8 times the clinical exposure. The lowest observed effect level (LOEL) was 60 mg/kg/day in the 6 month carcinogenicity study in TgrasH2 transgenic mice (relative exposure 17 times the clinical exposure, based on AUC). There was no indication of progression to a pre-neoplastic or neoplastic state in this model. However, the relevance of human c-Ha-ras gene overexpression to the progression of chronic inflammation and hypertrophy to carcinogenesis is unknown. Gall bladder toxicity was not observed in the shorter duration studies, including the 13 week mouse study at doses up to 300 mg/kg/day, corresponding to systemic exposure 60 times the clinical AUC.

The rat does not have a gall bladder, so this species is not a suitable model for investigating gall bladder toxicity. Minimal focal mucosal degeneration and oedema was observed in the gall bladders of dogs in the 4 week study (paritaprevir dose 20 mg/kg/day, 92 times the clinical AUC), but there was no evidence of progression in longer duration studies, and there were no gall bladder findings in the 13 week study. In the pivotal 9 month study, the NOEL for gall bladder changes was 20 mg/kg/day (88 times the clinical AUC), and only one male dosed with paritaprevir at 80 mg/kg/day for 9 months (214 times the clinical AUC) exhibited minimal epithelial necrosis. It is possible that the relatively lower severity of adverse gall bladder toxicity in this species is related to the correspondingly lower liver to plasma concentration ratio for paritaprevir.

Genotoxicity

Genotoxicity studies were GLP compliant, and the range of studies and their design accorded with ICH guidelines,[14] using appropriate concentrations or doses and controls. Paritaprevir did not induce mutations in a bacterial reverse mutation assay, but was clastogenic in human lymphocytes in vitro. No evidence of genotoxicity was found in an in vivo rat bone marrow micronucleus assay and an ex vivo liver Comet assay in rats in which liver exposure was confirmed. In rat tissue distribution studies, radioactivity was detected in the bone marrow 4 hours after oral dosing, so the bone marrow is likely to have been exposed to paritaprevir in the micronucleus assay. The weight of evidence provided indicates a low potential for paritaprevir genotoxicity. In previously evaluated studies ritonavir was inactive in in vitro tests (Salmonella typhimurium and mouse lymphoma cells) for gene mutation, and in in vitro (human lymphocytes) and in vivo (mouse micronucleus) tests for clastogenicity.

Carcinogenicity

The carcinogenic potential of paritaprevir by the oral route was assessed in transgenic TgrasH2 transgenic mice[15] following daily dosing for 26 weeks, and in a conventional 2 year oral carcinogenicity study in rats. The choice of transgenic model is considered acceptable.[16] The group sizes used (25/sex) and duration of dosing (26 weeks) were appropriate for the species,[17,18] Group sizes and selection of dose levels in the 2 year rat study were appropriate. Overall, the carcinogenic potential testing was in accordance with the relevant ICH guidelines.[19,20,21]

[14] ICH S2(R1): Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use.
[15] A Tg-rasH2 mouse is a transgenic mouse, carrying the three copies of human prototype c-Ha-ras oncogenes with endogenous promoter and enhancer in tandem.
[16] CPMP/SWP/2592/02/Rev 1; CHMP SWP conclusions and recommendations on the use of genetically modified animal models for carcinogenicity assessment. 23 June 2004
[17] MacDonald, J et al. The utility of genetically modified mouse assays for identifying human carcinogens: a basic understanding and path forward. *Toxicol. Sci.* 2004; 77: 188–194.
[18] Morton, D., et al. The Tg rasH2 mouse in cancer hazard identification. *Toxicol. Pathol.* 2002; 30: 139–146.
[19]CPMP/SWP/2877/00. Note for guidance on carcinogenic potential. 25 July 2002.

In the mouse study, a concurrent positive control group (N-nitroso-N-methylurea-treated) was included and tumours expected from administration of a mutagen were observed, confirming the validity of the study. There were no paritaprevir related neoplastic findings in any of the treated groups (≤ 300 mg/kg/day PO; systemic exposure 38 times the clinical AUC). There was no indication of progression of gall bladder inflammation or hyperplasia to a pre-neoplastic or neoplastic state in this model. However, the relevance of human c-Ha-ras gene overexpression to the progression of chronic inflammation and hypertrophy to carcinogenesis is unknown, and so the possibility of neoplastic progression cannot be excluded. However, the frequency and severity of gall bladder hyperplasia showed a clear dependence on time of exposure.

There were no treatment related increases in tumour development in the rat study at systemic exposure levels up to 9 times the clinical AUC, which is considered adequate.

Reproductive toxicity

Good laboratory practice compliant reproductive toxicity studies were submitted and examined fertility (in rats), embryofetal toxicity (mouse and rat) and pre/postnatal development (rats). The mouse was selected over the rabbit as an initial toxicokinetic study identified vehicle tolerability problems. Adequate animal numbers were used during appropriate gestational periods. Relative exposure in the rat fertility study was only 3 times the clinical AUC, but was somewhat higher in the embryofetal and pre/postnatal development studies in this species. Systemic exposure in the mouse embryofetal development study was up to 98 fold the clinical AUC. The clinical route (PO) was used in all studies.

Studies in rats found very limited placental transfer into fetal tissues, with measurable levels found only in the liver, at approximately one tenth the concentration in maternal plasma. Paritaprevir was detected in the milk of lactating rats, with a milk: plasma radioactivity concentration ratio of 0.224 estimated at their respective C_{max} values. The hydrolysis product M13 was the dominant radioactive species (84.1% of total radioactivity).

There was no adverse effect on male or female fertility up to and including the highest dose combination (up to 300/30 mg/kg/day PO, associated with exposure approximately 3 times the clinical AUC). There were no treatment related embryofetal development findings in rats and mice at systemic exposures 8 and 98 fold the clinical AUC, respectively. Results from pre/postnatal development study in rats were unremarkable, with no evidence of treatment related toxicity up to and including the highest dose (300/30 mg/kg/day PO; systemic exposure17 times the clinical AUC).

Table 4: Relative exposure; paritaprevir

Species	Study	Dose (mg/kg/day)	$AUC_{0-24\ h}$ (µg·h/mL)	Exposure ratio#
Rat (Crl:CD1[ICR])	Fertility	PAR 30	0.236	0.03
		PAR 60	14.44	2
		PAR 300	23.55	3

[20] CPMP/ICH/299/95 Note for guidance on carcinogenicity: testing for carcinogenicity of pharmaceuticals. March 1998.
[21] EMEA/CHMP/ICH/383/1995 ICH Topic S1C(R2). Dose selection for carcinogenicity studies of pharmaceuticals. October 2008.

Species	Study	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (µg·h/mL)	Exposure ratio#
		RTV 30	21.7	2
	Embryofetal development (main study) GD17	PAR 30	2.31	0.3
		RTV 15	8.46	0.9
		PAR 100	45.2	65
		RTV 15	8.22	0.9
		PAR 450	58.6	8
		RTV 45	26.2	2.8
Mouse CD-1	Embryofetal development (main study) GD15	PAR 30	224	32
		PAR 100	631	90
		PAR 300	686	98
		RTV 30	49.7	5.2
Rat (Crl:CD1[ICR])	Pre/postnatal development	PAR 30	0.345*	0.05
		RTV 30	18.1*	1.9
		PAR 60	5.36*	0.8
		RTV 30	20.2*	2
		PAR 300	116*	17
		RTV 30	17*	1.8
Human (healthy volunteers)	steady state PAR	150 mg/day	6.99	–
Human (healthy volunteers)	steady state RTV	100 mg/day	9.47	-

= animal: human plasma $AUC_{0-24\,h}$. * = maternal plasma AUC

Pregnancy classification

The sponsor has proposed Pregnancy Category B1[22] for paritaprevir. The reference regarding animal data in the pregnancy category statement for B1 is consistent with the results from the nonclinical assessment. This category would be appropriate if the clinical data indicates that paritaprevir has indeed been taken by a limited number of pregnant

[22] Pregnancy category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

women and women of childbearing age without an evidence of an increase in the frequency of malformation or indirect harmful effects. When combined with ritonavir (Pregnancy Category B3[23]) or ribavirin (Pregnancy Category X[24]) then the higher pregnancy category takes precedence. This is discussed in the evaluation of the combination products Viekira Pak and Viekira Pak–RBV.

Photosafety

No nonclinical phototoxicity studies have been submitted based on supporting clinical safety information from Phase III clinical studies. Although paritaprevir absorbs light in the range 290 to 700 nm and maximal molar extinction coefficient values exceed 1 x 10^3 $Lmol^{-1}cm^{-1}$, the results of photostability testing, DEREK in silico photosafety prediction modelling[25], the lack of detectable radioactivity in the skin or eye in tissue distribution studies and the absence of skin or ocular toxicity in repeat dose oral toxicity studies are supportive of the lack of phototoxicity potential. The sponsor's justification for the lack of nonclinical phototoxicity data is in accordance with the relevant guideline, based on the lack of distribution to exposed tissues.[26]

Impurities

The proposed specifications for impurities and degradants in the drug substance are below ICH levels,[27] or have been adequately qualified.

Paediatric use

No studies in juvenile animals were submitted. The sponsor justified the absence of such studies on the absence of any toxicological finding that would be considered to be more severe or to manifest differently to that in an adult, and no anticipated differences in metabolism between the adult and paediatric populations.

Nonclinical summary and conclusions - paritaprevir

- The overall quality of the submitted dossier for the paritaprevir component of Viekira Pak and Viekira Pak–RBV was high. All pivotal safety studies were conducted under GLP conditions.
- In vitro, paritaprevir inhibited the activity of NS3/4A protease from HCV strains of genotypes 1a, 1b and 4a with nanomolar potency and inhibited the replication of these strains in subgenomic HCV replicon assays. Paritaprevir had lower potency at NS3/4A protease from other HCV genotypes (2a, 2b and 3a).
- NS3 mutations F43L, R155G/K/S, A156T and D168A/E/F/H/N/V/Y, or combinations of V36M, F43L, Y56H or E357K with R155 or D168 variants conferred resistance to paritaprevir genotype 1a, and A156T, D168A/H/V/Y, either alone or in combination with Y56H for genotype 1b. Cross resistance may be seen with some other NS3 protease inhibitors, as mutations at R155 and A156 are also associated with resistance to most other NS3 protease inhibitors, while mutations at D168 are common to most macrocyclic NS3 inhibitors. However, certain variants associated with resistance to

[23] Pregnancy category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.
[24] Pregnancy category X: Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.
[25] DEREK is computer based predictive software for toxicity prediction
[26] CHMP/ICH/752211/2012 Photosafety Evaluation of Pharmaceuticals. S10 Step 4, 13 November 2013.
[27] CPMP/ICH/2737/99 ICH Topic Q3A (R2). Impurities in new drug substances. Note for guidance on impurities testing: Impurities in new drug substances.

telaprevir, boceprevir and a number of other NS3 inhibitors having a linear scaffold (V36A/M, T54A, V55A, Q80R/K, A156S, and V170A) may be susceptible to paritaprevir based on the results of the in vitro virology data.

- Paritaprevir showed no relevant antiviral activity evident against HIV-1 and HBV, and protease activity was highly specific for HCV NS3. No off-target activities are predicted during clinical use.
- Based on findings in the combined set of safety studies, paritaprevir is not expected to have any adverse effects on CNS, respiratory, gastrointestinal or cardiovascular function during clinical use.
- Paritaprevir is a high molecular weight, lipophilic compound subject to active efflux, and to moderate to high rates of metabolism by CYP3A4, resulting in high first pass hepatic metabolism. Absorption in rats was low, while oral bioavailability was moderate in the dog, and there was a pronounced food effect in this species. Markedly increased levels of systemic exposure were achieved in animals by co-dosing with the CYP3A4 inhibitor ritonavir, and this corresponds to the clinical situation. Plasma protein binding by paritaprevir was very high, but was similar in all species. In rats, tissue distribution of radioactively labelled material was mainly limited to the gastrointestinal tract and excretory organs. Liver concentrations were higher than plasma levels in mice, rats and dogs.
- Routes of metabolism were similar across species, and included CYP mediated oxidation and amide hydrolysis. Unchanged paritaprevir was the dominant circulating species, and none of the metabolites circulating in plasma exceeded 10% of total drug related material. Following oral dosing, paritaprevir was predominantly excreted in the bile and eliminated via the faeces in mice, rats, dogs and humans.
- Inducers or inhibitors of CYP3A4, P-gp, BCRP and the hepatic organic anion transporter proteins OATP1B1 and OATP1B3 may alter the systemic and/or hepatic exposure to paritaprevir. In vitro studies indicate paritaprevir has the potential to affect the oral absorption of co-administered drugs that are substrates for P-gp, BCRP and MRP2, and affect the disposition of co-administered drugs that are substrates for OATP1B1 andOATP1B3.
- Paritaprevir had a very low oral toxicity in single dose toxicity studies in rats and dogs in which plasma exposures reached up to 9 and 41 times the clinical exposure (based on AUC).
- GLP compliant repeat dose toxicity studies were conducted in mice (up to 6 months), rats (up to 3 months) and dogs (up to 9 months), using the oral route, and with ritonavir co-administration. The gallbladder was a target for toxicity in mice, characterised by focal erosion or ulceration, inflammation and epithelial hyperplasia. The effect was seen in two 6 month studies with a NOEL of 30 mg/kg/day (systemic exposure 4.8 times the clinical AUC) and a LOEL of 60 mg/kg/day (17 times the clinical AUC), but was not seen in studies of up to 13 weeks duration. Gall bladder toxicity was less severe in dogs, and the NOEL in the 9 month study was 20 mg/kg/day (88 times the clinical AUC), which may be reflective of the lower liver to plasma concentration ratio for paritaprevir in this species compared to the mouse. Rat studies are not relevant, since this species lacks a gall bladder.
- Paritaprevir was not genotoxic in a bacterial reverse mutation assay, in in vivo bone marrow micronucleus and ex vivo liver Comet assays in rats, but it was clastogenic in human lymphocytes in vitro. Overall, the weight of evidence provided indicates a low potential for paritaprevir genotoxicity.
- No drug related tumours were evident in transgenic TgrasH2 mice treated for 6 months with paritaprevir. Although there was no indication of progression of gall

bladder inflammation or hyperplasia to a pre-neoplastic or neoplastic state, the relevance of human c-Ha-ras gene overexpression to the progression of chronic inflammation and hypertrophy to carcinogenesis is unknown, and so the possibility of neoplastic progression cannot be excluded. A standard 2 year rat carcinogenicity assay found no treatment related neoplasia.

- GLP compliant reproductive toxicity studies were submitted and examined fertility (in rats), embryofetal toxicity (mouse and rat) and pre/postnatal development (rats). The mouse was selected over the rabbit as an initial toxicokinetic study identified vehicle tolerability problems. Adequate animal numbers were used during appropriate gestational periods. Relative exposure in the rat fertility study was only 3 times the clinical AUC, but was somewhat higher in the embryofetal and pre/postnatal development studies in this species. Systemic exposure in the mouse embryofetal development study was up to 98 fold the clinical AUC. The clinical route (PO) was used in all studies.
- In reproductive toxicity studies, placental transfer into fetal rat tissues was very limited, with measurable levels found only in the liver. Paritaprevir and its hydrolysis product M13 were detected in the milk of lactating rats. There was no adverse effect on male or female fertility in this species at systemic exposures approximately 3 times the clinical AUC, and no treatment related embryofetal development findings in rats and mice at systemic exposures 9 and 180 fold the clinical AUC, respectively. No evidence of toxicity was seen in the offspring of rats dosed at up to 300 mg/kg/day in the peri/postnatal toxicity study (systemic exposure17 times the clinical AUC).
- The phototoxic potential for paritaprevir was not investigated, but is considered to be negligible.

Ombitasvir

The overall quality of the nonclinical dossier for the ombitasvir part of Viekira Pak and Viekira Pak-RBV was high. All relevant safety and toxicity studies were conducted according to GLP standards.

The sponsor included a number of studies on ombitasvir that were not evaluated and excluded from the overall assessment (Study Nos. R&D/14/0208, R&D/14/0093, R&D/14/0271, R&D/14/0085, R&D/14/0091, R&D/14/0086 and R&D/14/0087). As these studies mostly pertained to environmental toxicity assessments, these were not considered relevant to the current application.

Pharmacology - ombitasvir

Primary pharmacology - ombitasvir

All submitted pharmacodynamic studies were conducted under in vitro conditions, with no nonclinical proof-of-concept studies provided to show effects of ombitasvir in animal models of HCV infection.

Antiviral efficacy - ombitasvir

Efficacy studies showed that ombitasvir was a highly potent antiviral agent against six genotypes of NS5A. This was demonstrated using a HCV expression system consisting of Huh-7 cells transfected with the different genotype HCV replicons. Picomolar inhibition of viral replication was demonstrated for all tested genotypes (genotypes 1a-H77, 1b-Con1, 2a, 2a JFH-1, 2b, 3a, 4a; EC_{50} range: 0.2 to 4.5 pM), except for genotype 6a which was the least sensitive (EC_{50}: 366 pM). Inhibitory potency was also found to be partially abrogated

by the presence of 40% human plasma by approximately 12 fold, suggesting that in vitro measures of potency may over-represent the likely potency of ombitasvir in a clinical setting. Ombitasvir showed no evidence of being cytotoxic in a standard MTT assay[28], with a calculated therapeutic index (Ratio of TD_{50}[29]:EC_{50}) 2 million fold. Co-treatment of Huh-7 cells expressing genotype 1b-Con1 with interferon–α for a 3 week period showed synergistic reduction of HCV RNA. Negligible antiviral activity was noted by human major metabolites of ombitasvir, M23, M29, M36 and M37 against genotypes 1a-H77 and 1b-Con1. Metabolites M29 and M36 showed negligible activity against genotypes 2a, 2b, 3a, 4a, 5a and 6a.

Resistance and cross-resistance - ombitasvir

Resistance to ombitasvir was assessed in all HCV genotypes, although emphasis was placed on the dominant HCV genotypes 1a and 1b. Mutations of NS5A that conferred resistance to ombitasvir were identified under conditions of chronic and high exposure to ombitasvir (3 weeks and up to 1000 times the EC_{50}). Mutations at residues M28, Q30 and Y93 were found to be the most prevalent for genotype 1a and L28 and Y93 for genotype 1b.Extent of resistance was high for genotype 1a mutants of the Y93H, M28T, Y93C and Q30R variants, showing resistance 41000, 8900, 1700 and 810 fold the EC_{50} (2.7 pM in WT 1a-H77), while for genotype 1b mutants L28T and Y93H conferred resistance 430 and 50 fold the EC_{50} (1.2 pM in WT 1b-Con1). Of the emergent mutants, the M28T mutant of genotype 1a showed substantial resistance to ombitasvir but no impairment to viral replication efficiency. For genotype 1b mutant L31F conferred approximately 9 fold resistance to ombitasvir and a slight increase (approximately 30%) in replication efficiency. For the other HCV genotypes, mutations at residue 28 (Genotype 2a: F28S; genotype 2b: L28F; genotype 3a: M28T; genotype 4a: L28V; genotype 5a: L28I) and 93 (genotype 2b and genotype 3a: Y93H) were the most prevalent and brought about resistances ranging between approximately 20 and up to 6700 fold the EC_{50}. Substitutions at residues 30 and 93 are known to occur with other NS5a inhibitors. In particular, substitution of the Y93 residue is regarded as a class-defining resistance mutation because it is frequently observed with inhibitor substances.[30]

Cross resistance was assessed against known mutant variants of NS3 protease and NS5B polymerase and found no difference in ombitasvir sensitivity between these variants and wild type forms of 1a and 1b.

Secondary pharmacodynamics and safety pharmacology - ombitasvir

High throughput screening assays were performed with ombitasvir and three human major metabolites (M29, M36 and M23) against a standard battery of protein targets. Whilst the parent compound showed weak affinity for neurokinin2 (NK_2) receptors, all three metabolites have significant affinity for numerous secondary targets. M29 inhibited ligand binding of P2Y receptors[31] (approximately 50% inhibition of specific binding), M36 significantly inhibited the dopamine transporter (approximately 75.1% inhibition; IC_{50} 3.2 μM), while M23 competed for the ligand of gamma aminobutyric acid (GABA)-gated Cl-channels (97.4% inhibition; IC_{50} 1.5 μM) and showed significant binding for A3, BZD, BB, CB1, 5-HT5a, sigma, and Na^+ channel site 2. However, taking into consideration the high plasma protein binding exhibited by ombitasvir,

[28] The MTT assay is a colorimetric assay for assessing cell metabolic activity and can be used to measure toxicity by my measuring cell viability.
[29] TD_{50} is the median toxic dose (the dose at which toxicity occurs in 50% of cases)
[30] Belda O, Targett-Adams P. Small molecule inhibitors of the hepatitis C virus-encoded NS5A protein. *Virus Research*. 2012; 170: 1 –14.
[31] P2Y receptors belong to the superfamily of heptahelical receptors that operate by binding or sensing signals outside the cell and then activating intracellular processes by coupling to heterotrimeric G proteins. The main signaling molecules or agonists recognized by the eight subtypes of P2Y receptors include adenine and uridine nucleotides (ATP, ADP, UTP, and UDP) and nucleotide sugars (UDP-glucose).

M29 and M36 (> 98%), circulating levels of unbound M23, M29 and M36 (AUC = 0.194, 0.669, 0.442 µg.h/mL, respectively) are going to be at least 1000 fold lower than any of the off-target IC_{50} values. Therefore, off-target effects by ombitasvir and its major metabolites are not anticipated.

Specialised safety pharmacology studies covered the cardiovascular, respiratory, gastrointestinal and central nervous systems, with most conducted according to GLP principles. None of these studies revealed specific hazards or organ system toxicities. One of the in vitro hERG channel assay studies reported modest reduction of channel currents by ombitasvir (IC_{50} = 5.1 µM or 4.56 µg/mL); however, in vivo investigations in dogs did not show ombitasvir to be arrhythmogenic at a maximum plasma level of 2.6 ± 0.35 µg/mL that was achieved with 60 mg/kg, PO at 6 hours post-dose.

Pharmacokinetics - ombitasvir

Absorption - ombitasvir

Ombitasvir, as a large (MW: 894.1 g/mol) lipophilic molecule, was minimally soluble in aqueous solutions. Inclusion of three different surfactants to customised diluents improved solubility, and subsequently oral bioavailability, in the tested animal species. Generally, however, bioavailability was low in most tested species (rats, dogs, monkeys and rabbits). Plasma exposure was highest in mice (approximately 3 x higher AUCs than for rats), which was the rationale for using mice as the preferred species in repeat dose toxicity studies. Low clearance (< 0.5 L/h/kg) was noted in all tested species. Elimination half-lives (t½) were longer in rodents (approximately 10 hours) compared to other tested species (approximately 7 h compared with. clinical t½: 21 hours). Pre-treatment with ritonavir augmented ombitasvir plasma levels, but there was no evidence of direct interference when ritonavir was co-administered with ombitasvir. Gender differences were observed in mice with males having plasma levels approximately 2 times higher than females. For this reason mouse toxicity studies used doses twice as high for female animals. Accumulation was generally not evident in mice. In rats and dogs, however, there was a progressive increase in AUC values over time. Out of all the animal models used, pharmacokinetic parameters of mice aligned closest with the clinical absorption profile of ombitasvir.

Distribution - ombitasvir

Plasma protein binding by ombitasvir was very high across all tested species (> 99%). Binding of major human metabolites, A-1538855 (M29) and A-1548255 (M36), was also high when tested against human and mouse plasma (≥ 96%). Ombitasvir showed low partitioning into RBC from whole blood in all species (Blood to plasma ratio: < 0.5). Tissue distribution in rats was slow and did not permeate across the blood brain barrier or into the lens of the eye. Complete elimination from plasma occurred by 24 to 48 hours post dose, whilst for tissues radioactivity was below levels of quantification by 168 hours post-dose. Studies in pregnant rats found extensive distribution of radiolabelled ombitasvir into the amniotic sac and placenta; however, actual placental transfer was not apparent (Fetal: maternal plasma ratio < 0.1).

Metabolism - ombitasvir

Very low biotransformation of ^{3}H-ombitasvir was noted with liver microsomes sourced from rats, dogs, monkeys and humans (> 85% of parent compound remained at t = 30 mins). Characterisation of this activity identified CYP 3A4, 2C8 and 3A5 as potential contributors to the metabolism of ombitasvir. Efforts to identify major metabolites found M23, a dianiline

amine hydrolysis product of ombitasvir, to be the only metabolite common to all tested species. T-butyl oxidation and demethylation of M23 forms a variety of downstream metabolites, including the human-only plasma metabolites M29, M36 and M37, which were only seen under in vivo conditions.

Excretion - ombitasvir

For all tested species (mouse, rat, dog and humans) ombitasvir and its metabolites were excreted through the faeces, with biliary transport identified as the likely pathway for excretion.

Conclusion - ombitasvir

There were sufficient similarities in the absorption profiles, level of plasma protein binding, extent of biotransformation and elimination pathways of ombitasvir in mice relative to the human pharmacokinetic profile for ombitasvir, to allow these animal models to serve as the predominant testing species appropriate models for assessing toxicity. The sponsor addressed uncertainties on the two major metabolites unique to human plasma (M29 and M36) in a series of exploratory studies in mice that were considered appropriate.

Pharmacokinetic drug interactions - ombitasvir

Ombitasvir was not found to be a significant inducer of the liver enzymes CYP1A2, 2B6 and 3A4, nor was it found to have significant inhibitory activity against CYPs 1A2, 2B6, 2C9, 2C19, 2D6 and 3A4. Moderate inhibition of CYP 2C8 (IC_{50} approximately 7.4 μM) and UGT1A1 was noted (IC_{50} approximately 2.12 μM). In vitro investigations showed that ombitasvir was not a substrate or inhibitor of efflux (P-gp, BCRP, MRP2, MATE1, MATE2K) or uptake (OATP1B1, OATP1B3, OAT1, organic anion transporter3 OAT3, OCT1, OCT2) transporters. However, mice lacking P-gp and BCRP had several folds higher plasma levels of radiolabelled ombitasvir compared to wild-type mouse strains, suggesting that ombitasvir may be a substrate of one or both of these transporters. No further exploratory investigations were conducted to ascertain which of the two transporters were responsible. Overall, ombitasvir has minor drug interaction potential, with interaction possible with CYP2C8 and UGT1A1 and potential as a substrate of either P-gp and/or BCRP.

Toxicology - ombitasvir

Acute toxicity - ombitasvir

No single dose toxicity studies were conducted with ombitasvir. In view of the absence of acute toxicities noted in the repeat-dose toxicity and safety pharmacology studies, the lack of dedicated single dose toxicity studies is considered acceptable.

Repeat-dose toxicity - ombitasvir

The sponsor submitted a number of repeat dose toxicity studies that were conducted in mice, rats and dogs. All studies used the clinical route (oral) and all pivotal studies were GLP compliant. Study durations employed for the pivotal studies were appropriate for the proposed period of use of the clinical product (3 months) with the pivotal mouse study being of 6 months duration, the rat was 3 months and the dog was 6 months duration.

Design aspects of the studies were generally consistent with relevant guidelines on repeat dose toxicity testing.[32]

Relative exposure - ombitasvir

Relative exposure ratios are calculated based on clinical $AUC_{0\text{-}24h}$ values that were determined from a study in healthy volunteers (Study No. R&D/14/0050). Exposures attained in the pivotal toxicity studies were adequate multiples of clinical plasma levels.

Table 5: Relative exposure to ombitasvir in repeat-dose toxicity and carcinogenicity studies- ombitasvir

Species	Study duration	Sex	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (µg.h/mL)	Exposure ratio#
Mouse [Tg(Hras)] Study No. R&D/12/574	26 week [Carcinogenicity]	male	2.5	2.67	2
			10	10.7	7.5
			150	36.6	26
		female	5	2.98	2.1
			20	12.4	8.7
			150	37	26
Mouse [CD-1] Study No. R&D/11/561	6 month [Pivotal toxicity] Sampling day: 182	male	5	3.57	2.5
			20	10.5	7.4
			200	40.8	29
		female	10	3.38	2.4
			40	17.9	12.6
			200	32.1	23
Rat [SD] Study No. R&D/10/1472	3 month [Pivotal toxicity] Sampling day: 91	male/ female	10	10.7/9.2	7.5/6.5
			30	20.4/25.4	14.4/18
			300	22.4/35.3	16/25
Dog [Beagle] Study No. R&D/10/1371	6 month [Pivotal toxicity] Sampling day: 189	male/ female	4	8.5/6	6/4.2
			20	54/41.5	38/29
			100	90/77	63.4/58.2

[32] CPMP/SWP/1042/99 Rev 1 Corr* Guideline on repeated dose toxicity.

Species	Study duration	Sex	Dose (mg/kg/day)	$AUC_{0-24\ h}$ (µg.h/mL)	Exposure ratio#
Study R&D/14/0500 Human (healthy volunteers)	Steady state	–	25 mg/day	1.42	–

= animal:human plasma $AUC_{0-24\ h}$; Bolded = NOAEL

Also exposures attained in mouse toxicity studies on human metabolites M29 (A-1538855) and M36 (A-1548255) were adequate multiples of levels reported in human subjects (> 20 times clinical AUC levels). Relative exposure is summarised in Table 6.

Table 6: Relative exposure to ombitasvir metabolites M29 and M36 in mouse toxicity studies - ombitasvir

Study details	Dose (mg/kg/day)	$AUC_{0-24\ h}$ (µg.h/mL)	Exposure ratio#
Study No. R&D/13/760 4 week repeat dose toxicity [M29; Clinical AUC: 0.669 µg.h/mL]	1	3.49	5.2
	2	7.03	10.5
	3.5/3.0	15.8/18.1	24/27
Study No. R&D/13/701 4 week repeat dose toxicity [M36; Clinical AUC: 0.442 µg.h/mL]	1.5	3.07	7
	3	6.55	15
	6	16.8	38
Study No. R&D/13/548 Developmental toxicity study [M29; Clinical AUC: 0.669 µg.h/mL]	1	2.24	3.3
	2.5	7.76	11.6
	4.5	17.4	26
Study No. R&D/13/549 Developmental toxicity study [M36; Clinical AUC: 0.442 µg.h/mL]	1.5	1.68	3.8
	3	4.65	10.5
	6	11.6	26

= animal: human plasma $AUC_{0-24\ h}$; Bolded = NOAEL

Major toxicities - ombitasvir

No specific targeted toxicities were evident in any of the repeat dose toxicity studies. Clinical signs were minor or sporadic and generally non-dose dependent in nature.

In the mouse differences between the ombitasvir treated and vehicle treated groups could not be distinguished nor could distinct treatment and dose dependent effects be discerned. In one of the non-GLP studies (Study No. R&D/10/493) there were small but significant elevations to liver enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST) and glutamate dehydrogenase (GLDH) in males that received ombitasvir doses of 28.5 and 95.1 mg/kg/day for 2 weeks. Histopathological examinations also showed (minimal to mild) liver necrosis in these groups; however, there were no

corresponding changes in female mice. Since these effects were not seen in mouse studies at higher doses and longer duration, these are not considered toxicologically significant.

No specific toxicities were identified in the rat repeat dose studies. Treatment related changes in rats were minimal with sporadic findings that were not consistent for all treated groups. Similar to findings from a non-pivotal mouse study, there were apparent dose dependent elevations in AST (and to a lesser degree, ALT) levels in male (but not female) treated rats (Study No. R&D/09/1241). This was accompanied by observed hepatocytic necrosis in the high dose treated males.

High incidence of vacuolation of villi in duodena and jejuna of dogs in the 6 month pivotal study appeared to be related to ombitasvir treatment. No other associated effects were present (for example GIT disturbances or abnormal excreta) but the effect was seen in nearly all animals from both the male and female medium and high dose groups (20 and 100 mg/kg/day). A 3 month GLP study in dogs also reported histopathological changes to the jejunum (dilated lacteals) in high dose group males and females (100 mg/kg/day), which also coincided with treatment and dose dependent occurrence of mucoid faeces. The toxicological significance of these findings and their relevance to clinical use are uncertain. Effects seen at these doses (20 and 100 mg/kg/day) were representative of plasma exposures of at least 34 and 61 times the clinical AUC and thus were at levels not anticipated to be attained clinically, and not of toxicological concern. At the NOAEL for the pivotal dog study (4 mg/kg/day) the relative exposure was 4 to 6 times the clinical AUC.

Additional toxicity studies on the nonclinical safety of the human metabolites M29 and M36 found no evidence of adverse effects at up to 4 weeks exposure in mice. Overall, treatment related changes to ombitasvir were minor and sporadic in nature, were not consistently seen in both sexes or found to be dose dependent. Therefore ombitasvir is not anticipated to exert any targeted toxicities when used at the proposed clinical dose levels.

Genotoxicity - ombitasvir

Ombitasvir was not shown to be mutagenic in a bacterial reverse mutation assay or clastogenic in in vitro (using human lymphocytes) and in vivo clastogenicity assays (using mouse micronucleus assay). Studies were generally consistent with guideline recommendation as outlined in 3BS6a and all studies were GLP compliant.

Human (plasma) metabolites of ombitasvir, A-1538855 (M29) and A-1548255 (M36) were also negative for mutagenicity and clastogenicity in a bacterial reverse mutation assay (Study No. R&D/13/487) and in an in vitro chromosomal aberration assay (Study No. R&D/13/485), respectively. Concentrations tested in the chromosomal aberration assay were high enough to exceed those measured in plasma at clinical steady state following a single 25 mg oral dose of ombitasvir (Highest tested concentration of ombitasvir 400 µg/mL compared with. approximately C_{max} for M29 and M36 of < 100 ng/mL or at plasma concentration after 24 hours (C_{24h}) approximately 30 to 50 ng/mL).

The genotoxic potential of ombitasvir impurities was not determined;[33] however, bone marrow samples were collected from mice used in a 4 week repeat-dose toxicity study to assess clastogenicity at a later stage if required. The Nonclinical Summary stated that there were no structural alerts when the impurities were run through either DEREK or CaseUltra in silico software for predictions of likely genotoxicity; however no further detail was provided. Discussion on the adequacy of impurity qualification studies was presented.

[33] Genotoxicity studies are not required for impurities with no strucutural alerts and < 1 mg intake per ICH M7

Carcinogenicity - ombitasvir

Ombitasvir was not found to be carcinogenic in a 26 week study using transgenic mice (CByB6F1-Tg (HRAS)2Jic; Tg Hras). The study design (group sizes, use of toxicokinetic cohorts and duration of study) was appropriate and consistent with ICH guideline recommendations on carcinogenicity testing.[34], [35], [36] Dose selection was based on a one month repeat dose toxicity study in these mice (Study No. R&D/10/096), in which the highest tested dose (150 mg/kg/day) was well tolerated by animals and deemed the highest dose in the carcinogenicity study. The relative plasma exposure (based on AUC) at this dose was approximately 29 times the clinical AUC, which is acceptable. The sponsor also indicated that the in-life part of the 2 year rat carcinogenicity study was completed and that the finalised report will be available by April 2015.

Survival rates were similar across all dose groups and negative controls. Aside from a few spontaneous tumour and non-neoplastic observations, there were no specific neoplastic or other histopathological findings that could be clearly ascribed to the effects of treatment. The positive control group (N-nitroso-N-methylurea (NMU)) showed a higher incidence of tumours and a higher number of mortalities, confirming that the exposure period and experimental systems used were sufficient for assessing carcinogenicity. Overall, based on the findings from this study, as well as the negative genotoxicity findings, ombitasvir is not anticipated to pose a carcinogenic risk.

Reproductive toxicity - ombitasvir

Reproductive toxicity of ombitasvir was determined in mice and rabbits using standard GLP compliant studies that encompassed all stages of development (fertility, embryofetal development and peri-/postnatal development) and included almost all relevant exposure periods. Study designs were generally satisfactory with regard to group sizes, timing and duration of treatment, as per the relevant Note for Guidance on reproductive toxicity.[37] Mice instead of rats were used as the primary rodent species in these studies because higher systemic exposures to ombitasvir are attained with mice than rats (or monkeys).

Dosing in mice was sufficiently high with relative exposures (based on either AUC or body surface area (BSA)) up to 40 times higher than clinical levels. Relative exposures for rabbits however were low when expressed as a function of plasma levels (< 5 times clinical AUC).

Table 7: Relative exposure in reproductive toxicity studies based on plasma levels (AUC0-24h) - ombitasvir

Species	Study	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (µg.h/mL)	Relative Exposure#
Mouse (CD-1)	Embryofetal development (R&D/11/369)	15	13.6	10
		50	40	28
		150	38	27
Rabbit	Embryofetal	10	3.4	2.4

[34] ICH 3BS8a The need for carcinogenicity studies of pharmaceuticals
[35] CPMP/ICH/140/95 ICH S1A Need for carcinogenicity studies of pharmaceuticals.
[36] CPMP/ICH/299/95 ICH Topic S1B Not for guidance on carcinogenicity: testing for carcinogenicity of pharmaceuticals.
[37] CPMP/ICH/386/95. ICH Topic S5(R2) Detection of toxicity to reproduction for medicinal products and toxicity to male fertility

Species	Study	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (µg.h/mL)	Relative Exposure#
(NZW)	development (R&D/11/406)	60	6.3	4.4
Human(healthy volunteers)	steady state	25 mg	1.42	–

= animal: human plasma $AUC_{0-24\,h}$; ^Based on PK parameters derived from healthy volunteers (Study No. R&D/14/0050)

Table 8: Relative exposure in reproductive toxicity studies based on body surface area (BSA) comparisons when plasma data were not available - ombitasvir

Species	Study	Dose (mg/kg/day)	Dose (mg/m2/day)	Dose ratio#
Mouse (CD-1)	Fertility	10	30	1.8
		40	120	7.3
		200	600	36.4
	Peri-/postnatal development (R&D/)	10	30	1.8
		40	120	7.3
		200	600	36.4
Human(healthy volunteers)	steady state	25 mg/day	16.5	–

Dose ratio = animal dose (mg/m2/day): human dose (mg/m2/day); ^Based on PK parameters derived from healthy volunteers (Study No. R&D/14/0050);

Placental transfer was negligible in mice and rabbits (fetal-maternal plasma ratio < 0.1).

Excretion of ombitasvir in milk was demonstrated in rats (Milk: plasma ratio: 3.93), of which levels declined to below quantification limits by 48 hours post dose. Characterisation of the metabolites excreted in milk found that although unchanged ombitasvir was the predominant species present, low levels of metabolites M19, M23, M24 and M26 were also detected in milk.

No differences were observed in the mating and fertility parameters of ombitasvir and vehicle treated groups. Oestrus cycling was not affected, and although sperm quality and characteristics were not assessed, absence of adverse outcomes on mating indices and pregnancy rates suggest no effect on male reproductive function. Overall, ombitasvir did not affect male or female fertility in mice, with the NOAEL established at ≥ 200 mg/kg/day, PO (approximately 36 times the clinical AUC).

In embryofetal development studies ombitasvir had no adverse effects on mouse and rabbit litter parameters. Maternal clinical signs were generally minor (for example soft faeces in rabbits) or sporadic in nature and thus considered unrelated to treatment. In the mouse, sporadic external abnormalities were not dose dependent and occurred at lower than historical control rates. In rabbits there were a number of malformations noted at 60 mg/kg/day (at a relative exposure ratio 4.4 times the clinical AUC) including microphthalmia, micrognathia and cleft palate. While incidences of these abnormalities were higher than historical control rates and suggested a treatment-dependent cause, corresponding fetal plasma levels of ombitasvir

were negligible (fetal: maternal plasma ratio approximately 0.01, based on mean plasma concentrations) and therefore embryofetal harm at these exposure levels would be expected to be remote. Furthermore, a preliminary dose range finding embryofetal development study did not observe developmental abnormalities in a higher dose group (200 mg/kg/day).

A peri-/postnatal development study in mice found no evidence of impairments to functional development or developmental milestones (that is behaviour, motor activity, sexual maturity and subsequent fertility) in pups. One male and one female pup each from the high dose treated group were found dead several days after maternal treatment had ceased (postnatal day 23 and 26, respectively with maternal treatment ceased on postnatal day 20). As no other clinical signs were noted these deaths are not considered related to ombitasvir treatment. Whilst ombitasvir excretion in milk was not determined in mice, in this study ombitasvir was still detected in the plasma of pups the day after treatment of dams was ceased, suggesting significant levels of ombitasvir are passed through milk. As F1 generation pups went on to successfully mate with no detrimental effect on litter parameters, the NOAEL for postnatal developmental effects in mice was established at ≥ 200 mg/kg/day, PO (approximately 36 times the clinical AUC).

Pregnancy classification – ombitasvir

The sponsor has proposed Pregnancy Category B1[22] for Viekira Pak and Category X[24] for Viekira Pak-RBV based on its inclusion of ribavirin, which itself has a Pregnancy Category of X. As there were no adverse embryofetal development findings noted in mice or rabbit treated with ombitasvir, a Pregnancy Category B1 category for ombitasvir is considered acceptable. On whether a Pregnancy Category B1 is acceptable for the Viekira Pak combination will depend on whether findings from embryofetal development studies with paritaprevir, ritonavir and/or dasabuvir are also consistent with Pregnancy Category B1.

Local tolerance

The sponsor did not conduct dedicated local tolerance studies on ombitasvir. Histopathological changes in duodenal and jejunal tissue (dilated lacteals and vacuolation of villi) noted in the pivotal 6 month dog study were of uncertain toxicological significance since they were not accompanied by other associated treatment related changes and occurred at exposure levels at least 34 times the clinical AUC. Overall, ombitasvir was found to be well tolerated when administered by the clinical route of administration.

Impurities - ombitasvir

The proposed specifications for drug substance and drug product ombitasvir impurities that were above ICH qualification thresholds have been adequately qualified.

Paediatric use - ombitasvir

The sponsor did not propose a paediatric indication for Viekira Pak/Viekira Pak-RBV nor did they provide nonclinical juvenile toxicity studies.

Nonclinical summary and conclusions - ombitasvir

- AbbVie Pty. Ltd. has applied to register Viekira Pak and Viekira Pak-RBV, which contain a fixed-dose combination tablet of paritaprevir, ritonavir and ombitasvir, and a separate tablet containing dasabuvir. The latter product, Pak-RBV also includes ribavirin tablets. This evaluation report concerns nonclinical data submitted to support the inclusion of the HCV NS5A inhibitor, ombitasvir. The quality of nonclinical data was found to be generally high and all relevant pivotal safety studies were conducted according to GLP.

- Ombitasvir displayed picomolar potency against replicons expressing NS5A from HCV genotypes 1a, 1b, 2a, 2b, 3a, 4a, 5a and 6a (EC_{50} range for inhibition of viral replication: 1 to 366 pM). Human metabolites, M29 and M36, inhibited viral replication of HCV genotypes with substantially lower potency than parent ombitasvir (EC_{50} values ≥ 279,000 fold higher than ombitasvir).
- Characterisation of resistant variants identified high prevalence of mutations at sites Q30R, Y93H/Y93C and M28T/M28V for genotype 1a and sites Y93H and L28T for genotype 1b. These mutations conferred resistance to ombitasvir that was 810 fold (Q30R), 41,000 fold (Y93H), and 8,900 fold resistant (M28T) to ombitasvir for genotype 1a, and 430 fold (L28T) and 50 fold resistant (Y93H) for genotype 1b. In most cases these mutations also impaired replication efficiencies, with the exception of the M28T mutant in which efficiencies were not affected. Resistant variants of genotypes 2a, 2b, 3a, 4a, 5a and 6a were also reported at similar residue sites of substitution but the extent of resistance was lower than that seen for genotype 1a.
- While ombitasvir did not have any significant off-target effects, three of its major human metabolites had affinity for unrelated targets. M29 inhibited P2Y receptor binding (approximately 50% of specific binding), M36 inhibited the dopamine transporter (IC_{50} 3.2 μM), while M23 inhibited GABA gated chloride channels (IC_{50} 1.5 μM). Safety pharmacology studies did not reveal any significant or clinically relevant effects on the CNS, cardiovascular, gastrointestinal or respiratory systems.
- Ombitasvir demonstrated low bioavailability (< 50%), slow absorption (T_{max} > 3 hours for most species) and low clearance. High plasma protein binding was noted for both ombitasvir (> 99%) and its major human metabolites (> 95%) in all tested species. Ombitasvir did not cross the blood brain barrier or bind to pigmented tissue. Biotransformation, likely carried out by CYPs 3A4, 2C8 and 3A5, was low (> 90% of parent remained after a 4 hour incubation with hepatocytes). Excretion was chiefly through the faecal route, with biliary excretion likely involved. Drug interaction potential is likely to be low, although possible interactions were highlighted with CYP2C8 and UGT1A1.
- Repeat dose toxicity studies were conducted in mice (up to 6 months), rats (up to 3 months) and dogs (up to 6 months) using the clinical (oral) route. In the rodent studies, changes were sporadic and were not found to be related to ombitasvir treatment. In dogs, a high incidence of histological changes to duodena and jejuna (vacuolation of villi and dilated lacteals) was deemed treatment related but occurred at plasma levels that were 34 and 60 times the clinical AUC and are therefore unlikely to be of significant toxicological concern.
- Ombitasvir and its major human plasma metabolites, M29 and M36, were not found to be mutagenic or clastogenic in a standard battery of in vitro and in vivo genotoxicity assays. Ombitasvir was not found to be carcinogenic in a 26 week transgenic mouse study. A 2 year rat carcinogenicity study is currently ongoing; the study report should be submitted when available.
- Although placental transfer was found to be negligible in mice and rabbits, milk transfer of ombitasvir and its metabolites was demonstrated in rats and implied in mice. Ombitasvir did not affect the fertilities of either male or female treated mice. Fetal malformations seen in rabbits at doses that were 4.4 times the clinical AUC were regarded as unlikely to be toxicologically related since fetal plasma levels of ombitasvir were negligible and exposure was low (fetal: maternal plasma ratio approximately 0.01). There was no evidence of treatment related effects on developmental milestones and fertilities of rat pups exposed to ombitasvir during the peri/postnatal period.

- Overall, there were no major deficiencies identified in the nonclinical dossier of Viekira Pak that related to ombitasvir.

Dasabuvir

The overall quality of the submitted dossier for the dasabuvir component of Viekira Pak and Viekira Pak-RBV was high. All pivotal safety studies were conducted under GLP conditions.

Pharmacology - dasabuvir

Primary pharmacology – dasabuvir

Dasabuvir was developed as a non-nucleoside inhibitor of the NS5B RNA-dependent RNA polymerase of HCV. Inhibition of NS5B is intended to impair HCV replication. The efficacy studies submitted assessed the inhibitory activity of dasabuvir in in vitro enzyme assays and standard subgenomic HCV replicon assays. No proof of the concept studies was conducted in animal models of HCV. This is not considered a major deficiency.[38]

In vitro, dasabuvir inhibited the activity of NS5B polymerase from HCV strains of genotypes 1a and 1b with nanomolar potency (IC_{50} 4.2 nM [range 2.2 to 10.7 nM; n = 7]; approximately equivalent to the clinical free C_{min} of 5.5 nM).[39] Dasabuvir had lower potency (> 200 times) at polymerases from other HCV genotypes (2a, 2b, 3a and 4a). Dasabuvir is unlikely to be active against these genotypes at the proposed clinical dose. The EC_{50} of dasabuvir against standard laboratory genotype 1a and 1b strains (H77 and Con1, respectively) in subgenomic HCV replicon assays was 7.7 nM and 1.8 nM, respectively. The potency of dasabuvir in subgenomic HCV replicon assays was reduced by approximately 12 fold in the presence of 40% human plasma. Dasabuvir had similar efficacy against a panel of genotype 1a and 1b isolates in the HCV subgenomic replicon assay; EC_{50} 0.77 nM (range 0.4 to 2.1 nM; n = 11) and 0.46 nM (range 0.2 to 2.0 nM; n = 10), respectively.

The M1 metabolite of dasabuvir had 30 to 40% lower potency than dasabuvir against standard genotype 1a and 1b laboratory strains in the subgenomic HCV replicon assay. Given the C_{max} for M1 (1.3 µM) in human subjects is higher than the EC_{50} against these genotypes in the replicon assay (143 nM and 26 nM against genotype 1a-H77 and genotype 1b-Con1, respectively, in the presence of human plasma), this metabolite is likely to contribute to the antiviral activity of dasabuvir.

Resistance and cross-resistance – dasabuvir

Mutations in NS5B that conferred some resistance to dasabuvir were identified from in vitro studies (treatment emergent mutations in HCV replicon assays) and early clinical studies, as well as from literature reports of mutations conferring resistance to other NS5B polymerase inhibitors. Mutations at C316, S368, A395, N411, M414, E446 (genotype 1a only), Y448, A553, G554, S556 or D559 (or combinations of these) conferred resistance to dasabuvir (EC_{50} > 5.5 nM) (Table 9).

Mutations C326Y and M414T have been reported to confer resistance to the nonnucleoside inhibitor, JTK-853[40] (not yet registered), that binds with the palm site and

[38] FDA Draft Guidance for Industry: Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment

[39] Based on a C_{trough} of 269 µM and assuming a free fraction of 1%.

[40] Ando, I. et al. Preclinical characterization of JTK-853, a novel nonnucleoside inhibitor of the hepatitis C virus RNA-dependent RNA polymerase. *Antimicrob Agents Chemother*2012; 56: 4250–4256.

β-hairpin region of the HCV polymerase. Therefore, treatment emergent dasabuvir resistant strains may also be resistant to JTK-853, and vice versa.

Table 9: Mutations in NS5B that conferred resistance to dasabuvir in HCV replicon assays

Mutation	Fold loss of activity	Mutation	Fold loss of activity
C316Y	190 to 1472 (1a), 1200 to 1569 (1b)	E446Q	17 (1a)
C316H	229 (1b)	Y448C	400 to 940 (1a), 200 to 414 (1b)
A395G	10 (1a)	Y448H	250 to 975 (1a), 11 to 100 (1b)
S368T	65 to 139 (1b)	A553T	152 (1a), 120 (1b)
N411S	12 to 84 (1b)	A553V	24 to 120 (1b)
M414I	8 (1a), 17 (1b)	G554S	198 (1a)
M414T	32 to 61 (1a), 26 to 270 (1b)	S556G	27 to 84 (1a), 12 to 32 (1b)
M414V	5 (1a), 18 (1b)	S556R	261 (1a), 3 (1b)
N444K	23 (1a)	D559G	110 (1b)
E446K	54 (1a)	Y561H	21 (1a)

Mutations at M423 (to M423V/T/I) in the polymerase thumb domain have been reported to confer resistance to the nonnucleoside polymerase inhibitors, NNI-1,[41] filibuvir,[42] lomibuvir[43] and VX-222[44] and the mutation P459L has been reported to confer resistance to the nonnucleoside inhibitor, TMC647055.[45] The M423T and P495L mutations had no effect on dasabuvir potency; suggesting dasabuvir may be effective in patients carrying HCV genotypes 1a and 1b that are resistant to NNI-1, filibuvir, lomibuvir and VX-222 by virtue of a M423T mutation and TMC647055 by virtue of a P495L mutation. Unfortunately, the efficacy of dasabuvir against other mutations conferring resistance to these inhibitors (L419M, R422K, M426A, I482L/N/T, A486S/T/V, L392I and V494A) was not assessed. Therefore, it is unknown if dasabuvir will be effective against genotype 1a and 1b HCV strains that are resistant to these other nonnucleoside inhibitors. Future studies with dasabuvir should assess efficacy against these mutant variants.

[41] Le Pogam, S. Selection and characterization of replicon variants dually resistant to thumb- and palm-binding nonnucleoside polymerase inhibitors of the hepatitis C virus. *J Virol.* 2006; 80: 6146–6154.
[42] Troke, PJF. et al. Characterization of resistance to the nonnucleoside NS5B inhibitor filibuvir in hepatitis C virus-infected patients. *Antimicrob Agents Chemother.* 2012; 56: 1331–1341.
[43] Fenaux, M. et al. Preclinical characterization of GS-9669, a thumb site II inhibitor of the hepatitis C virus NS5B polymerase. *Antimicrob Agents Chemother.* 2013; 57: 804–810.
[44] Jiang, M. et al. Genotypic and Phenotypic Analysis of HCV Variants Observed in Clinical Studies of VX-222, a Nonnucleoside NS5B Polymerase Inhibitor. *Antimicrob Agents Chemother.* pii: 2014; AAC.03052-14.
[45] Devogelaere, B. et al. TMC647055, a potent nonnucleoside hepatitis C virus NS5B polymerase inhibitor with cross-genotypic coverage. *Antimicrob Agents Chemother*. 2012; 56: 4676–4684.

The S282T mutation which has been reported to confer resistance to the NS5B polymerase nucleoside inhibitor, sofosbuvir,[46] did not confer resistance to dasabuvir. The S96T mutation, which has also been reported to confer resistance to nucleoside NS5B polymerase inhibitors [45] did not confer resistance to dasabuvir, suggesting dasabuvir may still be active in genotype 1a and 1b variants that are resistant to nucleoside inhibitors.

Combination studies - dasabuvir

Dasabuvir showed additive to synergistic antiviral activity when tested in combination with ombitasvir at most concentrations, with only slight antagonism evident at the lowest concentrations tested. Dasabuvir and ribavirin in combination showed additive to synergistic activity.

Secondary pharmacodynamics

Dasabuvir had no significant inhibitory activity against a number of human and mammalian DNA-dependent DNA polymerases and DNA-dependent RNA polymerases, and an RNA-dependent DNA polymerase (IC_{50} values ≥ 76 μM; > 3,600 times the clinical free C_{max}). Therefore, dasabuvir is not expected to interfere with DNA replication or transcription in host cells. In in vitro assays, dasabuvir had no antiviral activity against HIV-1 or HBV strains at concentrations significantly greater than would be expected clinically. Therefore, dasabuvir is not expected to have an effect on HIV-1 or HBV infection.

In a screen of 80 mammalian receptors, ion channels and transporters, neither dasabuvir nor M1 had any clinically-relevant inhibitory activity. No off-target activities are predicted during clinical use.

Safety pharmacology – dasabuvir

Specialised safety pharmacology studies covered the CNS, cardiovascular, respiratory and gastrointestinal systems. No significant effects on CNS, respiratory or gastrointestinal function was seen in rats with ≤ 30 mg/kg PO dasabuvir (exposure ratio based on C_{max} [ERC_{max}] 5) in the safety pharmacology studies. In the repeat dose toxicity studies in which higher doses were used, there were no clinical signs of adverse CNS, respiratory or gastrointestinal effects in mice (at ≤ 5000 mg/kg PO), rats (at ≤ 400 mg/kg PO) or dogs (at ≤ 60 mg/kg PO). Exposures at these doses were 26 to 39 times the clinical C_{max} for dasabuvir, while the estimated exposures to M1 were 61 times the clinical C_{max} in mice, approximately equivalent to the C_{max} in rats and subclinical in dogs.[47]

In vitro, dasabuvir inhibited hERG K+ tail current (IC_{50} 0.3 μg/mL; 29 times the clinical free C_{max}) but there was no effect on action potential duration in isolated dog Purkinje fibres (at ≤ 14.9 μg/mL; 1450 times the clinical free C_{max}), and QT prolongation was not observed in dogs given IV or high oral doses of dasabuvir (ERC_{max} ≤ 26).[48] Dasabuvir (at ≤ 15 mg/kg PO) did not induce emesis in ferrets (ERC_{max} approximately 1). Overall, dasabuvir is not expected to have any adverse effects on CNS, respiratory, gastrointestinal or cardiovascular function during clinical use. Unfortunately, the M1 metabolite is a very minor metabolite in dogs, and estimated exposures to this metabolite would have been subclinical at the highest tested dose in dogs. Furthermore, the potential for this metabolite to prolong the QT interval was not assessed in in vitro assays. Therefore, no comment can be made from the Module 4 data as to the potential for M1 to affect electrocardiogram (ECG) parameters in patients.

[46] SOVALDI Product Information document.
[47] Assuming exposures to M1 were approximately equivalent to the dasabuvir exposure in mice (based on metabolism studies), 3% and 0.05% dasabuvir exposures in rats and dogs, respectively.
[48] Based on data from the pivotal repeat-dose toxicity study which achieved higher exposures than the safety pharmacology studies.

Pharmacokinetics - dasabuvir

An in vitro study indicated dasabuvir had the potential for high oral absorption. In a regional absorption study in dogs, the greatest absorption was observed from the jejunum. The oral bioavailability of dasabuvir free acid was high in dogs (95.9%) and much lower in rats and monkeys (20 to 25% and 4.5%, respectively). The rate of absorption was similar in animal species (mice, rats, rabbits, dogs and monkeys) and human subjects (T_{max} 1 to 4 h), though C_{max} tended to occur later at higher doses in dogs (T_{max} 7 to 15 h). Following IV dosing, the elimination half-life was similar in rats and monkeys (t½ 2 to 4 h) and longer in dogs (approximately 20 h). The apparent half-life in human subjects was similar to that seen in rats and monkeys (5.9 h). There were no sex differences in pharmacokinetic parameters in mice, dogs and monkeys, while female rats had higher exposures (AUC) than their male counterparts at equivalent doses. The reason for this is unknown. Exposures to dasabuvir were lower with repeat once daily dosing to mice and rats. This was not seen with twice daily dosing to rats or once daily dosing to dogs and monkeys. There was no evidence of accumulation in animal species or human subjects.

M1 was a major metabolite in mice, rabbits and human subjects with exposures (AUC) 46 to 100% those of the parent, but was only a minor metabolite in rats and monkeys (exposures 1.5 to 3% those of the parent). Only trace levels were seen in dogs (exposures approximately 0.05% those of the parent). As a result, exposures to M1 were subclinical in the toxicity studies with dogs.

Plasma protein binding by dasabuvir and M1 was high (0.1 to 1.1% free fraction) and independent of concentration in all species (mice, rats, dogs, monkeys and humans). There were no meaningful differences in protein binding in the plasma from human subjects with varying degrees of hepatic or renal impairment. Dasabuvir preferentially distributed into the plasma compartment in rat, dog, monkey and human blood (blood to plasma ratio 0.6 to 0.7). The volume of distribution was greater than total body water in rats, dogs, monkeys and human subjects, suggesting extensive extravascular distribution. Consistent with this, tissue distribution in rats after oral administration of radiolabelled dasabuvir was rapid and wide. Highest concentrations were seen in organs involved in absorption and excretion (including the liver), as well as the Harderian gland and adrenal gland. There was minimal penetration of the blood brain barrier (brain levels were approximately 10% of plasma levels). Liver concentrations of dasabuvir were higher than plasma levels (liver: plasma ratios 36, 6.5 and 231 in rats, dogs and monkeys).

Metabolites of dasabuvir were formed by hydroxylation (to M1), followed by sulfation, glucuronidation, oxidation, oxidation and glucuronidation, or demethylation. Unchanged drug was the predominant circulating drug related species in rats, dogs and humans, while both unchanged drug and M1 were significant circulating species in mice. No circulating metabolites were detectable in dogs. Aside from M11 and an unidentified metabolite (U1), all circulating human metabolites were also seen in the plasma of at least one animal species. In vitro studies indicated a major role for CYP2C8, a lesser role of CYP3A4 and a minor role for CYP2D6 in the formation of M1 from dasabuvir.

Following oral dosing, excretion of dasabuvir and/or its metabolites was predominantly via the faeces in mice, rats, dogs and human subjects. Following IV dosing, biliary excretion was significant in rats.

While the M1 metabolite is only a very minor metabolite in dogs, this metabolite is formed in other animal species used in the toxicity studies. The two human specific (circulating) metabolites are only minor drug related species in human subjects and their absence in animal species is not expected to impact the validity of the toxicity studies. Overall, the pharmacokinetic profile of dasabuvir in rats and dogs is considered adequately comparable for these animal species to serve as models for toxicity.

Pharmacokinetic drug interactions - dasabuvir

Effect of other drugs on dasabuvir

As dasabuvir is metabolised by CYP2C8 and 3A4 and is a substrate for P-gp and BCRP, inhibitors/inducers of these CYP enzymes and transporters may alter the exposure of dasabuvir. While dasabuvir is not a substrate for OATP1B1 or OATP1B3, the M1 metabolite is (KM 1.30 μM and 1.71 μM, respectively). The M1 metabolite was also a substrate for BCRP in vitro.

The clinical overview states that co-administration of dasabuvir with ketoconazole (a CYP3A/P-gp inhibitor) resulted in an increase (by 42%) in dasabuvir exposure (AUC) and the AUC of dasabuvir decreased by 70% with co-administration of the CYP3A inducer, carbamazepine in human subjects. The AUC of dasabuvir was decreased by 30% when this drug was co-administered with the P-gp/BCRP/OATP1B1/OATP1B3 inhibitor, but was unaffected when dasabuvir was co-administered with the OATP1B1 inhibitor, atazanavir. Co-administration of dasabuvir with the CYP2C8 inhibitor, gemfibrozil, resulted in a 1,025% increase in dasabuvir exposures in patients. Overall, the in vivo data confirm the predictions from in vitro data.

Effect of dasabuvir on other drugs

Dasabuvir was an inhibitor of P-gp, BCRP and MRP2. As the IC_{50} values were < 0.1 times the intestinal concentration (16.7, 15.6 and 52 μM, respectively), dasabuvir has the potential to affect the oral absorption of co-administered drugs that are substrates for these transporters.[11] However, co-administration of dasabuvir with the P-gp substrate, digoxin, had no effect on the exposure of human subjects to the latter compound. Both dasabuvir and M1 were inhibitors of OATP1B1 and OATP1B3 (IC_{50} values 0.9 and 6.6 μM for dasabuvir against OATP1B1 and OATP1B3, respectively, and 2.6 and 9.7 μM for M1 against OATP1B1 and OATP1B3, respectively). As the IC_{50} values for dasabuvir against these transporters are < 25 fold the unbound hepatic inlet concentration,[49] dasabuvir has the potential to alter the disposition of co-administered drugs that are substrates for these hepatic transporters. The AUCs of pravastatin (an OATP1B1 substrate) and rosuvastatin (an OATP1B1/B3 and BCRP substrate) were increased (by 82% and 159%, respectively) when these compounds were co-administered with dasabuvir (in combination with ombitasvir, paritaprevir and ritonavir) in human subjects. While dasabuvir is likely to contribute to this effect, it is also possible that one or more of the other drugs (for example ritonavir or paritaprevir) also contribute to the increase in exposure to pravastatin and rosuvastatin.

Dasabuvir was an inhibitor of UGT1A1 (IC_{50} 0.92 μM). As the IC_{50} value is < 50 times the unbound clinical C_{max} dasabuvir has the potential to alter the disposition of co-administered drugs that are substrates for this enzyme. In a clinical drug-drug interaction study, an increase in raltegravir (an UGT1A1 substrate) exposure (AUC increased by 134%) was observed when this drug was co-administered with dasabuvir (with ombitasvir, paritaprevir and ritonavir. Dasabuvir (and possibly ombitasvir) is likely to contribute to this effect. Thus, the in vivo data confirm the in vitro predictions.

Dasabuvir had no clinically relevant inhibition on CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4 activity and no clinically relevant effect on bile salt export pump (BSEP), OAT1, OCT1, OCT2, OAT3, MATE1 and MATE2K transporter activity. Likewise, no clinically relevant inhibition of CYP1A2, 2B6, 2D6, 3A4, 2A6, 2C8, 2C9 and 2C19 and UGT1A1 enzyme activity and BSEP, OCT1, OCT2, OAT1, OAT3, MATE1 and MATE2K transporter activity was observed with M1. Neither dasabuvir (at ≤ 10 μM; approximately 450 times the clinical free C_{max}) nor M1 (at ≤ 50 μM; 3,800 times the clinical free C_{max}) induced CYP1A2, 2B6 or

[49] Assuming an absorption rate constant (ka) of 0.1 min-1 and a fraction absorbed from the gut to the portal vein (Fa) of 1 according to the EMA guideline above.

3A4 activity. While both dasabuvir and M1 were weak time dependent inhibitors of CYP3A4, this is not expected to be clinically relevant.

Toxicology - dasabuvir

Acute toxicity - dasabuvir

No single dose toxicity studies were conducted with dasabuvir. This is considered acceptable as there is sufficient information from the safety pharmacology and repeat-dose toxicity studies to assess the acute toxicity of dasabuvir.[50]

Repeat-dose toxicity

Pivotal repeat dose toxicity studies were of up to 3 months duration in mice, 6 months duration in rats and 9 months duration in dogs, and were conducted under GLP conditions. The duration of the pivotal studies, the species used group sizes and the use of both sexes was consistent with ICH guidelines.[13] While the clinical route (PO) was used in all studies, the clinical dosing regimen (twice daily) was only used in the pivotal rat study and shorter term mouse and rat studies. This is not expected to affect the validity of the toxicity studies, given the high exposures achieved and the significantly longer plasma half-life of dasabuvir in dogs than in rodents and human subjects (see pharmacokinetics). Animals were exposed for the full 24 hours. Doses used are considered generally acceptable, achieving high relative exposures to dasabuvir (Table 10). Doses in mice, however, were a little excessive, exceeding the limit dose as recommended in ICH M3(R2).[13] Estimated exposures to M1 were up to approximately 30 times the clinical exposure in mice, but were generally subclinical in rats and dogs[47] (based on a clinical AUC of 7.78 µg·h/mL for M1).

Table 10: Relative exposure in repeat-dose toxicity and carcinogenicity studies - dasabuvir

Species	Study duration	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (µg·h/mL)	Exposure ratio#
Mouse (CD-1)	13 weeks (R&D/09/1187)	600	63.0	5
		2000	156	11
		5000	205	15
Mouse (TgHRAS)	26 weeks (R&D/12/262) [carcinogenicity]	200	51.2	4
		600	119	9
		2000	265	19
Rat (SD)	6 months (R&D/08/1422)	25 (BD)	31.5/74.3 (male/female)	2/5

[50] EMA/CHMP/SWP/81714/2010: Questions and answers on the withdrawal of the 'Note for guidance on single dose toxicity'

Species	Study duration	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (µg·h/mL)	Exposure ratio#
		100 (BD)	51.8/170 (male/female)	4/12
		400 (BD)	119/319 (male/female)	9/23
Dog (Beagle)	9 months (R&D/09/310)	10	169	12
		30	520	38
		60	839	61
Human (healthy volunteers)	steady state	[250 mg BD]	13.7	–

= animal: human plasma $AUC_{0-24\,h}$; animal data were obtained from the final day of dosing; average of male and female data for mice and dogs

Major toxicities - dasabuvir

No consistent target organs for toxicity were identified. The lungs were a target organ for toxicity in rats. An increased incidence and severity of alveolar histiocytosis was observed in rats treated with ≥ 25 mg/kg BD PO dasabuvir (exposure ratio based on AUC [ERAUC] 2 to 5). A NOEL was not established and pulmonary histiocytosis had not completely reversed after a 1 month treatment free period, though the severity had lessened over this period. This lesion is consistent with phospholipidosis. Phospholipidosis is a common finding for cationic amphiphilic drugs, which have been approved for a wide range of clinical indications. It is uncertain if phospholipidosis in animals is predictive for humans and it is also uncertain if it is merely an adaptive response or has toxicological implications.[51, 52, 53] As there was no evidence of phospholipidosis in mice and dogs at much higher exposures, rats may be more sensitive to this effect, and the pulmonary changes are likely to have minimal clinical relevance. Phospholipidosis was also observed in rats treated with ritonavir. This should be considered when assessing the toxicity of the combination of drugs in Viekira Pak.

The NOAEL in mice and dogs was 5,000 mg/kg/day and 30 mg/kg/day, respectively, resulting in respective exposures 15 and 38 times the clinical AUC. At higher exposures in mice, inflammation and irritation was evident in the gastrointestinal tract. This was associated with the oral administration of a large amount of material, resulting in a local irritant effect. These findings are not considered clinically relevant.

At higher exposures in dogs, changes were evident in the adrenal gland (cortical hypertrophy/hyperplasia), liver (hepatocellular vacuolation) and lymphoid tissues

[51] Alakoskela, J.-M. et al. Screening for the drug-phospholipid interaction: correlation to phospholipidosis. *ChemMedChem* 2009; 4: 1224–1251.
[52] Reasor, M.J., et al. Drug-induced phospholipidosis: issues and future directions. *Expert. Opin. Drug Saf.* 2006; 5: 567–583.
[53] Reasor, M.J. and S. Kacew. Drug-induced phospholipidosis: are there functional consequences? *Exp. Biol. Med.* 2001; 226: 825–830.

(lymphoid depletion). Given the high exposures at which these occurred, they are not considered clinically relevant.

Genotoxicity - dasabuvir

The potential genotoxicity of dasabuvir was investigated in the standard battery of tests, conducted in accordance with ICH guidelines.[14] All assays were appropriately validated and conducted under GLP conditions. Dasabuvir was not mutagenic in bacterial mutation assays or clastogenic in vitro (in human lymphocytes) or in vivo (in the rat micronucleus test). The potential genotoxicity of M1 is likely to have been adequately assessed in the in vitro assays (based on the levels of M1 formed in in vitro incubations with rat microsomes). Estimated exposures to M1 in the rat micronucleus study are subclinical and therefore the clastogenic potential of M1 has not been adequately assessed. This is not considered to be a major deficiency. Given the absence of mutagenic and clastogenic activity in in vitro assays and the absence of drug related tumours in the mouse carcinogenicity study at relatively high exposures, the weight of evidence indicates both dasabuvir and M1 are not genotoxic.

Carcinogenicity - dasabuvir

The carcinogenic potential of dasabuvir by the oral route was assessed in transgenic Tg.rasH2 mice following daily dosing for 26 weeks. Given the intended patient group and intended duration of dosing (12 weeks) in combination with the negative findings in genotoxicity studies, carcinogenicity studies in a single species is considered acceptable.[54] The sponsor indicated a 2 year rat carcinogenicity study is currently in progress. This should be submitted to the TGA in a subsequent submission as soon as it is available. The choice of transgenic model is considered acceptable. The group sizes used (25/sex) and duration of dosing (26 weeks) was appropriate for the species.[17, 18] A concurrent positive control group (N-nitroso-N-methylurea-treated) was included and tumours expected from administration of a mutagen were observed, confirming the validity of the study. There were no dasabuvir-related neoplastic findings in any of the treated groups (≤ 2,000 mg/kg/day PO; greater than the limit dose). The relative exposure at the highest tested dose was acceptable (ERAUC 19 for dasabuvir and estimated ERAUC 34 for M1). Therefore, based on this study, dasabuvir is not expected to pose a carcinogenic risk during clinical use. This should be confirmed with the 2 year rat carcinogenicity currently in progress.

Reproductive toxicity - dasabuvir

A standard set of GLP compliant reproductive toxicity studies was submitted and examined fertility (in rats), embryofetal toxicity (rats and rabbits) and pre/postnatal development (rats). Adequate animal numbers were used during appropriate gestational periods. Maximum doses in rats were acceptable, achieving several multiples of the clinical dasabuvir exposure (Table 11). While exposure ratios in rabbits were generally low (maximum ERAUC 6), absorption was apparently saturated at the highest tested dose in the pivotal embryofetal development toxicity study, and therefore maximum exposures were achieved. Estimated exposure to M1 was approximately equivalent to the clinical AUC in rats and 5 times the clinical AUC in rabbits[55] at the highest tested doses. The clinical route (PO) was used in all studies with the clinical dosing regimen (twice daily) used in the rat studies.

Fertility was unaffected in rats when treated males were paired with treated females (≤ 400 mg/kg BD; ERAUC 12 in males and 18 in females). No adverse effects on fertility are

[54] ICH S1A: Guideline on the need for carcinogenicity studies of pharmaceuticals.
[55] Assuming M1 exposures were 46% of the parent.

predicted in patients. Placental transfer of dasabuvir and/or its metabolites was observed in rats and rabbits with fetal levels of dasabuvir 11 to 19% and 28 to 54% those of maternal levels in rats and rabbits, respectively. No adverse embryofetal effects were observed in either rats or rabbits at the highest tested doses; 400 mg/kg BD PO (ERAUC 24) in rats and 400 mg/kg/day PO (ERAUC 6) in rabbits.

Table 11: Relative exposure in reproductive toxicity studies - dasabuvir

Species	Study	Dose (mg/kg/day)	$AUC_{0-24\ h}$ (µg·h/mL)	Exposure ratio#
Rat (SD)	Fertility (R&D/09/1012)	30 [BD]	34.7/60.0 (male/female)	2.5/4
		150 [BD]	83.2/160 (male/female)	6/12
		400 [BD]	162/250 (male/female)	12/18
	Embryofetal development (R&D/09/105)	30 [BD]	59.1	4
		150 [BD]	212	15
		400 [BD]	329	24
	Pre-/postnatal development (R&D/12/272)	25 [BD]	76.3	6
		100 [BD]	223	16
		400 [BD]	302	22
Rabbit (NZW)	Embryofetal development (R&D/09/104)	100	23.8	1.7
		200	37.1	3
		400	83.5	6
Human(healthy volunteers)	steady state	[250 mg BD]	13.7	–

= animal:human plasma $AUC_{0-24\ h}$

Transfer of drug related material into milk was shown to be very high in lactating rats (exposures to dasabuvir were similar in milk and maternal blood). The metabolite profile was similar to that in blood. Dasabuvir was detected in the plasma of breast fed pups with plasma levels 10 to 16% of maternal plasma levels. Nonetheless, no adverse effects on gestation length, parturition or postnatal development were evident in rats at high doses (≤ 400 mg/kg BD PO dasabuvir; ERAUC 22).

Pregnancy classification - dasabuvir

The sponsor has proposed Pregnancy Category B1 for Viekira Pak (which lacks ribavirin). This pregnancy category is consistent with the absence of any drug related findings in adequately conducted reproductive toxicity studies with dasabuvir. However, embryofetal development studies with paritaprevir, ritonavir and ombitasvir will also need to be considered to determine if this category is applicable. The sponsor has proposed

Pregnancy Category X for Viekira Pak-RBV. This is consistent with the pregnancy category for ribavirin and is considered appropriate.

Phototoxicity

The nonclinical overview states that dasabuvir absorbs light between 290 and 700 nm, with a maximal molar extinction coefficient of 1.9 x 10^4 $M^{-1}cm^{-1}$ at 290 nm, which exceeds the threshold cited in ICH S10.[26] In the tissue distribution study in pigmented rats, there was no specific retention or affinity in skin that could be attributed to melanin, though the elimination half-life was longer than that in blood (and some other tissues). Skin levels of drug related material were similar to blood levels. However, phototoxic reactions with dasabuvir cannot be ruled out. As a minimum, the sponsor should have conducted an in vitro assay to assess the phototoxic potential of dasabuvir.

Impurities – dasabuvir

The proposed specifications for impurities in the drug substance have been adequately qualified. There are no degradants in the drug product requiring qualification.

Paediatric use - dasabuvir

No specific studies in juvenile animals were submitted.

Comments on the safety specification of the risk management plan

Results and conclusions drawn from the nonclinical program for dasabuvir detailed in the nonclinical safety specification of the sponsor's draft risk management plan are in general concordance with those of the nonclinical evaluator. However, a discussion of the pulmonary findings observed in the pivotal 6 month repeat-dose toxicity study in rats appears to have been omitted. References to alveolar histiocytosis in rats and its potential clinical relevance should be discussed in this section.

Nonclinical summary and conclusions - dasabuvir

- The overall quality of the submitted dossier for the dasabuvir component of Viekira Pak and Viekira Pak-RBV was high. All pivotal safety studies were conducted under GLP conditions.
- In vitro, dasabuvir inhibited the activity of NS5B polymerase from HCV strains of genotypes 1a and 1b with nanomolar potency and inhibited the replication of these strains in subgenomic HCV replicon assays. The M1 metabolite of dasabuvir had 30 to 40% lower potency than dasabuvir. Dasabuvir had lower potency at polymerases from other HCV genotypes (2a, 2b, 3a and 4a) and is unlikely to be active against these genotypes at the proposed clinical dose.
- Mutations at C316, S368, A395, N411, M414, E446 (genotype 1a only), Y448, A553, G554, S556 or D559 (or combinations of these) in NS5B conferred resistance to dasabuvir. Cross resistance may be seen with some other nonnucleoside inhibitors but cross resistance with nucleoside inhibitors may be unlikely.
- Dasabuvir had no significant inhibitory activity against a number of human and mammalian DNA-dependent DNA polymerases and DNA-dependent RNA polymerases. No off-target activities are predicted during clinical use.
- Based on findings in the combined set of safety studies, dasabuvir is not expected to have any adverse effects on CNS, respiratory, gastrointestinal or cardiovascular

function during clinical use. However, as the M1 metabolite is only a very minor metabolite in dogs, no comment can be made from the nonclinical data as to the potential for M1 to affect ECG parameters in patients.

- The oral bioavailability of dasabuvir free acid was high in dogs and much lower in rats. The rate of absorption was similar in animal species and human subjects. Plasma protein binding by dasabuvir and M1 was high. In rats, tissue distribution of drug related material was rapid and wide. Liver concentrations of dasabuvir were higher than plasma levels. M1 was a major metabolite in mice, rabbits and human subjects, but was only a minor metabolite in rats and monkeys. Only trace levels were seen in dogs. In vitro studies indicated a major role for CYP2C8, a lesser role of CYP3A4 and a minor role for CYP2D6 in the formation of M1 from dasabuvir. Excretion of dasabuvir and/or its metabolites was predominantly via the biliary/faecal route in animals and humans.
- Inducers/inhibitors of P glycoprotein, BCRP, CYP2C8 or CYP3A may alter the systemic exposure to dasabuvir. In vitro studies indicate dasabuvir has the potential to affect the oral absorption of co-administered drugs that are substrates for BCRP and MRP2, and affect the disposition of co-administered drugs that are substrates for OATP1B1, OATP1B3 and UGT1A1.
- Repeat dose toxicity studies were conducted in mice (up to 13 weeks), rats (up to 6 months) and dogs (up to 9 months) using the oral route. The lungs were a target organ for toxicity in rats with an increased incidence and severity of alveolar histiocytosis, consistent with phospholipidosis, observed in treated animals. A NOEL was not established. No clinically-relevant findings were seen in mice or dogs.
- Dasabuvir was not genotoxic in the standard battery of tests. No drug related tumours were evident in transgenic Tg.rasH2 mice treated for 6 months with dasabuvir.
- A standard set of GLP compliant reproductive toxicity studies was submitted and examined fertility (in rats), embryofetal toxicity (rats and rabbits) and pre/postnatal development (rats). There were no drug related findings. Placental transfer of dasabuvir and/or its metabolites was observed in both rats and rabbits. Transfer of drug related material into milk was shown to be very high in lactating rats.
- The phototoxic potential of dasabuvir is uncertain (no study).

Introduction – new fixed dose combination

General comments - new fixed dose combination

Hepatitis C Virus (HCV) is prone to develop resistance to antiviral drugs owing to the rapid rate and error prone nature of its replication. It has been proposed that all single nucleotide-mutant drug resistant viruses and all combinations of double nucleotide mutant viruses pre-exist in most treatment naïve patients,[56] and therefore treatment regimens have been developed based on co-administration of 2 or more antiviral agents having different mechanisms of action. The sponsor has applied to register two fixed dose combinations of 3 new DAAs for the treatment of chronic infection Viekira Pak and (in combination with ribavirin) Viekira Pak-RBV. Viekira Pak is proposed to be used for the treatment of genotype 1b HCV infection without cirrhosis, while Viekira Pak-RBV is proposed to be used for treatment of genotype 1a (with and without cirrhosis) and genotype 1b patients with cirrhosis. The recommended oral dose of Viekira Pak is two

[56] Strahotin, C.S. and Babich, M. Hepatitis C variability, Patterns of resistance and impact on therapy. *Advances in Virology* 2012*;* 2012 Article ID 267483, 10 pages.

paritaprevir/ ritonavir /ombitasvir 75/50/12.5 mg tablets once daily and one dasabuvir 250 mg tablet twice daily. When used in combination with ribavirin (Viekira Pak-RBV), the recommended dose of ribavirin depends on the patient's body weight (< 75 kg = 1,000 mg and ≥ 75 kg = 1,200 mg), and is taken twice daily.

The overall quality of the submitted dossier for Viekira Pak and Viekira Pak-RBV was high. All pivotal safety studies were conducted under GLP conditions. The submitted nonclinical dossier consisted of studies conducted with the individual agents paritaprevir (mostly in combination with the pharmacokinetic booster ritonavir), ombitasvir and dasabuvir, which have been evaluated separately (see above). In addition, previously evaluated nonclinical studies with ritonavir alone were submitted. This evaluation report addresses studies pertinent to the combination product, which includes pharmacology and pharmacokinetic drug interaction studies, and combination toxicity studies with dasabuvir, interferon plus ribavirin, paritaprevir and ritonavir plus ribavirin, and paritaprevir and ritonavir plus ombitasvir.

According to the TGA adopted EU guideline on fixed dose combination products,[57] for new active substances being developed for use in a fixed dose combination, a complete nonclinical development programme for each individual active substance would normally be expected to be supplemented by bridging studies with the combination. In addition, for a fixed dose combination containing approved compounds for long term use where experience of concomitant use is lacking, a 3 month repeat dose toxicity study in an appropriate species is generally recommended. The sponsor has not conducted comprehensive combination toxicity studies with the 3DAAs, citing a newer FDA draft guidance document.[58] According to this document, the need for combination toxicology studies may be waived for DAA combinations that are expected to treat patients with limited or no treatment options, or to improve response rates in patients at risk of serious morbidity or expected to be a substantial improvement over approved therapies, under the following conditions:

- Mechanisms of action or in vitro data of potential off-target effects of the individual drugs do not suggest a potential for additive or synergistic toxicity of a serious nature;
- Studies in animals or humans of absorption, distribution, metabolism and excretion of the individual drugs show no potential for an unmanageable interaction (one that cannot be addressed with dose adjustments) or serious toxicity for the combination;
- Toxicology studies of at least 3 months duration) of the individual drugs show a substantial safety margin for the intended clinical dose(s) or exposures;
- Phase I clinical data in healthy volunteers or HCV infected subjects receiving the individual drugs show no substantial or unmanageable safety concerns. Phase I data should include single- and multiple-dose pharmacokinetic and safety trials, at minimum. Additional safety data from Phase I and Phase II trials are encouraged and may be needed if one or more of the drugs demonstrate a potential serious safety risk;
- There are no concerning overlapping toxicities for the individual drugs based on animal toxicology studies and Phase I or Phase II clinical data; and
- Clinically significant PK based drug interactions are considered unlikely or can be reliably managed with dose adjustments such that safety margins based on individual drug exposures are not exceeded.

[57] EMEA/CHMP/SW/258498/2005 Guideline on the nonclinical development of fixed combinations of medical products. 24 January, 2008.
[58] Guidance for Industry. Chronic hepatitis C virus infection: developing direct-acting antiviral drugs for treatment. October 2013. US Department of Health and Human Services, FDA, CDER. Revision 1.

Pharmacology - new fixed dose combination

Primary pharmacology - new fixed dose combination

All 3DAAs act on separate and distinct targets on the HCV viral protein to prevent replication. The efficacy studies submitted in Module 4 assessed the inhibitory activity of the 3 agents in in vitro enzyme assays and standard subgenomic HCV replicon assays. No proof-of-concept studies were conducted in animal models of HCV. This is not considered a major deficiency.[5]

Paritaprevir is an inhibitor of HCV non-structural protein (NS) 3/4A protease in vitro, which is necessary for the proteolytic cleavage of HCV polyproteins, and is essential for viral replication. Paritaprevir inhibited genotype 1 HCV NS3/4A protease in vitro, with IC_{50} values against genotypes 1a and 1b with sub-nanomolar potency, compared with the clinical free C_{min} of 0.36 nM[59] (see Table 12). In cell culture using subgenomic HCV replicon assays the EC_{50} values against standard laboratory genotype 1a and 1b strains (H77 and Con1, respectively) in subgenomic HCV replicon assays were 0.94 to 1.0 nM and 0.21 to 0.32 nM, respectively, and potency was reduced 24 to 27 fold in the presence of 40% human plasma (to 23 nM and 8.7 nM, respectively). Paritaprevir had similar efficacy against a panel of genotype 1a and 1b isolates in the HCV subgenomic replicon assay; EC_{50} 0.86 nM (range 0.43 to 1.87 nM; n = 11) and 0.058 nM (range 0.033 to 0.087 nM; n = 9), respectively. Paritaprevir also showed some activity against genotype 4a, with IC_{50} for NS3/4A protease determined at 0.1 to 0.16 nM, and the EC_{50} against cell culture replicons containing genotype 4a determined to be 0.09 nM. Efficacy against genotype 6a was also sub-nanomolar (EC_{50} = 0.68 nM). Investigation of other genotypes indicated that their inhibition by paritaprevir is unlikely to be clinically significant.

In vitro efficacy studies showed that ombitasvir was a highly potent antiviral agent against NS5A from HCV genotypes 1a and 1b, as well as genotypes 2a, 2b, 3a, 4a and 5a, with EC_{50} values against these strains in subgenomic HCV replicon assays below the clinical free C_{min} of 32.4 pM[60] (see Table 12). Activity against genotype 6a is unlikely to be clinically relevant. The potency of ombitasvir in subgenomic HCV replicon assays was reduced by approximately 12 fold in the presence of 40% human plasma. Negligible antiviral activity against genotype s 1a-H77 and 1b-Con1 was noted by the human major metabolites of ombitasvir, M29 and M36.

In vitro, dasabuvir inhibited the activity of NS5B polymerase from HCV strains of genotypes 1a and 1b with nanomolar potency (IC_{50} 4.2 nM [range 2.2 to 10.7 nM; n = 7]; approximately equivalent to the clinical free C_{min} of 5.5 nM[61]). Dasabuvir had lower potency (> 200 times) at polymerases from other HCV genotypes (2a, 2b, 3a and 4a). Dasabuvir is unlikely to be active against these genotypes at the proposed clinical dose. The EC_{50} of dasabuvir against standard laboratory genotype 1a and 1b strains (H77 and Con1, respectively) in subgenomic HCV replicon assays was 7.7 nM and 1.8 nM, respectively. The potency of dasabuvir in subgenomic HCV replicon assays was reduced by approximately 12 fold in the presence of 40% human plasma. Dasabuvir had similar efficacy against a panel of genotype 1a and 1b isolates in the HCV subgenomic replicon assay; EC_{50} 0.77 nM (range 0.4 to 2.1 nM; n = 11) and 0.46 nM (range 0.2 to 2.0 nM; n = 10), respectively.

The M1 metabolite of dasabuvir had 30 to 40% lower potency than dasabuvir against standard genotype 1a and 1b laboratory strains in the subgenomic HCV replicon assay. Given the C_{max} for M1 (1.3 μM) in human subjects is higher than the EC_{50} against these genotypes in the replicon assay (143 nM and 26 nM against genotype 1a-H77 and

[59] Based on a paritaprevir C_{trough} of 2.6 nM and assuming a free fraction of 1.37%
[60] Based on ombitasvir C_{trough} of 32.4 nM and assuming a free fraction of < 0.1%
[61] Based on a dasabuvir C_{trough} of 269 μM and assuming a free fraction of 1%.

genotype 1b-Con1, respectively, in the presence of human plasma), this metabolite is likely to contribute to the antiviral activity of dasabuvir.

Table 12 compares the in vitro antiviral efficacy data for the 3DAAs against HCV laboratory strains and clinical isolates of genotypes 1a and 1b, as well as for other genotypes. Based on the in vitro data provided, it is anticipated that all 3 agents would inhibit HCV genotypes 1a and 1b at clinically relevant concentrations.

Table 12: Summary of antiviral efficacy data for ombitasvir, paritaprevir and dasabuvir

Drug C_{min} (free)	Target	Enzyme inhibition GT 1a and 1b IC_{50} (nM)	Antiviral activity HCV GTs 1a & 1b EC50	Activity against other HCV genotypes
ombitasvir C_{min} = 32.4 pM	NS5A	Not applicable	Laboratory strains: GT 1a – 14.1 pM GT 1b – 5 pM Panel of clinical isolates: GT 1a – 0.66 pM GT 1b – 1.03 pM	Laboratory strains: EC_{50} values (pM): GT 2a – 12 GT 2a JFH-1 – 0.8 GT 2b – 4.3 GT 3a – 19 GT 4a – 1.7 GT 5a – 3.2 GT 6a - 366
paritaprevir C_{min} = 0.36 nM	NS3/4A protease	0.043 to 0.43	Laboratory strains: GT 1a (H77) – 0.94 to 1.0 nM GT 1b (Con1) – 0.21 to 0.32 nM Panel of clinical isolates: 1a: 0.86 nM [range 0.43 to 1.87, n = 11] 1b: 0.058 nM [range 0.033 to 0.087, n = 9)	EC50 values (nM): GT 4a = 0.09 GT 6a = 0.68 GT 2aJFH-1 = 5.3 GT 3a = 19
dasabuvir C_{min} = 5.5 nM	NS5B RNA polymerase	4.2 [range 2.2 to 10.7; n = 7]	Laboratory strains: GT 1a (H77) – 7.7 nM GT 1b (Con1) – 1.8	> 200 fold lower potency against GTs 2a, 2b, 3a & 4a

Drug C_{min} (free)	Target	Enzyme inhibition GT 1a and 1b IC_{50} (nM)	Antiviral activity HCV GTs 1a & 1b EC50	Activity against other HCV genotypes
			nM Panel of clinical isolates: 1a: 0.77 nM [range 0.4 to 2.1, n = 11] 1b: 0.46 nM [range 0.2 to 2.0, n = 10)	
dasabuvir metabolite M1		Not tested	Laboratory strains (EC50 in presence of human plasma): GT 1a (H77) – 143 nM GT 1b (Con1) – 26 nM	Not tested

Pairwise combinations of paritaprevir, ombitasvir, dasabuvir and ribavirin showed additive to synergistic HCV genotype 1 antiviral activity when tested in short term culture assays.

Resistance and cross-resistance

Mutations in the target viral proteins that conferred resistance to the individual 3DAAs were identified from in vitro studies (treatment emergent mutations in HCV replicon assays) and early clinical studies.

Paritaprevir

Variants at amino acid positions 43, 155, 156 and 168 in genotype 1a generally conferred greater than 7 fold resistance to paritaprevir in vitro, while substitutions at 23, 36, 54 to 56, 80 and 357 were only associated with small (≤ 3 fold) increases in resistance. Resistance mutations V36L/M, F43L or E357K in combination with R155K or a D168 substitution increased the fold resistance of the latter mutation a further 2 to 7 fold. For the genotype 1b strain, substitutions at amino acid positions 155 and 168 were associated with increased resistance to paritaprevir. Substitutions at amino acid positions 54, 55 and 170 were not notably more resistant to paritaprevir, while some substitutions at position 156 were associated with modestly increased resistance. Clinically, the most common variants observed in NS3 in genotype 1 infected subjects that conferred resistance to paritaprevir were R155K and D168A/V/Y, either alone or in combination of V36M, Y56H or E357K in genotype 1a, and D168V alone and in combination with Y56H in genotype 1b.

Mutations at amino acid position 155 and 156 that are likely to confer resistance to paritaprevir based on the in vitro studies are also associated with resistance to most other NS3 protease inhibitors,[9] and hence patients that have failed therapy with other NS3/4A inhibitors may not be susceptible to paritaprevir (and vice versa). However, certain variants associated with resistance to telaprevir, boceprevir and a number of other NS3 inhibitors currently under development or more recently introduced to the market (V36A/M, T54A, V55A, Q80R/K, A156S, and V170A) may be susceptible to paritaprevir based on the results of the in vitro virology data. Mutations at position 168 are common to

most macrocyclic NS3 inhibitors including paritaprevir, but these variants are susceptible to NS3 inhibitors having a linear chemical scaffold, such as telaprevir and boceprevir.

Ombitasvir

Mutations at residues M28, Q30 and Y93 were found to be the most prevalent for genotype 1a and L28 and Y93 for genotype 1b in vitro. The magnitude of resistance was high for genotype 1a mutants of the Y93H, M28T, Y93C and Q30R variants, showing fold resistances of 41,000, 8,900, 1,700 and 810 respectively, while genotype 1b mutants L28T and Y93H conferred fold resistances of 430 and 50, respectively. Of the emergent mutants, the M28T mutant of genotype 1a showed substantial resistance to ombitasvir and no impairment to viral replication efficiency. For genotype 1b mutant L31F conferred approximately 9 fold resistance to ombitasvir and a slight increase (approximately 30%) in replication efficiency. Substitutions at residues 30 and 93 are known to occur with other NS5a inhibitors. In particular, substitution of the Y93 residue is regarded as a class defining resistance mutation because it is frequently observed with inhibitor substances.[30] Cross-resistance studies against known mutant variants of NS3 protease and NS5B polymerase found no difference in ombitasvir sensitivity between these variants and wild type forms of 1a and 1b. Clinically, the most common variants observed in NS5A in genotype 1 infected subjects that conferred resistance to ombitasvir were M28T, M28V, Q30R, H58D, and Y93N in genotype 1a, and Y93H in genotype 1b.

Dasabuvir

Mutations at C316, S368, A395, N411, M414, E446 (genotype 1a only), Y448, A553, G554, S556 or D559 (or combinations of these) conferred resistance to dasabuvir (EC_{50} > 5.5 nM; approximately 7 fold increase over wild type EC_{50}).Mutations C326Y and M414T have been reported to confer resistance to the non-nucleoside inhibitor, JTK-853 (not yet registered),[40] that binds with the palm site and β-hairpin region of the HCV polymerase. Therefore, treatment emergent dasabuvir resistant strains may also be resistant to JTK-853, and vice versa. Mutations at M423 (to M423V/T/I) in the polymerase thumb domain have been reported to confer resistance to the non-nucleoside polymerase inhibitors, NNI-1,[41]filibuvir,[42] lomibuvir[43] and VX-222[44] and the mutation P459L has been reported to confer resistance to the nonnucleoside inhibitor, TMC647055[45]. The M423T and P495L mutations had no effect on dasabuvir potency; suggesting dasabuvir may be effective in patients carrying HCV genotypes 1a and 1b that are resistant to NNI-1, filibuvir, lomibuvir and VX-222 by virtue of a M423T mutation and TMC647055 by virtue of a P495L mutation. Unfortunately, the efficacy of dasabuvir against other mutations conferring resistance to these inhibitors (L419M, R422K, M426A, I482L/N/T, A486S/T/V, L392I and V494A) was not assessed. Therefore, it is unknown if dasabuvir will be effective against genotype 1a and 1b HCV strains that are resistant to these other nonnucleoside inhibitors. Future studies with dasabuvir should assess efficacy against these mutant variants.

The S282T mutation which has been reported to confer resistance to the NS5B polymerase nucleoside inhibitor, sofosbuvir,[46] did not confer resistance to dasabuvir. The S96T mutation, which has also been reported to confer resistance to nucleoside NS5B polymerase inhibitors [45] did not confer resistance to dasabuvir, suggesting dasabuvir may still be active in genotype 1a and 1b variants that are resistant to nucleoside inhibitors.

Clinically, the most common variants observed in NS5B in genotype 1 infected subjects that conferred resistance to dasabuvir were C316Y, M414T, Y448H, G554S and S556G in genotype 1a, and C316Y, M414T, Y448H, and S556G in genotype 1b.

The ability of drug-resistant cells to form colonies in the presence of a single drug or drugs in combination was evaluated in long term replicon survival assays. In pair wise combinations of paritaprevir, ombitasvir, and dasabuvir at concentrations 10 fold over their respective EC_{50}, colony numbers were reduced by more than 100 fold by two drugs

as compared to each drug alone. When all three drugs were combined at concentrations of 5 fold above their respective EC_{50}, no drug resistant colonies survived.

Secondary pharmacodynamics and safety pharmacology

Paritaprevir, ombitasvir and dasabuvir showed no clinically relevant antiviral activity against HIV-1 and HBV. Dasabuvir had no significant inhibitory activity against a number of human and mammalian DNA-dependent DNA polymerases and DNA-dependent RNA polymerases, and an RNA-dependent DNA polymerase (IC_{50} values ≥ 76 μM; > 3,600 times the clinical free C_{max}). Therefore, dasabuvir is not expected to interfere with DNA replication or transcription in host cells. Secondary pharmacodynamics and safety pharmacology data were discussed. Overall, there are no off target activities predicted during clinical use, and no evidence of clinically relevant secondary pharmacological activity. However, the potential for the dasabuvir metabolite M1 to affect ECG parameters was not adequately investigated, since exposures were probably subclinical in the cardiovascular safety pharmacology study in dogs, in which it was only a minor metabolite.

Pharmacokinetics - new fixed dose combination

The assessments of the nonclinical pharmacokinetics for the individual compounds (paritaprevir, ombitasvir and dasabuvir) are provided in the individual evaluation reports (above) and only considerations relevant to the combination product are discussed below.

Overall, the nonclinical data submitted for the three compounds were considered to adequately support the animal models used in the toxicology studies. The pharmacokinetic profile of paritaprevir in mice, rats and dogs was considered adequately comparable for those animal species to serve as models for toxicity. There were sufficient similarities in the absorption profiles, level of plasma protein binding, extent of biotransformation and elimination pathways of ombitasvir in mice relative to the human pharmacokinetic profile for ombitasvir, to allow these animal models to serve as the predominant testing species appropriate models for assessing toxicity. The sponsor addressed uncertainties on the two major ombitasvir metabolites unique to human plasma (M29 and M36) in a series of exploratory studies in mice that were considered appropriate. With respect to dasabuvir, while the M1 metabolite is only a very minor metabolite in dogs, this metabolite was formed in other animal species used in the toxicity studies. The two human specific (circulating) dasabuvir metabolites are only minor drug related species in human subjects and their absence in animal species was not expected to impact the validity of the toxicity studies. Overall, the pharmacokinetic profile of dasabuvir in rats and dogs was considered adequately comparable for these animal species to serve as models for toxicity.

Pharmacokinetic drug interactions

Potential drug interactions were investigated in a comprehensive nonclinical study package, and the potential relevance was estimated using EMA[11] or FDA[62] guidelines. Nonclinical findings of potential clinical relevance are summarised in the two tables below. The main concerns for the individual components of Viekira Pak are interactions with strong inducers of CYP3A4 such as carbamazepine, and it is noted that this is included as a contraindication in the PI document. Dasabuvir is also a substrate for CYP2C8, and its exposure is likely to be increased if co-administered with inhibitors of this

[62] Guidance for Industry. Drug interaction studies – study design, data analysis, implications for dosing, and labelling recommendations. FDA CDER, Draft guidance (February 2012)

enzyme. All components of Viekira Pak are substrates of P-gp and BCRP, although the degree of sensitivity varies. In addition, paritaprevir is a substrate for the hepatic organic anion transporters OATP1/3, and plasma concentrations are likely to increase if it is co-administered with OATP, BCRP or P-gp inhibitors such as atazanavir and cyclosporine.

Ritonavir is responsible for the major CYP mediated drug interaction potential through its strong inhibition of CYP3A4. Paritaprevir inhibition of OATP transporters is likely to have clinical implications for co-administration of OATP substrates. Inhibition of P-gp and BCRP are also of possible clinical relevance based on nonclinical data.

Potential drug interactions based on interactions between the individual components of Viekira Pak and metabolising enzymes and drug transporters were reviewed by the sponsor in reports RD13811 and RD13893.

Table 13: paritaprevir/ritonavir/ombitasvir/dasabuvir as victims†

Compound	Substrate for Enzyme or Transporter	Nonclinical Findings	Clinical Relevance
paritaprevir	CYP3A4	K_m = 6.1 µM; V_{max} = 15.7 pmol/min/pmol	Confirmed; Predominantly responsible for oxidative metabolism of paritaprevir, and was the rationale behind inclusion of ritonavir in the formulation; CYP3A4 inhibitor ketoconazole further increased plasma AUC (by 98%); Carbamazepine reduced AUC by 71% (contraindicated)
	P-gp	Inhibited by LY335979 and cyclosporin A in vitro; KO mouse studies indicate this and BCRP involved in biliary clearance	Confirmed (AUC increased 94% by OATP1B1 inhibitor atazanavir and 72% by P-gp/BCRP/OATP1B1/B3 inhibitor cyclosporin)
	BCRP	Slight inhibition by BCRP inhibitor K0143	
	[a]OATP1B1	K_m for uptake 0.18 µM	
	[a]OATP1B3	K_m for uptake 0.089 µM	
ritonavir	CYP3A4	substrate	AUC increased by 57% when co-administered with ketoconazole;

Compound	Substrate for Enzyme or Transporter	Nonclinical Findings	Clinical Relevance
			AUC decreased by 87% when co-administered with carbamazepine
	P-gp, OATPB1/B3	P-gp substrate; No active uptake by OATP1B1/3 expressed in HEK cells	C_{trough} concentrations increased by 40-49% when co-administered with cyclosporine and atazanavir
	OATP1B1		
Ombitasvir	CYP3A4	K_{m2} = 71 µM; V_{max2} = 0.004 nmol/min/pmol; K_{m1} = 7.1 µM; V_{max1} = 0.0001 nmol/min/pmol;	AUC unchanged when co-administered with ketoconazole; AUC decreased 30% when co-administered with carbamazepine
	CYP2C8	K_m = 79.1 µM; V_{max} = 0.001 nmol/min/pmol;	Unlikely
	P-gp, BCRP	Contradictory: Ombitasvir was not a substrate of P-gp or BCRP mediated efflux *in vitro,* but mice lacking these transporters had increased exposure levels	AUC unchanged when co-administered with cyclosporine; C_{max} decreased by 23% when co-administered with atazanavir
Dasabuvir	CYP2C8	CYP2C8 inhibitor quercetin inhibited *in vitro* metabolism in human liver microsomes by 60%	Confirmed (AUC increased 1025% by gemfibrozil)
	CYP3A4	CYP3A inhibitor ketoconazole inhibited *in vitro* metabolism in human liver microsomes by 30%	Confirmed (AUC increased 42% by ketoconazole; decreased 70% by carbamazepine
	P-gp	Inhibited by LY335979 and cyclosporin A *in vitro*	Confirmed C (AUC decreased 21% by OATP1B1 inhibitor atazanavir and 30% by P-gp/BCRP/OATP1B1/B3

Compound	Substrate for Enzyme or Transporter	Nonclinical Findings	Clinical Relevance
	BCRP	Inhibited by BCRP inhibitor K0143	inhibitor cyclosporin)
Dasabuvir M1	BCRP	Inhibited by BCRP inhibitor K0143	Not tested
	OATP1B1	K_m = 1.30 µM	
	OATP1B3	K_m = 1.71 µM	

† Data taken from reports RD13893 and RD13811 [a]: Studies in KO mice indicate that OATP transporters affect the distribution between liver and plasma.

Table 14: paritaprevir/ombitasvir/dasabuvir as perpetrators

Compound	Substrate for Enzyme or Transporter	Nonclinical Findings	Clinical Relevance
paritaprevir	CYP2C8	Reversible inhibitor; IC_{50} = 13 µM	Not anticipated (R-value 1.01[62]); lack of safety signals in patients taking loperamide and zopiclone
	CYP3A4	Minimally induced (approx.. one third the effect of rifampin)	Unlikely to be relevant based on co-formulation with ritonavir (see below)
	UGT1A1	IC_{50} = 3.6 µM	Unlikely (clinical study showed 34% decrease in raltegravir exposure with the 3DAA regimen, but individual contribution unknown)
	P-gp	IC_{50} = 38.1 µM	Likely in intestine only ($[I_2]/IC_{50}$ > 10) [62]
	BCRP	IC_{50} = 0.59 to 14.4 µM	($[I_2]/IC_{50}$ > 10 and $[I_1]/IC_{50}$ > 0.1[62]
	OATP1B1	IC_{50} = 0.031 µM	Likely (R-value 1.88 to 3.07) [62] Clinical study showed increased rosuvastatin & pravastatin exposure with the 3DAA regimen, but individual contribution unknown
	OATP1B3	IC_{50} = 0.017 µM	Likely (R-value 2.60 to 4.77) [62] Clinical study showed increased rosuvastatin & pravastatin exposure

Compound	Substrate for Enzyme or Transporter	Nonclinical Findings	Clinical Relevance
			with the 3DAA regimen, but individual contribution unknown
Ritonavir	CYP3A4	Potent inhibitor	Kinetic booster for paritaprevir; will have clinical implications for all co-administered CYP3A4 substrates; This inhibitory effect is likely to dominate over slight induction effect of paritaprevir
	P-gp	IC_{50} = 0.35 µM (vesicle), > 50 µM (cell based)	Possible, but individual contribution of ritonavir to P-gp and BCRP inhibition in the 3DAA regimen is difficult to discern
	BCRP	IC_{50} = 24 µM (vesicle), 66 µM (cell based)	
	OATP1B1	IC_{50} = 0.5 µM	Clinical study showed increased rosuvastatin & pravastatin exposure with the 3DAA regimen, but individual contribution unknown
	OATP1B3	IC_{50} = 0.6 µM	
	OCT1	IC_{50} = 2.5 µM	Ritonavir (and other compounds in the 3DAA regimen) have low potential for clinically relevant interactions with renal transporters; Clinically, tenofovir exposure was similar following co-administration with the 2DAA and 3DAA regimens
	OAT1	IC_{50} = 14 µM	
	OAT3	IC_{50} = 8.1 µM	
	MATE1	IC_{50} = 3.3 µM	
	MATE2K	IC_{50} = 90 µM	
	BSEP	IC_{50} = 0.1 µM	
Ombitasvir	UGT1A1	IC_{50} = 2.1 µM	Possible; (clinical study showed 34% decrease in raltegravir exposure with the 3DAA regimen, but individual contribution unknown)
Dasabuvir	CYP2C9	IC_{50} = 9 µM	Unlikely (R-value 1.08) [62] Confirmed clinically (lack of interaction with warfarin)
	CYP2C8	IC_{50} = 17 µM	Unlikely
	CYP2C19	IC_{50} = 18 µM	Unlikely; (clinical study showed 38% reduction in omeprazole AUC)

Compound	Substrate for Enzyme or Transporter	Nonclinical Findings	Clinical Relevance
	UGT1A1	IC_{50} = 0.92 µM	Possible; (clinical study showed 34% decrease in raltegravir exposure with the 3DAA regimen, but individual contribution unknown)
	OATP1B1	IC_{50} = 0.9 µM	Unlikely (R-value = 1.06)
	OATP1B3	IC_{50} = 6.6 µM	Unlikely (R-value = 1.01)
	P-gp	IC_{50} = 16.7 µM	Possible, but not confirmed clinically (no increase in digoxin exposure when co-administered as part of 3DAA regimen)
	BCRP	IC_{50} = 15.6 µM	
M1	UGT1A1	IC_{50} = 6.53 µM	See above
	OATP1B1	IC_{50} = 2.6 µM	Unlikely (R-values = 1.03 & 1.01)
	OATP1B3	IC_{50} = 9.7 µM	

Toxicology - new fixed dose combination

Paritaprevir

The main target organ for paritaprevir associated toxicity was the gallbladder. In mice, focal erosion or ulceration of the gall bladder epithelium was characterised by focal necrosis and loss of mucosal epithelial cells, transmural fibrosis and inflammation, extending into the lamina propria, tunica muscularis and serosa. Hypertrophic or hyperplastic tissue was often found adjacent to the areas of mucosal erosion. The effect showed only partial recovery. There was no indication of progression to a pre-neoplastic or neoplastic state in this model. However, the relevance of human c-Ha-ras gene overexpression to the progression of chronic inflammation and hypertrophy to carcinogenesis is unknown. Gall bladder toxicity was not observed in the shorter duration studies, including the 13 week mouse study at doses up to 300 mg/kg/day, corresponding to systemic exposure 60 times the clinical AUC. The effect was not observed in the rat since this species lacks a gall bladder. Minimal focal mucosal degeneration and oedema was observed in the gall bladders of dogs in the 4 week study, but there was no evidence of progression in longer duration studies, and there were no gall bladder findings in the 13 week study. In the pivotal 9 month study, the NOEL for gall bladder changes was 20 mg/kg/day (88 times the clinical AUC), and only one male dosed with paritaprevir at 80 mg/kg/day for 9 months (214 times the clinical AUC) exhibited minimal epithelial necrosis. It is possible that the relatively lower severity of adverse gall bladder toxicity in this species is related to the correspondingly lower liver to plasma concentration ratio for paritaprevir.

The sponsor submitted 1 and 3 month toxicology studies in rats, in which ribavirin was co-administered with paritaprevir and ritonavir. There were no novel toxicities or exacerbation of previously reported toxicities. A 4 week safety study in CD-1 mice given low oral doses of a combination of paritaprevir, ritonavir and ombitasvir found no

evidence of toxicity associated with levels of systemic exposure 2.7, 2.4 and 3.3 times the respective clinical AUC values.

Ritonavir

Repeat dose toxicity studies with ritonavir were previously evaluated by the TGA. Toxicological findings which are relevant to the doses of ritonavir co-administered with paritaprevir were hepatotoxicity in the rat, including multinucleated hepatocytes, hepatocytomegaly and single cell necrosis, and thyroid follicular cell hypertrophy, associated with elevated thyroid stimulating hormone concentrations. Biliary hyperplasia and chronic pericholangitis were seen at higher doses. Hepatic pathology was associated with increased serum enzyme activities. Ocular changes were seen in rodents at doses higher than those administered in the current application. Effects included retinal degeneration and hypertrophy of the retinal pigment epithelial (RPE) cells, and electroretinography carried out in one study showed changes indicative of compromised retinal function. Retinal lesions were thought to be manifestations of phospholipidosis, and there was a widespread occurrence of microgranulomas in the 3 and 6 month rat studies, primarily in the liver, lungs and lymphoid tissues. In the dog, hepatotoxicity was manifest mainly as increased serum enzyme activities (for exampleγ glutamyltransferase) and hepatocytic hydropic degeneration, although pericholangitis was seen in one study. Low incidences of testicular and prostatic degeneration/atrophy were also seen in this species, but there were no thyroid or ocular changes.

Ocular effects were not seen in the studies submitted with the current application to support the safety of paritaprevir co-dosed with ritonavir, as the doses of ritonavir administered were below the LOEL for this effect. Alveolar histiocytosis, thought to be consistent with phospholipidosis, was observed in repeat dose studies with dasabuvir in rats (see below).

Ombitasvir

No specific toxicities were identified in the mouse or rat repeat dose studies. Treatment related changes in rats were minimal with sporadic findings that were not consistent for all treated groups. Similar to findings from a non-pivotal mouse study, there were apparent dose dependent elevations in AST (and to a lesser degree, ALT) levels in male (but not female) treated rats, accompanied by observed hepatocytic necrosis in the high dose treated males.

A high incidence of vacuolation of villi in the duodena and jejuna of dogs in the 6 month pivotal study appeared to be related to ombitasvir treatment. Effects were seen at doses corresponding to plasma exposures of at least 34 and 61 times the clinical AUC, and thus are not considered to be a toxicological concern. At the NOAEL for the pivotal dog study (4 mg/kg/day) the relative exposure was 3 times the clinical AUC. Additional toxicity studies on the nonclinical safety of the human metabolites M29 and M36 found no evidence of adverse effects at up to 4 weeks exposures in mice.

Dasabuvir

No consistent target organs for toxicity were identified. The lungs were a target organ for toxicity in rats. An increased incidence and severity of alveolar histiocytosis was observed in rats at exposure ratios based on AUC [ERAUC] of 2 to 5. A NOEL was not established and pulmonary histiocytosis had not completely reversed after a 1 month treatment free period, though the severity had lessened over this period. This lesion is consistent with phospholipidosis. Phospholipidosis is a common finding for cationic amphiphilic drugs, which have been approved for a wide range of clinical indications. It is uncertain if phospholipidosis in animals is predictive for humans and it is also uncertain if it is merely an adaptive response or has toxicological implications.[51, 52, 53] As there was no evidence of phospholipidosis in mice and dogs at much higher exposures, rats may be more sensitive

to this effect, and the pulmonary changes are likely to have minimal clinical relevance. The NOAEL in mice and dogs was 5,000 mg/kg/day and 30 mg/kg/day, respectively, resulting in respective exposures 15 and 38 times the clinical AUC. At higher exposures in mice, inflammation and irritation was evident in the gastrointestinal tract. This was associated with the oral administration of a large amount of material, resulting in a local irritant effect. These findings are not considered clinically relevant. At higher exposures in dogs, changes were evident in the adrenal gland (cortical hypertrophy/hyperplasia), liver (hepatocellular vacuolation) and lymphoid tissues (lymphoid depletion). Given the high exposures at which these occurred, they are not considered clinically relevant.

Combination toxicity studies with dasabuvir included a 13 week repeat dose study with ribavirin in rats, and two 4 week repeat dose studies in combination with ribavirin and interferon-γ (IFN-γ) in cynomolgus monkeys. Dosing with ribavirin was associated with a slight reduction in erythrocytic parameters in both species. Co-administration of RBV and/or IFN-γ did not notably affect the toxicokinetics of dasabuvir.

Genotoxicity

No combination genotoxicity studies were submitted. Paritaprevir was not genotoxic in a bacterial reverse mutation assay, in in vivo bone marrow micronucleus and ex vivo liver Comet assays in rats, but it was clastogenic in human lymphocytes in vitro. Overall, the weight of evidence provided indicates a low potential for paritaprevir genotoxicity. Ombitasvir (and its major human plasma metabolites, M29 and M36) and dasabuvir were not found to be mutagenic or clastogenic in a standard battery of in vitro and in vivo genotoxicity assays.

In previously evaluated studies (bacterial reverse mutation and mouse lymphoma assays for gene mutation, and human lymphocytes in vitro and mouse micronucleus assay in vivo for clastogenicity), ritonavir showed no mutagenic potential.

Evidence of genotoxicity for ribavirin is summarised in the approved PI document for Rebetol. According to this document, ribavirin was positive in the Balb/3T3 cell transformation assay in vitro. The results in the mouse lymphoma (L5178Y) assay were equivocal, but ribavirin was clastogenic in vivo in a mouse micronucleus assay. Ribavirin was negative in a range of other assays for gene mutations (Salmonella typhimurium, host mediated assay) and chromosomal damage (dominant lethal assay in rats).

Carcinogenicity

No combination carcinogenicity studies were submitted. No drug related tumours were evident in transgenic Tg.rasH2 mice treated for 6 months with paritaprevir, ombitasvir or dasabuvir alone. There was no indication of progression of gall bladder inflammation or hyperplasia to a pre-neoplastic or neoplastic state in the transgenic mouse study with paritaprevir, although the relevance of human c-Ha-ras gene overexpression to the progression of chronic inflammation and hypertrophy to carcinogenesis is unknown. However, there were no treatment related increases in tumour development in the rat carcinogenicity study with paritaprevir at systemic exposure levels up to 9 times the clinical AUC. It is noted that lifetime carcinogenicity studies with ombitasvir and dasabuvir are due to be submitted to the TGA in April 2015.

Two year carcinogenicity studies were previously conducted in rodents, at ritonavir dietary levels of 50, 100 and 200mg/kg/day in mice, and 7, 15 and 30 mg/kg/day in rats. In male mice there was a dose dependent increase in the incidence of hepatocellular adenomas, and adenomas and carcinomas combined, both reaching statistical significance only at the high dose. In female mice there were small, statistically significant increases in these tumour incidences only at the high-dose. In rats, there were no tumorigenic effects.

The systemic exposure levels for ritonavir in the paritaprevir carcinogenicity studies were 3.2 and 4.6 fold the proposed clinical exposure for Viekira Pak.

According to the approved PI document for Rebetol, there was no evidence of carcinogenicity for ribavirin in exposure levels in conventional rodent carcinogenicity studies or in a 26 week carcinogenicity study using the heterozygous p53 (+/-) mouse model. However, systemic exposure levels in these studies were near to or below human exposure under therapeutic conditions (ranging from 0.1 to 1.2).

Reproductive toxicity

Pregnancy classification

The sponsor has proposed Pregnancy Category B1[22] for Viekira Pak, based on the lack of adverse reproductive findings for the individual agents; paritaprevir, ombitasvir and dasabuvir (see individual evaluation reports above for full details). While it is accepted that individually a pregnancy categorisation of B1 is appropriate for paritaprevir, ombitasvir and dasabuvir alone, ritonavir alone is in Category B3[23] however, and so the product Viekira Pak should also be B3, unless an adequate scientific justification is provided.

The developmental toxicity studies previously submitted to support the registration of ritonavir included an embryofetal development study in the rat (study RD94024) in which the following effects were observed (as stated in the approved PI document for Norvir):

> 'In rats, early resorptions decreased fetal body weight and ossification delays and developmental variations occurred at a maternally toxic dosage of 75 mg/kg/day. A slight increase in the incidence of cryptorchidism was also noted in rats given 35 mg/kg/day.'

The maternal plasma AUC values in this study were 45.2 and 34.3 µg.h/mL, respectively, which corresponds to relative exposures of 5 and 3.6 times the clinical exposure with Viekira Pak.

In the current application, there was no evidence of embryofetal toxicity in the rat in study RD09847 at paritaprevir/ritonavir doses of up to 400/45 mg/kg/day during organogenesis. The systemic exposure for ritonavir in this study was only 2.8 times the proposed clinical exposure with Viekira Pak. Thus, based on systemic exposure, the new data are consistent with a NOEL for cryptorchidism in the rat being greater than 2.8 but less than 3.6 times the clinical exposure level. Taking into account the new data, a change in pregnancy categorisation for ritonavir from B3 to B1 is not justified based on the animal data alone.

The proposed Pregnancy Category X[24] for Viekira Pak-RBV is appropriate based on the existing pregnancy categorisation of ribavirin.

In the sponsor's response (April 2015) the pregnancy categorisation of B3 has been accepted.

Phototoxicity

The nonclinical overview states that dasabuvir absorbs light between 290 and 700 nm, with a maximal molar extinction coefficient of 1.9×10^4 $M^{-1}cm^{-1}$ at 290 nm, which exceeds the threshold cited in ICH S10.[26] In the tissue distribution study in pigmented rats, there was no specific retention or affinity in skin that could be attributed to melanin, though the elimination half-life was longer than that in blood (and some other tissues). Skin levels of drug related material were similar to blood levels. However, phototoxic reactions with dasabuvir cannot be ruled out. As a minimum, the sponsor should have conducted an in vitro assay to assess the phototoxic potential of dasabuvir.

Impurities

The proposed specifications for impurities and degradants in the drug substance are below ICH levels,[27] or have been adequately qualified.

Paediatric use

No studies in juvenile animals were submitted. The sponsor justified the absence of such studies on the absence of any toxicological finding that would be considered to be more severe or to manifest differently to that in an adult, and no anticipated differences in metabolism between the adult and paediatric populations.

Comments on the safety specification of the risk management plan

The sponsor has addressed a number of potential issues raised in the first round evaluation. The following comments refer to version 1.2 of the RMP, submitted with the S31 response on 27th February 2015.

Results and conclusions drawn from the nonclinical program are in general concordance with those of the nonclinical evaluator, with the following exceptions:

The key safety findings from the nonclinical studies begins by referring to studies in the dog and rat, whereas in fact the systemic exposure was considered to be a limiting factor in the latter species, so that the sponsor chose to continue the toxicology programme in the mouse.

Nonclinical summary and conclusions - new fixed dose combination

Summary

- The sponsor has applied to register two fixed dose combinations of 3 new DAAs for the treatment of chronic infection, Viekira Pak and (in combination with ribavirin) Viekira Pak-RBV. Viekira Pak is proposed to be used for the treatment of genotype 1b HCV infection without cirrhosis, while Viekira Pak-RBV is proposed to be used for treatment of genotype 1a (with and without cirrhosis) and genotype 1b patients with cirrhosis.
- Recommended oral dose rate is paritaprevir 150 mg/ritonavir 100 mg/ombitasvir 25 mg once daily and dasabuvir 250 mg twice daily (500 mg/day). When used in combination with ribavirin (Viekira Pak-RBV), the recommended dose of ribavirin is 1000 to 1200 mg twice daily (2000 to 2400 mg/day), depending on body weight.
- The overall quality of the submission was high. Pivotal safety studies were conducted under GLP conditions. Studies conducted with the individual agents paritaprevir (mostly in combination with the pharmacokinetic booster ritonavir), ombitasvir and dasabuvir have been evaluated separately (see above). This section addresses studies pertinent to the combination product. Limited combination toxicology studies were submitted, in accordance with ICH guideline M3 (R2)[63] and the FDA draft guidance document for HCV 3DAA treatments.[58]
- All 3DAAs act on separate and distinct targets on the HCV viral protein to prevent replication. The efficacy studies submitted in the nonclinical dossier assessed the inhibitory activity of the 3 agents in in vitro enzyme assays and standard subgenomic HCV replicon assays.

[63] ICH guideline M3 (R2) – questions and answers. EMA/CHMP/ICH/507008/2011.

- Paritaprevir inhibits HCV non-structural protein (NS) 3/4A protease. The EC_{50} values against genotype 1a and 1b clinical isolates in the HCV subgenomic replicon assay were 0.86 nM (range 0.43 to 1.87 nM; n = 11) and 0.058 nM (range 0.033 to 0.087 nM; n = 9), respectively. Potency was reduced 24 to 27 fold in the presence of 40% human plasma (to 23 nM and 8.7 nM, respectively). Paritaprevir also showed some activity against genotype 4a, (EC_{50} = 0.09 nM), and to a lesser extent genotype 6a (EC_{50} = 0.68 nM).
- Ombitasvir inhibits HCV NS5A. The mean EC_{50}s against replicons containing NS5A from a panel of treatment naïve genotype 1a and 1b isolates in the HCV replicon cell culture assay were 0.66 pM (range 0.35 to 0.88 pM; n = 11) and 1.0 pM (range 0.74 to 1.5 pM; n = 11), respectively. The potency of ombitasvir was reduced by approximately 12 fold in the presence of 40% human plasma. Ombitasvir also showed activity against replicon cell lines constructed with NS5A from single isolates representing genotypes 2a, 2b, 3a, 4a and 5a (EC_{50} values of 12, 4.3, 19, 1.7 and 3.2 pM, respectively, which are all below the below the clinical free C_{min} of 32.4 pM). Activity against genotype 6a is unlikely to be clinically relevant (EC_{50} value = 366 pM). Negligible antiviral activity against genotype s 1a-H77 and 1b-Con1 was noted by the human major metabolites of ombitasvir, M29 and M36.
- Dasabuvir inhibits NS5B polymerase. The EC_{50} values against a panel of genotype 1a and 1b clinical isolates in the HCV subgenomic replicon assay were 0.77 nM (range 0.4 to 2.1 nM; n = 11) and 0.46 nM (range 0.2 to 2.0 nM; n = 10), respectively, and the potency of dasabuvir in subgenomic HCV replicon assays was reduced by approximately 12 fold in the presence of 40% human plasma. The M1 metabolite of dasabuvir had 30 to 40% lower potency than dasabuvir against standard genotype 1a and 1b laboratory strains in the subgenomic HCV replicon assay. Dasabuvir had a lower potency (> 200 times) at polymerases from other HCV genotypes (2a, 2b, 3a and 4a), and is unlikely to be active against these genotypes at the proposed clinical dose.
- Based on the in vitro data, it is anticipated that all 3 agents would inhibit HCV genotypes 1a and 1b at clinically relevant concentrations. Pairwise combinations of paritaprevir, ombitasvir, dasabuvir and ribavirin showed additive to synergistic HCV genotype 1 antiviral activity when tested in short term culture assays. Colony survival was reduced by more than 100 fold compared to each drug alone in long term replicon survival assays in which pairwise combinations were tested at concentrations 10 fold over their respective EC_{50} values. No drug resistant colonies survived when all three drugs were combined at concentrations of 5 fold above their respective EC_{50} values.
- NS3 mutations F43L, R155G/K/S, A156T and D168A/E/F/H/N/V/Y, or combinations of V36M, F43L, Y56H or E357K with R155 or D168 variants conferred resistance to paritaprevir genotype 1a, and A156T, D168A/H/V/Y, either alone or in combination with Y56H for genotype 1b. Cross resistance may be seen with some other NS3 protease inhibitors, as mutations at R155 and A156 are also associated with resistance to most other NS3 protease inhibitors, while mutations at D168 are common to most macrocyclic NS3 inhibitors. However, certain variants associated with resistance to telaprevir, boceprevir and a number of other NS3 inhibitors having a linear scaffold (V36A/M, T54A, V55A, Q80R/K, A156S, and V170A) may be susceptible to paritaprevir based on the results of the in vitro virology data.
- NS5A substitutions M28T/V, Q30E/R, H58D, Y93C/H/L/N in genotype 1a reduced susceptibility to ombitasvir by 58 to 67,000 fold. In genotype 1b, substitutions L28T, L31F/V and Y93H reduced susceptibility to ombitasvir 8 to 661 fold. In general, combinations of ombitasvir resistance-associated substitutions in HCV genotype 1a or 1b replicons further reduced ombitasvir antiviral activity.

- Substitutions C316Y, M414I/T, N444K, E446K/Q, Y448C/H, A553T, G554S, S556G/R, and Y561H in HCV NS5B genotype 1a reduced susceptibility to dasabuvir by 5 to 1472 fold. G558R and D559G/N were observed as treatment emergent substitutions but the activity of dasabuvir against these variants could not be evaluated due to poor replication capacity. In genotype 1b, substitutions C316H/N/Y, S368T, N411S, M414I/T/V, Y448C/H, A553V, S556G and D559G in HCV NS5B reduced susceptibility to dasabuvir by 5 to 1,569 fold. Dasabuvir retained full activity against replicons containing substitutions S282T in the nucleoside binding site, M423T in the lower thumb site, and P495A/S, P496S or V499A in the upper thumb site.
- The 3DAAs showed no clinically relevant antiviral activity against HIV-1 and HBV. Dasabuvir had no significant inhibitory activity against a number of human and mammalian DNA-dependent DNA polymerases and DNA-dependent RNA polymerases, and an RNA-dependent DNA polymerase, and thus is not expected to interfere with DNA replication or transcription in host cells. Off target activities are not predicted during clinical use. However, the potential for the dasabuvir metabolite M1 to affect ECG parameters was not adequately investigated.
- The nonclinical pharmacokinetic data adequately supported the animal models used in the toxicology studies for all 3DAAs.
- The main concerns for the individual components of Viekira Pak are interactions with strong inducers of CYP3A4 such as carbamazepine, and it is noted that this is included as a contraindication in the PI document. In addition, dasabuvir is a substrate for CYP2C8, and its exposure is likely to be increased if co-administered with inhibitors of this enzyme.
- All components of Viekira Pak are substrates of P-gp and BCRP. Paritaprevir is a substrate for the hepatic organic anion transporters OATP1/3, and plasma concentrations are likely to increase if it is co-administered with OATP, BCRP or P-gp inhibitors such as atazanavir and cyclosporine.
- Paritaprevir inhibition of OATP transporters is likely to have clinical implications for co-administration of OATP substrates. Inhibition of P-gp and BCRP are also of possible clinical relevance based on nonclinical data.
- Paritaprevir administration was associated with gallbladder toxicity in two 6 month repeat dose studies in mice (consisting of focal erosion or ulceration, inflammation and epithelial hyperplasia; NOEL = 30 mg/kg/day or 4.8 times the clinical AUC; LOEL = 60 mg/kg/day or 17 times the clinical AUC). Gall bladder toxicity was less severe in dogs (NOEL = 20 mg/kg/day, or 88 times the clinical AUC).
- Vacuolation of villi and dilated lacteals in the duodena and jejuna of dogs were observed in repeat dose toxicity studies with ombitasvir. These effects were observed at plasma levels that were 34 and 60 times the clinical AUC.
- Toxicities observed in previously evaluated repeat-dose studies with ritonavir include hepatotoxicity in the rat and dog, and thyroid follicular cell hypertrophy (associated with elevated thyroid stimulating hormone concentrations) in rats. Biliary hyperplasia and chronic pericholangitis were seen in rats at higher doses. Retinal lesions in rodents were thought to be manifestations of phospholipidosis, and there was also a widespread occurrence of microgranulomas, primarily in the liver, lungs and lymphoid tissues. Low incidences of testicular and prostatic degeneration or atrophy were also seen in dogs.
- None of the previously reported effects of ritonavir were seen in the studies submitted with the current application to support the safety of paritaprevir co-dosed with ritonavir, as the doses of ritonavir administered were below the LOEL for these effects. Alveolar histiocytosis, thought to be consistent with phospholipidosis, was also

observed in repeat dose studies with dasabuvir in rats. Phospholipidosis is a common finding for cationic amphiphilic drugs, which have been approved for a wide range of clinical indications, and it is uncertain if phospholipidosis in animals is predictive for humans.

- The only combination repeat dose toxicity studies were 4 and 13 week toxicology studies in rats, in which ribavirin was co-administered with paritaprevir and ritonavir, a 13 week combination study with dasabuvir and ribavirin in rats, and two 4 week studies of dasabuvir with ribavirin and IFN-γ in cynomolgus monkeys. There were no novel toxicities or exacerbation of previously reported toxicities, and no evidence of pharmacokinetic interactions.
- A 4 week safety study in CD-1 mice given low oral doses of a combination of paritaprevir, ritonavir and ombitasvir found no evidence of toxicity associated with levels of systemic exposure 2.7, 2.4 and 3.3 times the respective clinical AUC values.
- Genotoxicity, carcinogenicity and reproductive toxicity studies were submitted with the individual agents. There were no genotoxicity or carcinogenicity concerns, but 2 year carcinogenicity studies in rats with dasabuvir and with ombitasvir have not yet been submitted (expected in April 2015).
- In previously evaluated embryofetal toxicity studies in rats with ritonavir alone, early resorptions, decreased fetal body weight and ossification delays and developmental variations occurred at a maternally toxic dosage of 75 mg/kg/day, while a slight increase in the incidence of cryptorchidism was also noted in rats given 35 mg/kg/day. These doses corresponded to systemic exposures 5 and 3.6 times the proposed clinical exposure with Viekira Pak. Thus, based on systemic exposure, the new data are consistent with a NOEL for cryptorchidism in the rat being greater than 2.8 but less than 3.6.
- It is considered that the sponsor should have conducted an in vitro assay to assess the phototoxic potential of dasabuvir.

Conclusions and recommendation

- Only limited combination toxicology studies were submitted, which is in accordance with a new FDA draft guidance document for HCV 3DAA treatments, and is considered to be acceptable.
- Based on the in vitro data, it is anticipated that all 3 agents would inhibit HCV genotypes 1a and 1b at clinically relevant concentrations. Additive to synergistic HCV genotype 1 antiviral activity was demonstrated in short term culture assays.
- Off target activities are not predicted during clinical use. However, the potential for the dasabuvir metabolite M1 to affect ECG parameters was not adequately investigated.
- The main concerns for the individual components of Viekira Pak are interactions with strong inducers of CYP3A4, as well as the potential to increase exposure for dasabuvir if co-administered with inhibitors of CYP2C8. In addition, exposures of one or more of the individual DAAs may be increased if co-administered with OATP, BCRP or P-gp inhibitors.
- Paritaprevir inhibition of OATP transporters is likely to have clinical implications for co-administration of OATP substrates. Inhibition of P-gp and BCRP are also of possible clinical relevance based on nonclinical data.
- There were no nonclinical concerns from the limited combination repeat-dose toxicity studies submitted, and no major concerns based on the toxicological profiles of the individual agents.

- While a pregnancy category of B1 is appropriate for paritaprevir, ombitasvir and dasabuvir alone it is noted that ritonavir alone has a pregnancy category of B3. The nonclinical data do not support a change for ritonavir to B1, as requested by the sponsor.
- There are no nonclinical objections to the registration of Viekira Pak and Viekira Pak-RBV.
- The evaluator also recommended some changes to the PI document but details of these are beyond the scope of the AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

It is estimated that 130 to 210 million people worldwide are infected with HCV with 2 to 4 million new infections annually. Approximately 300,000 Australians were infected with HCV in 2011. Acute infections become chronic in 70% to 90% of cases and this leads commonly to cirrhosis, chronic liver failure, hepatocellular carcinoma, liver transplantation and death. After 20 years of infection, 20 to 30% of patients will have progressed to cirrhosis, 5 to 10% will have developed end stage liver disease, and 4 to 8% will have died of liver related causes. HCV has six genotypes and multiple subtypes with genotypes 1 to 3 distributed worldwide. Genotypes 1a and 1b account for 60% of global HCV infections. In Australia, the most common genotypes are 1a and 1b (54% prevalence) and 3a (37% prevalence). Genotype 4 is most prevalent in North Africa and the Middle East but it is spreading to Europe and the rest of the world through immigration and IV drug use. Until recently, the standard of care treatment for chronic HCV infection for all genotypes was the combination of pegylated interferon (pegIFN) and ribavirin (RBV) for 48 weeks. The response to this treatment varies according to HCV genotype and host interleukin 28B (IL28B) genotypic subtypes (CC, CT, TT). Patients with the IL28B CC genotype are able to mount stronger immune responses to the HCV virus and spontaneous viral clearance rates and responsiveness to antiviral therapy are enhanced. In patients with genotype 1 infection, sustained viral response rates (SVR) following pegIFN/RBV therapy are only 45% in treatment naïve patients and significantly lower in prior relapsers and non-responders. Moreover, the side effect profile of pegIFN/RBV is unfavourable with a high incidence of lethargy, fatigue, depression and anaemia.

The NS3/4A protease inhibitors boceprevir, telaprevir, sofosbuvir and simeprevir used singly in combination with pegIFN/RBV have improved SVR rates in treatment naïve and treatment experienced patients, and shortened treatment duration to 24 weeks in many patients (Table 15). However, these combinations are associated with increased rates and severity of adverse events (AEs), including rash in addition to the common side effects of pegIFN/RBV. Simeprevir is well tolerated and has the advantage of once daily dosing. However, telaprevir and boceprevir both require three times a day (TID) therapy.

Table 15: Sustained virologic response rates 24 weeks after stopping treatment in subjects with HCV genotype 1

Regimen	Treatment Duration (weeks)	Treatment-Naïve	Partial Responder to pegIFN/RBV	Null Responder to pegIFN/RBV
Boceprevir + pegIFN/RBV	28 – 48	63%	52%[a]	38%[b]
Cirrhotic (F4) subset	48	42%[c]	not available	not available
Telaprevir + pegIFN/RBV	24 – 48	75%[d]	61%[e]	31%[e]
Cirrhotic (F4) subset	24 – 48	54%[d]	33%[e]	19%[e]
Simeprevir + pegIFN/RBV	24 – 48	80%[f]	65%[g]	53%[g]
F3/F4 subset	24 – 48	68%[f]	not available	not available
Sofosbuvir + pegIFN/RBV	12	89%[h]	not available[i]	not available[i]
Cirrhotic (F4) subset	12	80%[h]		

RGT = response guided therapy; SVR_{12} = sustained virologic response 12 weeks postdosing; SVR_{24} = sustained virologic response 24 weeks postdosing

a. Victrelis SmPC – SVR_{24} 48 weeks from RESPOND-2.
b. Victrelis USPI – SVR_{24} from PROVIDE.
c. Victrelis USPI – SVR_{24} 48 weeks from SPRINT-2.
d. Incivo SmPC – SVR_{24} RGT composite from studies C211, 108 (ADVANCE), and 111 (ILLUMINATE).
e. Incivo SmPC – SVR_{24} 48 weeks from C216 (REALIZE).
f. Olysio USPI – SVR_{12} RGT composite from QUEST 1 and QUEST 2.
g. Olysio USPI – SVR_{24} 48 weeks from ASPIRE.
h. Sovaldi SmPC – SVR_{12} 12 weeks from NEUTRINO.
i. Sovaldi USPI estimates a 71% response rates in prior pegIFN/RBV nonresponders based on rates in patients with multiple negative predictors of response.

The three DAAs in Viekira Pak have different mechanisms of action, they all have potent activity against HCV genotype 1, and they have non-overlapping viral resistance profiles. They also appear to have non-overlapping toxicity with RBV. Current EMA guidelines are based on 24 to 48 weeks of therapy with one or more DAAs in combination with pegIFN/RBV. However, the guidelines recognise the rapidly developing therapeutic area and the potential value of combination DAA therapy. Paritaprevir, ombitasvir and dasabuvir are potent DAAs but resistance develops to each agent when used as monotherapy. It is proposed that the combination of the three direct acting antiviral agents (3DAA) used in Viekira Pak will obviate the need for concomitant pegIFN/RBV therapy, increase SVR rates compared with approximately 75% for 1-DAA + pegIFN/RBV combination therapy in treatment naïve patients, shorten treatment duration from 24 to 12 weeks, and improve safety and tolerability.

Contents of the clinical dossier

The submission contained the following clinical information:

- Sixty one clinical pharmacology studies, including 59 that provided PK data and 5 that provided pharmacodynamic data.
- Two population PK analyses.
- Six pivotal efficacy/safety studies: M11-646 (Sapphire-I), M13-098 (Sapphire-II), M13-389 (PEARL-II), M13-961 (PEARL-III), M14-002 (PEARL-IV), M13-099 (TURQUOISE II).
- Multiple Phase I and II studies used to justify the selected regimen, dose and treatment duration.

- Five other efficacy/safety studies: M12-114, M13-386, M12-746, M12-998, M14-103. Also included in the submission is the preliminary report of a long-term follow-up study (M13-102) of all patients who have received 3DAA in a Phase II or III study. This will assess the long-term durability of virologic response and the persistence rates of resistant variants.
- Two additional efficacy/safety studies not directly related to the proposed indication: M11-652 in patients with genotype 1a or genotype 1b infection given 3DAA +/- RBV for 8, 12 or 24 weeks; and M13-393 in patients with genotype 4 infection treated with a 2DAA combination.
- Pooled efficacy and safety analyses, Integrated Summary of Efficacy (ISE), Integrated Summary of Safety (ISS).

The submission also contained a Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

All studies were conducted according to the principles of good clinical practice (GCP).

Pharmacokinetics

Studies providing pharmacokinetic data

Summaries of the PK studies were provided. Table 16 below shows the studies relating to each PK topic.

Table 16: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
PK in healthy adults	Absorption	M11-389	Effect of food on the BA of paritaprevir/ritonavir/ ombitasvir co-formulated tablet
		M14-196	PKs of dasabuvir commercial and clinical Phase III formulations
	Absolute bioavailability (BA)	M11-030	Absolute BA of dasabuvir
	BA	M12-995	BA of two test tablet formulations of dasabuvir
		M10-749	Single-ascending dose of paritaprevir alone and interaction with ritonavir
		M10-	BA of SDD and hard gelatin capsule

PK topic	Subtopic	Study ID	*
		797	(HGC) formulations of paritaprevir
		M11-388	BE between test paritaprevir/ritonavir tablet co-formulation and free combination
		M12-683	BA of different dosage strengths of paritaprevir and ritonavir co-formulated compared with free combination
		M12-115	BA of HME and SDD formulations of ombitasvir
		M12-647	Comparison of coated and uncoated ombitasvir HME tablets
		M13-391	BA of different dosage strengths of paritaprevir, ritonavir and ombitasvir co-formulated tablets with free combination
		M13-331	Comparison of optimised and Phase II tablet formulations of dasabuvir
		M13-387	Comparison of candidate tablets of ombitasvir
		M14-356	BE between commercial formulations of US and Australian ribavirin tablets
	Food Effect	M10-923	Effect of food on paritaprevir
		M12-116	Antiviral activity and food effect of single and multiple doses of ombitasvir
		M13-300	Effect of food on dasabuvir optimised tablets
	Ascending Single dose	M12-351	Comparison of 3 single doses of paritaprevir SDD Formulation
		M11-032	Single ascending doses of dasabuvir
	Multi-dose	M10-861	Multiple-ascending doses of paritaprevir
		M10-	Multi-dose PKs of dasabuvir

PK topic	Subtopic	Study ID	*
		687	
		M12-187	Multi-dose PKs of ombitasvir and paritaprevir/ritonavir
		M11-603	PKs of multi-dose dasabuvir plus paritaprevir/ ritonavir
	ADME	M10-789	ADME of [^{14}C] paritaprevir/ritonavir
		M12-186	ADME of [^{14}C]ombitasvir
PK in special popn	Target population HCV Genotype 1 infected subjects	M10-351	Antiviral activity, and PKs of single and multiple doses (2 Days) of dasabuvir
		M11-602	PKs, and antiviral activity of multi-dose paritaprevir/ ritonavir, dasabuvir, or ABT-072 each administered alone
	Hepatic impairment	M12-215	PKs of a single dose of co-administered ombitasvir, dasabuvir, and paritaprevir/ ritonavir
	Renal impairment	M12-193	PKs of a single dose of co-administered ombitasvir, dasabuvir, and paritaprevir/ ritonavir
	Other special pop'n	M12-221	PKs of multi-dose of ombitasvir and paritaprevir/ ritonavir in Han Chinese, Japanese, and Caucasians
		M12-688	PKs of a single dose of paritaprevir/ ritonavir in Han Chinese, Japanese and Caucasians
		M12-181	PKs of ombitasvir in Han Chinese, Japanese, and Caucasians
		M13-505	PKs of the co-formulated paritaprevir/ ritonavir /ombitasvir in Han Chinese and Japanese
		M11-384	PKs of paritaprevir/ritonavir in Japanese males
		M11-385	PKs of paritaprevir/ritonavir in Han Chinese

PK topic	Subtopic	Study ID	*
DDIs	Atazanavir	M13-394	DDIs between paritaprevir/ ritonavir with ombitasvir + dasabuvir and atazanavir
	Ketoconazole	M12-189	DDIs between paritaprevir/ ritonavir with ombitasvir + dasabuvir and ketoconazole
	Gemfibrozil	M12-196	DDIs between paritaprevir/ ritonavir + dasabuvir and gemfibrozil
	Warfarin	M12-198	DDIs between paritaprevir/ ritonavir with ombitasvir + dasabuvir and warfarin
	Omeprazole	M12-199	DDIs between paritaprevir/ ritonavir with ombitasvir + dasabuvir and omeprazole
	Carbamazepine	M14-027	DDIs between paritaprevir/ ritonavir with ombitasvir + dasabuvir and carbamazepine
	Digoxin	M12-201	DDIs between paritaprevir/ ritonavir with ombitasvir + dasabuvir and digoxin
	Rosuvastatin or pravastatin	M12-200	DDIs between paritaprevir/ ritonavir with ombitasvir + dasabuvir and rosuvastatin or pravastatin
	LPV (lopinavir)/r	M13-492	DDIs between paritaprevir/ ritonavir with ombitasvir + dasabuvir and LPV/ritonavir
		M14-031	DDIs between paritaprevir/ritonavir with ombitasvir + dasabuvir and LPV/r
	Darunavir	M13.506	DDIs between paritaprevir/ritonavir with ombitasvir + dasabuvir and darunavir
		M12-202	DDIs between paritaprevir/ritonavir with ombitasvir + dasabuvir and darunavir
	Emtricitabine + tenofovir	M13-783	DDIs between paritaprevir/ritonavir with ombitasvir + dasabuvir and emtricitabine + tenofovir

PK topic	Subtopic	Study ID	*
	Atripla	M13-104	DDIs between paritaprevir/ritonavir with ombitasvir + dasabuvir and Atripla
	Rilpivirine	M13-782	DDIs between paritaprevir/ritonavir with ombitasvir + dasabuvir and rilpivirine
	Raltegravir	M13-392	DDIs between paritaprevir/ritonavir with ombitasvir + dasabuvir and raltegravir
	CsA	M13-103	DDIs between paritaprevir/ritonavir with ombitasvir + dasabuvir and cyclosporine (CsA)
	Tacrolimus	M13-491	DDIs between paritaprevir/ritonavir with ombitasvir + dasabuvir and tacrolimus
	Methadone	M12-997	DDIs between paritaprevir/ritonavir with ombitasvir + dasabuvir and methadone
	Buprenorphine, norbuprenorphine and naloxone	M13-100	DDIs between paritaprevir/ritonavir with ombitasvir + dasabuvir and buprenorphine, norbuprenorphine and naloxone
	Ethinyl estradiol + norgestimate	M12-205	DDIs between paritaprevir/ritonavir with ombitasvir + dasabuvir and ethinyl estradiol + norgestimate
	Escitalopram or duloxetine	M12-204	DDIs between paritaprevir/ritonavir with ombitasvir + dasabuvir and escitalopram or duloxetine
	Alprazolam or zolpidem	M14-324	DDIs between paritaprevir/ritonavir with ombitasvir + dasabuvir and alprazolam or zolpidem
	Furosemide or amlodipine	M14-325	DDIs between paritaprevir/ritonavir with ombitasvir + dasabuvir and furosemide or amlodipine
PPK	Healthy subjects	R&D/13/690	PPKs of dasabuvir in healthy subjects
	Target	RD 13-	PPK of 3DAAs + ritonavir and ribavirin

PK topic	Subtopic	Study ID	*
	population	1098 PPK	in Phase I and 2b studies
		RD 14-0047 PPK	PPK of 3DAAs + ritonavir and ribavirin in Phase III studies

* Indicates the primary aim of the study. ADME - absorption, distribution, metabolism and excretion.† Bioequivalence of different formulations. BA – bioavailability § Subjects who would be eligible to receive the drug if approved for the proposed indication. CsA – cyclosporine. DDI - drug-drug interaction

None of the PK studies had deficiencies that excluded their results from consideration.

For further details of the evaluation of the PK studies please see Attachment 2.

Evaluator's conclusions on pharmacokinetics

Absorption

- Following a single oral dose (150 mg/100 mg/25 mg) of the to be marketed co-formulation of paritaprevir/ritonavir/ombitasvir under non-fasting conditions the C_{max}, T_{max}, t½ and AUC extrapolated to time infinity (AUC_{inf}) values for paritaprevir were 1,580 ng/mL, 4.9 hours, 5.2 hours and 7,660 ng.h/mL, respectively. For ritonavir these values were: 1,510 ng/mL; 4.4 hours; 4.4 hours and 9,210 ng.h/mL, respectively, and for ombitasvir were: 127 ng/mL, 5.2 hours, 29.0 hours and 1,670 ng.h/mL. Following a single oral dose of the to be marketed dasabuvir 250 mg tablet under non-fasting conditions the C_{max}, T_{max}, t½ and AUC_{inf} values for dasabuvir were 699 ng/mL, 3.47 hours, 7.07 hours and 6,050 ng.h/mL, respectively.
- The absolute bioavailability of paritaprevir and ombitasvir has not been determined.
- The absolute bioavailability of a 400 mg oral tablet dose of dasabuvir compared to an intravenous microdose of approximately 85 µg of ^{14}C-dasabuvir was 46%.
- Only a single dosage form and strength is proposed for the proposed to be marketed co-formulated paritaprevir/ritonavir/ombitasvir (75 mg/50 mg/12.5 mg) and dasabuvir 250 mg tablets.
- A number of different formulations of the active drugs were used during the clinical trial program.
- In the presence of 100 mg ritonavir, the Phase II SSD tablet formulation of paritaprevir had a lower bioavailability (55% and 49% lower C_{max} and AUC_{inf}, respectively) than the 200 mg paritaprevir hard gelatin capsule (HGC) used in early Phase I clinical trials.
- Following administration of the co-formulated paritaprevir/ritonavir 150 mg/100 mg (that is the proposed recommended dose) the C_{max} and AUC_{inf} of paritaprevir were 1.53 fold and 1.35 fold higher than following administration of 150 mg of the paritaprevir SSD tablet co-administered with the 100 mg ritonavir capsule.
- The C_{max} and AUC_{inf} values for the uncoated ombitasvir HME tablet, which was used in Phase II studies onwards, were 1.9 fold and 1.75 fold higher, respectively, relative to the ombitasvir SDD tablet used in the initial Phase I trials.
- Later in the development program a coated ombitasvir HME tablet was developed, which was bioequivalent with the uncoated HME tablet.

- Following administration of a triple co-formulated tablet containing paritaprevir/ritonavir/ ombitasvir the C_{max} and AUC_{inf} of paritaprevir were 1.93 fold and 1.63 fold higher than the corresponding values obtained for the free combination. By contrast, ritonavir exposure following administration of the triple co-formulated tablet was similar to ritonavir exposure following dosing with the free combination and ombitasvir exposures were bioequivalent.
- The commercial tablet formulation of dasabuvir was bioequivalent with the formulation used in the Phase III clinical trials.
- Following administration of the proposed daily dose of the co-formulated paritaprevir/ritonavir/ombitasvir tablet, a moderate fat breakfast increased the C_{max} and AUC_{inf} of paritaprevir by 4.67 and 3.11 fold, respectively, compared to when the co-formulation was administered under fasted conditions. The C_{max} and AUC_{inf} values for of ritonavir were increased by 1.63 and 1.49 fold, respectively, and the C_{max} and AUC_{inf} of ombitasvir increased by 2.27 and 1.82 fold, respectively.
- Following administration of a 250 mg dose of the optimised Phase III tablet formulation a moderate fat breakfast increased the C_{max} and AUC_{inf} of dasabuvir by 1.53 and 1.3 fold compared to when dasabuvir was administered under fasted conditions.
- Following co-administration of single doses of paritaprevir with ritonavir the PKs of paritaprevir were nonlinear and increased supra proportionally with dose. Following 14 days QD dosing with paritaprevir/ ritonavir 200/100 mg, paritaprevir C_{max} and AUC_t were approximately 2.3 fold and 1.68 fold higher, respectively, following 14 days dosing with 200/100 mg QD than following a single dose.
- For the ombitasvir SSD tablets between doses of 1.5 mg to 50 mg, the dose normalised C_{max} and AUC_{inf} increased with dose indicating that at these dose the PKs of ombitasvir were non-linear and increased greater than dose proportionally. By contrast, at higher doses the PKs were dose linear. Following 10 days QD dosing with 25 mg ombitasvir the C_{max} and AUC_{0-24} values of ombitasvir increased approximately 1.49 fold and 1.56 fold, respectively, compared to administration of a single dose.
- Following 21 days dosing with 25 mg ombitasvir SSD and 14 days with co-administered paritaprevir/ritonavir 250 mg SSD/100 mg SGC (starting on Day 8), the accumulation ratios for paritaprevir C_{max} and AUC_{24} were 3.81 and 2.60, respectively. The accumulation ratios for ritonavir over this period the accumulation ratios for C_{max} and AUC_{24} were 2.29 and 1.67, respectively, and for ombitasvir were 0.83 and 0.91, respectively.
- The dose normalised C_{max} and AUC of dasabuvir tablets were very similar at doses of 1,200 and 1,600 mg. By contrast for the capsule formulation of dasabuvir, dose normalised C_{max} and AUC_{inf} appeared to decrease with dose for doses up to 200 mg and for doses greater than 1,200 mg. The accumulation ratios comparing the AUC_{12} following 10 days and a single dose of dasabuvir ranged from 0.95 to 1.65.
- Following 21 days of dosing with paritaprevir/ritonavir (250 mg SSD/100 mg SGC) QD + ombitasvir HME 200 mg QD + dasabuvir 400 mg tablet twice daily (BD), the accumulation ratios for paritaprevir C_{max} and AUC_{24} were 2.32 and 1.89, respectively; for ritonavir they were 1.64 and 1.82, respectively; for ombitasvir they were 0.90 and 1.12; and for dasabuvir were 0.905 and 0.974.
- When dosed QD, a 50% increase in paritaprevir dose from 200 mg to 300 mg increased mean C_{max} and mean AUC by 5 to 6 fold. Increasing the BD dose from paritaprevir 50 to 100 mg increased the C_{max} and AUC by 4 to 5 fold.

- Following BD dosing with dasabuvir the C_{max} values following the morning dose were higher than the values following the evening dose.

Distribution

- Following the administration of two paritaprevir/ritonavir/ombitasvir (75/50/12.5 mg) co-formulated tablets (total dose of 150/100/25 mg) with a moderate fat breakfast, the volume of distribution (Vd/F) values for paritaprevir, ritonavir and ombitasvir were 400 L, 97.3 L and 717 L, respectively.
- The Vd/F of dasabuvir following a 250 mg dose of the optimised, to be marketed, tablet formulation was 517 L.
- Paritaprevir, ritonavir, ombitasvir and dasabuvir partitioned preferentially into the plasma compartment with blood to plasma concentration ratios of 0.68, 0.60, 0.49 and 0.7 in humans.

Metabolism

- Paritaprevir, ritonavir, ombitasvir and dasabuvir are primarily metabolised in vitro by: CYP3A4; CYP3A; CYP3A4/5 and CYP2C8; and CYP2C8, respectively.
- Five inactive paritaprevir metabolites have been identified in human plasma and the breakdown of total drug related material based on AUC_t was that 88.9% represented unchanged paritaprevir, 7.8% M2, 3.2% M29 and there were trace levels of M3, M13 and M6.
- Only a single ritonavir metabolite, M2, was identified in plasma and there was a mean 30 fold excess of parent drug over metabolite in systemic circulation between 2 and 12 h after oral dosing.
- The primary ombitasvir metabolites in plasma, based on AUC_t, were M29 (which represented 31.2% of the drug related material in plasma), M36 (21.4%), M23 (15%) and M37 (13.9%). By contrast, the parent drug ombitasvir represented only 8.85% of the administered dose in plasma. A number of other metabolites were also identified (M5, M25, M26 and M34) but each of these represented less than 5% of the administered dose. None of the ombitasvir metabolites had in vitro antiviral activity.
- Seven dasabuvir metabolites were identified in plasma including dasabuvir M1, M2, M3, M4, M5, M6 and trace levels of metabolite M11. Unchanged parent was the most prominent component in plasma representing 58.1% of total plasma radioactivity followed by the active metabolite M1 (21.4% of total plasma radioactivity), which has similar in vitro antiviral activity to dasabuvir. Following a single oral dose of the proposed commercial formulation of dasabuvir 250 mg under non-fasting conditions, the C_{max}, T_{max}, t½ and AUC_{inf} values for the active M1 metabolite of dasabuvir were 244 ng/mL, 4 h, 6.4 h and 2,120 ng.h/mL, respectively.
- A pharmacogenetic analysis indicated that there were no significant genetic abnormalities that were consistently associated with exposures of paritaprevir or dasabuvir.

Excretion

- Following administration of [^{14}C] paritaprevir/ritonavir 200/100 mg, 96.5% of the radioactive dose of paritaprevir was recovered in the faeces (representing 88% of radioactive dose) and urine (8.8%) within approximately 8 days. Unchanged parent drug accounted for only 1.1% and 0.05% of the total radioactivity in faeces and urine, respectively, with the major components being m29 in faeces, which accounted for 59.9% of radioactive dose, and M13 in urine, which accounted for 8.6%.

- Following administration of 600 mg dose of [^{14}C] ritonavir, 97.6% of radioactive dose was recovered in the urine and faeces of humans within approximately 6 days. Faecal excretion was the major route of elimination, accounting for 86.4% of the dose, whereas, urinary excretion accounted for 11.3%.
- Following a 25 mg oral dose of [^{14}C] ombitasvir under non-fasting conditions approximately 90.3% of the radioactive dose was recovered in faeces and a further 0.6% was recovered in urine within 8 days. Unchanged drug accounted for 87.8% of total radioactivity recovered in faeces and although a number of metabolites were detected in the faeces, including M2, M3, M5, M6, and M9, each represented less than 1% of administered dose.
- Two hundred forty hours following a single oral dose of 400 mg [^{14}C] dasabuvir, 94.4% of administered radioactivity was recovered in faeces and a further 2.20% was recovered in urine. Unchanged drug accounted for 26% and 0.03% in faeces and urine, respectively. Dasabuvir M1 was the most abundant metabolite in faeces representing 31.5% of administered dose.

Inter-subject variability

Following the proposed dose of the to be marketed formulation of paritaprevir/ritonavir/ombitasvir under non-fasted conditions inter-subject variability on C_{max} and AUC_{inf} values for paritaprevir, ritonavir and ombitasvir were > 100%, approximately 50% and 28%, respectively. For the proposed commercial formulation of dasabuvir, 250 mg the %CV values for dasabuvir C_{max} and AUC_{inf} were 44% and 46%, respectively.

Pharmacokinetics in the target population

- Following a single dose of paritaprevir/ritonavir 200 mg/100 mg in naïve HCV genotype 1 infected subjects the mean C_{max} and AUC_{24} values for paritaprevir were 1,753 ng/mL and 10,478 ng.h/mL, respectively, and for ritonavir were 917 ng/mL and 7,104 ng.h/mL, respectively. Over the dose range examined paritaprevir demonstrated greater than dose proportional increases following single doses. Paritaprevir exposures were 80% to 310% higher on Day 3 compared to Day 1.
- Following multiple oral doses of 5 to 50 mg ombitasvir SDD under non-fasting conditions in HCV genotype 1 infected treatment naïve subjects the C_{max} and AUC_{24} values for a 25 mg dose of ombitasvir were 35.9 ng/mL and 337 ng.h/mL, respectively and following 3 days of QD dosing were 24.8 ng/mL and 319 ng.h/mL, respectively. Following single doses there were greater than dose proportional increases in ombitasvir exposure in this population.
- Following 400 and 800 mg BD dosing for 3 days, dose normalised C_{max} and AUC_{12} values following a single dose indicated that there was a slightly greater than dose proportional increase in dasabuvir exposure, whereas on Day 3, exposures increased in a slightly less than dose proportional manner with increasing dasabuvir doses.

Inter-subject variability of PK in target population based on PPK modelling

- Inter-subject variability in paritaprevir apparent clearance (CL/F) and apparent volume of central compartment (Vc/F) was 166% and 265%, respectively and the residual unexplained variability (RUV) was 100%.
- Inter-subject variability values for ritonavir CL/F and VcF were 85% and 210%, respectively and the RUV was 71%.
- Inter-subject variability values for ombitasvir CL/F, Vc/F and Vp/F were 30%, 59% and 59%, respectively, and the RUV was 37%.

- Inter-subject variability values on dasabuvir CL/F and Vc/F were 62% and 73%, respectively, and the RUV was 55%.

Pharmacokinetics in subjects with impaired hepatic function

Following a single dose of 25 mg ombitasvir, 400 mg dasabuvir, and paritaprevir/ritonavir 200/100 mg under non-fasting conditions: mild hepatic impairment induced a ± 35% difference in AUC_{inf} for each of the active drugs; moderate hepatic impairment decreased the AUC_{inf} values for ritonavir, ombitasvir, dasabuvir and dasabuvir M1 by 30%, 30%, 16% and 57%, respectively, whereas, exposure to paritaprevir increased by approximately 62%; severe hepatic impairment increased the AUC_{inf} values for paritaprevir, ritonavir, dasabuvir and ABT-M1 by 10.5 fold, 1.13 fold, 4.25 fold and 1.77 fold, respectively, whereas, the AUC_{inf} of ombitasvir decreased by 54%. The % unbound fraction (fu) of DAAs and ritonavir were up to approximately 30% different in subjects with hepatic impairment and healthy control subjects, except for dasabuvir % fu, which was approximately 50% lower in subjects with mild and moderate hepatic impairment compared to healthy control subjects and ombitasvir % fu in subjects with severe hepatic impairment, which was approximately 2.24 fold higher than in healthy control subjects.

Pharmacokinetics in subjects with impaired renal function

Following administration of the 3DAA regimen with ritonavir, the AUC_{inf} of paritaprevir increased by 1.19 to 1.45 fold in subjects with mild to severe renal impairment compared to healthy subjects, ritonavir AUC_{inf} increased by 1.42 to 2.14 fold; and dasabuvir AUC_{inf} increased by 1.21 fold to 1.50 fold. In contrast, ombitasvir exposure was relatively unaffected by renal impairment.

Ethnicity

Following co-administration of ombitasvir 25 mg QD HME, paritaprevir/ritonavir 150/100 mg QD, and dasabuvir 400 mg BD for 21 days to Han Chinese, Japanese and Caucasian subjects, compared to Caucasians the AUC_{24} values for ombitasvir in Chinese and Japanese subjects were 1.18 and 1.30 fold higher, respectively. For paritaprevir, the AUC_{24} values were 2.47 and 2.91 fold higher in Chinese and Japanese subjects, respectively. For ritonavir, the AUC_{24} values were 1.24 and 1.06 fold higher in Chinese and Japanese subjects, respectively. For dasabuvir, the AUC_{24} values were 1.11 and 1.29 fold higher in Chinese and Japanese subjects, respectively and for dasabuvir M1 were 1.35 to and 1.50 fold higher, respectively.

Effect of ritonavir on paritaprevir exposure

Compared to when 300 mg paritaprevir was administered alone, co-administration with 100 mg ritonavir resulted in significant increases in paritaprevir C_{max}, which increased from 121 ng/mL to 3,397 ng/mL, and AUC_{inf}, which increased from 391 to 18,534 ng.h/mL.

Effect of paritaprevir/ritonavir on ombitasvir exposure

Compared to when 25 mg paritaprevir was administered alone for 7 days co-administration with a single dose of paritaprevir/ritonavir 250/100 mg increased the C_{max} and AUC_{24} of ombitasvir by 1.59 and 1.62 fold, respectively.

Effect of ombitasvir on paritaprevir/ritonavir exposure

Compared to when paritaprevir/ritonavir 250/100 mg was administered alone for 14 days, co-administration with a single dose of 25 mg ombitasvir had little to no effect on C_{max} and AUC_{24} of paritaprevir or ritonavir.

Effect of dasabuvir on paritaprevir/ritonavir

Co-administration of 100 mg dasabuvir BD with paritaprevir/ritonavir 200/100 mg increased the paritaprevir C_{max} from 2,520 to 3,140 ng/mL and paritaprevir AUC_{24} from

9,890 to 14,400 ng.h/mL. Ritonavir exposure was also increased in the presence of dasabuvir with the AUC_{24} of ritonavir increasing from 7,140 to 8,160 ng.h/mL.

Effect of paritaprevir/ritonavir on dasabuvir

Following co-administration of 100 mg dasabuvir BD with paritaprevir/ritonavir 200/100 mg QD the C_{max} and AUC_{12} values for dasabuvir was similar to when dasabuvir administered alone.

Effect of dasabuvir on paritaprevir/ritonavir + ombitasvir

Following co-administration of paritaprevir/ritonavir 150/100 mg QD + ombitasvir 25 mg QD with dasabuvir 400 mg BD for 14 days, paritaprevir exposure more than doubled. By contrast, the effect of dasabuvir on ritonavir and ombitasvir exposure was smaller with ritonavir AUC_{24} increasing from 10,100 to 13,700 ng.h/mL and ombitasvir AUC_{24} from 1,210 to 1,540 ng.h/mL.

Drug-drug interactions having a large effect on PKs (≥ ± 50%)

- Paritaprevir AUC values were increased by the co-administration of ketoconazole, rosuvastatin, lopinavir (LPV)/ritonavir, cyclosporine (CsA) or atazanavir by 1.98, 1.52, 2.17, 1.72 and 1.94 fold, respectively and decreased by tacrolimus and carbamazepine, by 1.51 and 3.4 fold, respectively.
- Ritonavir AUC was increased by the presence of ketoconazole or LPV/ritonavir by 1.57 and 2.05 fold, respectively, whereas, carbamazepine decreased the AUC by 7.9 fold.
- Ombitasvir AUC was decreased by 1.5 fold following co-administration with carbamazepine.
- Dasabuvir AUC was increased by the presence of gemfibrozil by 11.25 fold and decreased by carbamazepine or combined oral contraceptive (COC) by 3.3 and 2.08 fold, respectively.
- Dasabuvir M1 AUC was decreased by the co-administration of gemfibrozil or carbamazepine by 4.6 and 1.6 fold, respectively.
- In the presence of the 3DAAs + ritonavir the AUC values for pravastatin, rosuvastatin, rilpivirine, raltegravir, CsA, tacrolimus, buprenorphine, norbuprenorphine, norelgestromin (NGMN), norgestrel (NG) and amlodipine by 1.82, 2.59, 2.5, 2.34, 5.82, 57.1, 2.07, 1.84, 2.60, 2.54 and 2.57 fold, respectively.
- Co-administration of Atripla with the 3DAAs + ritonavir resulted in high number AEs therefore the 2 combination therapies should not be co-administered.

Drug-drug interactions having an intermediate effect on the PKs (< ± 50%)

- Co-administration of ketoconazole, gemfibrozil, pravastatin, darunavir or rilpivirine increased the AUC of paritaprevir by 1.42, 1.38, 1.13, 1.29 and 1.19 fold, respectively, whereas, emtricitabine/tenofovir, COC, duloxetine, zolpidem or amlodipine decreased the AUC of paritaprevir by 16%, 34%, 17%, 32% and 22%, respectively.
- Co-administration of tacrolimus or COC decreased the AUC of ritonavir by 13% and 29%, respectively.
- LPV/ritonavir increased the steady state ombitasvir AUC_{24} by 1.17 fold, whereas, atazanavir or darunavir decreased the AUC by 17% and 14%, respectively.
- Co-administration of emtricitabine/tenofovir, atazanavir, darunavir or CsA decreased the AUC of dasabuvir by 15%, 18%, 6% and 30%, respectively.
- Co-administration of emtricitabine/tenofovir, atazanavir, darunavir, COC or zolpidem decreased the AUC of dasabuvir M1 by 10%, 11%, 17%, 46% and 17%, respectively.
- Co-administration of paritaprevir/ritonavir/ombitasvir + dasabuvir decreased the AUC of omeprazole, darunavir, escitalopram and duloxetine by 39%, 25%, 13% and

25% and increased the AUC of naloxone, S-desmethylcitalopram and alprazolam by 1.28, 1.36, 1.34 fold.

Drug-drug interactions having little to no effect on PKs

- Co-administration of warfarin + Vitamin K1, digoxin, omeprazole, norethindrone (NET), alprazolam, escitalopram or furosemide had little no effect on the PKs of the 3DAAs + ritonavir.
- Co-administration of emtricitabine/tenofovir did not affect the exposure to ombitasvir or ritonavir.
- Co-administration of ketoconazole or tacrolimus had little to no effect on the PKs of ombitasvir or dasabuvir.
- Co-administration of pravastatin, rilpivirine, duloxetine, zolpidem and amlodipine had no effect on the PKs of ritonavir, ombitasvir or dasabuvir PKs.
- Gemfibrozil had little to no effect on ritonavir AUC_{inf}.
- Co-administration of the 3DAAs + ritonavir had little to no effect on the PKs of atazanavir, R- or S-warfarin, carbamazepine, digoxin, emtricitabine, tenofovir, R- and S-methadone, ethinyl estradiol (EE), NET, zolpidem or furosemide.
- Two studies examined the PPK of paritaprevir/ritonavir/ ombitasvir + dasabuvir in HCV genotype 1 infected subjects. In both studies, paritaprevir and ritonavir data was best fit to a one compartment model with first order absorption and elimination. By contrast, one study predicted that ombitasvir and dasabuvir data was best described by a one compartment model, whereas, the other study identified a 2 compartment model for these drugs.
- Covariates that were consistent across both two studies were: gender on paritaprevir and dasabuvir CL/F and ombitasvir Vd; and age, gender and body weight on ombitasvir CL/F.

Limitations of PK studies

- No studies examined the PKs of the 3DAAs in pregnant or breast feeding women or children (< 18 years of age).
- Studies to determine the absolute bioavailability of paritaprevir and ombitasvir have not been conducted.
- No studies contained in the clinical section of the evaluation materials have specifically examined the absorption, distribution, metabolism and excretion (ADME) of dasabuvir.
- The effect of raltegravir on the PKs of paritaprevir/ritonavir/ombitasvir/dasabuvir was not examined.
- No studies examined the effect of opioid like substances on the PKs of the 3DAAs + ritonavir. This is of concern as the PPK study, RD14-0047 PPK, identified concomitant opioid use as a significant covariant of paritaprevir clearance.
- It would have been more clinically relevant if the drug-drug interactions (DDIs) between paritaprevir/ritonavir/ombitasvir + dasabuvir and escitalopram or duloxetine had been examined on steady state levels of the anti-depressants rather than single doses as in Study M12-204, especially considering that CYP3A4 is a major contributor to the metabolism of escitalopram.
- Study M14-324 would have been more clinically relevant if it was conducted with steady state levels or at least following multiple daily doses of alprazolam.

- There are a number of inconsistencies between the PPK models defined for ombitasvir and dasabuvir in the two PPK studies.

Pharmacodynamics

Studies providing pharmacodynamic data

Summaries of the pharmacodynamic studies were provided. Table 17 shows the studies relating to each pharmacodynamic topic.

Table 17: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	Primary aim of the study
Secondary Pharmacology	Effect on QT	M12-990	QT effects of therapeutic and supratherapeutic doses
		M12-680	QT effects of therapeutic and supratherapeutic doses

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

For further details of the evaluation of the Pharmacodynamics please see Attachment 2.

Evaluator's conclusions on pharmacodynamics

Mechanism of action

Paritaprevir is a potent NS3/NS4A[64] protease inhibitor, ombitasvir is a NS5A inhibitor and dasabuvir is a NS5B polymerase inhibitor. Ritonavir is a potent CYP3A4 inhibitor.

Primary PD effects

Paritaprevir

In vitro studies indicate that paritaprevir potently inhibits the enzymatic activity of genotype 1a and 1b HCV NS3 proteases and genotype 1a and 1b replication. By contrast, paritaprevir is relatively less potent at inhibiting NS3 proteases from genotypes 2 and 3 and had no detectable inhibitory activity against endogenous human proteases or antiviral activity for HBV or HIV-1. The most common variants detected in NS3 that conferred resistance to paritaprevir were R155K, A156T, D168A/V/Y, V36M+R155K, and Y56H+D168V in genotype 1a; and R155K, D168K and D168V in genotype 1b.

Ombitasvir

Ombitasvir is a potent inhibitor of genotype 1 HCV replication in sub genomic HCV replicon cell culture assays, whereas, it has no in vitro antiviral activity against either HIV-1 or HBV. The most common variants observed in NS5A that conferred resistance to ombitasvir were M28T, M28V, Q30R, Y93C, and Y93H in genotype 1a; and Y93H in genotype 1b.

Dasabuvir

Dasabuvir is a potent inhibitor of HCV polymerases from genotype 1a and 1b strains. It was also a relatively weak inhibitor of HCV polymerases from genotypes 2 to 4. By

[64]NS3/NS4A = non-structural protein 3/ non-structural protein 4A

contrast, dasabuvir exhibited no significant inhibitory activity for endogenous human/mammalian polymerases or antiviral activity for either HIV-1 or HBV. The most common variants detected in NS5B that conferred resistance to dasabuvir were C316Y, M414T, Y448H, G554S, and S556G in genotype 1a; and C316Y, M414T, Y448H, and S556G in genotype 1b.

Antiviral activity in humans

- Four hours following dosing with ombitasvir, the mean decline in $\log_{10}$ HCV RNA viral load from baseline was statistically significantly greater than following placebo administration.
- Six hours following dosing with dasabuvir, all dose groups displayed decreased levels of HCV RNA and greater decreases through 12 hours after the first dose.
- Following multiple doses of paritaprevir/ritonavir, the mean maximum decrease from baseline in $\log_{10}$ HCV RNA levels was 4.03 $\log_{10}$ international units (IU)/mL and for dasabuvir was 1.02 $\log_{10}$ IU/mL. For subjects who received placebo the maximum decrease was 0.36 $\log_{10}$0 IU/mL HCV RNA.

Secondary pharmacodynamic effects

Therapeutic and supratherapeutic doses of paritaprevir/ritonavir/ombitasvir + dasabuvir did not prolong QT interval.

Time course of pharmacodynamic effects

The effects of ombitasvir and dasabuvir on baseline HCV RNA levels occur rapidly and statistically significant decreases are seen by 4 hours and 6 hours, respectively, after drug administration.

Relationship between drug concentration and pharmacodynamic effects

The antiviral effects of paritaprevir and ombitasvir were not dose dependent.

Following 100 mg QD, 100 mg BD and 600 mg BD, but not 600 mg QD, doses of dasabuvir the antiviral effects of dasabuvir were dose dependent.

Limitations of PD studies

No studies examined the gender and age related differences in pharmacodynamic response.

No studies examined PD interactions.

Dosage selection for the pivotal studies

Selection of the combination regimen, dosage and treatment duration was based on multiple Phase I and Phase II studies listed in Table 18.

Table 18: Studies used for regimen, dose and duration recommendation

Phase	Study (Planned N)	Study Design	Regimen
1	M12-187[a] (N = 52) (PK interaction)	Single-center, multiple-dose, open-label study designed to assess the PK and safety of ABT-267, ABT-450/r, and ABT-072 or ABT-333 when coadministered under nonfasting conditions	ABT-450/r + ABT-267 ± ABT-333 (or ABT-072)
1	M12-221[a] (N = 90) (PK Interaction)	Single-center, multiple-dose, open-label study designed to assess the PK and safety of ABT-267, ABT-450/r, and ABT-333 when coadministered under nonfasting conditions in Han Chinese, Japanese, and Caucasian subjects	ABT-450/r + ABT-267, ABT-450/r + ABT-267 + ABT-333
1	M10-351 (N = 24) (Substudy 2, HCV-infected subjects)	Treatment-naive HCV-GT1-infected subjects 2-day monotherapy, dose escalation, double-blind, placebo-controlled, nonfasting study conducted according to a randomized, sequential design (Substudy 2)	ABT-333
1	M12-116 (N = 18) (Substudy 4, HCV-infected subjects)	Randomized, double-blind, placebo-controlled, sequential substudy designed to assess the safety, tolerability, antiviral activity, and PK of ABT-267 3-day monotherapy (Substudy 4)	ABT-267
2	M10-380 (N = 30)	Blinded, randomized, multiple-dose, placebo-controlled study exploring the safety, tolerability, and antiviral activity of ABT-333 2-day monotherapy in HCV GT1-infected subjects	ABT-333, ABT-333 ± pegIFN ± RBV
2	M13-386 (N = 24)	Multicenter, open-label study to evaluate the safety, tolerability, PK, and antiviral activity of ABT-267 as 2-day monotherapy followed by ABT-267 coadministered with ABT-450/r, ABT-333, and RBV for 12 weeks in treatment-naive HCV GT1-infected subjects	ABT-267, ABT-267 + ABT-450/r + ABT-333 + RBV
2	M12-114 (N = 39)	A blinded, randomized, placebo-controlled, dose-ranging study to evaluate the safety, PK, and antiviral activity of ABT-267 in combination with pegIFN/RBV in treatment-naive subjects with chronic HCV GT1 infection	ABT-267, ABT-267 + pegIFN/RBV
2	M11-602 (N = 75)	A blinded, randomized, placebo-controlled, dose ranging study to evaluate the safety, tolerability, PK, and antiviral activity of multiple doses of ABT-450 with ritonavir (ABT-450/r), ABT-333, or ABT-072 each administered alone and in combination with pegIFN/RBV in treatment-naive subjects with chronic HCV GT1 infection	ABT-450/r, ABT-333, ABT-072, ABT-450/r + pegIFN/RBV ABT-333 + pegIFN/RBV ABT-072 + pegIFN/RBV
2	M12-746 (N = 45)	Multicenter, open-label, sequential, 3-arm, combination treatment study of a regimen of ABT-450/r, ABT-333, and RBV in HCV GT1-infected treatment-naive adults and previous nonresponders to pegIFN/RBV treatment	ABT-450/r and ABT-333 with RBV
2	M11-652 (N = 560)	Randomized, open-label, multicenter study to evaluate the safety and efficacy of ABT-450/r and ABT-267 and/or ABT-333 ± RBV for 8, 12, or 24 weeks in treatment-naive or null responders to previous pegIFN/RBV treatment	ABT-450/r + ABT-333 + RBV ABT-450/r + ABT-267 + RBV ABT-450/r + ABT-267 + ABT-333 ± RBV
2	M12-998 (N = 60)	Multicenter, open-label, 2 sequential arm, combination treatment study exploring the antiviral activity, safety, and PK of ABT-267 and ABT-450/r ± RBV in HCV GT 1-, 2-, or 3-infected, treatment-naive adults	ABT-267 + ABT-450/r ± RBV

Table 18(continued): Studies used for regimen, dose and duration recommendation

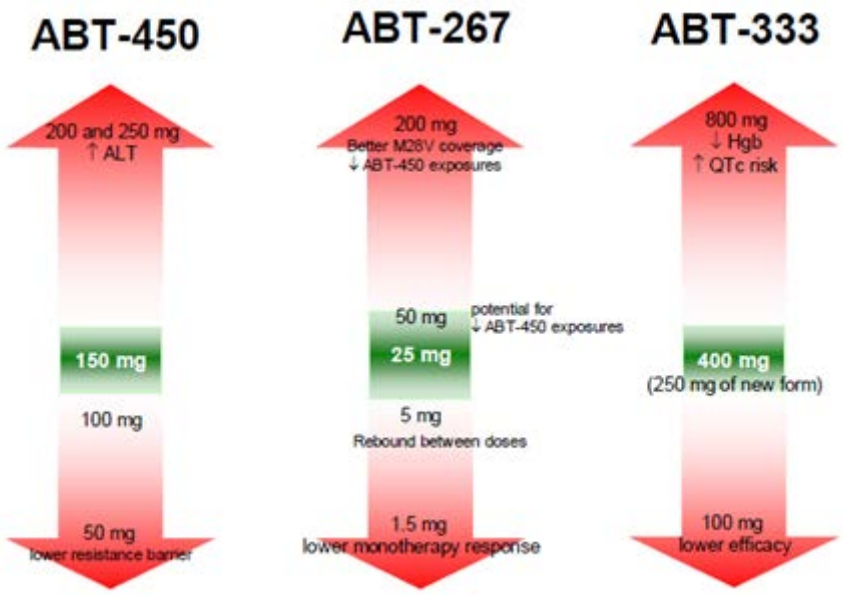
Phase	Study (Planned N)	Study Design	Regimen
2	M13-393[b] (GT1b, N = 80)	Randomized, open-label, combination treatment study to assess the PK, safety, and efficacy of the 2-DAA regimen of ABT-450/r and ABT-267 administered ± RBV	ABT-450/r + ABT-267 ± RBV
2	M12-536[b] (GT1b, N = 80)	Randomized, open-label study of 2 doses of ABT-450/r and 2 durations (12 and 24 weeks) to evaluate antiviral activity and PK of ABT-450/r and ABT-267 in HCV GT1b-infected and GT2-infected Japanese adults	ABT-450/r + ABT-267

a. Studies in healthy volunteers.

b. Used in discussion of the combination rule, but not used to justify the regimen chosen for Phase 3, as they had no results available before the Phase 3 studies began.

As stated in the Dose Duration report (R&D/14/0150), the doses for each of the 3DAAs that were to be used in the Phase III studies were determined by the examination of a combination of factors. These included comparisons of: viral load decline for different doses following monotherapy; virologic failure rates when the different doses were combined with peg-IFN plus RBV; virologic failure rates when the different doses were combined with other DAAs in the absence of interferon; and the resistance profile following monotherapy and IFN-free DAA combination regimens with the different doses. In addition, the safety profiles for the 3DAAs when combined with peg-IFN plus RBV and IFN-free DAA combination regimens were examined, as were the exposure-response relationships correlating exposures of paritaprevir, ombitasvir and dasabuvir to viral load and lab safety parameters. Finally, the PK interactions in healthy subjects between the 3DAAs and commonly prescribed and potentially co-administered medications were also taken into account. A summary of the principle drug characteristics that were used to determine the doses for each of the 3DAAs in Phase III are shown in Figure 7.

Figure 7: Summary of DAA doses selected for Phase III and to be marketed regimen with rationale for selection ABT-450 = paritaprevir; ABT-267 = ombitasvir and ABT-333 = dasabuvir



Comment: Conventional dose ranging studies are not feasible in chronic HCV infection because of the dangers of viral resistance in patients who receive potentially suboptimal treatment. This is particularly relevant with a novel 3DAA combination. The dosage and regimen selected for the Phase III studies was appropriate after consideration of a large body of in vitro and in vivo pre-clinical and Phase I and II data. For the Phase II and III studies, the optimal treatment duration was assumed to be 12 weeks but SVR were compared in different patient groups during treatment periods of 8, 12 and 24 weeks.

Efficacy

Studies providing efficacy data

For details of the evaluation of the studies providing efficacy please see Attachment 2.

Evaluator's conclusions on efficacy

Conclusions on clinical efficacy for the proposed indication of "*the treatment of genotype 1 chronic hepatitis C infection, including patients with cirrhosis*".

The study program was based on current US and EU guidelines for the treatment of chronic HCV infection, and scientific advice on study design and methodology was sought from the FDA and EMA. All studies were conducted according to the principles of GCP and patient numbers were adequate in the overall population and most subgroups. The eligibility criteria were appropriate with adequate representation of the most important patient groups defined by HCV genotype sub-type, prior treatment experience and the presence or absence of cirrhosis. Patients with significant hepatic and renal impairment were excluded, and also patients with co-infection with HIV. However, PK studies in these patient subgroups have been conducted leading to clear dosage recommendations and precautions in the PI. There were adequate numbers of males and females but few elderly patients were studied. In addition, the great majority of patients were White and efficacy in other racial groups, particularly Asians, needs further study. The potential influence of IL28B genotype sub-types was addressed in all the pivotal studies and no interactions were demonstrated.

The primary efficacy endpoint for all studies was sustained virologic response 12 weeks post-dosing rates in patients with chronic HCV genotype 1 infection. Within this population, important subgroups with known differing response rates to telaprevir + pegIFN/RBV were identified and analysed. These subgroups include patients with genotype 1a and genotype 1b infection, cirrhotic and non-cirrhotic patients, treatment naïve and treatment experienced patients, and other subgroups defined by IL28B status, gender, race, age, body mass index (BMI), baseline fibrosis score, baseline HCV RNA level and baseline interferon gamma-induced protein 10 (IP-10). SVR_{12} rates for the 3DAA + RBV combination in non-cirrhotic, treatment naïve and treatment experienced patients with genotype 1a and genotype 1b infection were compared with placebo in two pivotal Phase III studies. In the 770 patients who received active treatment during the 12 week double blind treatment period, the overall SVR_{12} rate was 96.2% (95% confidence interval (CI): 94.9%, 97.6%), and the rates were comparable in all subgroups including genotype subtype and prior treatment experience. The SVR_{12} rate was markedly superior to historical rates achieved by comparable patient groups treated with telaprevir + pegIFN/RBV. On treatment virologic failure and post treatment relapse occurred in only 2% of patients, and SVR_{12} almost completely predicted SVR_{24} rates. In the double blind studies, there was prompt normalisation of abnormal baseline liver function tests (LFTs) in most patients given active treatment. These studies confirmed the value of 3DAA + RBV given for 12 weeks in all non-cirrhotic patient groups with HCV genotype 1 infection.

The 3DAA + RBV and 3DAA 12 week treatment regimens were compared in non-cirrhotic, treatment naïve and treatment experienced patients with genotype 1a and genotype 1b infection in another three pivotal Phase III studies of similar design. In these studies, 398 and 505 patients were treated with 3DAA + RBV and 3DAA, respectively. In these studies, SVR_{12} rates of 90.2% to 100% were achieved across all patient groups, all markedly superior to historical rates with telaprevir + pegIFN/RBV. Only in treatment naïve genotype 1a patients treated with 3DAA were SVR_{12} rates lower than in other groups (90.2%). Only in this sub-group was an additional benefit obtained with the addition of RBV to the treatment regimen. However, an SVR_{12} rate of > 90% is still exceptional and 3DAA is a valid treatment option for patients intolerant of RBV. The 3DAA + RBV 12 week regimen was assessed in a single study in compensated cirrhotic patients with genotype 1 infection. SVR is more difficult to achieve in cirrhotic patients so the 3DAA regimen was not assessed, and the 3DAA + RBV regimen was given for 24 weeks in cirrhotic prior null responders. Outstanding SVR_{12} rates were achieved in cirrhotic patients with genotype 1b infection (99% overall), and in patients with genotype 1a infection (91% overall).

Dasabuvir has insufficient potency against HCV genotype 4 so a 2-DAA +/- RBV regimen was tested in this group of patients. An interim analysis of an on-going, open label, exploratory study with small patient numbers to date has demonstrated SVR_{12} rates of 100% and 90.9% in the 3DAA + RBV and 3DAA groups respectively. The data do not merit an indication for use in patients with genotype 4 infection but they are strongly encouraging and warrant further studies.

Safety

For a full evaluation of the safety please see Attachment 2.

Studies providing safety data

In the pivotal efficacy studies, the following safety data were collected:

- General AEs were assessed, documented and reported in accordance with ICH GCP and classified according to Medical Dictionary for Regulatory Activities (MedDRA) criteria.
- AEs of particular interest included LFT abnormalities, skin rash and anaemia. Hepatic safety was assessed by an independent specialist liver panel.
- Laboratory tests, including chemistry, haematology, urinalysis, HCV RNA and IL28B genotyping were performed by [information redacted] at Indianapolis, Geneva and Singapore.

Pivotal studies that assessed safety as a primary outcome

No studies were presented.

Dose response and non-pivotal efficacy studies

The dose response and non-pivotal efficacy studies provided safety data, assessed and categorised using the same methodology as the pivotal studies.

Other studies evaluable for safety only

No studies submitted.

Patient exposure

The majority of patients were male (57.3%) with a mean age of 51.6 years. A total of 214 (8.1%) patients were aged ≥ 65 years. The large majority of patients was White (90.5%) and 6.2% were Hispanic or Latino. A total of 2,632 patients with HCV genotype 1 infection

were exposed to the 3DAA combination, with or without RBV, for up to 24 weeks. A total of 380 patients had compensated cirrhosis. In the All Treated Analysis Set, the median exposure in each treatment group was 84 days with > 95% of patients exposed for more than 60 days of treatment. A total of 2,044 patients were exposed to 3DAA + RBV for 511.4 patient-years (PY), and 588 patients were exposed to 3DAA for 134.4 PY. Exposure in the All Treated Analysis Set was 586.2 PY in Whites, 41.8 PY in Hispanics or Latinos, 41.7 PY in Blacks, and 10.7 PY in Asians. Exposure in patients with compensated cirrhosis was 124.94 PY.

Comment: Further studies in Asian populations are in progress.

However, following co-administration of ombitasvir 25 mg QD HME, paritaprevir/ritonavir 150/100 mg QD, and dasabuvir 400 mg BD for 21 days to healthy Han Chinese, Japanese and Caucasian subjects, Study M12-221 indicated that relative to the values in Caucasians, the paritaprevir AUC_{24} values were 2.47 and 2.91 fold higher in Han Chinese and Japanese subjects, respectively, and the dasabuvir M1 AUC values were 1.35 and 1.50 fold higher in Han Chinese and Japanese subjects, respectively. For the other components of Viekira Pak changes in AUC were less than 1.3 fold between the 3 groups.

In addition, Study RD 13-1098 PPK identified that the ritonavir trough plasma concentration ($C_{\tau,ss}$) in HCV genotype 1 infected subjects of Hispanic/Latino ethnicity was approximately 156% higher than in non-Hispanic/Latino patients.

Safety issues with the potential for major regulatory impact

For a full evaluation of the safety please see Attachment 2.

Liver toxicity

No major issues were identified with the exception of a potential interaction between 3DAA and oestrogen containing medications.

Haematological toxicity

The known association of RBV with anaemia was confirmed but no issues related to 3DAA were identified.

Safety related to drug-drug interactions and other interactions

The sponsor has provided an extensive examination of the possible drug-drug interactions for Viekira Pak in healthy subjects. Studies have examined the interaction of the 3DAAs with: inhibitors of CYP2C8, CYP3A4 and P-gp; other drugs that are substrates for CYP1A1, CYP1A2, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP3A4, CYP3A5, P-gp and OATP1B1/B3; and an inducer of CYP3A. In addition, the interaction between the 3DAAs and: other antiviral drugs; commonly co-administered immune suppressants; commonly co-administered opioid substitutions; and commonly co-administered drugs; have also been examined.

As identified in the dose selection section of this report there is evidence to suggest that co-administration of drugs that increase the proposed level of paritaprevir exposure by 1.5 fold or greater may result in elevations in ALT and drugs that induce a 2 fold increase dasabuvir exposure may decrease haemoglobin and increase the risk to QTc elongation; whereas, drugs that induce a large increase in ombitasvir exposure (approximately 8 fold) may result in reduced paritaprevir exposure. By contrast, co-administered drugs that lower the levels of exposure to the 3DAAs may result in increased resistance and lower efficacy for HCV1.

The principle DDIs in regards to safety were therefore the interactions between: paritaprevir and ketoconazole, rosuvastatin, LPV/ritonavir, CsA or atazanavir, which resulted in paritaprevir AUC increases of 1.98, 1.52, 2.17, 1.72 and 1.94 fold, respectively, and with

carbamazepine, which induced a 3.4 fold decrease in paritaprevir AUC; and the interactions between dasabuvir and gemfibrozil, which increased dasabuvir AUC by 11.25 fold, and carbamazepine or COC which decreased dasabuvir AUC by 3.3 and 2.08 fold, respectively. Finally, co-administration of Atripla with the 3DAAs + ritonavir resulted in a large number of AEs, indicating that the 2 combination therapies should not be co-administered.

Post-marketing data

Not applicable. This is a new drug application.

Evaluator's conclusions on safety

The rationale for the development of this novel combination product is sound as viral resistance to the individual components is inevitable. However, assessment of safety and tolerability raises some unique issues as it is a fixed dose combination of three new chemical entities. Safety related to the individual components relies heavily on pre-clinical data, and limited data from Phase I and II studies in healthy subjects and patients. It also relies on the premise that the safety of the individual components can be assumed if the combination is shown to be safe. This assumption can be validly made based on the data presented.

The safety of the 3DAA combination has been assessed in treatment naïve and treatment experienced patients with HCV genotype 1a and genotype 1b infection, with and without compensated cirrhosis. The safety of the 3DAA + RBV combination was compared with placebo in the two pivotal studies, M11-646 and M13-098. The frequency of AEs was significantly higher in the active group compared with placebo although the pattern of AEs was comparable with the known AE profile of RBV. The safety of the 3DAA + RBV and 3DAA combinations was compared in three pivotal studies, M13-389, M13-961 and M14-002. All AE categories were reported more frequently in the 3DAA + RBV group compared with the 3DAA group. Although the data were generated from different studies, the frequency of AEs in the 3DAA and the placebo groups were comparable. In all studies, most AEs were of mild to moderate intensity. The frequency of Grade 3 or 4 ADRs and SAEs was low and none of the three deaths was considered to be drug related. Study drug compliance was high and discontinuations due to AEs occurred in only 1% of patients, confirming the tolerability of the combinations.

In the placebo controlled studies, the most common adverse drug reactions (ADRs) were pruritus, fatigue, nausea, asthenia, insomnia and anaemia, all of which occurred more commonly in the 3DAA + RBV group. In the regimen controlled studies, the same ADRs also occurred more commonly in the 3DAA + RBV group compared with the 3DAA group. However, ADRs in the placebo group (of the placebo controlled studies) were each reported more frequently than in the 3DAA group (of the regimen controlled studies). The only exception was pruritus which was reported in 4.3% and 6.1% of the respective groups. With the benefit of hindsight, it is regrettable that there are no direct comparisons of 3DAA and placebo in a Phase III study. Safety and tolerability were comparable in all patient sub-groups. Only 8% of patients were aged > 65 years but the frequency of ADRs was similar to the younger population. Most patients were Caucasian and further studies in Asian populations are required. An exploratory study of 2-DAA + RBV in patients with genotype 4 infection was also well tolerated and the data add weight to the overall safety profile of the 3DAA combination.

AEs of special interest based on approved HCV therapies including pegIFN/RBV and DAAs were also assessed. In the placebo controlled and regimen controlled studies, anaemia AEs were reported in 5.3% to 7.5% of the 3DAA + RBV groups, compared with only one patient in the 3DAA group and no patients in the placebo group. The results suggest that anaemia (and hyperbilirubinaemia) related to the 3DAA + RBV combination can be attributed

exclusively to the haemolytic anaemia associated with RBV. There was a prompt improvement in LFTs in all active treatment groups indicating a reduction in liver inflammation due to suppression of viral replication. There were transient marked elevations in ALT in approximately 1% of patients, most often during the first two weeks of treatment. However, there were no associated bilirubin elevations and the abnormalities were self-limiting. With the exception of pruritus, the frequency of skin AEs in the active treatment groups was comparable to placebo. Most rashes were mild or moderate in severity and there were no cases of the serious reactions seen with DAAs such as telaprevir. No studies have directly compared the safety profiles of the 3DAA with pegIFN/RBV or other DAAs. However, the overall safety profile of 3DAA with or without RBV is clearly superior to any other approved pegIFN/RBV or DAA + pegIFN/RBV combination therapy.

First round benefit-risk assessment

First round assessment of benefits

The benefits of Viekira Pak and Viekira Pak-RBV in the proposed usage are:

- In patients with HCV genotype 1 infection given the recommended dosage schedules (3DAA with or without RBV for 12 weeks or 24 weeks), SVR_{12} was achieved by 97% of non-cirrhotic patients with HCV genotype 1 infection, and 95% of patients with cirrhosis.
- The 3DAA combination alone is a viable and effective therapeutic option in patients intolerant of RBV.
- SVR_{12} rates in all patient groups were notably higher with 3DAA than with other approved combinations.
- Shorter treatment duration than other approved regimens (12 or 24 weeks versus 24 or 48 weeks).
- Very low rates of on-treatment virologic failure (0.5%) and post treatment relapse (1.6%).
- Almost 100% post treatment durability of response.
- Comparable efficacy in other sub-groups defined by IL28B status, gender, race, age, BMI, baseline fibrosis score, baseline HCV RNA level and baseline IP-10.
- Fixed dose regimens.
- Also the limited data from study M13-393 suggest efficacy as a 2-DAA combination in patients with HCV genotype 4 infection.
- Rapid normalisation of liver function tests in most patients (97% 3DAA + RBV, 15.8% placebo).
- Good safety profile with most AEs attributable to co-administered RBV. Pruritus (mostly mild) was the only potential specific safety signal detected.
- Well tolerated, contributing to good compliance (> 98%) and low discontinuation rates (0.3%).

First round assessment of risks

The risks of Viekira Pak and Viekira Pak-RBV in the proposed usage are:

- As yet unidentified ADRs.

- Potential interaction with oestrogen contraceptives (ALT elevation).
- As yet unidentified drug-drug interactions.
- ADRs associated with co-administered RBV.
- No data available in patients with decompensated liver disease or patients with moderate to severe renal impairment.
- Limited data in racial groups other than White.
- Emergence of resistant viral variants.
- No data in patients co-infected with HIV or HBV.
- No data available in liver transplant patients.

First round assessment of benefit-risk balance

The benefit-risk balance of Viekira Pak and Viekira Pak-RBV given the proposed usage, is highly favourable. The benefits of both products are summarised in relation to the tabulated indications in the proposed PIs shown below. In all patient subgroups, efficacy rates are outstanding and notably better than telaprevir-based therapy in the same subgroups. Viekira Pak is well tolerated. The risks associated with Viekira Pak relate largely to potential risks which have not been identified in the clinical trial program. The same risks apply to Viekira Pak-RBV with the addition of the well described toxicity associated with RBV.

Viekira Pak

Viekira Pak is indicated for both treatment naïve and treatment experienced patients with HCV genotype 1b infection without cirrhosis. SVR rates of > 95% can be anticipated without the addition of RBV.

In treatment naïve patients with a genotype 1a infection without cirrhosis, SVR rates were 97.0% in patients given Viekira Pak-RBV and 90.2% in patients given Viekira Pak. The addition of RBV confers additional benefit but outstanding SVR rates can still be achieved in patients who are intolerant of RBV.

The data do not support the use of Viekira Pak for any genotype subgroup other than 1b. It should not be recommended if the genotype 1 subtype is unknown, or for patients with mixed infections. Viekira Pak has not been tested in patients with cirrhosis.

Viekira Pak-RBV

Viekira Pak-RBV is indicated for treatment experienced patients with genotype 1a infection without cirrhosis. SVR was achieved by 93% of treatment naïve patients and > 95% of treatment experienced patients. As noted above, SVR rates > 90% may still be achieved with Viekira Pak in genotype 1 patients intolerant of RBV.

Viekira Pak-RBV is also indicated in patients with compensated cirrhosis and genotype 1 infection. SVR rates > 90% were achieved with higher rates in patients with genotype 1b infection compared with genotype 1a infection. There was a marginal benefit in in patients given 24 weeks rather than 12 weeks of therapy with SVR rates > 95%. However, there was a notable benefit in prior null responders given 24 weeks therapy compared with those given a 12 week regimen (95.2% versus 86.7%).

Table 19: Summary of treatment options

Patient Population	Treatment	Duration	Ribavirin Dosage
Genotype 1b, without cirrhosis	Viekira Pak	12 weeks	
Genotype 1a, without cirrhosis	Viekira Pak-RBV*	12 weeks	< 75kg = 1000mg ≥ 75kg = 1200mg Ribavirin is to be taken in two doses, morning and evening
Genotype 1 with cirrhosis	Viekira Pak-RBV*	12 weeks†	< 75kg = 1000mg ≥ 75kg = 1200mg Ribavirin is to be taken in two doses, morning and evening

*Viekira Pak without ribavirin can be considered as a therapeutic option for treatment naïve patients with genotype 1a infection without cirrhosis. Treatment decision should be guided by an assessment of the potential benefits and risks for the individual patient. †24 weeks of Viekira Pak–RBV is recommended for patients with genotype 1a-infection with cirrhosis who have had a previous null response to pegIFN and ribavirin. Viekira Pak-RBV ribavirin is recommended in patients with an unknown genotype 1 subtype or with mixed genotype1 infection.

First round recommendation regarding authorisation

Approval is recommended for the proposed indication of '*the treatment of genotype 1 chronic hepatitis C infection, including patients with cirrhosis*'. However, the approval is subject to incorporation of suggested changes to proposed PI and CMI and adequate response to clinical questions.

Clinical questions

Pharmacokinetics

Pharmacokinetics question 1

In studies M13-300 and M10-351, dasabuvir formulation appears to alter the effects of food on the bioavailability of dasabuvir. Can the sponsor please comment?

Pharmacokinetics question 2

The dose/exposure pattern of dasabuvir during Study M10-351 appears to be a little unusual. Can the sponsor please explain this behaviour in regards to dose normalised C_{max} and AUC for dasabuvir in Study M10-351 and why the results for the 1200 and 1600 mg doses are not consistent across the two studies?

Pharmacokinetics question 3

Regarding Study M10-861 can the sponsor please provide an explanation as to why accumulation of paritaprevir exposure was far less pronounced for the 300 mg paritaprevir dose compared to the 250 mg and 200 mg doses?

Pharmacokinetics question 4

Given the metabolic profile of R-warfarin, it is a little surprising that the PKs of R-warfarin were not affected by the presence of the 3DAAs + ritonavir (Study M12-198), considering that ritonavir is a potent inhibitor of CYP3A4. This possibly suggests that the PK interaction study should have instead examined steady state levels of warfarin. Can the sponsor please comment on whether a different result would be expected if this was the case?

Pharmacokinetics question 5

In Study M14-027, due to the inhibition of CYP3A4 induced by ritonavir should we not expect to see an increase in carbamazepine exposure in the presence of the 3DAAs + ritonavir?[65]

Pharmacokinetics question 6

It seems counter-intuitive that on the one hand ritonavir increases paritaprevir exposure (see Tables 6 and 7 in Attachment 2) but in Study M12-202 the additional dose of ritonavir decreases paritaprevir, can the sponsor please provide an explanation concerning the differences seen in paritaprevir PKs between Studies M13-506 and M12-202 described above?

Pharmacokinetics question 7

It is not clear why the sponsor has combined data from Arms 1 and 2 in which 3DAAs and 2 DAAs have been co-administered respectively, as Studies M13-394 and M12-189 indicate that co-administration of dasabuvir with paritaprevir/ritonavir/ombitasvir significantly affects the PKs of paritaprevir, ritonavir and ombitasvir. Can the sponsor please provide replacement Tables 4.57.1 and 4.57.2 in which the two data sets for Arm 1 and 2 have been separated?

Pharmacokinetics question 8

Given the results of RD14-0047 PPK indicate that concomitant opioid use may significantly affect paritaprevir clearance, can the sponsor please justify why the effects of co-administration of opioid like substances, in Studies M12-997 and M13-100, on the PKs of Viekira Pak were not examined?

Pharmacokinetics question 9

Given that for anti-depressants to be clinically effective they must attain steady state, why has Study M12-204 only examined the interaction between Viekira Pak and single doses of the anti-depressants, especially considering that CYP3A4 is a major contributor to the metabolism of escitalopram?

Pharmacokinetics question 10

As the US PI for Xanax states that alprazolam should be administered multiple times daily and for at least 3 to 4 days for maximum effect why has Study M14-324 only examined the interaction with Viekira Pak following a single dose of alprazolam? This is of particular importance given that potent CYP3A4 inhibitors can increase alprazolam plasma concentrations by up to 4 fold.

[65] Berbel GA et al. Protease inhibitor induced carbamazepine toxicity. *Clin Neuropharmacol* 2000: 23: 216-218

Pharmacodynamics

Pharmacodynamics question 1

Regarding Study M10-351, can the sponsor please provide an explanation as to why the 100 mg QD, 100 mg BD and 600 mg BD doses of dasabuvir have dose dependent antiviral effects, whereas, the 600 mg QD dose does not?

Efficacy

Efficacy question 1

Individual patient data and the percentages of some important protocol deviations are provided in the CSRs. However, it is unclear what percentages of patients had major deviations, how many had deviations leading to exclusion from the analyses of the primary endpoints, and on what basis these decisions were made. Please provide these data for each of the pivotal studies.

Efficacy question 2

The body of the M13-961 CSR Section 9.4.1 (Treatments) contains the following statement:

> *Subjects received paritaprevir/ritonavir/ombitasvir at 75 mg/50 mg/ 12.5 mg QD, dasabuvir 250 mg BD, and either placebo for RBV or weight based RBV 1,000 or 1,200 mg divided BD for 12 weeks. All study drugs were taken orally with food.*

In addition, the body of the M14-002 CSR Section 9.4.1 (Treatments) contains the following statement:

> *Subjects received paritaprevir/ritonavir/ombitasvir at 75 mg/50 mg/ 12.5 mg QD*

In each case the evaluator has assumed that paritaprevir/ritonavir/ombitasvir was actually given as two tablets of the stated dose QD and not one tablet either QD or BD. Please confirm.

Efficacy question 3

Studies M13-389 and M13-961 both assessed 3DAA with and without RBV. The RBV component in M13-961 was double blinded but M13-389 was conducted open label. Please provide a rationale for this difference in study design.

Efficacy question 4

In the pivotal studies, a non-inferiority margin of 10.5% was selected. Please provide a rationale for this choice.

Safety

Safety question 1

Was there a rationale for not including a 3DAA arm in addition to the 3DAA + RBV arms in the placebo controlled studies?

Second round evaluation of clinical data submitted in response to questions

For details of the sponsor's response and the evaluation of the response please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Viekira Pak and Viekira Pak-RBV in the proposed usage are unchanged from those identified in the first round assessment of benefits.

Second round assessment of risks

After consideration of the responses to clinical questions, the benefits of Viekira Pak and Viekira Pak-RBV in the proposed usage are unchanged from those identified in the first round assessment of risks.

Second round assessment of benefit-risk balance

The benefit-risk balance of Viekira Pak and Viekira Pak-RBV given the proposed usage, is favourable.

Second round recommendation regarding authorisation

Approval is recommended for the proposed indication of:

> *'the treatment of genotype 1 chronic hepatitis C infection, including patients with cirrhosis'*.

However, the approval is subject to incorporation of suggested changes to proposed PI (discussion of these is beyond the scope of the AusPAR).

V. Pharmacovigilance findings

NOTE: Please see the AusPAR for Viekira Pak-RBV (PM-2014-01438-1-2) for the pharmacovigilance findings for that product which is covered by a separate RMP.

Risk management plan

The sponsor submitted a Risk Management Plan RMP (in EU-RMP format) Version 1.0 (dated June 2014, DLP 24 January 2014) and Australian Specific Annex (ASA) Version 1.0 (dated June 2014 which was reviewed by the RMP evaluator.

The sponsor provided three RMPs in its submission, which were consistent in their contents and presentations:

- EU RMP for dasabuvir
- EU RMP for paritaprevir/ritonavir/ombitasvir
- 'Australian' RMP for paritaprevir/ritonavir/ombitasvir in combination with dasabuvir (primary RMP used in this evaluation report).

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 20.

Table 20: Ongoing safety concerns and missing information provided by the sponsor in their RMP submission for Viekira Pak (without ribavirin)

Ongoing safety concerns for Viekira Pak (without ribavirin)	
Important identified risk	• Drug-drug interactions • Post-baseline serum ALT elevations (general population) • Post-baseline serum ALT elevations (patients receiving systemic oestrogen-containing medications)
Important potential risk	Off-label use
Missing information	• Safety in paediatric subjects • Transplant subjects • HIV co-infected subjects • Subjects with Child Pugh B • HCV-infected patients with creatinine clearance ≤ 60 mL/min • Medication errors • Safety in pregnancy or during breastfeeding • Risks of resistance development

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities for important identified and important potential risks, and missing information items. Routine pharmacovigilance activities include targeted questionnaires for post-marketed serious hepatic events. Furthermore, additional activities are planned for some risks (Table 21).

Table 21: Additional pharmacovigilance activities planned by the sponsor

Additional activity	Objectives	Assigned safety concern	Status	Estimated planned submission of final data
Phase II/III randomised, open label study of paritaprevir /ritonavir/ombitasvir and dasabuvir with ribavirin in adults with genotype 1 HCV infection and HIV-1 co-infection. Study M14-004	Safety and efficacy	HIV co-infected patients	Ongoing	Phase II cohort in 3rd quarter 2014 Phase III cohort in November 2015

Additional activity	Objectives	Assigned safety concern	Status	Estimated planned submission of final data
Phase II open label, study of paritaprevir /ritonavir/ombitasvir and dasabuvir with or without ribavirin in adult liver transplant recipients with genotype 1 HCV Infection. Study M12-999	Safety and efficacy	Transplant patients	Ongoing	May 2014 (interim) December 2015 (final)
Study in moderate hepatic impairment.	Safety and efficacy	Subjects with Child Pugh B	Planned Draft study protocol unavailable	4th quarter 2015
Study in subjects with moderate to severe renal impairment	Safety and efficacy	HCV-infected patients with creatinine clearance ≤ 60 mL/min	Planned Draft study protocol unavailable	4th quarter 2015
Study of paritaprevir /ritonavir/ombitasvir and dasabuvir in paediatric subjects.	Safety and efficacy	Safety in paediatric subjects	Deferred Draft study protocol unavailable	Not declared
Phase III follow-up study in subjects who participated in Phase II or III clinical studies for the treatment of chronic HCV infection. Study M13-102	Assess resistance and durability of paritaprevir /ritonavir/ ombitasvir and dasabuvir therapy	Risks of resistance development	Ongoing	May 2016

Table 22: Additional pharmacovigilance activities conducted by the sponsor, but which are not in the pharmacovigilance plan

Additional activity	Assigned safety concern
M14-423 A Study to Evaluate Long-term Outcomes Following Treatment With paritaprevir/Ritonavir/ombitasvir (paritaprevir/ritonavir/ ombitasvir) and dasabuvir With or Without Ribavirin (RBV) in Adults With Genotype 1 Chronic Hepatitis C Virus (HCV) Infection (TOPAZ-I)	Long-term safety
M14-222 A Study to Evaluate Long-term Outcomes Following Treatment With paritaprevir/ritonavir/ombitasvir and dasabuvir With or Without Ribavirin (RBV) in Adults With Genotype 1 Chronic Hepatitis C Virus (HCV) Infection ((TOPAZ II))	Long-term safety
M13-004 Study to Evaluate the Efficacy and Safety of paritaprevir/ritonavir/ombitasvir in Japanese Adults With Subgenotype 1b Chronic Hepatitis C Virus (HCV) Infection (GIFT I)	Non-Caucasian patients
M14-153 Study to Evaluate the Efficacy and Safety of paritaprevir/ritonavir/ ombitasvir in Japanese Adults With Genotype 2 Chronic Hepatitis C Virus (HCV) Infection (GIFT II)	Non-Caucasian patients; Patients with genotype 2, 3, 4, 5 or 6 HCV infection
M14-250* Co-administration of paritaprevir/ritonavir/ombitasvir with ribavirin (RBV) in Adults With Genotype 4 (genotype4) Hepatitis C Virus (HCV) in Egypt	Patients with genotype 2, 3, 4, 5 or 6 HCV infection
M14-226 Ombitasvir/paritaprevir/ritonavir and Dasabuvir With or Without Ribavirin in Treatment naïve HCV Genotype 1-Infected Adults With Chronic Kidney Disease	Patients with severe renal impairment

*Limited applicability to Viekira Pak

Risk minimisation activities

The sponsor proposes no additional risk minimisation activities.

Reconciliation of issues outlined in the RMP report

Recommendation 1 in RMP report

It is recommended that the following important potential risk and missing information items should be added as ongoing safety concerns and become part of the pharmacovigilance plan for the 3DAA regimen:

Important potential risk

- Hypersensitivity (for the 3DAA regimen).

Missing information

- Patients with genotypes 2, 3, 4, 5 and 6 HCV infection
- Patients with HBV co-infection
- Non-Caucasian patients (including Asian or Australian Indigenous populations)
- Long-term safety
- Carcinogenicity data for ombitasvir and dasabuvir
- Effectiveness of hormonal contraception;
- Acute liver disease (other than HCV infection)
- Patients with portal hypertension
- Anaemia (for the 3DAA regimen)
- Hyperbilirubinaemia
- Patients with Child Pugh Score C/decompensated cirrhosis
- Patients over 70 years
- Patients with severe renal impairment

Sponsor's response

AbbVie acknowledges that there is a risk of hypersensitivity with any new chemical entity and the Australian package insert has language about this, as does the company core labelling. This language, however, is not based on specific data which implicates the 3DAA regimen with the risk of hypersensitivity, but is based on the theoretical risk for this type of event with any new chemical entity. AbbVie agrees to add this theoretical risk to the Australian Specific Annex (ASA) per TGA's request.

Missing information risks

The following as shown in Table 23 have been added as missing information risks in the approved EU RMP Version 1.2.

Table 23: missing information risks added to the revised RMP

Information added to RMP	
Important missing information	Safety in patients with hepatic impairment (Child-Pugh B)
	Safety in patients with renal impairment (creatinine clearance < 60 mL/min)
	Safety in post liver transplant patients
	Safety in patients co-infected with HIV-1
	Safety in pregnancy in patient using the 3DAA regiment without RBV
	Safety in patients co-infected with HBV
	Safety in elderly patients
	Safety in patients who have failed prior DAA treatments

Information added to RMP	
	Safety in genotype 4 infected patients with cirrhosis

Based on this revised table, AbbVie believes that the missing information in patients > 70 years of age, in HBV co-infected patients, renal impairment, and moderate hepatic impairment has been addressed.

AbbVie does not believe that a missing information risk should be added for acute liver disease. The 3DAA regimen has been developed for and has specific antiviral effect against hepatitis C. It is not indicated for treatment of other hepatic diseases, thus adding a missing information risk for acute liver disease is not appropriate given that the regimen is not indicated for use in other hepatic diseases. The section of the RMP that the RMP evaluator quotes is specifically based on exclusion criteria of the clinical trials in which patients were excluded if they had causes for liver disease other than HCV. This exclusion criteria was included as part of the clinical trial to allow for inclusion of subjects for chronic HCV infection and not liver disease due to another cause. Based on the indication for the regimen, a missing information risk is not believed to be necessary.

AbbVie does not believe that a missing information risk should be added for portal hypertension. Patients with Child Pugh B (moderate hepatic impairment) are included as missing information in the 3DAA RMP v1.2 and use of the 3DAA regimen is contraindicated for use in patients with Child Pugh C (severe hepatic impairment).

AbbVie does not believe that a missing information risk should be added for genotypes 2 to 6. The 3DAA regimen is not indicated for use in these genotypes. In addition, off label use (including use in genotypes other than those indicated) is included as a potential risk in the 3DAA RMP. Finally, dasabuvir is less effective in genotypes other than 1, thus this regimen will not be submitted for indications in these other genotypes.

In addition, because one of the identified risks with the 3DAA regimen is ALT elevations, a category 3 post authorisation safety studies (PASS) protocol is being developed and is under review by the EMA. This protocol is designed to evaluate frequency of grade 3^{+} ALT elevations in the real world (post-market) and to evaluate whether there are any acute hepatic outcomes related to these elevations (Part III Pharmacovigilance Plan of the v 1.2 RMP). Because the 3DAA regimen is used for 3 or 6 months, a specific risk for long-term safety is not included in the RMP. Clinical trials have been followed through 48 weeks post-DAA dosing, and no safety signals have been identified during this follow-up period. In addition, persistence of resistance and 5 year long-term studies to evaluate impact of achieving SVR on hepatic outcomes are underway and are included in v1.2 of the RMP.

A missing information risk for non-Caucasians, including the Australian Indigenous populations has been added to the ASA per TGA's request.

Missing information for carcinogenicity

The rat carcinogenicity studies for dasabuvir and ombitasvir will be available in April of 2015 and will be submitted at that time.

Anaemia is an identified risk in the ribavirin annex and it is identified as an important class effect in Section SVII 5.2 of the 3DAA RMP. AbbVie does not believe that it should be added as an important identified risk of the 3DAA regimen without ribavirin.

The graphs below are from the ISS. When ribavirin is not used with the 3DAA regimen (regimen controlled studies), the decline from baseline in haemoglobin is similar to the placebo arm in the placebo controlled studies.

Figure 8: Mean change from baseline in haemoglobin (g/L) (placebo controlled analysis set)

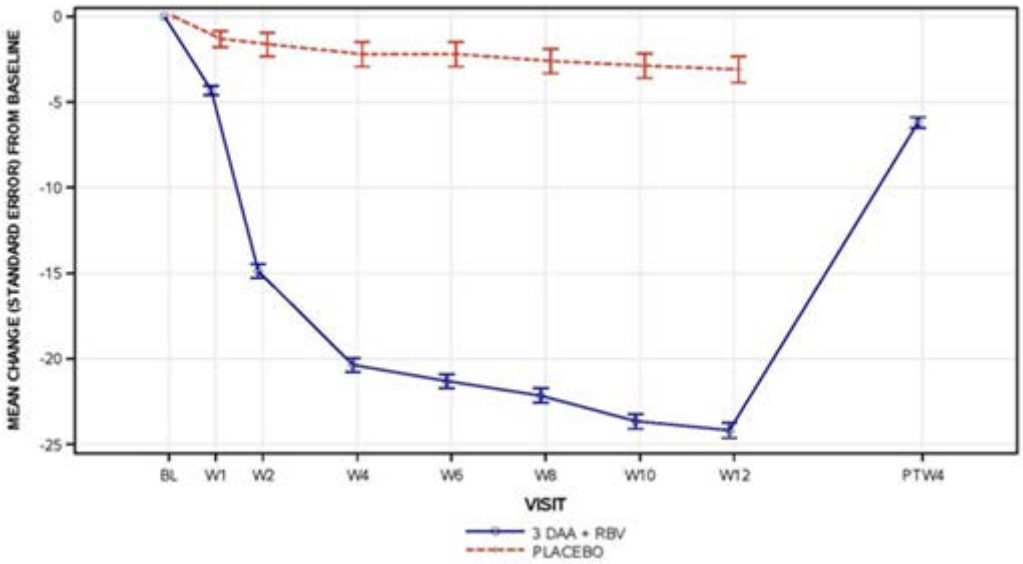
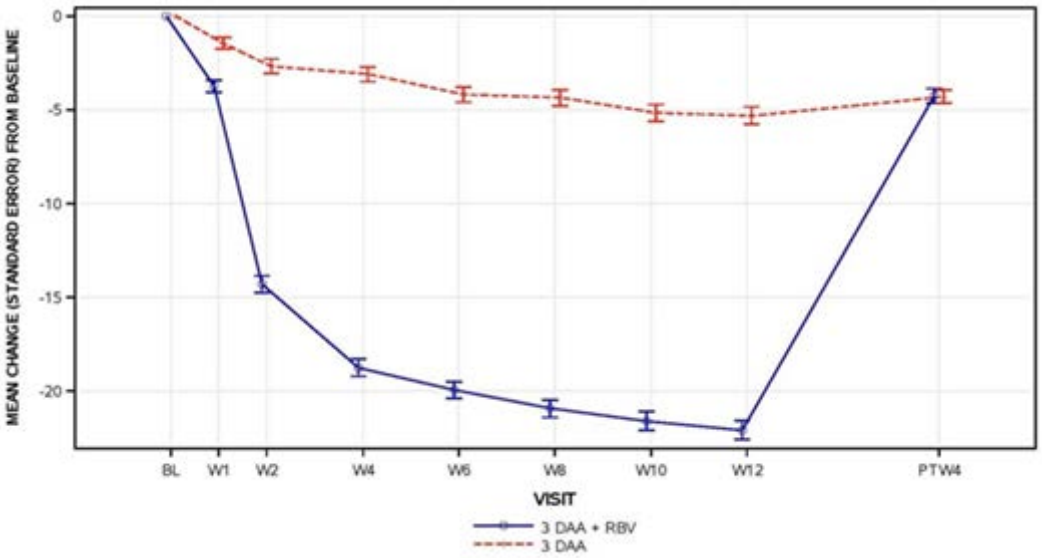


Figure 9: Mean change from baseline in haemoglobin (g/L) (regimen controlled analysis set)



For the risk of hyperbilirubinaemia, the sponsor notes that this risk is categorized in Section SVII 5.2 of the 3DAA RMP. Elevations in total, predominantly indirect bilirubin are a known effect of the use of ribavirin related haemolysis and due to inhibition of the OATP bilirubin transporter by paritaprevir. As described in the ISS, when ribavirin is not used with the 3DAA regimen, the rate of hyperbilirubinaemia is greatly reduced (see graphs below). Thus, based on the known effect of ribavirin on haemolysis, ribavirin enhances the hyperbilirubinaemia effect when it is taken with the 3DAA regimen. AbbVie does not believe that hyperbilirubinaemia should be added as an identified risk for the 3DAA regimen without ribavirin. This has been agreed to by the RMP evaluator.

Figure 10: Mean change from baseline in total bilirubin (µmol/L) (placebo controlled analysis set)

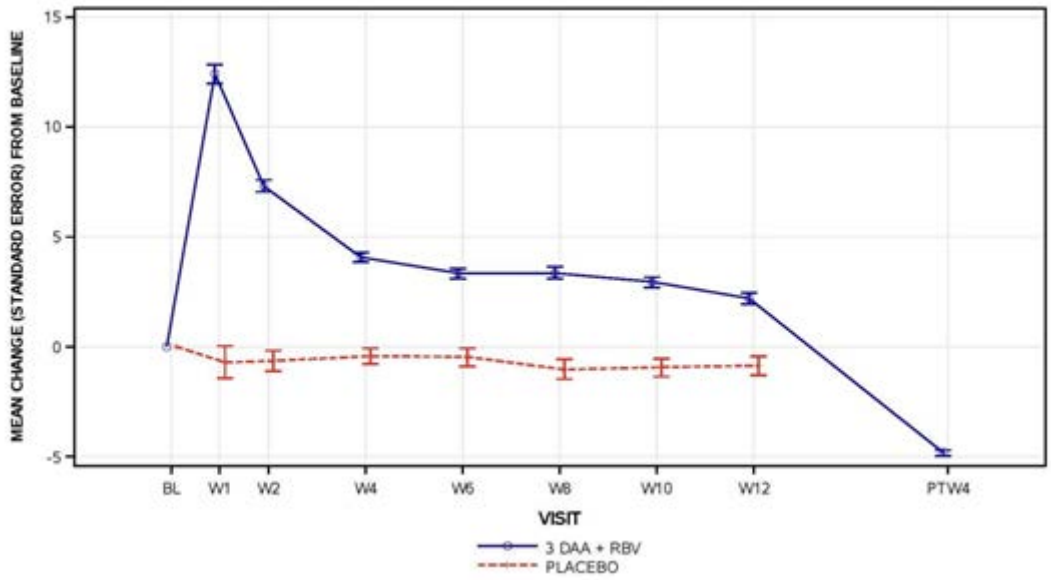
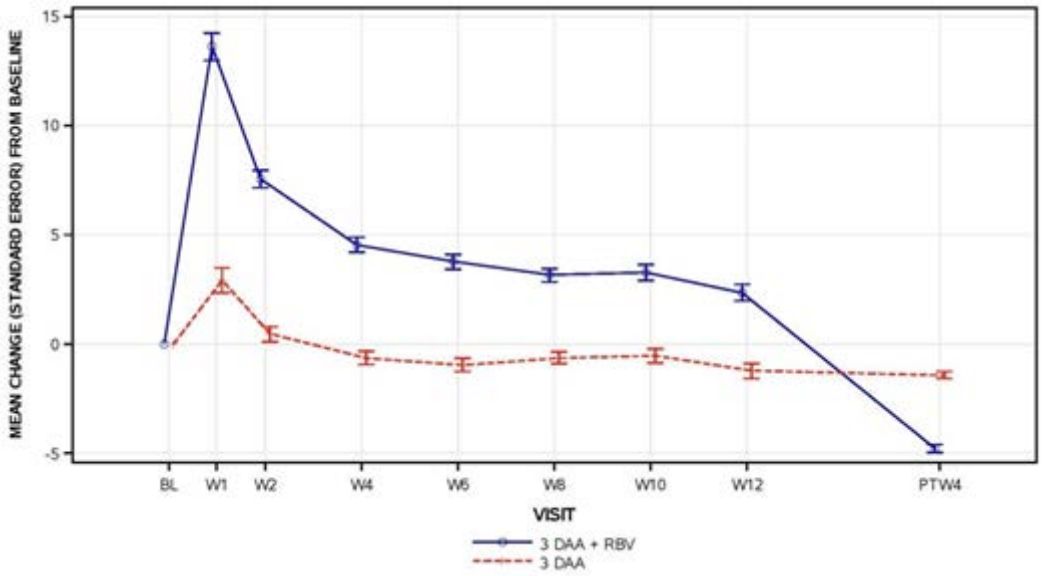


Figure 11: Mean change from baseline in total bilirubin (µmol/L) (regimen controlled analysis set)



Effectiveness of hormonal contraception

A Phase I study in healthy volunteers has been conducted with the DAA regimen and oral contraceptives. This study included arms with ethinyl estradiol (EE) containing oral contraceptives and progestin (PG)-only contraceptives [Study M12-205].
Co-administration of the progestin-only oral contraceptive, norethindrone, with the paritaprevir/ritonavir/ombitasvir plus dasabuvir regimen did not affect exposures (C_{max}, AUC and C_{trough}) of norethindrone (≤ 17% decrease). No dose adjustment is needed for norethindrone when administered with the 3DAA regimen. With the co-administration of norethindrone and the 3DAA regimen, paritaprevir C_{max} and AUC values increased by 24%, and 23%, respectively. Ritonavir C_{max} and AUC values showed less than a 27% increase.

Ombitasvir exposures (C_{max} and AUC) were comparable to those without norethindrone co-administration. No dose adjustment for the DAAs is recommended as the increase in

paritaprevir exposures when co-administered with a progestin-only oral contraceptive, norethindrone, is not expected to have a clinically meaningful impact on DAA safety.

As an example of a progestin only product, norethindrone (Micronor Australian PI) has been available by prescription since 1957 as a progestational agent, and has been used extensively in the treatment of amenorrhea, menstrual irregularity, functional uterine bleeding, infertility, habitual and threatened abortion, premenstrual tension, and dysmenorrhea. More recently, it has been utilized as the progestational component of several oral contraceptives, in combination with ethinyl estradiol or its 3-methyl ether. A new concept of contraception has evolved from the investigations of the progestational components, namely, the use of continuous low level doses in amounts which produce contraception and, at the same time, permit menstrual bleeding. These progestin only contraceptives may be used with the DAA regimen and were included for evaluation in the Phase I study described above.

The Australian PI contains language about the use of at least 2 effective forms of birth control. Ethinyl estradiol containing contraceptives are contraindicated based on the safety issue with ALT elevations; therefore, progestin only contraceptives would need to be considered if a hormonal form of birth control is being used. In addition, non-hormonal forms of birth control should also be considered. These include effectiveness barrier methods. These methods do not interact with the DAA regimen, so if at least 2 forms of contraception are used; this would comply with the Australian Viekira PAK-RBV PI. In addition, this would comply with the PIs for ribavirin, which is a teratogen and for which two effective forms of birth control are required.

Based on this, AbbVie does not believe that a missing information risk for effectiveness of hormonal contraceptives is needed in the 3DAA RMP or the ASA.

RMP evaluator's comment

This is considered acceptable as previously agreed.

Recommendation 2 in RMP report

a. The safety concern 'Transplant patients' should be altered to include transplants other than liver transplants; and

b. The sponsor did not consider the incidence of gallbladder related adverse events as clinically significant. This item will be reviewed in the second round as an important potential risk.

Sponsor's response

This change has been made in the revised RMP.

In the 3DAA RMP Module SII, the preclinical finding of adverse histopathological findings in the gallbladder is described. In this section, it is also described that these findings were isolated to one species and were observed in a 6 month study at exposures which were 31 fold above human clinical exposures. In addition, similar findings were not observed in the 3 month study at exposures which reached 60 fold above human clinical exposures. In Section SVIII of Version 1.0 of the RMP, findings using a Standardised MedDRA Queries (MedDRA SMQ) were described showing that there was a low rate of gallbladder events in the Phase II-III dataset, and this rate was much lower than observed epidemiological studies in an HCV infected population. Based on this, AbbVie did not carry this risk forward. AbbVie maintains this and in the approved EU RMP Version 1.2, the risk of gallbladder findings is not listed as an important potential risk.

In addition, the following are based on the preclinical findings:

- Repeat dose toxicity studies (CD-1 mice) and dose selection (TgHras mice): No gallbladder findings were observed in the 3 month study in CD-1 mice at exposures up to 417 µg.hr/mL. In the 6 month study in CD-1 mice, gallbladder findings consisted of

focal erosion/ulceration, inflammation and epithelial hypertrophy/hyperplasia in some mice at paritaprevir exposures ≥ 220 µg.hr/mL. The severity score for the erosions/ulcerations varied from minimal to moderate, whereas the remaining changes were classified as minimal to mild. Changes in the gallbladders of the recovery mice were limited to minimal epithelial hypertrophy/hyperplasia in one male and acute inflammation in two males administered 300/30 mg/kg/day. The lack of erosions/ulcerations in the recovery animals and the minimal nature of the ongoing inflammation/hyperplasia/hypertrophy are consistent with a regressing change. For the carcinogenicity study in the transgenic mice, 300 mg/kg/day (paritaprevir/ritonavir) was selected as the high dose as it resulted in maximal feasible exposure in both the CD-1 mouse (6 month study) and the wild type TgHras mouse (1 month study) (300/30 mg/kg/day) in order to ensure that the potential for carcinogenicity was adequately evaluated from an exposure standpoint.

- Relevance of TgHras Mouse Strain[66]: AbbVie considers the 6 month study in the TgHras mouse to be a robust evaluation for detection of a carcinogenic risk, including the potential for progression of the gallbladder hypertrophy/hyperplasia to a neoplastic state. The TgHras mouse (CByB6F1-Tg(HRAS)2Jic) model was selected as it is an accepted model for evaluation of both genotoxic and nongenotoxic compounds. This mouse model has its own promoter/enhancer elements and harbors a single point mutation which induces high enhancer activity. Since the pathogenesis of human cancer is often multifactorial, AbbVie believes that the promoter/enhancer properties inherent to this mouse strain combined with the paritaprevir associated gallbladder hypertrophy/hyperplasia/inflammation would constitute a suitable model for evaluation of the overall paritaprevir carcinogenic risk.

Treatment with the tumour promoter 12-o-tetradecanolyphorbol-13-acetate (TPA) results in an epithelial hyperplastic response. The HrasG12V knock-in allele (Caggs-Cre/FR-HrasG12V model) has been shown to be sensitive to TPA. In this model, topical treatment with TPA results in tumours,[67] without the requirement for topical applications of the initiator 7,12-dimethylbenz(a)anthracene (DMBA). Also of interest are publications citing concordance between transgenic and non-transgenic mice with respect to evaluation of other compounds that result in hyperplasia (ethylene thiourea, p-cresidine, 4,4'-thiodianiline)[68],[69],[70] and for concordance in general between the TgHras model and the 2 year rat model.[71] Other evidence of the interaction of inflammation and Hras signaling in the progression of epithelial cell neoplasia has been identified in other models of Hras mutant mouse epithelial tumours.[72]

In summary, AbbVie believes that the risk for progression of gallbladder hypertrophy/hyperplasia/inflammation has been adequately evaluated. The lack of gallbladder findings at exposures approximately 60 fold exposures at the maximal clinical dose in the 3 month study coupled with the evidence of regression of these findings in the

[66] Morton D, et al. The Tg rasH2 Mouse in Cancer Hazard Identification. *Toxicologic Pathology*. 2002;30: 139-146.
[67] Chen X, et al. Transformation by HrasG12V is consistently associated with mutant allele copy gains and is reversed by farnesyl transferase inhibition. *Oncogene*. 2014;33:5442-5449
[68] Yamamoto S, et al. Validation of transgenic mice carrying the human prototype c-Ha-ras gene as a bioassay model for rapid carcinogenicity testing. *Environ Health Perspec.* 1998;106:57-69.
[69] Yamamoto S, et al. Rapid caricinogenicity testing system with transgenic mice harboring human prototype c-HRAS gene. *Lab An Sci.* 1997;47:121-125.
[70] National Toxicology Program (1993). Bioassay of 1-pheyl-3-methyl-5-prazolone for possible carcinogenicity (CAS No.89-25-8). Compendium of Abstracts from Long-Term Cancer Studies Reported by the National Toxicology Program from 1976 to 1992.
[71] Nambiar P, Morton D. The rasH2 model for assessing carcinogenic potential of pharmaceuticals. *Toxicol Pathol.* 2013;1:1058-1067.
[72] Wong, CE, et al. Inflammation and Hras signaling control epithelial-mesenchymal transition during skin tumor progression. *Genes and Development*. 2013;27:670-682.

6 month study is consistent with a transient change. Additionally, AbbVie believes that use of the TgHras transgenic model allowed investigation of the potential for progression of the hypertrophy/hyperplasia/inflammation to a neoplastic state by virtue of the promoter/enhancer activity of this model.

RMP evaluator's comment

a. This is considered acceptable in the context of this application.

b. The RMP evaluator has reviewed the non-clinical evaluation report and the sponsor's response and does not consider the incidence of gallbladder related adverse events as an important potential risk for Viekira Pak.

Recommendation 3 in RMP report

The ongoing Phase II/III study for HIV co-infected patients (M14-004) relates to Viekira Pak RBV not Viekira Pak. It is unclear from the submission whether the sponsor plans to undertake a study with co-infected HIV patients without ribavirin. The sponsor should state whether another study is planned.

Sponsor's response

The sponsor confirms that a protocol amendment for the study in HIV co-infection is planned to include an arm evaluating the 3DAA regimen without ribavirin in HCV genotype 1b infection.

RMP evaluator's comment

This is considered acceptable in the context of this application.

Recommendation 4 in RMP report

The proposed study investigating concomitant systemic oestrogen use should be added to the pharmacovigilance plan and the protocol made available to the TGA.

Sponsor's response

The proposed study investigating concomitant systemic oestrogen use has been added to the pharmacovigilance plan and the protocol has been included in the updated version (v 1.2) of the RMP. This study is a category 3 PASS protocol and will include evaluation of grade 3^{+} ALT elevations and risks factors for these elevations, including estrogens. Ethinyl estradiol (EE) estrogens are contraindicated with the DAA regimen, so among the risk factors, the risk of ALT elevation among non EE estrogen users will be explored. See Part III Pharmacovigilance Plan in the revised RMP.

RMP evaluator's comment

This is considered acceptable in the context of this application.

Recommendation 5 in RMP report

It is noted that the sponsor is already conducting or planning to conduct additional pharmacovigilance activities. These additional pharmacovigilance activities should be added to the pharmacovigilance plan.

Sponsor's response

The additional pharmacovigilance activities have been added to the pharmacovigilance plan in the updated version (v 1.2) of the RMP.

RMP evaluator's comment

This is considered acceptable in the context of this application.

Recommendation 6 in RMP report

Not all study protocols have been attached to the submission. The sponsor should provide the missing protocols, once available.

Sponsor's response

All available study protocols have been included in the updated version (v 1.2) of the RMP.

RMP evaluator's comment

This is considered acceptable in the context of this application.

Recommendation 7 in RMP report

The following missing information item requires additional pharmacovigilance activities in the pharmacovigilance plan: Effectiveness of hormonal contraception.

Sponsor's response

- A Phase I study in healthy volunteers has been conducted with the AbbVie DAA regimen and oral contraceptives. This study included arms with EE containing oral contraceptives and progestin (PG)-only contraceptives [Reference Study M12-205]. Co-administration of the progestin only oral contraceptive, norethindrone, with the paritaprevir/ritonavir/ombitasvir plus dasabuvir regimen did not affect exposures (C_{max}, AUC and C_{trough}) of norethindrone (≤ 17% decrease). No dose adjustment is needed for norethindrone when administered with the 3DAA regimen. With the co-administration of norethindrone and the 3DAA regimen, paritaprevir C_{max} and AUC values increased by 24%, and 23%, respectively. Ritonavir C_{max} and AUC values showed less than a 27% increase. Ombitasvir exposures (C_{max} and AUC) were comparable to those without norethindrone coadministration. No dose adjustment for the DAAs is recommended as the increase in paritaprevir exposures when co-administered with a progestin only oral contraceptive, norethindrone, is not expected to have a clinically meaningful impact on DAA safety.
- As an example of a progestin only product, norethindrone (reference Micronor Australian PI) has been available by prescription since 1957 as a progestational agent, and has been used extensively in the treatment of amenorrhea, menstrual irregularity, functional uterine bleeding, infertility, habitual and threatened abortion, premenstrual tension, and dysmenorrhea. More recently, it has been utilized as the progestational component of several oral contraceptives, in combination with ethinyl estradiol or its 3-methyl ether. A new concept of contraception has evolved from the investigations of the progestational components, namely, the use of continuous low level doses in amounts which produce contraception and, at the same time, permit menstrual bleeding.
- The Australian PI contains language about use of an effective form of birth control. EE containing contraceptives are contraindicated based on the safety issue with ALT elevations, so progestin only contraceptives would need to be considered if a hormonal form of birth control is being used. In addition, non-hormonal forms of birth control can also be considered. These include effectiveness barrier methods. These methods do not interact with the DAA regimen, so would comply with the Australian Viekira PAK PI. Based on this, AbbVie does not believe that a missing information risk for effectiveness of hormonal contraceptives is needed in the 3 DAA-RMP or the ASA.
- AbbVie's routine pharmacovigilance includes collection of reports in pregnancy both in clinical trials and in the post-market period. These reports are evaluated with data summarized in the periodic update safety reports (PSURs). Labelling updates or other pharmacovigilance activities are considered, when appropriate, to address any issues which are identified.

RMP evaluator's comment

This is considered acceptable in the context of this application.

It is noted that the Advisory Committee for the Safety of Medicines (ACSOM) provided the following comment: "The committee advised that while the Viekira Pak – oestrogen drug interaction was a safety signal that needed to be managed, additional pharmacovigilance activities to further evaluate the effectiveness of hormonal contraceptive agents when used in conjunction with Viekira Pak/Viekira Pak RBV were not necessary. Instead, information for patients and prescribers needed to be strengthened and aligned to the information in the Eu SmPC."

Recommendation 8 in RMP report

The following missing information items would benefit from additional pharmacovigilance activities in the pharmacovigilance plan:

- Patients with portal hypertension;
- Patients with HBV co-infection.

Sponsor's response

AbbVie does not believe that a missing information risk should be added for portal hypertension. Patients with Child-Pugh B (moderate hepatic impairment) are included as missing information in the 3DAA RMP, (new version now being submitted), and use of the 3DAA regimen is contraindicated for use in patients with Child-Pugh C (severe hepatic impairment).

Patients with HBV co-infection have been addressed in the updated version (v 1.2) of the RMP.

RMP evaluator's comment

This is considered acceptable in the context of this application.

Recommendation 9 in RMP report

The sponsor should state which of the different packaging forms is proposed for Australia.

Sponsor's response

Of the two packaging configurations shown, option 2 will only be supplied in Australia; a blister containing co-packaged paritaprevir/ritonavir/ombitasvir and dasabuvir. The ribavirin will be supplied in a separate bottle, but all components will be supplied in a single monthly carton. Additionally, the ribavirin bottle will be labelled "ribavirin film-coated tablets, as part of Viekira Pak-RBV combination therapy" and will not be sold as a separate component.

A description of the packaging has been added to the ASA.

RMP evaluator's comment

This is considered acceptable in the context of this application.

Recommendation 10 in RMP report

A table summarising the pharmacovigilance and risk minimisation activities for all of the specified ongoing safety concerns and missing information proposed for Australia should be included in the revised ASA.

Sponsor's response

An updated table summarizing the pharmacovigilance and risk minimization activities for all of the specified ongoing safety concerns and missing information has been included in the updated ASA.

RMP evaluator's comment

This is considered acceptable in the context of this application.

Recommendation 11 in RMP report

In addition, the 'Adverse Effects' section of the PI should be reviewed at the second round. The draft PI for Viekira Pak is potentially misleading when it cites 'pruritis was the only identified adverse reaction'. For example, Table 29 in Study M14-002, a randomised, double blind, controlled study revealed the following incidence of adverse events with the direct acting antivirals (without ribavirin) in the regimen controlled dataset: diarrhoea (16.1%), nausea (13.7%), fatigue (35.1%), back pain (5.9%), headache (28.3%), dizziness (6.3%) and insomnia (7.8%) and cough (5.9%). In particular there were more cases of memory impairment without RBV than with RBV (6.8% versus 1.0%, respectively; $p \leq 0.05$). The latter at the very least should be considered for inclusion in the PI.

Sponsor's response

Inclusion of adverse events in the table of the PI was based on a 5% cut off for events being reported at least 5% more frequently in the 3 DAA + RBV arms of the Placebo controlled arms when compared to the Placebo controlled arms. A side by side tabulation for these events was provided the Placebo controlled studies, the Regimen controlled studies (with and without RBV) and the study in patients with cirrhosis. Adverse events which did not occur at least 5% more often in the active versus the placebo arms were not represented.

AbbVie does not believe that memory impairment should be included in the PI. AbbVie confirms that there were 15 subjects who experienced an adverse event of memory impairment in Study M14-002. Of these, 1 subject was in Arm A who received 3 DAA + RBV for 12 weeks and 14 subjects were in Arm B who received 3 DAA for 12 weeks; this difference was likely a chance finding. First, if this adverse event was related to the 3DAA regimen, the rate of this event would be similar in both arms of Study M14-002 (the 3DAA only and the 3DAA + RBV arms). In addition, the rate of the adverse event varied across all trials suggesting that this event was not specifically related to the 3DAA component of the regimen.

The frequency for the adverse events of memory impairment across the Phase III studies included in the ISS is shown in Table 24.

Table 24: Frequency of the MedDRA PT of memory impairment across the Phase III studies included in the ISS

	Studies and Regimen									
MedDRA PT	M11-646 and M13-098 3-DAA + RBV N = 770	M11-646 and M13-098 Placebo N = 255	M13-961 3-DAA	M13-961 3-DAA + RBV	M13-389 3-DAA	M13-389 3-DAA + RBV	M14-002 3-DAA	M14-002 3-DAA + RBV	M13-099 3-DAA + RBV 12 weeks	M13-099 3-DAA + RBV 24 weeks
	n (%)									
Memory impairment	13 (1.7%)	6 (2.4%)	2/209 (1.0%)	0/210	2/91 (2.2%)	0/95	14/205 (6.8%)	1/100 (1.0%)	5/208 (2.4%)	12/172 (7.0%)

MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term

As shown in Table 24, the frequency of treatment emergent adverse event of memory impairment varies across the studies without a consistent pattern, suggesting that the higher frequency observed for the 3DAA only arm of Study M14-002 was a chance finding.

An additional evaluation was performed for this event in Study M14-002. In Study M14-002, the treatment emergent adverse event of memory impairment was noted in 15 subjects. The group characteristics of subjects experiencing this event are as follows:

- The mean age of these subjects is 53 years (range is 37 years to 61 years)
- Gender distribution was 8 males and 7 females

- The treatment day of onset of these events varied, ranging from Day 1 to Day 63
- All of the reported events were non-serious
- Fourteen out of 15 subjects reported former or current alcohol use.

Memory impairment may be associated with a number of factors including alcohol and drug abuse, heavy cigarette smoking, head injuries, stroke, sleep deprivation, severe stress, vitamin B12 deficiency, and illnesses such as chronic HCV infection, Alzheimer's disease and depression.[73] In addition, concomitant medications such as benzodiazepines are observed to be associated with memory impairment.[74] The 15 subjects reported a number of possible other contributing factors for the event of memory impairment including difficulty sleeping, depression, and alcohol use. The individual demographic and medical histories of subjects experiencing memory impairment or loss are presented in Table 25.

Table 25: Treatment emergent adverse events of memory impairment in Study M14-002

Subject	Age	Sex	Medical History	Concomitant Medications	History of Tobacco and Alcohol Use	Treatment Day of Onset	AE Reported	Seriousness of AE
	49	F	Glaucoma, headache, fatigue	Amoxicillin, latanoprost, dorzolamide eye drops, ibuprofen	None	63	Forgetfulness × 4 days	Nonserious
	40	M	Trouble sleeping, back pain	Trazodone, zofram, ibuprofen, tylenol, hydrocodone/homatropine	Former smoking and alcohol use	19	Increased Forgetfulness	Nonserious
	60	F	Hypertension, menopause, myopia	Lisinopril, ibuprofen	Never smoked. Current alcohol use	16	Forgetfulness × 62 days	Nonserious
	55	F	Hypertension, occasional headaches, menopause	Lisinopril	Former smoker and alcohol use	10	Forgetfulness × 103 days intermittently	Nonserious
	53	M	Alcohol withdrawal seizures, head injury, head surgery, jaw reconstruction	Albuterol inh, beclomethasone inh	Former smoker and alcohol use	5	Intermittent forgetfulness 1 day	Nonserious
	57	F	Depression, occasional headache, anxiety	Advil, cranberry, z-pack, vitamin B12 (for dietary supplement)	Current smoker, former alcohol use	43	Forgetful	Nonserious
	56	M	Insomnia, liver biopsy, GERD	Trazodone (1 day for insomnia)	Former smoker and alcohol use	15	Intermittent forgetfulness	Nonserious
	61	F	Hypertension, Meniere's syndrome, gastric bypass, GERD, postmenopausal	Omeprazole, claritin, vit D, hydrochlorothiazide, aleve, alprazolam	Never smoked. Former alcohol use	23	Intermittent Forgetfulness	Nonserious
	55	F	Mitral valve prolapse, IBS, rheumatoid fever, Stevens-Johnson's syndrome	Bisoprolol, alprazolam, tianeptine, calcium, zinc, tylenol, eye drops	Current smoker, former alcohol use	27	Intermittent Forgetfulness	Nonserious
	56	M	High blood pressure, insomnia, fatigue	Vit C, Vit D, Vit E, triamterene	Former smoker and alcohol use	2	Intermittent Forgetfulness	Nonserious
	39	F	Myopia, occasional headaches, IVDA, hypothyroidism	Levothyroxine, flonase, penicillin V, diflucan	Current smoker, former alcohol use	9	Intermittent forgetfulness	Nonserious
	59	M	Hypertension	Lisinopril	Former smoker and alcohol use	27	Intermittent Forgetfulness	Nonserious
	61	M	Hypercholesterolemia, anxiety	Pravastatin, excedrine, ativan, motrin	Former smoker and alcohol use	1	Intermittent Forgetfulness	Nonserious
	58	M	Fractured leg	Amoxicillin, oil of cloves	Current smoker and current alcohol use	5	Forgetfulness	Nonserious
	37	M	GERD, psoriasis, genital herpes, psoriasis	Omeprazole, co-codamol, ibuprofen, kaolin, and morphine	Former smoker, current alcohol use	43	Intermittent Forgetfulness	Nonserious

AE = adverse event

In summary, this review within Study M14-002 indicates that there are a number of confounding factors among the subjects who reported memory impairment, suggesting that the 3DAA regimen was not the cause for the event. This coupled with the variable rates across the 3DAA, 3DAA + RBV and placebo treatment arms suggest that this event is not associated with the 3DAA regimen.

[73] USNLM, NIH. Memory Loss: http://www.nlm.nih.gov/medlineplus/ency/article/003257.htm
[74] Ericson J Medical Daily: http://www.medicaldaily.com/5-common-prescription-drugs-may-cause-memory-loss-examples-and-alternatives-251443#.U-qRl3Cho64.email

In AbbVie's HCV clinical development program, the reported treatment emergent adverse events of memory impairment/memory loss occurred at a low frequency across the treatment groups. This was not a focus of safety data collection and events in all trials in the clinical development program were collected as standard treatment emergent events. A threshold of 5% was used for inclusion into the in-text tables for the study reports; hence, this event was noted in the in-text tables for Study M14-002, but not in the other study reports. The rate reported for the 3DAA arm of Study M14-002 was higher than in the 3DAA + RBV; however, this higher frequency was not observed in the other 3DAA only arms. In addition, if this event was due to the 3DAA component of the regimen, a similarly high rate might be expected across all study arms including those with 3DAA + RBV.

Furthermore, further evaluation of the subjects reporting memory impairment in Study M14-002 revealed that many subjects had confounding factors which may predispose to memory impairment and some were taking medications associated with memory impairment. Thus, a variety of other common conditions likely contributed to development of memory impairment. This analysis does not support an association between memory impairment and the 3DAA regimen.

RMP evaluator's comment

The sponsor's response is noted. While the RMP evaluator agrees that, at the 5% level, pruritis occurred more commonly with Viekira Pak treatment than with placebo treatment, the proposed PI is potentially misleading with the proposed wording.

The RMP evaluator recommends to the Delegate that the PI statement 'pruritis was the only identified adverse reaction' should be placed in context that is at the 5% level as this statement implies that there were no other treatment emergent adverse reactions to Viekira Pak with higher rates than placebo. This is considered acceptable in the context of this application.

Recommendation 12 in RMP report

It is recommended to the Delegate the PI for Viekira-Pak-RBV and the PI for Viekira-Pak be separate documents, as some of the prescribing information does not apply to both, in particular the teratogenicity of ribavirin.

Sponsor's response

There are separate package inserts for Viekira Pak and Viekira Pak-RBV.

RMP evaluator's comment

It is noted that the PI documents are now separate, as requested. This is considered acceptable in the context of this application.

Recommendation 13 in RMP report

It is recommended to the Delegate that the relevant information from a currently approved Australian PI document for ritonavir be included in the PI document for Viekira Pak, as ritonavir is part of the 3DAA regimen.

Sponsor's response

Relevant information from the ritonavir labelling has been added to the Viekira Pak-RBV Australian PI and the Viekira Pak Australian PI, so the sponsor does not believe that a separate ritonavir PI is necessary.

RMP evaluator's comment

The RMP evaluator considers this acceptable within the submitted application pending approval by the Delegate.

Recommendation 14 in RMP report

In the 'Contraindications' section, above the list of contraindicated agents, the PI should include a statement that these are extensively metabolised by CYP3A to enable prescribers to take appropriate care when considering other agents metabolised by CYP3A that are not listed.

Sponsor's response

The PI has been revised to include the following statement:

The following drugs are extensively metabolised by CYP3A and contraindicated with Viekira Pak (see 'Interaction with other medicines').

RMP evaluator's comment

The RMP evaluator considers this acceptable within the submitted application pending approval by the Delegate.

Recommendation 15 in RMP report

In the 'Indications' section, the Delegate may wish to consider inclusion of 'in adults' as per the EU SmPC (and PI for Victrelis), to clearly indicate Viekira Pak is only to be used in an adult population.

Sponsor's response

The sponsor has reviewed and will not include "adults" in the indications section. The PI does indicate that the regimen has not been studied in the paediatric population.

RMP evaluator's comment

The sponsor's response is noted and this matter will be referred to the Delegate.

Recommendation 16 in RMP report

In the 'Contraindications' section, the Delegate may wish to consider inclusion of astemizole and terfenadine (as per the EU SmPC for the co-formulated tablet) and fusidic acid and salmeterol (as per the EU SmPC for dasabuvir tablet).

Sponsor's response

Astemizole, terfenadine, fusidic acid, and salmeterol have been included in the list of contraindicated medications.

RMP evaluator's comment

This is considered acceptable in the context of this application for RMP purposes, subject to approval by the Delegate.

Recommendation 17 in RMP report

In the 'Contraindications' section, 'rifampin' should be changed to 'rifampicin', which is the approved name used in Australia.

Sponsor's response

"Rifampin" has been changed to "rifampicin."

RMP evaluator's comment

This is considered acceptable in the context of this application for RMP purposes, subject to approval by the Delegate.

Recommendation 18 in RMP report

In the 'Precautions' section, the PI should include a statement that herbal supplements such as milk thistle may decrease serum ALT, thereby interfering with evaluation of serum ALT with treatment of HCV.

Sponsor's response

AbbVie does not believe that language concerning milk thistle should be added to the Australian PI. First, in studies in patients infected with HCV, inconsistent findings have been observed with milk thistle use.[75,76] Further, there are no data with milk thistle and highly active direct acting antivirals such as the AbbVie DAA regimen showing that in the context of HCV viral clearance, milk thistle has an effect on serum ALT levels. Taking both things in context, addition of language about milk thistle in the PI, is not supported.

RMP evaluator's comment

This is considered acceptable in the context of this application for RMP purposes, subject to approval by the Delegate.

Recommendation 19 in RMP report

In the 'Precautions' section, the PI should include a statement that there is a dose-response relationship between paritaprevir (formerly veruprevir) and ALT level, and that appropriate monitoring should occur.

Sponsor's response

Proposed language has been added in the revised PI. The rationale for this language is included with the Australian PI response document.

RMP evaluator's comment

This is considered acceptable in the context of this application for RMP purposes, subject to approval by the Delegate.

Recommendation 20 in RMP report

In the 'Precautions' section, the PI should include a statement regarding the efficacy of hormonal contraception when used in conjunction with Viekira Pak.

Sponsor's response

The PI has been revised to include language about the use of non ethinyl estradiol containing contraceptives or non-hormonal contraceptive methods. See the response to recommendation 7 regarding efficacy of hormonal contraception.

RMP evaluator's comment

This is considered acceptable in the context of this application for RMP purposes, subject to approval by the Delegate.

Recommendation 21 in RMP report

In the 'Precautions' section, under 'Use in the Elderly', the PI should include a statement that safety and efficacy have not been established in patients over 70 years (or a statement to that effect).

Sponsor's response

[75] Yang Z, Zhuang L, et al. Effects and tolerance of silymarin (milk thistle) in chronic hepatitis C virus infection patients: a meta-analysis of randomized controlled trials. *Biomed Res Int*. 2014:941085. doi: 10.1155/2014/941085. Epub 2014 Aug 27.
[76] Gordon A, et al. Effects of Silybum marianum on serum hepatitis C virus RNA, alanine aminotransferase levels and well-being in patients with chronic hepatitis C. *J Gastroenterol Hepatol*. 2006; 21: 275-280.

The following statement has been added to the PI: "The safety and effectiveness of Viekira Pak has not been established in patients aged 70 years or over."

RMP evaluator's comment

This is considered acceptable in the context of this application for RMP purposes, subject to approval by the Delegate.

Recommendation 22 in RMP report

In the 'Precautions' section, under 'Use in the Elderly', the PI should include a statement on the experience in patients over 65 years.

Sponsor's response

The following information is included in the "Precautions" section under "Use in the Elderly:"

No dose adjustment of Viekira Pak is warranted in elderly patients. In Phase III clinical trials, 8.5% (174 out of 2053) of subjects were age 65 or over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects. The safety and effectiveness of Viekira Pak has not been established in patients aged 70 years or over.

RMP evaluator's comment

This is considered acceptable in the context of this application for RMP purposes, subject to approval by the Delegate.

Recommendation 23 in RMP report

In the 'Precautions' section, under 'Use in Pregnancy', the sponsor should determine the pregnancy category in conjunction with the nonclinical evaluator. It is noted that the sponsor is proposing category B1 for Viekira Pak without ribavirin, even though ritonavir is classified as category B3 and other Australian licensed HCV protease inhibitors such as Victrelis (boceprevir) PI 1 and Incivo (telaprevir) PI 2 are categorised as B2.

Sponsor's response

AbbVie believes that the Pregnancy Category of B1 for Viekira Pak without ribavirin is appropriate given current available information for ritonavir from the Antiviral Pregnancy Registry database. Please see the response for Viekira Pak-RBV and the lack of embryofetal effects with paritaprevir/ritonavir, ombitasvir or dasabuvir.

RMP evaluator's comment

The nonclinical evaluator recommended Pregnancy Category B3 as did the first round RMP evaluator. However, given the sponsor considers Viekira Pak should be categorised as B1, this matter will be referred to the nonclinical evaluation section for a determination.

Recommendation 24 in RMP report

In the "Interactions with other medicines: Potential for other drugs to affect Viekira Pak" section of the PI a statement should be included that CYP2C8 inhibitors can prolong the effect of dasabuvir and can increase the risk of experiencing AEs.

Sponsor's response

The following statement has been added to the "Interactions with other medicines" section: "Additionally, drugs that are strong CYP2C8 inhibitors may increase dasabuvir concentrations and can prolong the effect of dasabuvir potentially increasing the risk of dasabuvir related adverse effects."

RMP evaluator's comment

This is considered acceptable in the context of this application for RMP purposes, subject to approval by the Delegate.

Recommendation 25 in RMP report

In the 'Interactions with other medicines' section, under 'Potential for other drugs to affect Viekira Pak', the PI should additionally state that CYP3A4 inducers can potentially increase the risk of experiencing AEs (or a statement to that effect).

Sponsor's response

The following statement has been added to the PI under the "Potential for other drugs to affect Viekira Pak" heading: "CYP3A4 inducers can potentially increase the risk of experiencing adverse effects."

RMP evaluator's comment

This is considered acceptable in the context of this application for RMP purposes, subject to approval by the Delegate.

Recommendation 26 in RMP report

In the 'Interactions with other medicines' section, under 'Potential for other drugs to affect Viekira Pak', the PI should additionally include a statement that CYP3A4 inhibitors can potentially increase the exposure to paritaprevir up to 2 fold.

Sponsor's response

The following statement is included in the PI, immediately following the heading "Potential for other drugs to affect Viekira Pak": "Co-administration of Viekira Pak with strong inhibitors of CYP3A may increase paritaprevir concentrations up to 2 fold."

RMP evaluator's comment

This is considered acceptable in the context of this application for RMP purposes, subject to approval by the Delegate

Recommendation 27 in RMP report

In the 'Interactions with other medicines' section, the PI should additionally include representative examples of substrates of UGT1A1, BCRP, OATP1B1 and OATP1B3.

Sponsor's response

Representative examples of each of these substrates have been added to the PI: UGT1A1 (for example, raltegravir), BCRP (for example, rosuvastatin), OATP1B1 or OATP1B3 (for example, pravastatin).

RMP evaluator's comment

This is considered acceptable in the context of this application for RMP purposes, subject to approval by the Delegate

Recommendation 28 in RMP report

In the 'Dosage and Administration' section, the PI should contain a statement to swallow the Viekira Pak tablets whole (as per the EU SmPC).

Sponsor's response

The following statement has been added to "Dosage and Administration" section: Patients should be instructed to swallow the tablets whole (that is, patients should not chew, break or dissolve the tablet).

RMP evaluator's comment

This is considered acceptable in the context of this application for RMP purposes, subject to approval by the Delegate.

Recommendation 29 in RMP report

In the 'Dosage and Administration' section, the PI should contain a statement on 'missed doses' (as per US Product Label, Health Canada Product Monograph and EU SmPC). The instructions specify 12 hours for the co-formulated tablet as the critical period, and 6 hours for the dasabuvir tablet.

Sponsor's response

The PI has been revised to include the following information under "Dosage and Administration:"

> Missed Dose
>
> Inform patients that in case a dose of paritaprevir, ritonavir, ombitasvir is missed, the prescribed dose can be taken within 12 hours.
>
> In case a dose of dasabuvir is missed, the prescribed dose can be taken within 6 hours.
>
> If more than 12 hours have passed since ombitasvir, paritaprevir, ritonavir is usually taken or more than 6 hours have passed since dasabuvir is usually taken, the missed dose should NOT be taken and the patient should take the next dose as per the usual dosing schedule.
>
> Instruct patients not to take more than their prescribed dose of Viekira Pak to make up for a missed dose.

RMP evaluator's comment

This is considered acceptable in the context of this application for RMP purposes, subject to approval by the Delegate.

Recommendation 30 in RMP report

In the 'Dosage and Administration' section, the PI should contain a statement that while no dose adjustment of Viekira Pak is required for patients with mild renal impairment, there is no efficacy and safety data to support its administration in patients with moderate or severe renal impairment (or a statement to that effect).

Sponsor's response

This change has been made.

RMP evaluator's comment

This is considered acceptable in the context of this application for RMP purposes, subject to approval by the Delegate.

Recommendation 31 in RMP report

In the 'Precautions: Use in specific populations' section, the Delegate may consider reference to genotype 4 HCV for which Viekira Pak is seeking approval in the EU. Hence, strictly there is missing information for genotypes 2, 3, 5 and 6

Sponsor's response

A submission for genotype 4 will be part of a separate filing, so this is not included in the current PI.

RMP evaluator's comment

This is considered acceptable in the context of this application for RMP purposes, subject to approval by the Delegate.

The administration of Viekira Pak in patients with genotypes 2 to 6 (inclusive) may be considered under the Potential Risk of off-label use.

Recommendation 32 in RMP report

In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft consumer medicines information document be revised to accommodate the changes made to the product information document.

Sponsor's response

The CMI document will be updated appropriately.

RMP evaluator's comment

This is considered acceptable in the context of this application for RMP purposes, subject to approval by the Delegate.

Summary of recommendations

1. The nonclinical evaluator recommended Pregnancy Category B3 as did the first round RMP evaluator. However, given the sponsor considers Viekira Pak should be categorised as B1, this matter will be referred to the nonclinical evaluation section for a determination.
2. The RMP evaluator recommends to the Delegate that the PI statement 'pruritis was the only identified adverse reaction' should be placed in context that is at the 5% level as this statement implies that there were no other treatment emergent adverse reactions to Viekira Pak with higher rates than placebo.
3. It is noted that the sponsor has removed breastfeeding women from the Missing Information list. The sponsor should provide a compelling justification for this or reinstate this as a missing information item.
4. The sponsor should add drug-drug interaction information on atorvastatin to the proposed PI.
5. The sponsor should advise how patients will access/obtain the patient information sheet that contains individual dosing information.
6. The sponsor should provide the details of the planned education program to specifically address the risk of drug-drug interactions and appropriate contraception and how the effectiveness of the planned education program will be measured.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

The ACSOM advice has been reviewed by the RMP evaluator and relevant parts are incorporated in the second round report.

Suggested wording for conditions of registration

RMP

Implement RMP (in EU-RMP format) Version 1.2 (dated February 2015, DLP 24 January 2014) and Australian Specific Annex (ASA) Version 1.2 (dated February 2015) and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

A consequence of evaluating three new active substances and a new version of ribavirin is that there was a large amount of information. Key points are summarised here. Detailed information is provided in the reports for each respective submission (Viekira Pak, PM 2014-01436-1-2 and Viekira Pak-RBV, PM 2014-01438-1-2).

Registration of the proposed Viekira Pak and Viekira Pak-RBV combination therapy composite packs was recommended with respect to quality and biopharmaceutic aspects. All issues raised during the initial evaluation of this application were satisfactorily resolved apart from a minor PI issue and some labelling revisions.

Nonclinical

For the nonclinical evaluation, reports were provided for the individual new active substances (paritaprevir, ombitasvir and dasabuvir) as three separate attachments, in addition to the report for the fixed dose combination. Detailed information is provided in these reports.

There were no nonclinical objections to the registration of Viekira Pak and Viekira Pak-RBV. The overall quality of the submission was high. Only limited combination toxicology studies were submitted, which is in accordance with a new FDA draft guidance document for HCV 3DAA treatments, and was considered to be acceptable.

While a pregnancy category of B1 is appropriate for paritaprevir, ombitasvir and dasabuvir alone, it was noted that ritonavir alone has a pregnancy category of B3. The nonclinical data do not support a change for ritonavir to B1.This has been accepted by the sponsor with the recent response to the second round evaluation reports (29 April 2015).

Clinical

The submission contained the following information:

- 61 clinical pharmacology studies, including 59 that provided PK data and five studies that provided pharmacodynamic data.
- Two population PK analyses.
- Six pivotal efficacy/safety studies: M11-646 (Sapphire-I), M13-098 (Sapphire-II), M13-389 (PEARL-II), M13-961 (PEARL-III), M14-002 (PEARL-IV), M13-099 (TURQUOISE II).
- Multiple Phase I and II studies used to justify the selected regimen, dose and treatment duration.
- Five other efficacy/safety studies: M12-114, M13-386, M12-746, M12-998, M14-103. The preliminary report of a long-term follow-up study (M13-102) of all patients who had received 3DAA in a Phase II or III study was also included.
- Two additional efficacy/safety studies not directly related to the proposed indication: M11-652, a completed Phase II study in patients with genotype1 infection given 3DAA +/- RBV for 8, 12 or 24 weeks; and M13-393(PEARL-1), an ongoing study in patients with genotype4 infection treated with a 2DAA combination.
- Pooled efficacy and safety analyses, Integrated Summary of Efficacy, Integrated Summary of Safety.

Pharmacology and pharmacokinetics

Key points include the following:

A number of different formulations of the active drugs were used during the clinical trial program.

With regards to dose selection and dose duration, the evaluator commented that conventional dose ranging studies were not feasible in chronic HCV infection because of the dangers of viral resistance in patients who receive potentially sub-optimal treatment. This was particularly relevant to a novel 3DAA combination. The dosage and regimen selected for the Phase III studies was appropriate after consideration of a large body of in vitro and in vivo preclinical and Phase I and II data. For the Phase II and III studies, the optimal treatment duration was assumed to be 12 weeks but SVR rates were compared in different patient groups during treatment periods of 8, 12 and 24 weeks.

Paritaprevir displays nonlinear pharmacokinetics with the addition of ritonavir providing considerable boosting over and above the paritaprevir pharmacokinetics (Tables 26 and 27).

Table 26: Study M10-749. The mean ± SD PK parameters of ABT-450 (paritaprevir) in Sub study 1 after single dose administration

Pharmacokinetic Parameter	Group 1 300 mg ABT-450 (N = 6)	Group 2 600 mg ABT-450 (N = 6)	Group 3 900 mg ABT-450 (N = 6)
C_{max} (ng/mL)	121 ± 68.2	780 ± 599	5120 ± 3581
C_{max}/Dose (ng/mL/mg)	0.404 ± 0.227	1.30 ± 1.00	5.69 ± 3.98
T_{max} (h)	2.3 ± 0.5	1.8 ± 0.4	2.2 ± 0.4
$t_{½}^{\#}$ (h)	2.67 ± 0.64	2.72 ± 1.17	3.05 ± 1.60
AUC_t (ng•h/mL)	385 ± 190	1645 ± 729	8753 ± 7402
AUC_t/Dose (ng•h/mL/mg)	1.29 ± 0.63	2.74 ± 1.21	9.73 ± 8.23
AUC_∞ (ng•h/mL)	391 ± 189	1651 ± 729	8758 ± 7401
AUC_∞/Dose (ng•h/mL/mg)	1.30 ± 0.63	2.75 ± 1.21	9.73 ± 8.22
f_e (%)	0.009	0.021	0.096
CL_R (L/h)	0.091	0.079	0.125

\# Harmonic mean and pseudo SD.

Table 27: Study M10-749

	ABT-450/r			
ABT-450 Pharmacokinetic Parameter	Group 4 100/100 mg (N = 6)	Group 5 400/100 mg (N = 6)	Group 6 200/75 mg (N = 6)	Group 7 400/50 mg (N = 6)
C_{max} (ng/mL)	115 ± 78.4	10267 ± 5122	1055 ± 1167	7079 ± 5445
C_{max}/Dose (ng/mL/mg)	1.51 ± 0.78	25.7 ± 12.8	5.28 ± 5.83	17.7 ± 13.6
T_{max} (h)	4.2 ± 1.0	3.2 ± 1.2	3.5 ± 1.0	3.2 ± 1.7
$t_{½}^{\#}$ (h)	5.66 ± 0.99	4.89 ± 0.93	4.76 ± 0.66	4.02 ± 1.52
AUC_t (ng•h/mL)	962 ± 540	81071 ± 61514	5520 ± 5734	43968 ± 35097
AUC_t/Dose (ng•h/mL/mg)	9.62 ± 5.40	203 ± 154	27.6 ± 28.7	110 ± 87.7
AUC_∞ (ng•h/mL)	970 ± 542	81078 ± 61512	5530 ± 5741	43974 ± 35098
AUC_∞/Dose (ng•h/mL/mg)	9.70 ± 5.42	203 ± 154	27.7 ± 28.7	110 ± 87.7
f_e (%)	0.048	1.169	0.213	0.727
CL_R (L/h)	0.038	0.071	0.061	0.087

\# Harmonic mean and pseudo SD.

Bioavailability

Studies to determine the absolute bioavailability of paritaprevir and ombitasvir were not conducted. The sponsor provided a justification for this, based on the extensive PK evaluation which was accepted by the clinical evaluator.

The absolute bioavailability of a 400 mg oral tablet dose of dasabuvir compared to an intravenous microdose of approximately 85 µg of ^{14}C-dasabuvir was 46%. Study M13-331 assessed the relative bioavailability of the 250 mg dasabuvir optimised formulation intended for Phase III, compared to the 400 mg dasabuvir Phase IIb formulation. C_{max} and AUC_{inf} values for dasabuvir were bioequivalent following administration of the 250 mg optimised tablet and the 400 mg formulation (Table 28).

Table 28: Study M13-331

For the two one-sided test based on the analysis of log-transformed C_{max}, AUC_t and AUC_∞, the 90% confidence intervals for evaluating bioequivalence and the corresponding point estimates of relative bioavailability are shown in the following table.

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value[a]		Relative Bioavailability	
		Test	Reference	Point Estimate[b]	90% Confidence Interval
		ABT-333			
A vs. B	C_{max}	762	847	0.900	0.820 - 0.987
	AUC_t	5755	6018	0.956	0.892 - 1.025
	AUC_∞	5799	6061	0.957	0.893 - 1.025
		ABT-333 M1 Metabolite			
A vs. B	C_{max}	268	290	0.921	0.853 - 0.996
	AUC_t	1971	2108	0.935	0.879 - 0.994
	AUC_∞	2000	2140	0.934	0.880 - 0.992

Regimen A = ABT-333 250 mg optimized Phase 3 tablet under non-fasting conditions (Test)

Regimen B = ABT-333 400 mg Phase 2b tablet under non-fasting conditions (Reference)

a. Antilogarithm of the least squares means for logarithms.

b. Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

Food-effect

Exposures of all four drugs were increased by administration with a moderate or high fat meal, with the highest increases observed for paritaprevir and ombitasvir.[77] Following administration of the proposed daily dose of the co-formulated paritaprevir/ritonavir/ ombitasvir tablet, a moderate fat breakfast increased the C_{max} and AUC_{inf} of paritaprevir by 4.67 and 3.11 fold, respectively, compared to administration under fasted conditions. The C_{max} and AUC_{inf} of ombitasvir increased by 2.27 and 1.82 fold, respectively. For this reason, the proposed PI recommends that Viekira-Pak be taken with food, 'without regard to fat or calorie content', to maximise absorption.

Metabolism

Paritaprevir (paritaprevir), ritonavir, ombitasvir and dasabuvir are primarily metabolised in vitro by: CYP3A4; CYP3A; CYP3A4/5 and CYP2C8; and CYP2C8, respectively.

[77] Centre for Drug Evaluation and Research. Application number206619Orig1s000.Summary review http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/206619Orig1s000SumR.pdf

Excretion

Paritaprevir is primarily eliminated in the bile with minimal renal elimination1. Unchanged parent drug accounted for only 1.1% and 0.05% of the total radioactivity in faeces and urine respectively. Ombitasvir is predominately eliminated unchanged via the hepatobiliary route, with minimal renal elimination.[77] Unchanged parent drug accounted for 87.8% of total radioactivity recovered in faeces. Dasabuvir is primarily eliminated in the bile with minimal renal elimination1. Dasabuvir M1 was the most abundant metabolite in faeces representing 31.5% of administered dose, with unchanged parent drug accounting for 26% in faeces.

Hepatic impairment

A study of 24 patients, study M12-215, assessed the pharmacokinetics of the active constituents following a single dose of 25 mg ombitasvir, 400 mg dasabuvir, and 200mg paritaprevir/100mg ritonavir under non-fasting conditions in subjects with normal hepatic function(n = 7), subjects with mild stable chronic(n = 6), moderate stable(n = 6) to severe stable(n = 5) chronic hepatic impairment. The FDA summary report[77] summarised the findings as follows:

> Compared to subjects with normal hepatic function, there were only mild decreases or slight increases in AUCs for all three of the DAAs in Viekira Pak in mild hepatic impairment. In moderate hepatic impairment paritaprevir AUCs increased by 62%.
>
> In subjects with severe hepatic impairment, paritaprevir and dasabuvir AUCs increased by approximately 945% and 325%, respectively, and ombitasvir AUCs decreased by 54%. For this reason and given the exposure response relationship of paritaprevir and ALT elevations, Viekira Pak will be contraindicated in patients with severe hepatic impairment.

Renal impairment

A study of 24 patients, M12-193, administered a single dose of 2-DAA (paritaprevir/ritonavir + ombitasvir) and 3DAA (paritaprevir/ritonavir + ombitasvir + dasabuvir) combinations under non-fasting conditions suggested that no dose adjustment was necessary for patients with renal impairment. Data were limited to 6 subjects with normal renal function, and 6 subjects in each of the mild, moderate and severe renal impairment groups.

Ethnicity

The evaluator commented that exposure was higher in Asians and patient numbers in the Phase III studies were not sufficient to address possible racial differences. Study M12-221 indicated that relative to the values in Caucasians, the paritaprevir AUC_{24} values were 2.47 and 2.91 fold higher in Han Chinese and Japanese subjects, respectively, and the dasabuvir-M1 AUC values were 1.35 and 1.50 fold higher in Han Chinese and Japanese subjects, respectively. The evaluator provided a further response dated 24 April 2015 in reply to a query from the sponsor regarding wording of the PI in regards to Asian and Hispanic/Latino subjects. This will be addressed with the pre-ACPM response.

Drug-drug interactions

A number of drug-drug interaction studies were conducted as part of the clinical development program, with drugs likely to be co-administered with Viekira Pak and Viekira Pak-RBV.

Based on the results of these studies, drug-drug interactions were stratified into those having a large effect on pharmacokinetics (hence contra-indicated), those with an intermediate effect (dose adjustment recommended) and those with little or no effect on pharmacokinetics (dose adjustment not required).

Many of the clinically relevant drug interactions relate to paritaprevir being extensively metabolised by CYP3A4, with ritonavir a potent inhibitor of CYP3A4. CYP2C8 plays a major role in dasabuvir metabolism. The drugs in Viekira Pak also inhibit P-gp and organic anion transporting polypeptide (OATP) transporters, further increasing the possibility of drug-drug interactions.[77] Consequently, co-administration of Viekira Pak with strong inhibitors of CYP3A may increase paritaprevir and ritonavir concentrations and co-administration of Viekira Pak with drugs that inhibit CYP2C8 may increase dasabuvir concentrations. Conversely, drugs which are moderate or strong inducers of CYP3A or CYP2C8 may result in substantially lower concentrations of these agents and reduced therapeutic effect. Inhibition of P-gp and other transporters BCRP (Breast cancer resistance protein), OATP1B1 or OATP1B3 may also increase the plasma concentrations of the various components of Viekira Pak, as described in the PI. Ombitasvir does not appear to contribute to drug-drug interactions observed.[1]

Ribavirin

Viekira Pak will be given with ribavirin to many patients. Drug interaction studies were conducted without ribavirin, as ribavirin is not hepatically eliminated via the cytochrome P450 (CYP) system.[78]

The clinical evaluator raised several questions following round 1, in relation to the drug interaction studies for R-warfarin , carbamazepine, darunavir/ritonavir, methadone or buprenorphine/naloxone and escitalopram, most of which were satisfactorily addressed by the sponsor in their response. Outstanding issues were the timing of buprenorphine, when co-administered with 3DAA. This should be reflected in PI prior to registration, given that higher exposures were observed when given 4 hours after Viekira-Pak in study M13-100. The response to the second round evaluation reports (29 April 2015) has addressed the issue of timing of buprenorphine satisfactorily.

Population pharmacokinetics

The clinical evaluator report on the population PK studies in presented in Section 4.4.3 of Attachment 2, with the submission also considered by the Pharmaceutical Subcommittee (PSC) meeting 159 (24 November 2014).

The TGA was unable to engage an expert in pharmacometrics to review and replicate the results of the analyses. As a consequence, the population pharmacokinetics was not reviewed by PSC. The clinical evaluation report included an extensive consideration of possible reasons for different results concerning the absorption and elimination of ombitasvir and dasabuvir. The evaluator favoured the analysis RD 14-0047 PPK, indicating that the final model for ombitasvir was a one-compartment model and for dasabuvir was a two-compartment model.

Pharmacodynamics

Primary and secondary pharmacodynamics effects were studied through in vitro and in vivo studies, with three PK studies examining the antiviral activity of the DAAs in Viekira-Pak. The effect of genetic variations conferring resistance was discussed.

Two studies, M12-990 and M12-680 examined the effects of therapeutic and supra-therapeutic doses on QT in healthy subjects however the first study did not include a

[78] European Medicines Agency. Assessment report, Viekirax. Procedure No. EMEA/H/C/003839/0000, Committee for Medicinal Products for Human Use (CHMP) 20 November 2014. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003839/WC500183999.pdf

positive control (such as moxifloxacin). Therapeutic and supratherapeutic doses of paritaprevir/ritonavir/ ombitasvir + dasabuvir did not prolong QT interval.

No studies examined the gender- and age-related differences in pharmacodynamic response or pharmacodynamics interactions.

Efficacy

Data to support the proposed indications were primarily derived from six Phase III trials. All trials enrolled genotype-1 infected adults only and it was therefore possible to pool demographic data across the trials.[1]

The study reports included data for 12 week outcomes, with studies ongoing at the time of submission. The primary efficacy endpoint for all trials was the proportion of subjects achieving SVR_{12} (HCV RNA below the lower limit of quantification 12 weeks after the end of study treatment).

Within the study population, important subgroups with known differing response rates to telaprevir + pegIFN/RBV were identified and analysed. These subgroups included patients with genotype1a and genotype1b infection, cirrhotic and non-cirrhotic patients, treatment naïve and treatment experienced patients, other subgroups defined by IL28B status and relevant demographic characteristics.

The primary efficacy comparison in all six trials was the historical SVR rate of telaprevir plus pegylated interferon (pegIFN) with RBV therapy.[77]

Telaprevir and pegIFN/RBV were selected for comparison, because this regimen provided the highest SVR rates of all approved therapies at the time the studies were designed (Clinical Overview). While the evaluator commented that ideally an active control group of 1-DAA + pegIFN/RBV should have been included, the sponsor justified its exclusion on the grounds of difficulties of double dummy blinding injectable medications, blinding the well-known side effects of pegIFN/RBV and the currently approved DAAs, and the ethics of prolonged treatment with poorly tolerated combination therapies. This was deemed acceptable.

To demonstrate non-inferiority to the historic telaprevir rate, the lower bound of the 95% CI for the rate of SVR_{12} in 3DAA regimen with RBV had to exceed the upper bound for the control rate minus 10.5 percentage points (non-inferiority margin). This margin was chosen based on the most recent non-inferiority ILLUMINATE study for telaprevir.[79]

The study program was based on current US and EU guidelines for the treatment of chronic HCV infection, with scientific advice on study design and methodology sought from the FDA and EMA.

[79] Sherman KE et al. Response-Guided Telaprevir Combination Treatment for Hepatitis C Virus Infection. *N Engl J Med* 2011;365:1014-1024

Table 29: Pivotal Phase III trials[77]

Study	Design	Population	Number of subjects treated	Study arms, treatment duration	Study duration
Placebo controlled, no cirrhosis					
SAPPHIRE-I M11-646	Multicentre, randomised, double blind	genotype 1 (a and b) Treatment naïve without cirrhosis	631	Viekira Pak+RBV (12 weeks) Placebo	72 weeks
SAPPHIRE-II M13-098	Multicentre, randomised, double blind	genotype 1 (a and b) Treatment experienced without cirrhosis	394	Viekira Pak+RBV (12 weeks) Placebo	72 weeks
Viekira Pak-RBV versus VIEKIRA-Pak, no cirrhosis					
PEARL-II M13-389	Multicentre, randomised, open label	genotype 1b, Treatment experienced without cirrhosis	186	Viekira Pak+RBV (12 weeks) Viekira Pak (12 weeks)	60 weeks
PEARL-III M13-961	Multicentre, randomised, double blind	genotype 1b, Treatment naïve without cirrhosis	419	Viekira Pak+RBV (12 weeks) Viekira Pak (12 weeks)	60 weeks
PEARL-IV M14-002	Multicentre, randomised, double blind	genotype 1a Treatment naïve without cirrhosis	305	Viekira Pak+RBV (12 weeks) Viekira Pak (12 weeks)	60 weeks
Viekira Pak-RBV, cirrhosis					

TURQUOISE-II M13-099	Multicentre, randomised, open label	genotype 1 (a and b) Treatment experienced and treatment naïve with cirrhosis	380	Viekira Pak+RBV (12 weeks) Viekira Pak+RBV (24 weeks)	72 weeks

M11-646, SAPPHIRE-I[80]

Genotype 1, treatment naïve.

This was a Phase III, multicentre, randomised, double blind, placebo controlled safety and efficacy study of paritaprevir/ritonavir/ ombitasvir and dasabuvir co-administered with ribavirin (3DAA + RBV) in treatment naïve non-cirrhotic adults with genotype 1 chronic HCV infection. It was conducted at 79 centres in 13 countries. The primary efficacy objective was to show the non-inferiority in SVR_{12} rates after 12 weeks of treatment with 3DAA + RBV, compared with the historical SVR rate for telaprevir plus pegIFN/RBV.

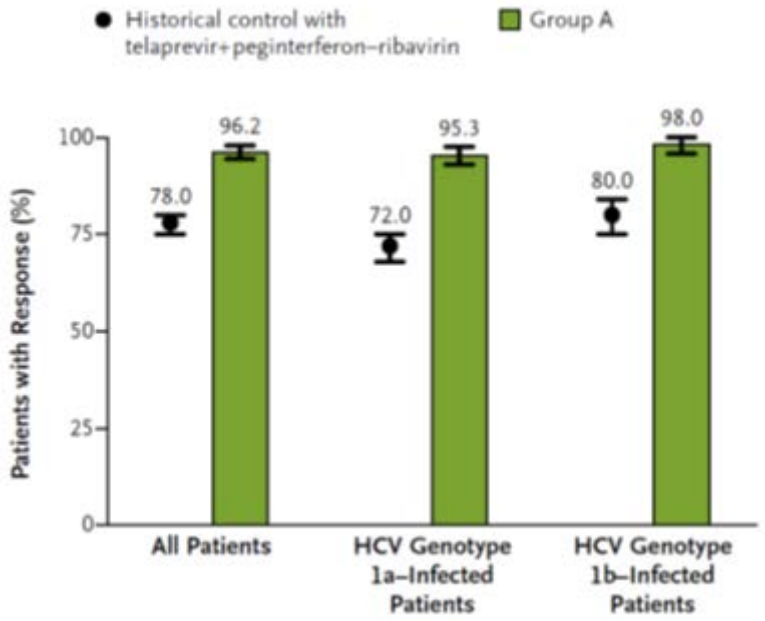
Approximately 600 patients were randomised to one of two arms in a 3:1 ratio to receive 3DAA + RBV for 12 weeks (Group A), or placebo 3DAA + RBV for 12 weeks followed by 3DAA + RBV for 12 weeks (Group B). In the double blind treatment period, randomisation was stratified according to HCV subtype (1a and non-1a) and IL28B genotype (CC and non-CC). The duration of the study was 72 weeks consisting of a double blind treatment period, an open label treatment period (for patients randomised to placebo) and a post dosing period. All patients who received active study drugs were followed for 48 weeks post treatment to monitor safety, HCV RNA, and the emergence and/or persistence of resistant viral variants.

Results

Sustained virologic response at 12 weeks post dosing (SVR_{12}) was achieved by 96.2% patients (95% CI: 94.5%, 97.9%). Both primary endpoints were achieved, namely non-inferiority and superiority compared with historical telaprevir based therapy (> 70% for the lower bound of the 95% CI non-inferiority threshold (LCB), and > 80% for the lower bound of the 95% CI superiority threshold). All patients achieved viral suppression. Virologic failure whilst on treatment was experienced by one patient (0.2%), one patient (0.2%) experienced viral rebound, and seven (1.5%) patients relapsed by post treatment Week 12. The remaining reasons for non-response were missing data or premature study discontinuation. Compliance was ≥ 95% in the patients who had on-treatment virologic failure or relapse.

[80] Feld J et al. Treatment of HCV with ABT-450/r – Ombitasvir and Dasabuvir with Ribavirin. *N Engl J Med* 2014;370:1594-1603

Figure 12: Rates of sustained virologic response (SVR_{12}) among all patients and according to HCV Genotype in the historical control group and in Group A[80]



Group A: patients receiving paritaprevir/r–ombitasvir and dasabuvir with ribavirin during the double blind period. Dots indicate the point estimates in the control group. I bars indicate 95% confidence intervals. Numbers above the confidence intervals are the rates of sustained virologic response.

M13-098, SAPPHIRE-II[81]

Genotype 1, treatment experienced

This was a Phase III, multicentre, randomised, double blind, placebo controlled safety and efficacy study of paritaprevir/ritonavir/ombitasvir and dasabuvir co-administered with ribavirin in pegIFN/RBV treatment experienced non-cirrhotic adults with genotype1 chronic HCV infection. It was conducted at 76 centres in 15 countries. The study design, efficacy assessments and endpoints were identical to study M11-646(SAPPHIRE-I) except that the population consisted of treatment experienced patients.

Results

SVR_{12} was achieved by 96.3% of patients (95% CI: 94.1%, 98.4%). Both primary endpoints were met as the 60% non-inferiority and 70% superiority LCB thresholds were achieved. There were no cases of on-treatment virologic failure; 2.4% of patients had virologic relapse by post treatment Week 12; and 1.3% discontinued drug treatment prematurely. SVR_{12} rates and 95% CIs were comparable in the randomisation strata based on previous pegIFN/RBV treatment failure (null responders, partial responders, and relapsers) (Table 24 Attachment 2), and in sub-groups defined by HCV genotype, IL28B genotype, gender, age, race, geographic region, BMI, baseline HCV RNA, baseline IP-10, and fibrosis stage (Table 30).

The clinical evaluator commented that the patient population was restricted to patients who had failed to achieve viral clearance following pegIFN/RBV and the prior use of any other antiviral agents, including DAAs, was excluded.

[81] Zeuzem S et al. Retreatment of HCV with ABT-450/r – Ombitasvir and Dasabuvir with Ribavirin. *N Engl J Med* 2014;370:1604-1614

Table 30: Study M11-098. Virologic response (SVR_{12}) for subgroups of the 3DAA + RBV treatment groups (intent to treat population)

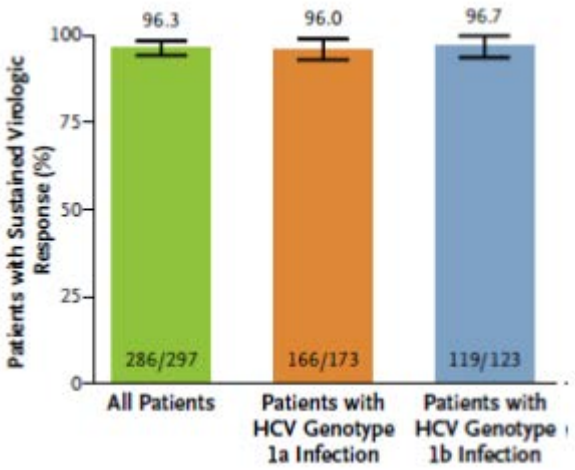
	3-DAA + RBV N = 297	
Subgroup	SVR_{12} Response Rate n/N (%)	95% Confidence Interval[a]
HCV genotype		
1a	166/173 (96.0)	93.0, 98.9
1b	119/123 (96.7)	93.6, 99.9
1 other	1 (100)	100.0, 100.0
Type of response to previous pegIFN/RBV treatment		
Null responder	139/146 (95.2)	91.7, 98.7
Definition 1[b]	136/143 (95.1)	91.6, 98.6
Definition 2[c]	3/3 (100)	not calculated
Partial responder	65/65 (100)	100.0, 100.0
Relapser	82/86 (95.3)	90.9, 99.8
IL28B		
CC	31/34 (91.2)	81.6, 100.0
Non-CC	255/263 (97.0)	94.9, 99.0
CT	194/200 (97.0)	94.6, 99.4
TT	61/63 (96.8)	92.5, 100.0
Sex		
Female	126/130 (96.9)	94.0, 99.9
Male	160/167 (95.8)	92.8, 98.8
Age		
< 65 years	269/277 (97.1)	95.1, 99.1
≥ 65 years	17/20 (85.0)	69.4, 100.0
< 55 years	155/159 (97.5)	95.1, 99.9
≥ 55 years	131/138 (94.9)	91.3, 98.6
Birth year		
< 1945	4/5 (80.0)	not calculated
1945 to 1965	202/210 (96.2)	93.6, 98.8
> 1965	80/82 (97.6)	94.2, 100.0
Race		
Black	21/22 (95.5)	86.8, 100.0
Non-black	265/275 (96.4)	94.2, 98.6
Ethnicity		
Hispanic or Latino	21/22 (95.5)	86.8, 100.0
None of the above	265/275 (96.4)	94.2, 98.6
Geographic region		
Australia/New Zealand	10/11 (90.9)	73.9, 100.0
Europe	145/150 (96.7)	93.8, 99.5
North America	131/136 (96.3)	93.2, 99.5
Country		
Australia	10/11 (90.9)	73.9, 100.0
Canada	18/18 (100)	100.0, 100.0
Czech Republic	5/5 (100)	not calculated
Denmark	5/6 (83.3)	not calculated
France	21/22 (95.5)	86.8, 100.0
Germany	13/13 (100)	100.0, 100.0
Ireland	7/7 (100)	not calculated
Italy	19/19 (100)	100.0, 100.0
Netherlands	7/7 (100)	not calculated
Portugal	15/15 (100)	100.0, 100.0
Russian Federation	18/19 (94.7)	84.7, 100.0
Spain	23/25 (92.0)	81.4, 100.0
United Kingdom	12/12 (100)	100.0, 100.0
United States	113/118 (95.8)	92.1, 99.4
Body mass index		
< 30 kg/m^2	231/238 (97.1)	94.9, 99.2
≥ 30 kg/m^2	55/59 (93.2)	86.8, 99.6

Table 30 (continued): Study M11-098. Virologic response (SVR_{12}) for subgroups of the 3DAA + RBV treatment groups (intent to treat population)

	3-DAA + RBV N = 297	
Subgroup	**SVR_{12} Response Rate n/N (%)**	**95% Confidence Interval[a]**
Baseline HCV RNA		
< 800,000 IU/mL	42/42 (100)	100.0, 100.0
≥ 800,000 IU/mL	244/255 (95.7)	93.2, 98.2
Baseline IP-10		
< 600 ng/L	192/199 (96.5)	93.9, 99.0
≥ 600 ng/L	74/77 (96.1)	91.8, 100.0
Missing	20/21 (95.2)	86.1, 100.0
Baseline HOMA-IR		
< 3 mmol/L × µIU/mL	166/173 (96.0)	93.0, 98.9
≥ 3 mmol/L × µIU/mL	55/56 (98.2)	94.7, 100.0
Missing	65/68 (95.6)	90.7, 100.0
Baseline fibrosis stage[d]		
F0-F1	197/202 (97.5)	95.4, 99.7
F2	50/53 (94.3)	88.1, 100.0
≥ F3	39/42 (92.9)	85.1, 100.0
History of diabetes		
No	272/283 (96.1)	93.9, 98.4
Yes	14/14 (100)	100.0, 100.0
History of depression or bipolar disorder		
No	220/229 (96.1)	93.6, 98.6
Yes	66/68 (97.1)	93.0, 100.0
History of bleeding disorders		
No	281/292 (96.2)	94.0, 98.4
Yes	5/5 (100)	not calculated
Former injection drug user		
No	196/205 (95.6)	92.8, 98.4
Yes	88/90 (97.8)	94.7, 100.0
Missing	2/2 (100)	not calculated

	3-DAA + RBV N = 297	
Subgroup	**SVR_{12} Response Rate n/N (%)**	**95% Confidence Interval[a]**
RBV dose modification		
No	267/278 (96.0)	93.8, 98.3
Yes	19/19 (100)	100.0, 100.0

Figure 13: Sustained virologic response (SVR_{12}) in the entire active regimen group and according to HCV Genotype [81]



The numbers at the bottom of each bar are the number of patients with a sustained response and the total number of patients. I bars indicate 95% confidence intervals.

M13-389, PEARL-II

Genotype1b, treatment experienced

This was a Phase III, multicentre, open label safety and efficacy study of paritaprevir/ritonavir/ombitasvir and dasabuvir with and without ribavirin in pegIFN/RBV treatment experienced non-cirrhotic adults with genotype1b chronic HCV infection. It was conducted at 43 centres in 10 countries.

The primary efficacy objective was to demonstrate non-inferiority in SVR_{12} rates in both arms after 12 weeks of treatment with 3DAA with and without RBV compared with the historical SVR rate of telaprevir plus pegIFN/RBV. Approximately 210 patients were to be randomised in a 1:1 ratio to receive either, 3DAA + RBV (Arm 1) or 3DAA without RBV (Arm 2). Randomisation was stratified according to the type of response to previous pegIFN/RBV treatment (null responder, partial responder, or relapser).The duration of the study was 60 weeks consisting of a 12 week treatment period, and a post-dosing observation period of up to 48 weeks to monitor safety, HCV RNA, and the emergence and/or persistence of resistant viral variants.

The original protocol included patients with genotype1a and genotype1b infection but this was amended to allow recruitment of only genotype1b infected patients. This amendment was made after two patients with genotype1a infection had been randomised.

Results

SVR_{12} was achieved by 96.6% of patients (95% CI: 92.8%, 100%) in the 3DAA + RBV group, and by 100% of patients (95% CI: 95.9%, 100%) in the 3DAA group. Both primary endpoints were met as the 64% non-inferiority LCB thresholds were achieved in both groups. There were no cases of on-treatment virologic failure, and no cases of virologic relapse by post-treatment Week 12. Two patients (2.3%) discontinued treatment prematurely, and one patient had missing SVR_{12} data. SVR_{12} rates and 95% CIs were comparable in the randomisation strata based on previous pegIFN/RBV treatment failure (null responders, partial responders, and relapsers) (Table 31), and in sub-groups defined by HCV genotype, IL28B genotype, gender, age, race, geographic region, BMI, baseline HCV RNA, baseline IP-10, and fibrosis stage (Table 32).

Table 31: Study M13-389. Virologic response (SVR_{12}) by randomisation strata (Intent to treat genotype 1b efficacy subset population)

Prior Response to Previous pegIFN/RBV Treatment	3-DAA + RBV N = 88 n/N (%)	3-DAA N = 91 n/N (%)
Null responder	29/31 (93.5) 95% CI[a]: 84.9, 100.0	32/32 (100) 95% CI[b]: 89.3, 100.0
Non/partial responder	24/25 (96.0) 95% CI[a]: 88.3, 100.0	26/26 (100) 95% CI[b]: 87.1, 100.0
Relapser	32/32 (100) 95% CI[b]: 89.3, 100.0	33/33 (100) 95% CI[b]: 89.6, 100.0
Total	85/88 (96.6) 95% CI[c]: 92.8, 100.0	91/91 (100) 95% CI[c]: 100.0, 100.0
Test for homogeneity across strata[d]	0.363	--

CI = confidence interval; DAA = direct-acting antiviral agent; GT1b = subgenotype 1b; pegIFN = pegylated interferon; RBV = ribavirin; SVR_{12} = sustained virologic response 12 weeks postdosing

a. Calculated using the normal approximation to the binomial distribution.

b. Calculated using the Wilson score method because the point estimate was 100%.

c. Calculated using a stratum-weighted proportion and variance.

d. From Pearson χ^2 test across strata within the treatment group. P value could not be calculated for the 3-DAA treatment group because SVR_{12} was 100% in all strata.

Table 32: Study M13-389. Virologic response (SVR_{12}) for pre specified subgroups (intent to treat genotype 1b efficacy subset population)

Subgroup	SVR_{12} Response Rate n/N (%): 95% CI[a]		Treatment
	3-DAA + RBV N = 88	3-DAA N = 91	Difference (95% CI[a])
Prior response to previous pegIFN/RBV			
Null responder	29/31 (93.5): 84.9, 100.0	32/32 (100): 100.0, 100.0	6.5 (–2.2, 15.1)
Partial responder	24/25 (96.0): 88.3, 100.0	26/26 (100): 100.0, 100.0	4.0 (–3.7, 11.7)
Relapser	32/32 (100): 100.0, 100.0	33/33 (100): 100.0, 100.0	not calculated
IL28B			
CC	10/10 (100): not calculated	7/7 (100): not calculated	not calculated
Non-CC	75/78 (96.2): 91.9, 100.0	84/84 (100): 100.0, 100.0	3.8 (–0.4, 8.1)
CT	54/56 (96.4): 91.6, 100.0	64/64 (100): 100.0, 100.0	3.6 (–1.3, 8.4)
TT	21/22 (95.5): 86.8, 100.0	20/20 (100): 100.0, 100.0	4.5 (–4.2, 13.2)
Sex			
Female	44/45 (97.8): 93.5, 100.0	37/37 (100): 100.0, 100.0	2.2 (–2.1, 6.5)
Male	41/43 (95.3): 89.1, 100.0	54/54 (100): 100.0, 100.0	4.7 (–1.6, 10.9)
Age			
< 65 years	70/73 (95.9): 91.3, 100.0	76/ 76 (100): 100.0, 100.0	4.1 (–0.4 , 8.7)
≥ 65 years	15/15 (100): 100.0, 100.0	15/15 (100): 100.0, 100.0	not calculated
< 55 years	35/36 (97.2): 91.9, 100.0	40/40 (100): 100.0, 100.0	2.8 (–2.6 , 8.1)
≥ 55 years	50/52 (96.2): 90.9, 100.0	51/51 (100): 100.0, 100.0	3.8 (–1.4 , 9.1)
Birth year			
< 1945	not applicable	5/5 (100): not calculated	not calculated
1945 to 1965	62/64 (96.9): 92.6, 100.0	63/63 (100): 100.0, 100.0	3.1 (–1.1, 7.4)
> 1965	23/24 (95.8): 87.8, 100.0	23/23 (100): 100.0, 100.0	4.2 (–3.8, 12.2)
Race			
Black	3/3 (100): not calculated	5/5 (100): not calculated	not calculated
Nonblack	82/85 (96.5): 92.5, 100.0	86/86 (100): 100.0, 100.0	3.5 (–0.4, 7.5)
Ethnicity			
Hispanic or Latino	1/2 (50.0): not calculated	1/1 (100): not calculated	not calculated
Not Hispanic or Latino	84/86 (97.7): 94.5, 100.0	90/90 (100): 100.0, 100.0	2.3 (–0.9, 5.5)

The clinical evaluator commented that efficacy rates in patients given 3DAA +/- RBV were comparable and that the results justify the recommendation for the use of 3DAA without RBV for 12 weeks in non-cirrhotic, treatment experienced patients with genotype1b infection.

Justification was sought from the evaluator for use of an open label design. The sponsor explained that Study M13-389(PEARL-II) was originally an ongoing Phase II study which was converted to a Phase III study. Conversion to a blinded study (including creation of blinded RBV/placebo) would have significantly delayed the Phase III program. The open label nature of the study design did not unduly affect the efficacy comparisons because the primary and secondary efficacy endpoints were based on laboratory measurements. Data from the blinded PEARL III (M13-961) and IV (M14-002) studies were able to assess the impact of RBV on the overall adverse event profile of the regimen.

Study M13-961, PEARL III

Treatment naïve, genotype1b infection.

This was a Phase III, randomised, multicentre, double blind, placebo controlled, safety and efficacy study of paritaprevir/ritonavir/ ombitasvir and dasabuvir with and without ribavirin in treatment naive non-cirrhotic adults with genotype1b chronic HCV infection. It was conducted at 50 centres in 11 countries. The primary efficacy objective was to demonstrate non-inferiority in SVR_{12} rates in both arms after 12 weeks of treatment with

3DAA with and without RBV compared with the historical SVR rate of telaprevir plus pegIFN/RBV.

Approximately 400 patients were randomised in a 1:1 ratio to receive either, 3DAA + RBV (Arm A) or 3DAA without RBV (Arm B). Randomisation was stratified according to the IL28B genotype. The duration of the study was 60 weeks consisting of a 12 week treatment period, and a post-dosing observation period of up to 48 weeks to monitor safety, HCV RNA, and the emergence and/or persistence of resistant viral variants.

Results

SVR_{12} was achieved by 99.5% of patients (95% CI: 98.6%, 100%) in the 3DAA + RBV group, and by 99.0% of patients (95% CI: 97.7%, 100%) in the 3DAA group. Both primary endpoints were met as the 73% non-inferiority LCB thresholds were achieved in both groups. There were no cases of on-treatment virologic failure in the 3DAA group. In the 3DAA + RBV group, one patient (0.5%) experienced virologic failure but there were no cases of virologic relapse in either arm. Two patients (1%) had missing SVR_{12} data but no patients discontinued drug treatment prematurely. SVR_{12} rates and 95% CIs were comparable in the randomisation strata based on IL28B genotype (CC versus non-CC), and in sub-groups defined by gender, age, race, geographic region, BMI, baseline HCV RNA, baseline IP-10, and fibrosis stage (Table 33).

Table 33: Study M13-961. Virologic response (SVR_{12}) for pre-specified subgroups (intent to treat population)

Subgroup	SVR_{12} Response Rate n/N (%): 95% CI[a] 3-DAA + RBV N = 210	3-DAA N = 209	Treatment Difference (95% CI[a])
IL28B, Breslow-Day[b] = 0.385 (0.377)[c]			
CC	44/44 (100.0): 100.0, 100.0	43/44 (97.7): 93.3, 100.0	–2.3 (–6.7, 2.1)
Non-CC	165/166 (99.4): 98.2, 100.0	164/165 (99.4): 98.2, 100.0	0.0 (–1.7, 1.7)
CT	126/127 (99.2): 97.7, 100.0	131/132 (99.2): 97.8, 100.0	0.0 (–2.1, 2.2)
TT	39/39 (100.0): 100.0, 100.0	33/33 (100.0): 100.0, 100.0	not calculated
Sex, Breslow-Day[b] = 0.056			
Female	103/104 (99.0): 97.2, 100.0	123/123 (100.0): 100.0, 100.0	1.0 (–0.9, 2.8)
Male	106/106 (100.0): 100.0, 100.0	84/86 (97.7): 94.5, 100.0	–2.3 (–5.5, 0.9)
Age, Breslow-Day[b] not calculated			
< 65 years	195/196 (99.5): 98.5, 100.0	188/190 (98.9): 97.5, 100.0	–0.5 (–2.3, 1.2)
≥ 65 years	14/14 (100.0): 100.0, 100.0	19/19 (100.0): 100.0, 100.0	not calculated
< 55 years	128/129 (99.2): 97.7, 100.0	131/133 (98.5): 96.4, 100.0	–0.7 (–3.3, 1.8)
≥ 55 years	81/81 (100.0): 100.0, 100.0	76/76 (100.0): 100.0, 100.0	not calculated
Birth year, Breslow-Day[b] not calculated			
< 1945	1/1 (100.0): not calculated	3/3 (100.0): not calculated	not calculated
1945 to 1965	112/113 (99.1): 97.4, 100.0	115/117 (98.3): 95.9, 100.0	–0.8 (–3.7, 2.1)
> 1965	96/96 (100.0): 100.0, 100.0	89/89 (100.0): 100.0, 100.0	not calculated
Race, Breslow-Day[b] not calculated			
Black	11/11 (100.0): 100.0, 100.0	11/11 (100.0): 100.0, 100.0	not calculated
Nonblack	198/199 (99.5): 98.5, 100.0	196/197 (99.5): 98.5, 100.0	0.0 (–1.4, 1.4)
Missing	none	0/1 (0.0): not calculated	not calculated
Ethnicity, Breslow-Day[b] = 0.525			
Hispanic or Latino	2/2 (100.0): not calculated	4/5 (80.0): not calculated	not calculated
None of the above	207/208 (99.5): 98.6, 100.0	203/204 (99.5): 98.6, 100.0	0.0 (–1.4, 1.3)
Region, Breslow-Day[b] = 0.380			
Europe	161/162 (99.4): 98.2, 100.0	161/162 (99.4): 98.2, 100.0	0.0 (–1.7, 1.7)
North America	48/48 (100.0): 100.0, 100.0	46/47 (97.9): 93.7, 100.0	–2.1 (–6.3, 2.0)

The evaluator commented that the study design and objectives were similar to study M13-389 (PEARL-II) with the exception that the population of HCV genotype1b infected patients was treatment naïve, and the RBV treatment was given double blind. The data from both studies failed to demonstrate any efficacy benefit with the addition of RBV to 3DAA given for 12 weeks in treatment naïve or treatment experienced patients with HCV genotype1b infection. Overall, the data supported the use of 3DAA without RBV for all non-cirrhotic patient groups with genotype1b infection.

M14-002, PEARL-IV

Treatment naïve, genotype1a infection.

This was a Phase III, randomised, multicentre, double blind, placebo controlled, safety and efficacy study of paritaprevir/ritonavir/ombitasvir and dasabuvir with and without ribavirin in treatment naive non-cirrhotic adults with genotype1a chronic HCV infection. It was conducted at 53 centres in Canada, UK and the US. The study design and primary objectives and efficacy endpoints were the same as for study M13-961, PEARL III.

Results

SVR_{12} was achieved by 97.0% of patients (95% CI: 93.7%, 100%) in the 3DAA + RBV group, and by 90.2% of patients (95% CI: 86.2%, 94.3%) in the 3DAA group. Both primary endpoints were met as the 65% non-inferiority LCB thresholds were achieved in both groups. All patients achieved virologic suppression but on-treatment virologic failure occurred in 1 (1.0%) patient in the 3DAA + RBV group, and six (2.9%) patients in the 3DAA group. In the 3DAA + RBV group, one patient (1.0%) experienced virologic relapse by post treatment Week 12 compared with 10 (5.2%) patients in the 3DAA group. One patient (1%) in each group had missing SVR_{12} data. In the 3DAA + RBV group, SVR_{12} rates and 95% CIs were comparable in the randomisation strata based on IL28B genotype (CC versus non-CC), and in sub-groups defined by gender, age, race, geographic region, BMI, baseline HCV RNA, and fibrosis stage (Table 34).

Table 34: Study M14-002. Virologic response (SVR_{12}) for pre specified subgroups (intent to treat population)

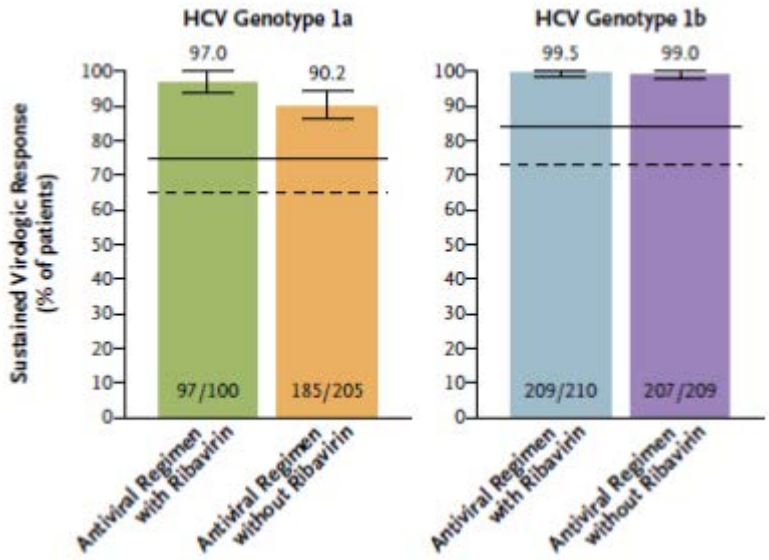
	SVR_{12} Response Rate n/N (%): 95% CI[a]		Treatment
Subgroup	3-DAA + RBV N = 100	3-DAA N = 205	Difference (95% CI[a])
IL28B, Breslow-Day[b] = 0.575 (0.601)[c]			
CC	31/31 (100): 100.0, 100.0	61/63 (96.8): 92.5, 100.0	–3.2 (–7.5, 1.2)
Non-CC	66/69 (95.7): 90.8, 100.0	124/142 (87.3): 81.9, 92.8	–8.3 (–15.6, –1.0)
CT	55/58 (94.8): 89.1, 100.0	92/105 (87.6): 81.3, 93.9	–7.2 (–15.7, 1.3)
TT	11/11 (100): 100.0, 100.0	32/37 (86.5): 75.5, 97.5	–13.5 (–24.5, –2.5)
Sex, Breslow-Day[b] = 0.470			
Female	30/30 (100): 100.0, 100.0	72/76 (94.7): 89.7, 99.8	–5.3 (–10.3, –0.2)
Male	67/70 (95.7): 91.0, 100.0	113/129 (87.6): 81.9, 93.3	–8.1 (–15.5, –0.7)
Age, Breslow-Day[b] = 0.065 (not calculated)[d]			
< 65 years	87/90 (96.7): 93.0, 100.0	172/192 (89.6): 85.3, 93.9	–7.1 (–12.8, –1.4)
≥ 65 years	10/10 (100): not calculated	13/13 (100): 100.0, 100.0	not calculated
< 55 years	49/52 (94.2): 87.9, 100.0	100/109 (91.7): 86.6, 96.9	–2.5 (–10.7, 5.7)
≥ 55 years	48/48 (100): 100.0, 100.0	85/96 (88.5): 82.2, 94.9	–11.5 (–17.8, –5.1)
Birth year, Breslow-Day[b] = 0.626			
< 1945	2/2 (100): not calculated	2/2 (100): not calculated	not calculated
1945 to 1965	69/71 (97.2): 93.3, 100.0	134/150 (89.3): 84.4, 94.3	–7.8 (–14.1, –1.6)
> 1965	26/27 (96.3): 89.2, 100.0	49/53 (92.5): 85.3, 99.6	–3.8 (–13.9, 6.2)
Race, Breslow-Day[b] = 0.444			
Black	10/10 (100): not calculated	23/27 (85.2): 71.8, 98.6	–14.8 (–28.2, –1.4)
Nonblack	87/90 (96.7): 93.0, 100.0	162/178 (91.0): 86.8, 95.2	–5.7 (–11.3, –0.1)
Ethnicity, Breslow-Day[b] = 0.317			
Hispanic or Latino	9/10 (90.0): not calculated	16/18 (88.9): 74.4, 100.0	–1.1 (–24.7, 22.5)
Not Hispanic or Latino	88/90 (97.8): 94.7, 100.0	169/187 (90.4): 86.1, 94.6	–7.4 (–12.6, –2.2)
Region, Breslow-Day[b] = not calculated			
Europe	8/8 (100): not calculated	19/19 (100): 100.0, 100.0	not calculated
North America	89/92 (96.7): 93.1, 100.0	166/186 (89.2): 84.8, 93.7	–7.5 (–13.2, –1.7)

Both treatments were superior to the historical control rate for telaprevir plus pegIFN/RBV therapy. Although the SVR rate was > 90% in the 3DAA group, it was not shown to be non-inferior to the 3DAA + RBV group. Virologic failure occurred in 2.0% of the 3DAA + RBV compared with 7.8% in the 3DAA group. Anaemia was reported in 42.0% of patients in the 3DAA + RBV group and 3.9% in the 3DAA group.

Overall, the study results confirmed high efficacy rates in HCV genotype1a infected patients, matching the rates observed in patients with genotype1b infection. SVR_{12} rates were higher with the addition of RBV to the treatment regimen. The evaluator commented that the high SVR_{12} rates in the 3DAA group (> 90%) could justify the use of 3DAA alone in patients with genotype1a infection who are intolerant to RBV.

Results: PEARL III and IV [82]

Figure 14: Sustained virologic response at 12 weeks after the end of treatment



The dashed horizontal lines indicate non-inferiority thresholds, based on the historical rate of sustained virologic response with telaprevir plus peginterferon–ribavirin. The solid horizontal lines indicate superiority thresholds, based on the historical rate with telaprevir plus peginterferon–ribavirin. I bars indicate 95% confidence intervals.

M13-099. TURQUOISE II

Genotype 1, treatment naïve and experienced, compensated cirrhosis.[83]

This was a Phase III, randomised, multicentre, open label safety and efficacy study of paritaprevir/ritonavir/ ombitasvir + dasabuvir with ribavirin in treatment naive and pegIFN/RBV treatment experienced adults with genotype 1a and 1b chronic HCV infection and compensated cirrhosis. It was conducted at 78 centres in North America and Europe. Randomisation was stratified according to previous pegIFN/RBV therapy (treatment experienced) or no previous therapy (treatment naive). The treatment experienced patients were stratified according to non-response to previous pegIFN/RBV treatment (null responder, partial responder, or relapser) and IL28B genotype. The treatment naïve patients were stratified by HCV genotype (1a or 1b).

The duration of the treatment period was either 12 or 24 weeks, followed by a 48 week post treatment period to monitor safety, HCV RNA, and the emergence and/or persistence of resistant viral variants. A final follow-up visit was conducted at Week 72.

Results

SVR_{12} was achieved by 91.8% of patients (97.5% CI: 87.6%, 96.1%) in the 12 week treatment group, and by 95.9% of patients (97.5% CI: 92.6%, 99.3%) in the 24 week group. Both primary endpoints were met as the 43% non-inferiority LCB thresholds were achieved in both groups.

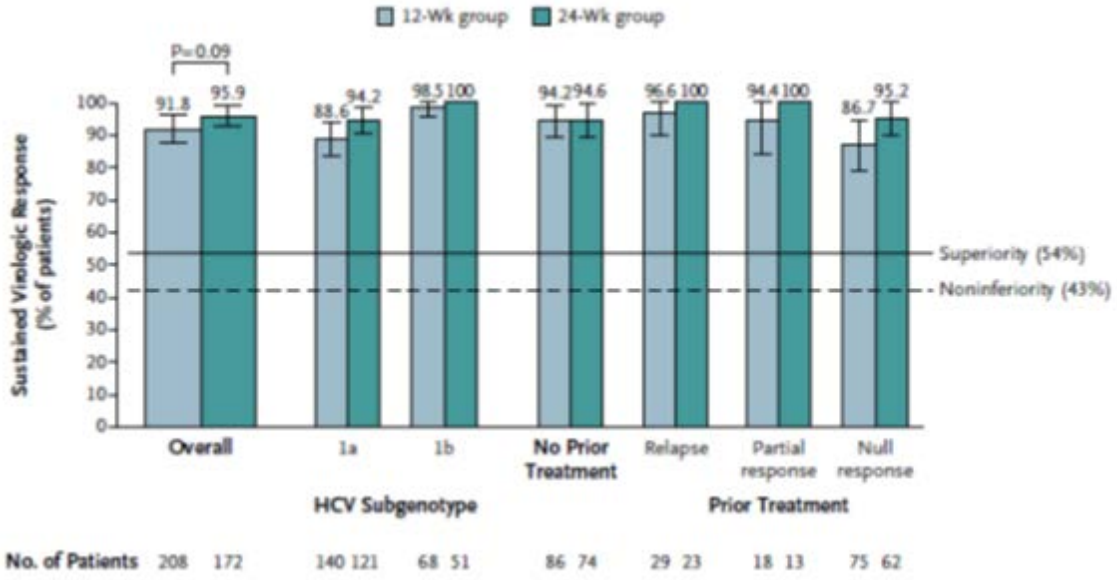
All patients achieved virologic suppression but on-treatment virologic failure occurred in 1 (0.5%) patient in the 12 week group and 3 (1.7%) patients in the 24 week group. In the 12 week group, 12 patients (5.9%) experienced virologic relapse by post treatment Week 12

[82] Ferenci P et al. ABT-450/r – Ombitasvir and Dasabuvir with or without Ribavirin for HCV. *N Engl J Med* 2014;370:1983-1992.
[83] Poordad F et al. ABT-450/r – Ombitasvir and Dasabuvir with Ribavirin for Hepatitis C with Cirrhosis. *N Engl J Med* 2014;370:1973-1982

compared with one (0.6%) patient in the 24 week group. No patients had missing SVR_{12} data. SVR_{12} rates by randomisation strata are shown below.

In both treatment groups, the SVR_{12} rates were higher in patients with genotype1b infection compared with genotype1a infection (98.5% versus 88.6% in the 12 week group, 100% versus 94.2% in the 24 week group). There were no meaningful differences in SVR_{12} rates between treatment naïve and treatment experienced patients with the exception of prior null responders with genotype1a infection in the 12 week arm (SVR_{12} 80.0%). In prior null responders, the SVR_{12} rate was higher in the 24 week group than in the 12 week group (95.2% versus 86.7%, respectively).

Figure 15: Sustained virologic response at post-treatment Week 12 in each treatment group, overall and according to subgroups[83]



To establish non-inferiority and superiority of ritonavir-enhanced paritaprevir, ombitasvir, dasabuvir, and ribavirin to the historical control (telaprevir plus peginterferon–ribavirin), the lower boundary of the confidence interval for the rate of sustained virologic response at post-treatment week 12 in each treatment group had to exceed 43% (dashed line) and 54% (solid line), respectively. All confidence intervals (I bars) are two-sided, with an overall alpha level of 0.05.

Other efficacy trials

Other efficacy trials are described in the clinical evaluation report (see Attachment 2) with a large Phase IIb trial also published.[84]

Study M13-393 (PEARL-1)

Study M13-393 (PEARL-1) Genotype 4 infection, treatment naïve and experienced, genotype1b infection, with and without cirrhosis, treatment naïve and experienced.

This was an open label, randomised, efficacy and safety study of the 2-DAA combination treatment (paritaprevir/ritonavir administered with ombitasvir with and without RBV) in adults with chronic HCV infection. The results presented were an interim analysis of the on-going study. The study objectives were to compare SVR_{12} rates in treatment naïve and treatment experienced patients with HCV genotype 4 infection and in patients with and without cirrhosis with HCV genotype1b infection.

Dasabuvir has no potent in vitro activity against HCV genotype 4, so it was not included in the treatment regimen in this study. These preliminary results showed that 2-DAA for 12 weeks

[84] Kowdley K et al. Phase 2b Trial of Interferon-free Therapy for Hepatitis C Virus Genotype 1. *N Engl J Med* 2014;370:222-232.

is effective in treatment naïve patients with HCV genotype 4 infection (SVR_{12} rate 90.9%). In the group with added RBV, 100% of patients achieved SVR_{12} with similar efficacy in treatment experienced patients.

It is noted that an indication for use in genotype 4 has not been sought by the sponsor but that Europe has included use for genotype 4 in their SmPC.

Analyses performed across trials

These are summarised in the CER (see Attachment 2) and not described in this Overview, given the results of the Phase III trials clearly demonstrated efficacy in relevant patient subgroups.

Influence of IL28B genotype

The potential influence of IL28B genotype sub-types was addressed in all the pivotal studies and no interactions were demonstrated. The FDA and EU reviews [1,77] reported that in non-cirrhotic genotype1a subjects with non-CC genotypes treated with 3DAA + RBV, the SVR_{12} rate was 95%, and when RBV was not included in the regimen the rate was lower at 87%, suggesting that ribavirin reduced the relapse rate, and that these subjects would benefit from the addition of RBV to their treatment regimen. SVR_{12} data in genotype1a treatment naive cirrhotic subjects with non-CC genotypes also suggested a benefit from 24 weeks over 12 weeks of treatment. Treatment naïve genotype1b subjects achieved SVR_{12} rates 99% regardless of IL28B genotype or the inclusion of RBV in the treatment regimen.[1]

Overall conclusions for clinical efficacy

The clinical evaluator concluded that the benefit-risk balance of Viekira Pak and Viekira Pak-RBV given the proposed usage was highly favourable with efficacy rates notably better than telaprevir based therapy in the same subgroups. The data did not support the use of Viekira Pak for any genotype subgroup other than 1b, although the evaluator did comment that in treatment naïve patients with genotype 1a infection without cirrhosis, the addition of ribavirin confers additional benefit but outstanding SVR rates could still be achieved in patients who are intolerant of ribavirin. Given the TGA is proposing separate PIs, this may need some clarification in the PI for Viekira Pak.

Potential for virological resistance, virologic failure

The potential for virological resistance was not discussed at length in the CER. ACSOM commented that the presence of resistance-associated polymorphic forms of HCV were not predictive of therapeutic failure of Viekira Pak and Viekira Pak RBV in clinical trials to date. However, routine clinical use will provide an opportunity for viral resistance to emerge and this should be kept under review. The FDA reviewer[1] commented that resistance testing demonstrated treatment emergent substitutions in all three DAA targets, and that the substitutions were those expected based on preclinical virologic testing. The FDA reviewer also commented that pre-treatment screening for resistance mutations will not be required. A detailed discussion of resistance is also included in the EU review for Viekirax,[78] (pp 77 84). Note that the clinical studies concluded that in non-cirrhotic genotype1a subjects, the addition of RBV appeared to decrease the relapse rate among those treated with 3DAA + RBV. Among cirrhotic (treatment experienced) subjects with genotype1a infection, the virologic failure rates were reduced with longer duration treatment.[1]

Safety

The overall safety profile of 3DAA with or without RBV was clearly superior to any other approved pegIFN/RBV or DAA + pegIFN/RBV combination therapy.

It expected that the majority of Australian patients will need to take with ribavirin, which carries a risk of haemolytic anaemia.

The FDA Summary Review[77] highlighted five pertinent clinical pharmacology issues for Viekira Pak, relevant to safety:

1. An exposure response relationship for paritaprevir for transaminase elevations and other safety parameters
2. Food effect
3. Increased exposures with hepatic impairment
4. Multiple drug-drug interactions, and
5. A drug-drug interaction with oestrogen based oral contraceptives (of unknown mechanism), that increases the frequency of transaminase elevations.

It is this Delegate's view that Viekira Pak and Viekira Pak RBV will be prescribed by appropriately qualified specialists. These matters can be handled appropriately by having adequate and well formatted information in the Product Information coupled with some risk minimisation activities directed at prescribers and patients.

While Viekira Pak and Viekira Pak RBV may cause transaminitis and hyperbilirubinaemia (the latter attributable to paritaprevir inhibition of the bilirubin transporter OATP1B1 and augmented when given with RBV), an association with progression to serious drug-induced liver disease including hepatic failure has not been established.[78]

The clinical evaluator commented that there were no direct comparisons of 3DAA and placebo in a Phase III study and that safety has not been compared with other DAAs. With respect to serious skin related reactions, it is notable that there was a lack of severe or serious rash related events in the pivotal studies. Most events were reversible and mild in severity.

Deaths and serious adverse events

The frequency of SAEs was low in all patient groups. Few SAEs and no deaths were attributed to 3DAA by the investigators. The clinical evaluator commented that patients with significant co-morbidities in the largely middle aged population were excluded and the tolerability in real world patients may prove to be less, but the safety profile of 3DAA in the Phase III studies was strongly encouraging.

Given the lack of post-marketing data currently available, as part of the pre-ACPM response, the sponsor has been requested to update the total number of patients exposed to Viekira Pak and Viekira Pak RBV and to report any new safety issues which have arisen, particularly serious adverse events or serious consequences of drug/drug interactions. A report of the compassionate use program in Australia for the use of these agents (including the number of patients supplied, details of adverse events) has also been requested.

Risk management plan

RMP evaluation and ACSOM advice
Following advice from ACSOM (13 February 2015) the Round 2 RMP reports were provided as separate documents for Viekira Pak (PM-2014-01436-1-2) and Viekira Pak RBV (PM-2014-01438-1-2) respectively.
The recommendations concerning outstanding issues for both submissions were satisfactorily addressed with the response to the first round reports (29 April 2015), with the exception of the wording in relation reporting of adverse reactions in the PI.
The RMP evaluator recommended to the Delegate that the PI statement 'pruritis was the only identified adverse reaction' should be placed in context that is at the 5% level as this statement implies that there were no other treatment-emergent adverse reactions to

Viekira Pak occurred with higher rates than placebo. The revised wording proposed by the sponsor required a minor amendment.

Risk-benefit analysis

Delegate's considerations

Discussion

This submission is unique, given the consideration of three new chemical entities for registration. Efficacy has been clearly demonstrated and represents a considerable advance over previous therapies. Safety is acceptable; however the potential for drug-drug interactions is a major consideration. Clear recommendations to prescribers, pharmacists and patients are required in the PI and CMI and through the proposed education programmes.

The current format of the Australian Product Information differs from that of the European SmPC, the US Prescribing Information and the Canadian Product Monograph, as separate PIs are proposed by the TGA for Viekira Pak and Viekira Pak-RBV (given the difference in pregnancy categorisation for ribavirin). This has implications for the presentation of the PI and the different patient populations for which Viekira Pak and Viekira Pak-RBV are respectively recommended. The Delegate feels that clearer guidance is needed for the Viekira Pak PI, given it is currently recommended for genotype1b only. Inclusion of dosing information related to ribavirin in the Viekira Pak PI may need to be reconsidered, as it may cause confusion for prescribers.

Studies have been conducted in a predominantly white male population; results have been presented for 12 week outcomes only, with 48 week outcomes awaited. Results have been compared to historical control rates with telaprevir and pegylated interferon/ribavirin therapy. While unconventional, this is deemed acceptable given the challenges blinding an injectable medication and the well-known side effects of pegylated interferon/ribavirin.

ACSOM noted that clinical trial exclusion criteria had been applied to patients with advanced disease, co-infection, co-morbidity and concomitant medication, resulting in a limited dataset on which to comment. Specifically, data were not presented for patients with HIV co-infection or in post-transplant settings although overseas evaluation reports confirm these studies have been conducted. [1,78] The sponsor is requested to provide an update of these studies and their intentions for Australia with the pre-ACPM response.

Given the paucity of post-marketing data currently available, as part of the pre-ACPM response, the sponsor has been requested to update the total number of patients exposed to Viekira Pak and Viekira Pak-RBV and to report any new safety issues which have arisen, particularly serious adverse events or serious consequences of drug/drug interactions. A report of the compassionate use program in Australia for the use of these agents has also been requested and will require comment by ACPM.

Subject to advice from ACPM and resolution of the product information, the Delegate proposes to register Viekira Pak combination therapy pack and Viekira Pak-RBV combination therapy pack for the for the treatment of genotype 1 chronic hepatitis C infection, including patients with compensated cirrhosis. Duration of therapy and addition of ribavirin are dependent on patient population. Registration is subject to implementation of the RMP (in EU-RMP format) Version 1.2 (dated February 2015, DLP 24 January 2014) and Australian Specific Annex (ASA) Version 1.2 (dated February 2015), any future updates as a condition of registration and resolution of the PI.

Summary of issues

These products each include three new active substances taken in combination with ritonavir. Some patients will also take ribavirin. Efficacy and safety from clinical trials are impressive. A major consequence of the use of these combinations is an extensive potential for drug-drug interactions, including a number of contraindicated combinations.

Issues for the sponsor

1. Please address the labelling queries from the quality evaluator in relation to the various Viekira Pak-RBV (submission PM-2014-01438-1-2) presentations; given the 'monthly' carton labels for the various presentations are not sufficiently distinguished.

Response from sponsor

AbbVie agrees to differentiate the monthly carton labels as requested by the quality evaluator and in line with TGAs 'Best practice guideline on prescription medicine labelling'. AbbVie only plan to launch Viekira Pak-RBV with either 600 mg ribavirin tablets (for 1200 mg/day dosing) or 200mg ribavirin tablets (for 1000 mg/day dosing or dose reduction if required).

2. Please provide a response to the evaluator comments sent 30 April 2015 regarding the concerns with current statement in the PI regarding race and ethnicity (with reference to Asian and Hispanic/Latino subjects).

Response from sponsor:

AbbVie respectfully disagrees to include the 2nd part of this statement ("however patient numbers in the clinical trials were not sufficient to address possible racial differences").

As summarized in the CER from the TGA, two PPK studies, RD 13-1098 PPK and RD 14-0047 PPK examined the population PKs of paritaprevir, ombitasvir and dasabuvir in HCV genotype 1 infected subjects. Study RD 14-0047 PPK included data from 2,348 subjects from Phase II and Phase III studies in which the HCV genotype 1 infected patients received the recommended dose of the co-formulated paritaprevir/ritonavir/ ombitasvir 150/100/25 mg tablets QD + dasabuvir 250 mg tablets BD. As suggested by the clinical evaluator, RD 14-0047 PPK provides the preferred and more reliable final PPK models for ombitasvir and dasabuvir.

In RD 14-0047 PPK, there were a total of 144 Hispanic/Latino subjects. Hispanic/Latino race was not a significant covariate on the disposition of paritaprevir, ombitasvir, dasabuvir or ritonavir.

In RD 14-0047 PPK, there were a total of 38 Asian subjects. Asian race was not a significant covariate on the disposition of paritaprevir, ombitasvir, dasabuvir or ritonavir. Post-hoc steady-state exposure data showed that paritaprevir, ombitasvir, dasabuvir and ritonavir exposures were generally comparable between Asian and Non-Asian (N = 2,310) HCV genotype 1 infected subjects, with a substantial portion of Non-Asian subjects having exposures higher than those observed in Asian subjects. In addition, the safety was also comparable between Asian and Non-Asian subjects.

Additional details on Asian versus Non-Asian comparison of Phase I data and Phase II/III data are summarized below.

Asian versus Non-Asian Subjects

The exposures of paritaprevir are highly variable across subjects (% coefficient of variation (CV) of approximately 80% across Phase I studies) and therefore, cross study or cross arm comparisons using small sample sizes can be misleading. The 3DAA arm of M12-221 (25 mg ombitasvir + 150/100 mg paritaprevir/ritonavir + 400 mg dasabuvir)

compared 6 subjects per ethnicity. Table 35 shows the mean AUC values from M12-221 and the means from other Phase I studies.

Table 35: Geometric mean AUC values for paritaprevir from M12-221 and other Phase I studies with the 3DAA regimen at steady state using the same formulation as M12-221

	Geometric Mean AUC (%CV) (ng*hr/mL)	
	Study M12-221 (N=6)	Other Phase 1 studies
Caucasian	1768 (83%)	2360-8250[a]
Chinese	7631 (94%)	
Japanese	9001 (44%)	

a. Range of geometric mean values across 10 study arms in studies conducted in US that used the same ABT-450/r 150/100 mg SDD formulation as in Study M12-221.

The geometric mean AUC of paritaprevir in Chinese subjects was in the range of geometric means of Caucasians in Phase I studies, and the geometric mean of AUC in Japanese subjects was only slightly higher than the maximum in Caucasians. Thus while the exposures of paritaprevir were higher in Asian subjects than Caucasians, the exact magnitude of the increase is difficult to quantify given the small sample size coupled with the high variability of paritaprevir exposures.

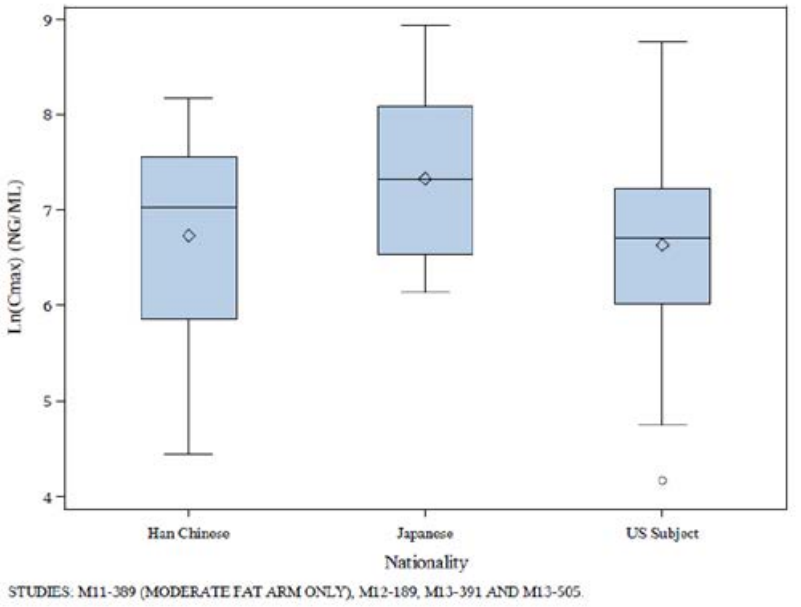
When a similar comparison was done across studies using the Phase III formulation with a higher number of subjects, the differences were much lower; comparable AUC values for paritaprevir in Chinese and only approximately 60% higher AUC values (7136 ng.hr/mL versus 4,556 ng.hr/mL) in Japanese subjects compared to the US subjects (Table 36 and Figure 16).

Table 36: Geometric mean AUC values for paritaprevir in Chinese, Japanese and US subjects using the Phase III formulation following single dose of paritaprevir/ritonavir/ombitasvir 150/100/25 mg

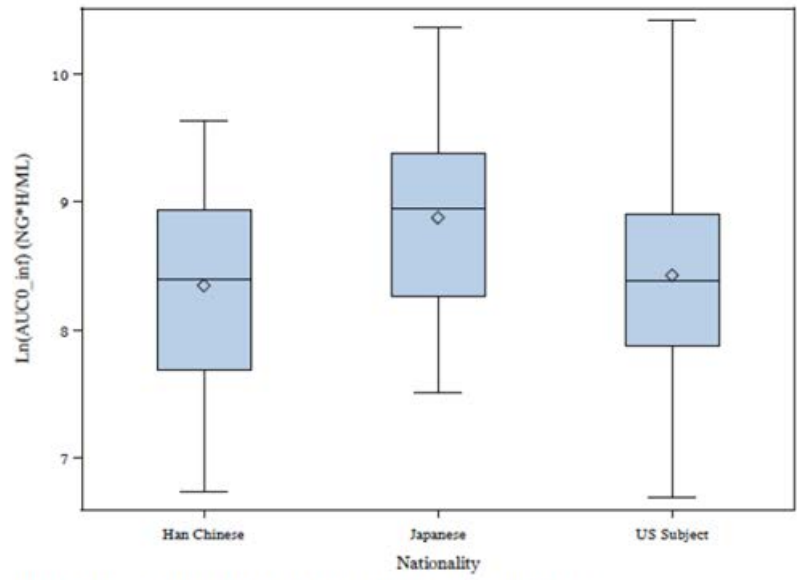
	Study (N)	Geometric Mean AUC (ng*hr/mL)
Chinese	M13-505 (N=23)	4219 (71%)
Japanese	M13-505 (N=24)	7136 (82%)
US subjects	Pooled (N=50)	4556[a]
	M11-389 (N=19)	5088 (107%)
	M11-391 (N=19)	3403 (55%)
	M12-189 (N=12)	6066 (46%)

a. Geometric mean ABT-450 AUC across Studies M11-389, M11-391 and M12-189

Figure 16: Paritaprevir C_{max} and AUC values in Caucasian and Asian Subjects across studies



STUDIES: M11-389 (MODERATE FAT ARM ONLY), M12-189, M13-391 AND M13-505.



STUDIES: M11-389 (MODERATE FAT ARM ONLY), M12-189, M13-391 AND M13-505.

Similarly, in Study M13-505, following administration of paritaprevir/ritonavir/ ombitasvir co-formulated tablets, ombitasvir AUC values in healthy Japanese and Chinese subjects were comparable or slightly higher (Japanese/US AUC ratio: 1.06 to 1.21, Chinese/US AUC ratio: 0.85 to 1.02) than ombitasvir AUC values in healthy US subjects (M11-389, M11-391 and M12-189).

Similar to the results from Study M13-505 with the Phase III formulation, a pooled analysis of 38 Asian subjects dosed in one of the 6 Phase III studies (M11-646, M13-098, M13-389, M13-961, M14-002, and M13-099) and supportive Phase II Study M14-103 showed only a modest increase in exposures of paritaprevir compared with the Non-Asian subjects. The geometric mean steady state exposures (maximum plasma concentration at steady state ($C_{max,ss}$) and $AUC_{24,ss}$) of paritaprevir, ombitasvir and dasabuvir for the Asian population (N = 38; 37 Asians and 1 White-Asian) were only 37% to 39%, 18% to 21% and 29% to 39% higher than for Non-Asians (N = 2,310), respectively (Table 37). There was significant overlap in the ranges of exposures between Asians and Non-Asians as shown in Figures 17, 18, 19 and 20. Eighteen of the 38 Asian subjects were female. Overall,

the results do not suggest a clinically meaningful impact of Asian race on the pharmacokinetics of paritaprevir, ombitasvir, dasabuvir or ritonavir.

Table 37: Comparison of paritaprevir, ombitasvir, dasabuvir and ritonavir steady-state exposures (C_{max} and AUC) between Asian and Non-Asian populations in global Phase III studies plus Study M14-103 (using the Phase III formulation and doses) (geometric mean values)

	AUC (ng*hr/mL)			C_{max} (ng/mL)		
	Non-Asians[a] (N = 2310)	Asians[b] (N = 38)	AUC Ratio (Asians/ Non-Asians)	Non-Asians[a] (N = 2310)	Asians[b] (N = 38)	C_{max} Ratio (Asians/ Non-Asians)
ABT-450	1790	2490	1.39	142	194	1.37
ABT-267	982	1190	1.21	54.4	64.2	1.18
ABT-333	9940	13800	1.39	596	768	1.29
Ritonavir	4400	4130	0.94	362	341	0.94

a. Includes subjects from Studies M11-646, M13-098, M13-099, M13-389, M13-961, M14-002, and M14-103 who had samples available for pharmacokinetic analyses.

Figure 17: Comparison of paritaprevir steady-state exposures (C_{max} and AUC) between Asian and Non-Asian populations in global Phase III Studies plus Study M14-103 (using the Phase III formulation and doses)

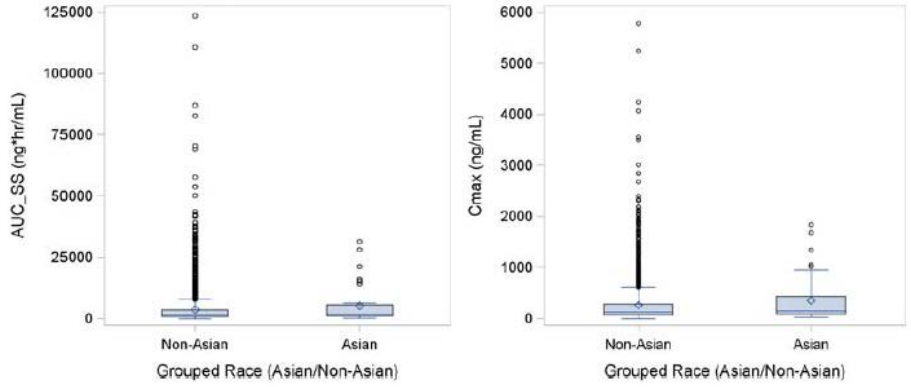


Figure 18: Comparison of ombitasvir steady state exposures (C_{max} and AUC) between Asian and Non-Asian populations in global Phase III Studies plus Study M14-103

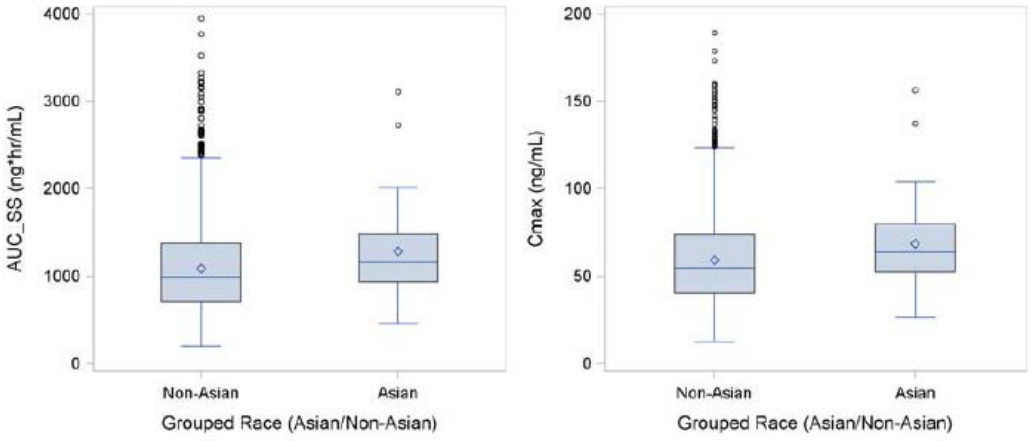


Figure 19: Comparison of dasabuvir steady state exposures (C_{max} and AUC) between Asian and Non-Asian populations in global Phase III Studies and M14-103

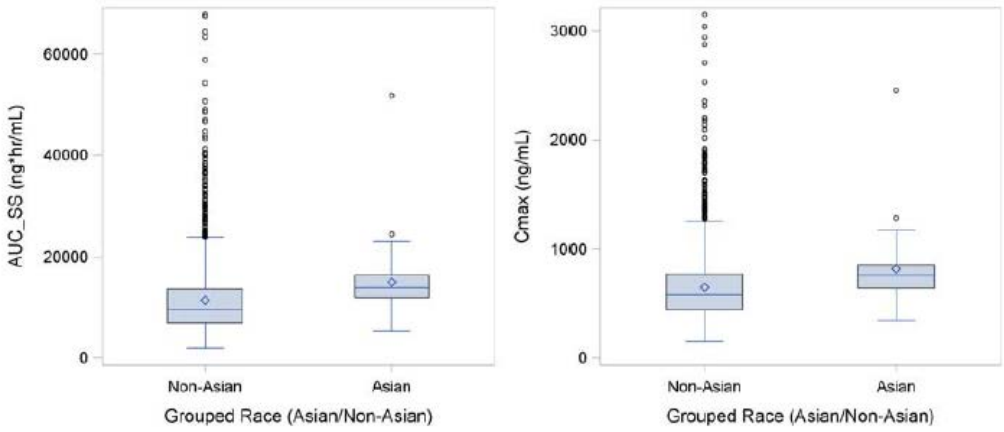
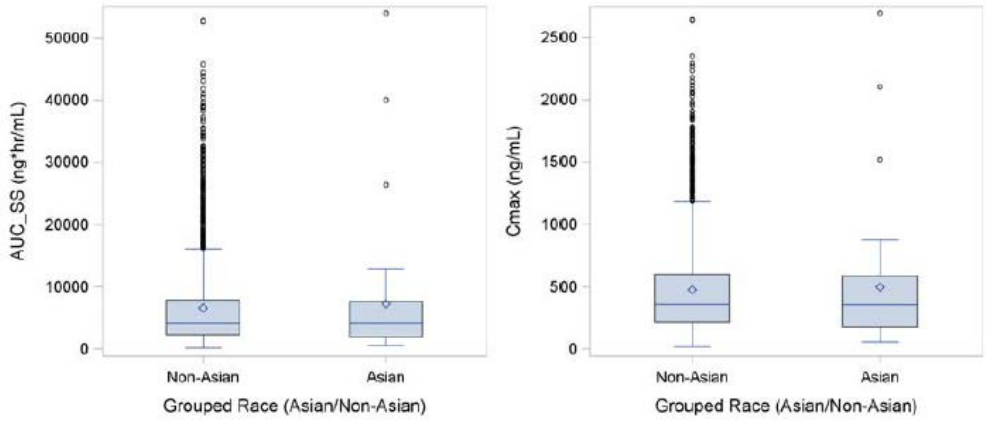


Figure 20: Comparison of ritonavir steady-state exposures (C_{max} and AUC) between Asian and Non-Asian populations in global Phase III Studies and M14-103



In summary, while the mean exposures in Asian subjects are higher (up to 60%, 20% and 40% for paritaprevir , ombitasvir and dasabuvir, respectively), the increases are modest and no change is required in the dosing recommendation for any of the compounds in the regimen.

Safety in Asian and Non-Asian HCV genotype1-infected subjects in the global 3DAA development program

A total of 38 Asian subjects participated in the 6 Phase III studies and supportive Phase II study (M14-103) in the global 3DAA development program. These Asian subjects received 12 weeks of 3DAA, 12 weeks of 3DAA + RBV, or 24 weeks of 3DAA + RBV depending upon the trial in which they participated.

Demographic characteristics of Asian subjects were comparable to those of Non-Asian subjects (Table 38) except that mean body weight was lower (67.9 kg versus 77.7 kg).

Baseline disease characteristics for Non-Asian and Asian subjects are presented in Table 39. Similar to Non-Asian subjects, the majority of Asian subjects was treatment naïve (71.1%) and had minimal fibrosis (F0 to F1, 63.2%). A total of 8 (21.2%) Asian subjects had compensated cirrhosis and 6 (15.8%) Asian subjects were null responders to previous pegIFN/RBV treatment. A higher percentage of Asian subjects had IL28B CC (65.8% versus 21.1%) and were infected with genotype1b (60.5% versus 46.3%) compared with Non-Asian subjects.

Table 38: Demographic characteristics of Asian and Non-Asian subjects in global Phase II and III studies

Characteristic	Non-Asian Subjects			Asian Subjects		
	3-DAA + RBV (N = 1810)	3-DAA (N = 503)	Total (N = 2313)[a]	3-DAA + RBV (N = 32)	3-DAA (N = 6)	Total (N = 38)[b]
Sex, n (%)						
Female	747 (41.3)	232 (46.1)	979 (42.3)	13 (40.6)	5 (83.3)	18 (47.4)
Male	1063 (58.7)	271 (53.9)	1334 (57.7)	19 (59.4)	1 (16.7)	20 (52.6)
Geographic region, n (%)						
US	740 (40.9)	230 (45.7)	970 (41.9)	13 (40.6)	2 (33.3)	15 (39.5)
European Union	801 (44.3)	179 (35.6)	980 (42.4)	12 (37.5)	2 (33.3)	14 (36.8)
Rest of world	269 (14.9)	94 (18.7)	363 (15.7)	7 (21.9)	2 (33.3)	9 (23.7)
Age distribution, n (%)						
< 65 years	1662 (91.8)	456 (90.7)	2118 (91.6)	30 (93.8)	5 (83.3)	35 (92.1)
≥ 65 years	148 (8.2)	47 (9.3)	195 (8.4)	2 (6.3)	1 (16.7)	3 (7.9)
Age, years						
Mean ± SD	52.1 ± 10.53	51.1 ± 11.33	51.8 ± 10.71	47.2 ± 12.00	46.8 ± 12.04	47.2 ± 11.84
Median	54.0	53.0	54.0	48.0	46.0	48.0
Minimum – maximum	18.0 – 71.0	21.0 – 70.0	18.0 – 71.0	26.0 – 66.0	34.0 – 67.0	26.0 – 67.0
Weight, kg						
Mean ± SD	77.8 ± 15.28	77.4 ± 15.56	77.7 ± 15.34	70.0 ± 13.63	56.8 ± 7.53	67.9 ± 13.69
Median	76.8	76.0	76.5	67.4	56.0	66.0
Minimum – maximum	41.5 – 129.0	46.0 – 129.0	41.5 – 129.0	45.0 – 110.0	47.6 – 68.0	45.0 – 110.0

a. Includes subjects from Studies M11-646, M13-098, M13-099, M13-389, M13-961, M14-002, and M14-103.
b. Includes subjects from Studies M11-646, M13-098, M13-099, M13-389, M13-961, and M14-002; no Asian subjects participated in Study M14-103.

Table 39: Baseline disease characteristics of Asian and Non-Asian subjects in global Phase II and III studies

Characteristic	Non-Asian Subjects			Asian Subjects		
	3-DAA + RBV (N = 1810) n (%)	3-DAA (N = 503) n (%)	Total (N = 2313)[a] n (%)	3-DAA + RBV (N = 32) n (%)	3-DAA (N = 6) n (%)	Total (N = 38)[b] n (%)
Prior HCV medication history						
Treatment naïve	1113 (61.5)	410 (81.5)	1523 (65.8)	23 (71.9)	4 (66.7)	27 (71.1)
PegIFN/RBV treatment-experienced	697 (38.5)	93 (18.5)	790 (34.2)	9 (28.1)	2 (33.3)	11 (28.9)
Type of response to previous pegIFN/RBV treatment						
Null responder	358 (19.8)	32 (6.4)	390 (16.9)	5 (15.6)	1 (16.7)	6 (15.8)
Partial responder	142 (7.8)	27 (5.4)	169 (7.3)	1 (3.1)	0	1 (2.6)
Relapser	197 (10.9)	34 (6.8)	231 (10.0)	3 (9.4)	1 (16.7)	4 (10.5)
HCV genotype/subtype						
1a	1038 (57.3)	202 (40.2)	1240 (53.6)	12 (37.5)	3 (50.0)	15 (39.5)
1b	771 (42.6)	300 (59.6)	1071 (46.3)	20 (62.5)	3 (50.0)	23 (60.5)
Other	1 (< 0.1)	1 (0.2)	2 (< 0.1)	0	0	0
IL28B genotype						
CC	379 (20.9)	110 (21.9)	489 (21.1)	21 (65.6)	4 (66.7)	25 (65.8)
CT	1097 (60.6)	302 (60.0)	1399 (60.5)	11 (34.4)	2 (33.3)	13 (34.2)
TT	334 (18.5)	91 (18.1)	425 (18.4)	0	0	0
Baseline fibrosis stage						
F0 – F1	1035 (57.2)	328 (65.3)	1363 (59.0)	18 (56.3)	6 (100)	24 (63.2)
F2	243 (13.4)	103 (20.5)	346 (15.0)	1 (3.1)	0	1 (2.6)
F3	158 (8.7)	69 (13.7)	227 (9.8)	5 (15.6)	0	5 (13.2)
F4	374 (20.7)	2 (0.4)	376 (16.3)	8 (25.0)	0	8 (21.1)
Missing	0	1	1	0	0	0
History of diabetes						
Yes	120 (6.6)	29 (5.8)	149 (6.4)	4 (12.5)	0	4 (10.5)
No	1690 (93.4)	474 (94.2)	2164 (93.6)	28 (87.5)	6 (100)	34 (89.5)
History of depression or bipolar disorder						
Yes	339 (18.7)	74 (14.7)	413 (17.9)	2 (6.3)	0	2 (5.3)
No	1471 (81.3)	429 (85.3)	1900 (82.1)	30 (93.8)	6 (100)	36 (94.7)

a. Includes subjects from Studies M11-646, M13-098, M13-099, M13-389, M13-961, M14-002, and M14-103.
b. Includes subjects from Studies M11-646, M13-098, M13-099, M13-389, M13-961, and M14-002; no Asian subjects participated in Study M14-103.
Note: Percentages are calculated on non-missing or non-unknown values.

An overview of treatment emergent adverse events is presented in Table 40. A majority of subjects (84.9% of Non-Asian subjects and 97.4% of Asian subjects, respectively)

experienced at least 1 treatment emergent adverse event. Most of these subjects experienced events that were mild in severity.

The most common adverse events (≥ 10.0% of Asian or Non-Asian subjects) are presented in Table 41 and were generally comparable between Non-Asian and Asian subjects. There was no apparent difference in the pattern of moderate to-severe adverse events between Asian and Non-Asian subjects.

The incidences of treatment emergent serious adverse events (2.6% in both Asian and Non-Asian subjects) and treatment emergent adverse events leading to discontinuation of study drug (0% and 1.0% in Asian and Non-Asian groups, respectively) were low. Only one Asian subject experienced a serious adverse event (subcutaneous abscess) that was considered to have no reasonable possibility of relatedness to 3DAA or RBV. No deaths were observed among Asian subjects (Table 40).

Laboratory abnormalities of special interest were also assessed for Asian and Non-Asian subjects (Table 42). The severity and frequency of laboratory abnormalities among Non-Asian and Asian subjects were generally similar.

In summary, in the global 3DAA development program, demographic and baseline characteristics in Asian and Non-Asian subjects were generally similar except for the lower body weight, higher percentage of IL28B-CC haplotype and higher percentage of genotype1b infection in Asian subjects, as expected. The safety profile of the 3DAA regimen in Asian and Non-Asian subjects were similar.

Therefore, there is a reasonable amount of data from Latino or Asian subjects in the global 3DAA development program. The sponsor considers that, for the Australian PI, the recommendation of "No dose adjustment is necessary for paritaprevir/ritonavir/ombitasvir or dasabuvir based on race or ethnicity." is appropriate, and stating the magnitude of differences between Asians and Non-Asians from population PK analysis is appropriate:

"Based on population pharmacokinetic analysis of data from Phase III clinical studies, Asian subjects had 18% to 21%, 37% to 39% and 29% to 39% higher ombitasvir, paritaprevir and dasabuvir exposures, respectively, than Non-Asian subjects. The ritonavir exposures were comparable between Asians and Non-Asians."

Table 40: Overview of treatment emergent AEs for Asian and Non-Asian subjects in global Phase III Studies and M14-103

	Non-Asian Subjects			Asian Subjects		
Category	3-DAA + RBV (N = 1810) n (%)	3-DAA (N = 503) n (%)	Total (N = 2313)[a] n (%)	3-DAA + RBV (N = 32) n (%)	3-DAA (N = 6) n (%)	Total (N = 38)[b] n (%)
Any adverse event	1585 (87.6)	378 (75.1)	1963 (84.9)	32 (100)	5 (83.3)	37 (97.4)
Any adverse event with a reasonable possibility of being related to DAA[c]	1259 (69.6)	274 (54.5)	1533 (66.3)	30 (93.8)	2 (33.3)	32 (84.2)
Any adverse event with a reasonable possibility of being related to RBV[c]	1319 (72.9)	220 (43.7)	1539 (66.5)	30 (93.8)	2 (33.3)	32 (84.2)
Any severe adverse event	66 (3.6)	6 (1.2)	72 (3.1)	0	0	0
Any grade 3 or 4 adverse event	82 (4.5)	10 (2.0)	92 (4.0)	1 (3.1)	0	1 (2.6)
Any serious adverse event	52 (2.9)	7 (1.4)	59 (2.6)	1 (3.1)	0	1 (2.6)
Any adverse event leading to discontinuation of study drug	21 (1.2)	2 (0.4)	23 (1.0)	0	0	0
Any adverse event leading to interruption of study drug	26 (1.4)	2 (0.4)	28 (1.2)	0	0	0
Any adverse event leading to RBV dose modifications	145 (8.0)	1 (0.2)	146 (6.3)	1 (3.1)	0	1 (2.6)
Any fatal adverse event	1 (< 0.1)	0	1 (< 0.1)	0	0	0
Deaths, including nontreatment-emergent	2 (0.1)	0	2 (< 0.1)	0	0	0

a. Includes subjects from Studies M11-646, M13-098, M13-099, M13-389, M13-961, M14-002, and M14-103.
b. Includes subjects from Studies M11-646, M13-098, M13-099, M13-389, M13-961, and M14-002; no Asian subjects participated in Study M14-103.
c. As assessed by the investigator.

Table 41: Treatment emergent AEs reported for ≥ 10.0% of Asian or Non-Asian subjects in global Phase III studies and M14-103

	Non-Asian Subjects			Asian Subjects		
Preferred Term	3-DAA + RBV (N = 1810) n (%)	3-DAA (N = 503) n (%)	Total (N = 2313) n (%)	3-DAA + RBV (N = 32) n (%)	3-DAA (N = 6) n (%)	Total (N = 38) n (%)
Any adverse event	1585 (87.6)	378 (75.1)	1963 (84.9)	32 (100)	5 (83.3)	37 (97.4)
Fatigue	586 (32.4)	134 (26.6)	720 (31.1)	14 (43.8)	1 (16.7)	15 (39.5)
Headache	517 (28.6)	128 (25.4)	645 (27.9)	11 (34.4)	1 (16.7)	12 (31.6)
Nausea	358 (19.8)	43 (8.5)	401 (17.3)	4 (12.5)	0	4 (10.5)
Pruritus	259 (14.3)	30 (6.0)	289 (12.5)	7 (21.9)	1 (16.7)	8 (21.1)
Insomnia	253 (14.0)	26 (5.2)	279 (12.1)	4 (12.5)	0	4 (10.5)
Diarrhoea	223 (12.3)	55 (10.9)	278 (12.0)	4 (12.5)	3 (50.0)	7 (18.4)
Asthenia	212 (11.7)	20 (4.0)	232 (10.0)	2 (6.3)	0	2 (5.3)
Rash	168 (9.3)	19 (3.8)	187 (8.1)	4 (12.5)	0	4 (10.5)
Cough	150 (8.3)	24 (4.8)	174 (7.5)	6 (18.8)	0	6 (15.8)
Dyspnoea	149 (8.2)	11 (2.2)	160 (6.9)	4 (12.5)	0	4 (10.5)
Decreased appetite	113 (6.2)	18 (3.6)	131 (5.7)	5 (15.6)	0	5 (13.2)
Nasopharyngitis	111 (6.1)	17 (3.4)	128 (5.5)	2 (6.3)	2 (33.3)	4 (10.5)
Dry skin	101 (5.6)	11 (2.2)	112 (4.8)	4 (12.5)	0	4 (10.5)
Dyspepsia	92 (5.1)	16 (3.2)	108 (4.7)	3 (9.4)	1 (16.7)	4 (10.5)

a. Includes subjects from Studies M11-646, M13-098, M13-099, M13-389, M13-961, M14-002, and M14-103.
b. Includes subjects from Studies M11-646, M13-098, M13-099, M13-389, M13-961, and M14-002; no Asian subjects participated in Study M14-103.
Note: Order is by decreasing frequency in non-Asian subjects.

Table 42: Key laboratory parameters by grade during the treatment period for Asian and Non-Asian subjects in global Phase III studies and M14-103

	Non-Asian Subjects			Asian Subjects		
Postbaseline Grade	3-DAA + RBV (N = 1810) n/N (%)	3-DAA (N = 503) n/N (%)	Total (N = 2313)[a] n/N (%)	3-DAA + RBV (N = 32) n/N (%)	3-DAA (N = 6) n/N (%)	Total (N = 38)[b] n/N (%)
Hemoglobin						
At least Grade 2	122/1804 (6.8)	0/ 503	122/2307 (5.3)	1/32 (3.1)	0/6	1/38 (2.6)
ALT						
At least Grade 2	46/1804 (2.5)	9/ 503 (1.8)	55/2307 (2.4)	1/32 (3.1)	0/ 6	1/38 (2.6)
At least Grade 3	23/1804 (1.3)	1/ 503 (0.2)	24/2307 (1.0)	1/32 (3.1)	0/ 6	1/38 (2.6)
AST						
At least Grade 2	29/1803 (1.6)	5/ 503 (1.0)	34/2306 (1.5)	1/32 (3.1)	0/ 6	1/38 (2.6)
At least Grade 3	11/1803 (0.6)	1/ 503 (0.2)	12/2306 (0.5)	0/32	0/ 6	0/38
Alkaline Phosphatase						
At least Grade 2	1/1804 (< 0.1)	0/ 503	1/2307 (< 0.1)	0/32	0/ 6	0/38
At least Grade 3	0/1804	0/ 503	0/2307	0/32	0/ 6	0/38
Total Bilirubin						
At least Grade 2	471/1804 (26.1)	31/503 (6.2)	502/2307 (21.8)	15/32 (46.9)	0/ 6	15/38 (39.5)
At least Grade 3	84/1804 (4.7)	2/503 (0.4)	86/2307 (3.7)	4/32 (12.5)	0/ 6	4/38 (10.5)
Creatinine Clearance						
At least Grade 2	63/1803 (3.5)	13/ 503 (2.6)	76/2306 (3.3)	2/32 (6.3)	1/ 6 (16.7)	3/38 (7.9)

a. Includes subjects from Studies M11-646, M13-098, M13-099, M13-389, M13-961, M14-002, and M14-103.
b. Includes subjects from Studies M11-646, M13-098, M13-099, M13-389, M13-961, and M14-002; no Asian subjects participated in Study M14-103.
Note: N indicates the number of subjects with a postbaseline value.

3. Please ensure there are regular updates to the PI in line with emerging data from clinical trials. In particular, please submit the data relating to special groups including HCV/HIV co-infection (M14-004), post-transplant (M12-99) and the results of the completed studies for this current submission (when available) as a formal future submission to the TGA. The Delegate notes that the data supporting use in patients with genotype 4 infection will be submitted.

Response from sponsor

We agree to submit the data relating to special groups including HCV/HIV co-infection (M14-004), post-transplant (M12-999) and the results of the completed studies for this current submission (when available).

4. Please provide the most recent version of the patient dosing card and information sheets for both Viekira Pak and Viekira Pak-RBV with the pre-ACPM response (as described in the response to the second round reports, RMP evaluation).

Response from sponsor

Please refer to the sponsor's response to Question 3 in the request for ACPM advice response from sponsor section below.

Proposed action

The Delegate had no reason to say, at this time, that the applications for Viekira Pak and Viekira Pak-RBV should not be approved for registration.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. The potential for virological resistance with the use of Viekira Pak and Viekira Pak-RBV.
2. The adequacy and clarity of the PI with respect to contra indications and drug-drug interactions sections, noting the Delegate's proposed changes and the presentation of overseas PI.
3. The clarity of the CMI, patient dosing card and information sheets (see RMP second round report, recommendation 1.12, PM-2014-01438-1-2 (Viekira Pak-RBV).
4. With reference to Viekira Pak and the proposed PI, is the broad indication proposed for genotype 1 infection for Viekira Pak acceptable, given the data only support use in genotype 1b? Also, is clearer guidance needed for the Viekira Pak PI indicating it is currently recommended for genotype1b only? Should dosing information related to ribavirin be omitted?
5. The updated safety data and report of the compassionate use program anticipated with the pre-ACPM response.
6. Does the PI require further qualification in regards to race and ethnicity for Asian and Hispanic/Latino patients?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

AbbVie Pty Ltd welcomes the opportunity to provide comments on the evaluation and proposed actions in relation to the applications to register Viekira Pak and Viekira Pak-RBV.

AbbVie agrees with the assessment of the Delegate in the Request for ACPM's Advice dated 5 May 2015.

The committee was requested to provide advice on the following specific issues:

1. The potential for virological resistance with the use of Viekira Pak and Viekira Pak-RBV

AbbVie Comment:

All interferon-free DAA combination therapies for genotype 1 infection that are approved or under review, including Viekira Pak and Viekira Pak-RBV, are associated with a risk for selection of resistance among patients who fail treatment. In particular, regimens like Viekira Pak, sofosbuvir/ledipasvir, and daclatasvir/asunaprevir combinations each of which contains an NS5A inhibitor, all lead to emergence of NS5A resistant variants among patients who fail treatment.

The risk of resistance development and the persistence of resistant variants were studied in an analysis presented at the International Liver Congress in Vienna in April 2015 (Krishnan et al.)[85]. In this analysis, among subjects who received the regimen in the proposed Viekira Pak and Viekira Pak-RBV labels, the overall rate of virologic failure was 1.8%. Among those patients who did fail, the majority showed emergence of resistance associated variants in at least one target gene (NS3, NS5A, and NS5B). However, NS3 variants (which might result in cross resistance to other protease inhibitors) decreased in frequency over 48 weeks of follow-up. NS5B variants tended to persist over 48 weeks, but these variants do not confer cross resistance to any polymerase inhibitors (nucleoside or nonnucleoside) currently approved (for example sofosbuvir) or in late-stage development, so they would not have any impact on re-treatment. The NS5A variants in this analysis persisted over 48 weeks (96% were still present at 48 weeks).

However, long term persistence appears to be a characteristic of NS5A resistant variants in general, and is not specific to Viekira Pak or Viekira Pak-RBV. In another analysis presented at the International Liver Congress (Wyles et al)[86], patients who developed NS5A resistant variants after treatment with ledipasvir-containing regimens were studied. Among these patients 95% of the NS5A resistant variants were still present after 48 weeks of follow-up. The consistency of these findings confirms previous results demonstrating the persistence of NS5A resistant variants. However, the clinical significance of these variants is still uncertain, as optimal re-treatment regimens have yet to be defined. These re-treatment options may include combinations of currently available therapies, or newer, "next-generation" agents with in vitro activity against resistant strains.

In summary, in clinical trials the risk of virologic failure in patients treated with the regimens in the proposed Viekira Pak and Viekira Pak-RBV labels was 1.8%, indicating that resistance will not be a concern for the large majority of patients treated with these regimens. For those patients who do experience treatment failure, the impact of resistance on options for re-treatment is likely to be similar for Viekira Pak treated patients and for patients treated with other interferon-free DAA combination regimens.

2. *The adequacy and clarity of the PI with respect to contra-indications and drug-drug interactions sections, noting the Delegate's proposed changes and the presentation of overseas PI.*

AbbVie Comment:

The sponsor has agreed with the requests of the Delegate to update the PI in line with the EU SmPC and US PI as proposed in the Request for ACPM's advice, along with a recent update to the CCDS regarding hypersensitivity and drug-drug interactions with quetiapine.

3. *The clarity of the CMI, patient dosing card and information sheets (see RMP second round report, recommendation 1.12, PM-2014-01438-1-2)*

AbbVie Comment

AbbVie Pty Ltd believes the CMI, patient dosing card and information sheets proposed in the response and the response to the evaluation reports provide sufficient information to the patient with respect to the dosing regimen.

Please refer to the CMI, patient dosing card and the overview of the proposed information sheet provided.

[85] Krishnan P. et al. Long term follow up of treatment emergent resistance associated variants in NS3, NS5A and NS5B with paritaprevir/r-, ombitasvir- and dasabuvir based regimens. *Journal of Hepatology* 2015; 62: S220

[86] Dvory-Sobol H et al (including Wyles D) Long term persistence of HCV NS5A variants after treatment with NS5A inhibitor ledipasvir. *Journal of Hepatology* 2015; 62: S221

4. *With reference to Viekira Pak and the proposed PI, is the broad indication proposed for genotype 1 infection for Viekira Pak acceptable, given the data only support use in genotype 1b? Also, is clearer guidance needed for the Viekira Pak PI indicating it is currently recommended for genotype1b only? Should dosing information related to ribavirin be omitted?*

AbbVie Comment:

AbbVie proposes to retain the broad indication for genotype 1 in the Viekira Pak PI. Per Dosing and Administration, Viekira Pak without ribavirin can be considered as a therapeutic option for treatment naïve patients with genotype 1a infection without cirrhosis (see clinical trials). Treatment decisions should be guided by an assessment of the potential benefits and risks and available alternative therapies for the individual patient. As the potential exists for use of Viekira Pak in patients with genotype1a infection, the broader indication should be retained.

5. *The updated safety data and report of the compassionate use program anticipated with the pre-ACPM response*

AbbVie Comment:

The adverse reactions update which includes updated safety data and a report of the compassionate use program has been provided as an appendix to this response.

6. *Does the PI require further qualification in regards to race and ethnicity for Asian and Hispanic/Latino patients?*

AbbVie Comment:

Please refer to the sponsor's response to Delegate's "Issues for the sponsor" Question 2 above.

Advisory Committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Viekira Pak tablets containing paritaprevir 75 mg, ritonavir 50 mg and ombitasvir 12.5 mg fixed dose combination tablets, co-packaged with dasabuvir 250 mg tablets has an overall positive benefit–risk profile for the indication;

> *Viekira Pak is indicated for the treatment of genotype 1 chronic hepatitis C infection, including patients with compensated cirrhosis. Duration of therapy and addition of ribavirin are dependent on patient population (see DOSAGE AND ADMINISTRATION, PRECAUTIONS, CLINICAL TRIALS).*

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed PI and CMI amendments

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI)and specifically advised on the inclusion of the following:

- The PI/CMI should warn about the possibility of jaundice and dark urine as well as advice on the need for frequent blood tests.
- The PI should provide strong warnings about drug-drug interactions.

- The PI should include a statement such as the following, "however, patient numbers in the clinical trials were not sufficient to address possible differences in pharmacokinetics and toxicity profiles in specific ethnic groups such as Asian patients".
- Emphasise the potential consequences of pregnancy in the CMI given the teratogenicity of ribavirin and the contraindicated use of ethinyl oestradiol containing medicinal products.
- Add a statement to the effect that "Viekira Pak is recommended as first line treatment for genotype 1b infection, and second line (if ribavirin-intolerant) for genotype 1a infection" to the beginning of the Dosage and Administration section of the PI, referencing Table 16.

Specific Advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. The potential for virological resistance with the use of Viekira Pak and Viekira Pak-RBV.

The ACPM advised that there is a risk that virological resistance may develop. However, the ACPM considered that this is unlikely to be a significant problem in clinical practice, as the results seen in the pivotal clinical studies for proportion of patients achieving SVR_{12} were very high.

2. The adequacy and clarity of the PI with respect to contraindications and drug-drug interactions sections, noting the Delegate's proposed changes and the presentation of overseas product information.

The ACPM advised that the information in the PI with respect to the contraindications and drug-drug interactions sections should be amended as proposed by the Delegate. The ACPM noted the changes to the PI that had been made by the sponsor in response to the Delegate's comments.

The ACPM noted that the PI contraindicates use of Viekira Pak (with or without ribavirin) with ethinyl oestradiol containing medicinal products due to the potential for elevation of ALT. There was concern that a contraindication to oral contraceptives could be potentially problematic, given that ribavirin (which is included in Viekira Pak-RBV, but not Viekira Pak) is in Pregnancy Category X. However, the contraindication for oral contraceptives in the PI only applies to products that contain ethinyl oestradiol, and the PRECAUTIONS section of the PI recommends the use of alternative contraceptive agents or methods of contraception during Viekira Pak therapy.

3. The clarity of the CMI, patient dosing card and information sheets (see RMP second round report, recommendation 1.12, PM-2014-01438-1-2).

The ACPM considered that the CMI was complicated, but noted that the patient dosing chart was fairly clear. The ACPM advised that the CMI should include a warning about dark urine/jaundice and the need for frequent blood tests to check for liver function abnormalities.

The ACPM advised that the CMI should also include changes consistent with those made to the PI, particularly with respect to the contraindications and drug-drug interactions. The potential consequences of pregnancy should be emphasised in the CMI, given the teratogenicity of ribavirin and the contraindicated use of ethinyl oestradiol containing medicinal products.

4. With reference to Viekira Pak and the proposed PI, is the broad indication proposed for genotype 1 infection for Viekira Pak acceptable, given the data only support use in genotype 1b? Also, is clearer guidance needed for the Viekira Pak PI indicating it is

currently recommended for genotype1b only? Should dosing information related to ribavirin be omitted?

The ACPM noted that the results of study M14-002 (PEARL-IV, which compared 12 weeks treatment with Viekira Pak RBV versus Viekira Pak without ribavirin in treatment naïve patients with genotype1a infection, and without cirrhosis) reported SVR_{12} in 97% of patients treated with Viekira Pak RBV compared with 90% of those in the Viekira Pak treatment group. Although the results demonstrated an SVR rate of > 90% for treatment without ribavirin, this was not shown to be non-inferior to the treatment with ribavirin, but the ribavirin group showed significant toxicity (anaemia 42% versus 4%). Additionally, the results for both treatments were superior to the historical control rate for teleprevir plus pegIFN/RBV therapy.

The ACPM advised that the results of study M14-002, which reported high success rates in patients with genotype 1a infection, provided support for the indication for Viekira Pak (that is without ribavirin) for treatment of genotype 1 (1a or 1b) infection. It is recommended that a statement to the effect that "Viekira Pak is recommended as first line treatment for genotype 1b infection, and second line (if ribavirin intolerant) for genotype 1a infection" be added to the beginning of the Dosage and Administration section of the PI, referencing Table 16.

5. *The updated safety data and report of the compassionate use program anticipated with the pre-ACPM response.*

The ACPM noted that the sponsor's updated information on the compassionate use program indicated use in 431 patients to 17 April 2015. The updated safety data noted reports of hyperbilirubinaemia, elevated AST, and drug-drug interactions with quetiapine. The ACPM considered that this reinforced the need to have in the PI a warning about hyperbilirubinaemia under PRECAUTIONS plus a management plan, and strong warnings about drug-drug interactions.

6. *Does the PI require further qualification in regards to race and ethnicity for Asian and Hispanic/Latino patients?*

The ACPM noted that there are little data on Asian patients, but further studies are in progress. The ACPM noted that larger numbers of Hispanic/Latino patients were included in trials, but there were no obvious pharmacokinetic differences (except for ritonavir, where increased exposure was not clinically important).

The ACPM advised that, pending further data, the PI should include a statement such as the following, "however, patient numbers in the clinical trials were not sufficient to address possible differences in pharmacokinetics and toxicity profiles in specific ethnic groups such as Asian patients".

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Viekira Pak combined - paritaprevir/ritonavir/ombitasvir 75 mg/50 mg/ 12.5 mg film coated tablets and dasabuvir (as sodium salt) 250 mg film coated tablets composite pack blister pack for oral use indicated for:

> *Viekira Pak is indicated for the treatment of genotype I chronic hepatitis C infection, including patients with compensated cirrhosis. Duration of therapy and addition of ribavirin are dependent on patient population (see DOSAGE AND ADMINISTRATION, PRECAUTIONS, CLINICAL TRIALS).*

Specific conditions of registration applying to these goods

The Viekira Pak (combined paritaprevir/ritonavir/ombitasvir tablets and dasabuvir tablets) composite pack, Risk Management Plan (RMP): Version 1.2 of EU-RMP format (dated February 2015, DLP 24 January 2014) and Australian Specific Annex (ASA) Version 1.2 (dated February 2015) included with submission PM-2014-01436-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Viekira Pak approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at < https://www.tga.gov.au/product-information-pi> .

Attachment 2. Extract from the Clinical Evaluation Report

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