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Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Faldaprevir Boehringer Ingelheim

International non-proprietary name: Faldaprevir

Procedure no. EMEA/H/C/03720

Note

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

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List of abbreviations

ADME	Absorption distribution, metabolism and excretion
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BD	Below detection
BLQ	Below limit of quantitation
BMI	Body mass index
Cmax	Maximum concentration
CMH	Cochran-Mantel Haenszel
DAA	Direct-acting antiviral
DAVP	Division of antiviral products of US FDA
DILI	Drug-induced liver injury
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
DRV	Darunavir
eGFR	eGlomerular filtration rate
ETR	End of treatment response
ETS	Early treatment success
EVR	Early virologic response
FAS	Full analysis set
GMR	Geometric mean ratio
GT1	Genotype 1
HCV	Hepatitis C virus
HCV-1	Hepatitis C virus genotype 1
HIV	Human immunodeficiency virus
IU	International unit
LD	Loading dose
LLoQ	Lower limit of quantitation
LOCF	Last observation carried forward
LPTCF	Last post-treatment value carried forward
MedDRA	Medical dictionary for drug regulatory affairs
NPV	Negative predictive value
pegIFN	Pegylated interferon alfa
PfOS	Powder for oral solution
P-gp	P- glycoprotein
PI	NS3/4A protease inhibitor
PPS	Per protocol set
PPV	Positive predictive value
QT	ECG QT interval
RAV	Resistance-associated variant
RBV	Ribavirin
RdRp	RNA-dependent RNA polymerase
RGT	Response guided therapy
RNA	Ribonucleic acid
SAE	Serious adverse event
SCE	Summary of clinical efficacy
SCS	Summary of clinical safety
SGC	Soft gelatin capsule
SMQ	Standard MedDRA queries
SSC	Special search category
SVR	Sustained virologic response
SVR4	Sustained virologic response at 4 weeks after planned cessation of treatment
SVR12	Sustained virologic response at 12 weeks after planned cessation of treatment
SVR24	Sustained virologic response at 12 weeks after planned cessation of treatment
TD	Target detected
TE	Treatment experienced
TEN	Toxic epidermal necrolysis
TN	Treatment naïve
TND	Target not detected
VL	Viral load

1. Recommendations

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the application for faldaprevir in the treatment of chronic hepatitis C (CHC) in adults.

is not approvable since there are Major Objections on Quality. Details of these Major Objections are in section 6. Briefly, they relate to the following issues:

Drug substance: There is inadequate information on the three starting materials (BI 201335 peptide, BI 201335 sulfone and BI 201335 INRF 3 TS) used for the synthesis of faldaprevir. These are complex molecules that contribute significant structural fragments to the final drug substance and they need to be controlled appropriately to ensure consistent quality.

Drug product: There are concerns about the changes observed in the dissolution profiles of batches stored under non-refrigerated conditions. The changes are considered to be related to cross linking of the gelatin but a comprehensive evaluation and discussion has not been presented and the data presented are limited. The potential impact of this change on product performance needs to be addressed fully as this may affect the clinical performance of the product.

Questions to be posed to additional experts

None

Inspection issues

None

New active Substance status

Based on the review of the data faldaprevir is to be qualified as a new active substance in itself. See the separate report on NAS status.

2. Executive summary

2.1. Problem statement

Hepatitis C virus infection represents a major public health problem because of its potential to lead to serious or life-threatening chronic liver disease. Approximately 130 to 210 million individuals (3% of the world population) are chronically infected with HCV. The prevalence varies markedly from one geographic area to another and within the population assessed. In Western Europe, HCV prevalence ranges from 0.4% to 3%. The prevalence of HCV-related chronic liver disease is increasing, mainly due to the long lag of 20 years or more between initial infection and clinical manifestations of the disease.

Six HCV genotypes and a large number of subtypes have been described. They originated from diverse areas in Africa and Asia, and some of them have spread widely throughout the world. Genotype 1 (subtypes 1a and 1b) is by far the most prevalent genotype worldwide, with a higher prevalence of 1b in Europe and 1a in the US. Genotype 3a is highly prevalent in European intravenous drug users. This group is currently experiencing an increasing incidence and prevalence of infections related to HCV Genotype 4. Genotype 2 is found in clusters in the Mediterranean region, while Genotypes 5 and 6 are found more rarely.

HCV-associated liver disease progresses over several decades and is accelerated in the presence of cofactors such as alcohol consumption, diabetes mellitus (to which HCV itself appears to predispose), older age at acquisition, human immunodeficiency virus (HIV) co-infection or co-infection with other hepatotropic viruses. Depending on the presence of cofactors, between 10% and 40% of patients with chronic HCV infection will develop cirrhosis. Death related to the complications of cirrhosis may occur at an incidence of approximately 4% per year, whereas hepatocellular carcinoma (HCC) occurs in this population at an estimated incidence of up to 5% per year. Patients diagnosed with HCC have a 33% probability of death during the first year. HCV infection has become the leading cause of primary liver cancers in Europe.

Based on models from France to predict death rates due to HCV-related HCC, the peak mortality related for HCV infection is yet to come and currently available therapies are expected to have a modest impact on the mortality rate. These results probably also apply to most other European countries. In the United States the prevalence of HCV infection between the years 1999 and 2002 was 1.6%, approximately equal to 4.1 million persons who are positive for antibody to HCV (anti-HCV), 80% of whom are estimated to be viraemic. Hepatitis C is the principal cause of death from liver disease and the leading indication for liver transplantation in the US. Current medical opinion encourages treatment of HCV infection before cirrhosis and complications of chronic liver disease develop.

2.2. About the product

Faldaprevir is an orally bioavailable reversible inhibitor of the hepatitis C NS3/NS4A serine protease, a virally encoded enzyme that is critical for viral replication. Its physical-chemical properties are those of a low molecular weight peptidomimetic with poor aqueous solubility and high protein binding in human plasma.

HCV is a 9.6 kilobase single, positive-strand RNA virus and contains a long open reading frame which encodes several structural and non-structural viral proteins. The HCV serine protease is encoded by the NS3/NS4A protein and is essential for the proteolytic cleavage of the HCV translated polyprotein into HCV-specific non-structural enzymes such as the helicase and RNA-dependent RNA polymerase (RdRp) required for viral replication. HCV RdRp lacks a proof-reading function which contributes to the generation of a quasispecies (swarm) of closely related HCV RNA genomes within an individual.

Faldaprevir was optimised for inhibition of HCV genotype (GT) 1a/1b NS3/NS4A protease activity at concentrations below cytotoxicity. It is 2-fold more active against GT1b than GT1a *in vitro*. Faldaprevir inhibits NS3/NS4A proteases from HCV GT 4a, 5a and 6a *in vitro* at slightly higher concentrations while very much higher concentrations are needed to inhibit the proteases from GT2 and 3.

As a result, the clinical development of faldaprevir has focussed on treatment of GT1a and GT1b infections. All of the efficacy data for faldaprevir in the current application dossier concern its use in conjunction with pegylated interferon alfa-2a and ribavirin (PEG/RBV). The liquid-filled 120 mg soft gelatin capsule formulation was used in the Phase 2 and 3 studies as well as in many of the Phase 1 studies and this is the formulation intended to be marketed.

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

The applicant did not obtain advice from CHMP during the development programme. The content of this programme generally complies with the CHMP guidance regarding development of directly acting antiviral agents (DAAs) for treatment of HCV infections that was in place at the time.

Due to the timing of the clinical programme and by using unequal randomisation to minimise the risk of assignment to placebo, the applicant was able to recruit three placebo-controlled studies in which all patients (treatment naïve or experienced with respect to PEG/RBV) received either faldaprevir or placebo in combination with PEG/RBV. An additional study enrolled HIV/HCV co-infected patients who were randomised to one of two regimens of faldaprevir plus PEG/RBV. There is an ongoing study in Japanese patients in which faldaprevir is being used at two different regimens in conjunction with peg-IFN alfa-2b.

Around the same time that the Phase 3 studies commenced the protease inhibitors boceprevir and telaprevir received marketing authorisations for treatment of GT1 infections in combination with PEG/RBV. Faldaprevir has not been compared with either of these agents in studies reported in this application dossier. This is considered acceptable in light of the timing of the programme and the fact that the studies have provided a definitive comparison of faldaprevir with placebo so that the magnitude of the treatment effect can be clearly demonstrated.

At the time of filing there was an ongoing programme in which faldaprevir is being studied as a component of a DAA-only regimen. This is not a part of the current application.

The indication for use as proposed by the applicant is as follows:

Faldaprevir, in combination with peginterferon alfa and ribavirin, is indicated for the treatment of chronic genotype-1 hepatitis C virus (HCV) infection in adult patients with compensated liver disease including cirrhosis, and patients with human immunodeficiency virus (HIV)/HCV co-infection, who:

- are treatment-naïve, or
- have been previously treated with interferon-based treatment, including prior relapsers, partial responders and null responders (see sections 4.4 and 5.1)

The proposed posology is as follows:

Faldaprevir must only be prescribed and administered in combination with peginterferon alfa and ribavirin. For specific dosage instructions for peginterferon alfa and ribavirin, refer to their respective Summary of Product Characteristics.

Posology

The recommended dose of Faldaprevir is dependent on the patient population, as described below.

Treatment-naïve and prior relapser patients

Treatment begins with a loading dose of Faldaprevir 240 mg on the first day of treatment followed by Faldaprevir 120 mg on each day thereafter. For a detailed description and recommended duration of treatment, see Table 1.

Partial and null responder patients

Treatment begins with a loading dose of Faldaprevir 480 mg on the first day of treatment followed by Faldaprevir 240 mg on each day thereafter. For a detailed description and recommended duration of treatment, see Table 1.

Duration of treatment

The recommended duration of treatment with Faldaprevir is 12 weeks in combination with peginterferon alfa and ribavirin. HCV RNA levels should be monitored at treatment Weeks 4 and 12 to determine the treatment duration of peginterferon alfa and ribavirin and to assess for treatment futility.

Table 1. Recommended Treatment Duration (see also Table 2 for Treatment Futility Rules)

Treatment-Naïve and Prior Relapser Patients*			
HCV RNA	**Faldaprevir 120 mg, peginterferon alfa and ribavirin**	**Peginterferon alfa and ribavirin**	**Total treatment duration**
<25 IU/mL at Week 4, and <25 IU/mL target not detected at Week 12	12 weeks	Additional 12 weeks	24 weeks
≥25 IU/mL at Week 4 or detected at Week 12	12 weeks	Additional 36 weeks	48 weeks
Partial and Null Responder Patients **			
	Faldaprevir 240 mg, peginterferon alfa and ribavirin	**Peginterferon alfa and ribavirin**	**Total treatment duration**
All Patients	12 weeks	Additional 36 weeks	48 weeks

*On the first day of treatment patients receive a single loading dose of 240 mg
** On the first day of treatment patients receive a single loading dose of 480 mg

Patients with cirrhosis (treatment-naïve or experienced) may benefit from a total of 48 weeks treatment duration of peginterferon alfa and ribavirin (see section 5.2, *Clinical efficacy and safety*).

The prescribed dose of Faldaprevir must not be reduced or interrupted.

Missed dose

In case a dose of Faldaprevir is missed within 12 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of Faldaprevir as soon as possible. If the missed dose is noticed more than 12 hours after the time, the missed dose should be skipped and the next Faldaprevir dose should be taken at the normal dosing schedule.

Dosing with selected comedications

All patients requiring coadministration of Faldaprevir with moderate CYP3A inducers should take the 240 mg dose of Faldaprevir (see section 4.5).

HIV/HCV co-infected patients on an efavirenz-based antiretroviral regimen should take the 240 mg dose of Faldaprevir (see section 4.5).

Discontinuation of dosing

Discontinuation of treatment is recommended in all patients with:

(1) HCV RNA levels of greater than 100 IU/mL at Treatment Week 4 or 12; or

(2) Confirmed detectable HCV RNA levels at Treatment Week 24

Table 2. Treatment Futility Rules: All Patients

HCV RNA	*Action*
Week 4 or Week 12: Greater than 100 IU/mL	*Discontinue Faldaprevir and peginterferon and ribavirin*
Week 24: Detectable	*Discontinue peginterferon and ribavirin*

If peginterferon alfa is discontinued for any reason, Faldaprevir must also be discontinued.

Patients with hepatic impairment

No pharmacokinetic or safety data are available for use of Faldaprevir in HCV-infected patients with moderate or severe hepatic impairment, and appropriate doses have not been established.

Dose modification of Faldaprevir is not required when administered to hepatitis C patients with mild hepatic impairment [Child Pugh A, score 5-6] (see section 5.2, “Specific populations”).

Patients with renal impairment

No dose adjustment is necessary for Faldaprevir in HCV-infected patients with mild, moderate or severe renal impairment (see section 5.2, “Specific populations”).

Faldaprevir has not been studied in subjects with end-stage renal disease (ESRD) or subjects on hemodialysis (see section 5.2, “Specific populations”).

Older people

No dose adjustment is recommended based on age (see section 5.2, “Specific populations”).

Paediatric population

The safety and efficacy of Faldaprevir in children aged below 18 years have not yet been established.

No data are available.

Method of administration

Faldaprevir is taken orally with or without food.

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

GMP

All manufacturers and manufacturing sites have current GMP certifications. The QP at the batch release site (Boehringer Ingelheim Pharma GmbH & Co. KG) has provided a declaration (with audit date) confirming that the manufacturer of the drug substance and drug product operate in compliance with GMP guidelines.

GLP

All pivotal toxicity studies were conducted in compliance with GLP. The secondary pharmacodynamics studies and the pharmacokinetic studies were not conducted in compliance with GLP. The toxicokinetic studies were GLP compliant. Bridging toxicokinetic studies were not GLP compliant.

GCP

The Clinical Overview contains the following statement:

All studies employed up-to-date methodologies; were initiated after review and approval of the relevant ethics committees, institutional review boards, and regulatory authorities; and all were conducted according to ICH Good Clinical Practices guidelines.

The individual study reports carry statements of compliance with GCP.

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

- ***Legal basis***
  - The application has been made via the centralised procedure according to Regulation (EC) No 726/2004 and Article 3(1) Annex (3) i.e. mandatory scope for a new active substance.
  - The application has been made in accordance with Article 8(3) of Directive 2001/83/EC.
  - It concerns 120 mg soft capsules that contain the new active substance faldaprevir (as the sodium salt).
- ***Significance of paediatric studies***

Article 7 of the Paediatric Regulation applies. The PIP decision number is P/0301/2012.

- According to Article 14(9) of Regulation (EC) No 726/2004 the applicant sought an ***accelerated procedure***. This was granted by the CHMP 24 October 2013.
- ***CHMP guidelines/Scientific Advice***

  See section 2.3.

3. Scientific overview and discussion

3.1. Introduction

Faldaprevir is intended for treatment of chronic HCV GT1a and GT1b infections regardless of prior exposure to PEG/RBV and HIV-co-infection. All of the efficacy data for faldaprevir in the current application dossier concern it use in conjunction with PEG/RBV. The liquid-filled 120 mg soft gelatin capsule formulation was used in the Phase 2 and 3 studies as well as in many of the Phase 1 studies and this is the formulation intended to be marketed.

A different dose regimen is proposed for treatment-naïve (TN) patients and treatment-experienced (TE) patients who relapsed after a prior course of PEG/RBV alone vs. TE patients who were partial or null responders to prior PEG/RBV alone. In addition, while a fixed 12-week regimen of faldaprevir is proposed, the PEG/RBV regimen differs according to patient sub-group and for TN and TE relapsers a total of 24 weeks is proposed for those who meet the criteria for response-guided treatment (RGT). Currently there are no data on use of faldaprevir to treat patients who were not successfully treated with a prior course of PEG/RBV in conjunction with another directly acting antiviral agent (DAA).

3.2. Quality aspects

Drug substance

The dossier is provided without reference to an EDMF and all details relating to the synthesis of the drug substance are included in the section 3.2.S. submitted.

Faldaprevir sodium is synthesized as a single stereoisomer with five chiral centres. It is hygroscopic, poorly soluble in water and shows higher solubility in acidic and basic solutions. A single polymorph (Form A) is the only phase that has been produced by the drug substance synthesis during development.

The drug substance manufacture consists of five main steps and the last step consists of milling of the drug substance. The information on the manufacturing process is generally acceptable but further

information is needed on the milling process. Details of the manufacturing process, the starting compounds, raw materials, reagents, and solvents, catalysts, quantities and equipment used, yields at each step, are described in the dossier. Ethanol denatured with toluene is used at steps 2, 3, 4 and during the reprocessing steps. The specification for the ethanol includes a limit for potential benzene residues.

Three starting materials are used in the synthesis: BI 201335 peptide, BI 201335 sulfone and BI 201335 INRF 3 TS. All 3 starting materials are manufactured by external manufacturers via synthetic routes proprietary to the applicant. The starting materials, as described below, are complex molecules that contribute significant structural fragments to the final drug substance including chiral centres. Whilst the information presented is comprehensive the synthesis of these starting materials need to be controlled appropriately under GMP to ensure consistent quality. The starting materials should therefore be redefined to simpler, well characterized compounds and full details of the synthesis of faldaprevir from the newly defined starting materials should be provided with information on catalysts, solvents, reagents used in the synthetic processes together with evidence that the starting materials and intermediates are adequately controlled. Full details of the manufacturers and sites of manufacture should be provided. This point is raised as a Major Objection.

Starting material BI 201335 peptide is a dipeptide. There are three stereocenters in BI 201335 peptide and eight stereoisomers are possible. A brief summary of the synthesis has been provided with details of the materials and reagents used.

The applicant has stated that no Class 1 solvents are used in the synthesis. Appropriate declarations concerning the TSE status of the starting material should be provided from the suppliers taking account of the use of the amino acid derivatives.

A detailed discussion of the stereochemistry of the dipeptide and the eight potential stereoisomers has been provided.

A detailed investigation of the origin and fate of all potential impurities has been undertaken and extensive spiking experiments have been conducted for all specified impurities to justify the specification proposed for the starting material. Of the specified impurities controlled in the specification, 4 are derived from isomeric impurities in the synthetic precursors.

A detailed evaluation of potential genotoxic impurities has been provided which includes *in silico* analysis of the structures. The alkyl tosylates were identified as having a structural alert and thus the potential for residues has been addressed. Analytical results for 21 representative batches of BI 201335 peptide obtained from the two manufacturers have been presented. However, the results do not include assay results and several batches are outside of the proposed specification. The major impurity found at levels up to 3.8% is a residual synthetic precursor. The levels vary from 0.7- 3.8% and further comment should be provided. The proposed assay limits for BI 201335 peptide appear wide (93.0-103.0%) and are not supported by batch results. The limits proposed for total impurities (without the residual synthetic precursor) appear wide and should be addressed. Three HPLC methods used to control BI 201335 peptide and satisfactory details and acceptable validation data have been provided.

Further information is requested on the batch data for the dipeptide including full batch histories with details of manufacturers, batch sizes and dates of manufacture to ensure that the batches are representative of material to be used commercially. Assay results should be presented to support the proposed specification limits and further comment should be provided on the batches outside of specification and the variable content of the residual precursor impurity should be discussed. The specification proposed for starting material BI 201335 peptide should be revised to include tighter limits for assay and total impurities (without the residual precursor).

Starting material BI 201335 sulfone does not contain a chiral centre and shows no stereoisomerism. A brief summary of the synthesis has been provided with details of the materials and reagents used. The applicant has stated that no Class 1 solvents are used in the synthesis. A detailed investigation of the origin and fate of all potential impurities has been undertaken and detailed spiking experiments have been conducted for all specified impurities to justify the specification proposed for the starting material. Benzenesulfinic acid is a potential reaction by-product derived from sodium benzene sulfinate during the synthesis of BI 201335 sulfone. Potential residues of benzenesulfinic acid, benzenesulfonic acid and alkyl benzenesulfonates have been investigated and shown to be controlled. A detailed evaluation of potential genotoxic impurities has been provided which includes *in silico* analysis of the structures. The alkyl tosylates and alkyl benzenesulfonates were identified as having a structural alert and thus the potential for residues has been addressed. One specified impurity was shown to be Ames positive but to date this has not been found above 1ppm (HPLC-MS).

Analytical results for 23 representative batches obtained from four different manufacturers have been provided. However, the results do not include assay results and several batches are outside of the proposed specification with respect to one specified impurity and one batch with respect to 'any unspecified impurity'. Further information is requested on the batch data including full batch histories with details of manufacturers, batch sizes and dates of manufacture to ensure that the batches are representative of material to be used commercially. Assay results should be presented to support the proposed specification limits and further comment should be provided on the batches outside of specification. Batches of BI 201335 sulfone are reported to contain up to 13% residual dimethylformamide and the impact of this level of residual DMF on the stability of the starting material should be fully addressed.

Optional crystallisation from toluene is proposed in the final step of synthesis of the BI 201335 sulfone intermediate and the potential for benzene residues should be addressed.

Starting material BI 201335 INRF 3 TS has two stereocentres therefore four stereoisomers are possible. A brief summary of the synthesis is provided with details of the materials/reagents used. The applicant has stated that no Class 1 solvents are used in the synthesis. A detailed investigation of the origin and fate of all potential impurities has been undertaken and detailed spiking experiments have been conducted for all specified impurities to justify the specification proposed for the starting material.

A gradient HPLC method is used to control organic impurities and the two diastereoisomers; satisfactory details and validation data have been provided. A chiral HPLC method is employed to ascertain the enantiomeric purity; satisfactory details and validation data have been provided. Analytical results for 7 representative batches obtained from two different manufacturers only have been provided. However, the results do not include assay results and one batch was outside of the proposed specification with respect to INRF-3 acid, 'any unspecified impurity' and total diastereoisomers. Further information is requested on the batch data including full batch histories with details of manufacturers, batch sizes and dates of manufacture to ensure that the batches are representative of material to be used commercially. Assay results should be presented to support the proposed specification limits and further comment should be provided on the batches outside of specification.

A detailed evaluation of potential genotoxic impurities has been provided which includes *in silico* analysis of the structures. The alkyl tosylates were identified as having a structural alert and thus the potential for residues has been addressed.

The starting material INRF 3 TS was itself shown to be Ames positive but the downstream steps ensure levels above 0.5 ppm have not been found of INRF 3 TS or INRF-3 acid. INRF-3 acid is controlled as a specified impurity in the starting material as it is genotoxic; spiking experiments have confirmed that the limit of not more than 0.20 % for INRF-3 acid in the starting material ensures that the level of INRF-3 acid in the drug substance is below the threshold of toxicological concern.

The proposed starting materials in the synthesis are not considered acceptable for the following reasons:

BI 201335 peptide: this intermediate is synthesized from commercially available building blocks. Many peptide coupling reagents are genoxtoxic or give rise to genotoxic by-products and as such, the synthesis of the dipeptide should be carried out under GMP control. Furthermore, the building blocks and the dipeptide itself have weak UV chromophores and so new impurities may be difficult to detect.

BI 201335 sulfone: multiple synthetic routes could be envisaged for the synthesis of this compound and changes would not be subject to regulatory oversight. Potential routes include cross-coupling chemistry using heavy metal catalysts. The starting material from an earlier synthetic route is disclosed as genotoxic. The tosylate analogue which appears to also be a precursor to the sulfone would also therefore have genotoxic potential. It should be clarified whether the tosylate intermediate has been screened for genotoxicity. Thus, the synthesis of BI 201335 sulfone should be carried out under GMP control.

IN 201335 INRF 3 TS: The disclosed synthetic route to this starting material from racemic precursor consists of a kinetic resolution. However, the racemic precursor is not considered readily available and already contains the required diastereomeric relationship of the 2 chiral centres. The resolution is considered a purification step and should be carried out under GMP control. The synthetic route to the racemic INRF 3 HCl should be provided, including all transformations from a readily available starting material and the diastereocontrol discussed.

Control of the four isolated and purified synthesis intermediates is stated to be critical for the production of drug substance of consistently high quality. The applicant has stated that there are no critical process parameters in the synthesis apart from the control of the amount of base used at Step 1. Further information is requested on the four intermediates including full batch histories with batch sizes and dates of manufacture for the supporting batch data. The proposed specifications for the intermediates need revision to include tighter limits for specified, unspecified and total impurities in line with supporting batch data. Suitable assay methods should also be included for the individual intermediates.

A polymeric impurity formed during the synthetic process has only recently been discovered following investigation of a low assay result in one batch. Retrospective analysis has confirmed its prescence in batches with levels from < 0.1% to over 0.8%. It appears that this impurity forms only during the final step of the synthesis, however, it needs to be proven that this impurity can be controlled or removed and further information is requested on the conditions likely to favour its formation and in view of the levels reported (up to 0.8%) how it can be controlled and limited to the proposed specification level of ≤0.15%. If levels cannot be controlled to this limit satisfactorily the need for toxicological qualification will need to be considered and this point has been raised. Further information is also requested on the stability of the polymeric impurity and its likely bioavailability. The potential for the impurity to occur in the drug product and on storage needs to be addressed. This polymeric impurity is currently monitored using a HPTLC method. In the HPTLC system the impurity remains at the origin while the drug substance travels with the solvent front. Any other ‘impurities’ at the origin will interfere with the measurement of exact quantity.

The information provided on the elucidation of structure and the characteristics of the drug substance is comprehensive and uses standard techniques 1H and 13C NMR, LC/MS, FTIR, UV/VIS, elemental analysis. The absolute configurations of the five chiral centres of faldaprevir sodium were determined by Single Crystal X-ray Diffraction analysis. The solid state properties of faldaprevir sodium (Form A) were characterized by polymorphism screening experiments (high throughput and manual), polarized light microscopy (including thermomicroscopy), scanning electron microscopy, FTIR and Raman spectroscopy, solid-state nuclear magnetic resonance spectroscopy, thermal analysis (TG and DSC), X-ray powder diffraction (XRPD and VRH-XRPD), dynamic vapour sorption experiments.

The proposed drug substance specification is generally acceptable. The assay limits are wide compared to the batch data (min. 98.7%) and consideration should be given to tightening the limits.

The levels of two of the specified impurities, found in commercial scale batches are much lower than the proposed limits but both impurities are qualified toxicologically at the proposed limits so can be accepted. The limits for the other specified impurities do not exceed the qualification limit of 0.15%.

As tetrahydrofuran is used in the presence of HCl during the synthesis the formation and potential carry-over of 4-chlorbutanol to the final drug substance should be investigated and a suitable limit included in the drug substance specification or a suitable intermediate, if appropriate.

A suitable control on the particle size needs to be included to distinguish the final drug substance from un-milled material as the milled drug substance is needed for successful manufacture of the drug product.

Two batches exceed the specification limit proposed for the polymeric impurity (≤0.15%). Further comment should be provided on this observation and as indicated above the options for control and/or removal of this impurity should be addressed further.

A retest period of 48 months is proposed for the drug substance when stored protected from light. Studies have been carried out in accordance with current guidelines and in the proposed commercial container. This includes appropriate stress tests as well as long term and accelerated conditions.

Results are presented up to 36 months long term (25°C/60 % RH) as well as for 6 months under accelerated conditions (40°C/75 % RH). The batches used for the long term stability studies are approximately 28 – 54% of the commercial batch scale. The stability results show that the drug substance remains within specification and is stable when stored up to 36 months long term (25°C/60 % RH). Results will now be available up to 48 months and should be requested. Extrapolation is not approvable given the presence of a genotoxic impurity (INRF-3 acid) that is likely to increase on storage. Results should also be presented for the newly detected polymeric impurity before the proposed retest period is accepted.

In summary, the major concern arising with the drug substance is the need for redefinition of the proposed starting materials, BI 201335 peptide, BI 201335 sulfone and BI 201335 INRF 3 TS, to simpler, well characterized compounds controlled appropriately under GMP to ensure consistent quality.

Further information is needed on a number of aspects of the synthesis to ensure that appropriate controls are in place. The newly discovered polymeric impurity needs further investigation to ensure that, if formed, it can be removed to the specified level and a more appropriate control method should be investigated.

Drug product

The aim of the pharmaceutical development has been to develop an immediate-release solid oral dosage form considering the physicochemical and biopharmaceutical properties of the drug substance (BCS Class II) and the clinical and commercial dose requirements, consistent with the Quality Target Product Profile.

Two dosage forms have been used during the clinical development: 1) Oral drinking solutions (aqueous and lipid-based compositions) prepared using a Powder for Oral Solution (PfOS) and a co-supplied solvent 2) self-emulsifying drug delivery system SEDDS soft gelatin capsules. Efforts to develop alternative dosage forms were not successful. Two tablet formulations were considered in development and evaluated against a SEDDS formulation in dogs. Both tablet formulations showed markedly inferior in vivo exposure relative to a SEDDS formulation.

The formulation has been developed taking account of the physicochemical and biopharmaceutical properties of faldaprevir. A self-emulsifying drug delivery system (SEDDS) in a soft gelatin capsule with a liquid fill was chosen for development. The faldaprevir sodium is highly soluble in the lipid-based fill solution of the finished capsule and on exposure to the gastro-intestinal tract the drug product capsule shell dissolves, exposing the fill material to the aqueous gastro-intestinal environment. The components of the fill material spontaneously emulsify upon exposure to water. The selection of excipients and their corresponding levels was based on *in vitro* dispersion, stability, and *in vivo* bioavailability studies using various prototype SEDDS formulations.

Further information is needed on the formulation development. Given the lipophilic properties of the drug, and considering that the mechanism of release is quite different from solid state dissolution, solubility in dissolution media containing surfactants and in biorelevant gastric and intestinal dissolution media such as FaSSIF and FeSSIF should have been investigated in the development.

Further details should have been presented on the compatibility studies with excipients in particular those likely to form complexes. The inclusion of the antioxidant and of the choice of the antioxidant concentration should have been based on experimental data. The consumption of antioxidant during manufacturing and during storage should be evaluated to propose appropriate specification limits at release and shelf life.

The applicant has stated that changes in polymorphic form are not observed during manufacture and storage. However, phase conversion of form A into less soluble forms in the fill formulation may be initiated by the presence of impurities and further comment should be provided on this possibility.

In addition, form A is classified as variable hydrate and further discussion should be provided on the relationship between water content and solubility in formulation.

The applicant has not justified the volume and the composition of the medium used in dispersibility studies and has not investigated the kinetics of emulsification. Even though the *in vivo* and *in vitro* correlation is out of the scope of the product development, the link of the physical properties to *in vivo* performance deserves investigation. *In vivo* performance of the SEDDS is linked to the lipolysis phenomenon. Therefore the emulsification in different dissolution media simulating both fasted and fed conditions should be investigated.

It is noted that the viscosity of the bulk fill (and the temperature dependence) is not mentioned either in the preparation of bulk fill nor in the encapsulation process description. Since this parameter may influence both steps, it should be discussed.

It is stated that a relative bioavailability study was performed in Phase I in HV comparing the SEDDS soft gelatin capsules versus the oral drinking solutions and that this study showed that the SEDDS

capsule formulation was a suitable candidate for development. The results of the relative bioavailability study demonstrating bioequivalence study should be reported.

Any bridging studies between the various clinical batches, as well as between the two strengths used in clinical studies, should have been provided to demonstrate that the clinical batches do have the same biopharmaceutical properties. Even though the fill formulation is liquid, the capsular container is meant to disintegrate in the stomach in order to release the actives. Therefore at least a disintegration test should be provided to ensure the biopharmaceutical quality of the batches. Moreover the biopharmaceutical properties of the clinical batches would be useful to support the relevant release and shelf life specifications of the finished product.

The development of the manufacturing process has been discussed in detail.

The manufacturing process consists of three main operations: manufacture of the bulk fill solution, of the gel mass and of the finished capsules. The critical steps have been identified and controls applied have been discussed and are considered acceptable.

Process validation has been carried out on three consecutive, full-scale batches manufactured according to the proposed commercial manufacturing process at the commercial facility. The 3 batches are those used in the primary stability studies and are representative of the minimum production scale. The batch results show that the soft capsules can be manufactured reproducibly at a commercial scale in accordance with the proposed finished product specification.

For the ICP, the applicant stated that the visual inspection is sufficient to ensure that the drug substance is reproducibly dissolved. The company should confirm the validated mixing time and that there is no need for checking the solubilisation by assaying the bulk fill. Results showed consistency of moisture content values across the drying process and confirmed the minimum drying duration. This should be confirmed by the applicant as the validated drying time. It was noted that the content was consistently about 2% below the target label claim, but well within acceptance criteria. This was due to water migration from the capsule shell and prompted the subsequent target fill weight increase described in manufacturing process development. This should be validated in the final validation batches.

Confirmation should be given that the capsule weight remains constant through the washing procedure and that none of the gelatin coat dissolves. The applicant should comment on the effect on capsule quality on under- and over-drying and on the batch to batch variability of drying time.

Manufacturing process: QbD language is used in the “control of critical steps” section and the applicant talks of manufacture at “extreme ranges” of the process (mixing, disperser, sweeper speeds). However, no design space is applied for. The manufacturer should therefore confirm the relevant target set-points for the various operations and that no changes will be made outside of NORs without submission of variation procedures.

The information presented on excipients is generally acceptable. The specification proposed for gelatin is in line with Ph. Eur.

The specification proposed for mono/diglycerides of caprylic/capric acid is tighter than Ph. Eur. and takes account of the applicant’s experience with their related formulations. The specification is acceptable.

Confirmation should be provided on the TSE/BSE status of the gelatin, glycerol and glycerides (mono/diglycerides of caprylic/capric acid; triglycerides, medium-chain). Confirmation should be provided that appropriate controls are in place on the glycerol including tests for diethylene glycol and ethylene glycol.

The major issues with control of the drug product have been the challenges presented in developing a suitable dosage form and overcoming the problems of the genotoxic degradant, INRF-3 acid. Impurity INRF-3 acid is a critical degradation impurity in the drug product and is stability limiting. The control strategy for this impurity has been discussed in detail. INRF-3 acid is not detected in the drug substance during manufacture and is limited by storage under appropriate conditions. The limits proposed for INRF-3 acid at release are in line with current guidelines for genotoxic impurities; the wider limits proposed for shelf-life will be addressed in the non-clinical assessment report.

The limits proposed for two degradation products in the drug product are acceptable and are qualified toxicologically. The limits proposed for 'any unspecified degradation product' are acceptable and are in line with current guidelines. The limits proposed for 'total degradation product' are wide compared to the stability results but can be accepted based on the qualified limits accepted for the specified impurities.

The proposed dissolution test is based on two tiers of testing using the approach in the USP general chapter. Initially, the capsules are tested with Tier I medium (phosphate buffer pH 6.8 with 0.23% Tween 80 at 37°C). If samples fail in Tier I they are then tested at Tier II (- Tier 1 medium with pancreatin (≤ 1750 USP units of protease activity per litre). The validation data for the dissolution test has addressed the effect of paddle speed, vessel temperature, pH, etc. The use of the surfactant (Tween 80) has not been discussed in detail. The use of pancreatin in the Tier II test media is stated to be needed due to gelatin capsule shell cross-linking. The batch data presented includes dissolution profiles at 15, 20, 30, 45 and 60 minutes. All batches presented show dissolution at 30 minutes > 98% for all batches; at 15 minutes results are >90% for all batches.

Stability results from the batches stored under accelerated conditions (25°C/60 % RH and 30°C/75% RH) show changes in their dissolution and all 3 batches required Tier II test conditions by 6 months.

The changes in the dissolution have not been discussed in detail but are stated to be due to cross-linking of the gelatin on storage. There are no data to show that batches failing Tier I but meeting Tier II behave in the same way clinically as batches meeting Tier I criteria. The changes in dissolution and the implications for bioavailability need to be fully addressed should cross-linking of the gelatin shell or any other changes in the formulation be occurring. In the absence of evidence to confirm that the clinical performance of batches failing the dissolution test Tier I is unaffected, the Tier II testing should be removed from the drug product specification.

The applicant has stated that the test is a 'dispersion test' and not a true dissolution test because the drug substance is in solution within the capsule shell. The applicant has stated that 'an *in vitro-in vivo* correlation (IVIVC) with this dissolution method was not pursued. The *in vivo* absorption of the drug from a SEDDS formulation is complex and factors controlling it are not completely understood. Pharmacokinetic data from clinical studies using both powder for oral solution and capsule dosage forms indicate that adequate exposure is achieved with the drug product formulation.'

The applicant would normally be expected to demonstrate that the dissolution test is capable of discriminating between batches with manufacturing variables likely to impact on clinical performance. Evidence to demonstrate that the dissolution test is capable of discriminating between batches of differing manufacturing variables has not been presented and the applicant has stated that it was not feasible to develop a dissolution method that is discriminating for quality attributes of the drug product that would be predictive of *in vivo* performance. However, it is clear from the stability studies under accelerated conditions that the method is capable of discriminating between batches where the capsule fails to dissolve without the addition of pancreatin.

The limits proposed for dissolution in the drug product specification are wide compared to the batch data and stability results. The limits should be tightened in line with the clinical trial batches and Tier II testing should be removed from the drug product specification.

The drug product specification should include a chiral assay (or an achiral assay combined with a method for controlling the opposite enantiomer is acceptable in lieu of a chiral assay) and control on enantiomeric impurities in line with ICH Q6A (decision tree #5). A suitable disintegration test should be included for the capsule at release and shelf life.

Microbial purity testing should be routinely conducted at release and when sufficient analytical information is collected, a variation may be submitted to apply for a non-routine analysis frequency. The non-routine analysis frequency should be specified as one batch in every 10 or annually, whichever is earliest.

Further details are required on the secondary packaging materials for the drug product and for the container/closures used for storage and transportation of the bulk capsules. The transport conditions to the packaging site should be indicated and it should be confirmed that the stability data assure the holding time of bulk capsule including transport (duration and conditions).

Data on a significant number of exemplary batches should be given to justify absence of specifications for residual alcohols in the drug product. These should address also potential benzene residues arising from the ethanol.

The proposed shelf-life is 2 years when stored in the original blister in order to protect from moisture. The long term storage conditions proposed are in a refrigerator (2°C – 8°C) with a period of storage by the patient for up to 90 days below 30°C.

The stability studies have been conducted in accordance with ICH guidelines packaged in the proposed commercial blister packaging. The batches investigated are representative of the future commercial batches as they were manufactured at the commercial production site at commercial scale using the commercial manufacturing process.

The stability samples have been tested using the methods proposed for the drug product; the methods used for assay and impurities/degradation products are stability indicating.

Results of primary stability testing are presented for 12 months at long-term storage conditions refrigerator (2 °C – 8 °C) and for 6 months at accelerated conditions (25 °C/60% RH). Under long term storage conditions (2 °C – 8 °C), no appreciable changes were observed for any of the test parameters with the exception of water content which increased slightly for one batch. Statistical analysis of assay results shows no stability time trends or variability between batches at the long-term storage condition. Impurity INRF-3 acid remains within specification and all capsules meet Tier I test dissolution.

Under the accelerated storage condition (25 °C/60% RH) trends over time and/or batch variability were observed for INRF-3 acid, dissolution, and water content.

INRF-3 acid levels rise to 6ppm but remain within specification limit. Water content rises slightly but remains within specification. With regard to dissolution all 3 batches fail Tier I testing; one batch fails after one month, the other two at 6 months.

Results are also presented on batches stored at 30 °C/75% RH for a period of six months; these data are intended to support the proposed period of storage by the patient for up to 90 days at 30 °C. The results show that the genotoxic impurity INRF 3 acid increases from ≤1ppm to 10 ppm after 6 months but remains within the specification limit (15 ppm). Changes in dissolution are observed after one

month of storage; one batch fails at Tier I showing only 3% dissolution for one sample. After 3 months all 3 batches fail Tier I; all batches pass using the Tier II test conditions with the added pancreatin.

The data presented to support storage outside of refrigerated conditions up to 3 months are not acceptable. The results indicate changes in dissolution after one month that seem to be related to cross-linking of the gelatin in the capsule shells. The impact of this change on product performance has not been addressed.

The proposed storage at 30 °C for up to 90 days is not accepted. Storage should be restricted to the refrigerator until further data are presented to demonstrate that the changes in dissolution have no detrimental effect on the clinical performance of the product. An update should be provided on all on-going stability studies on the drug product to support the proposed shelf-life and long term storage conditions (2 °C – 8 °C). Extrapolation of the shelf life of 12 months is considered premature in view of the increase in the genotoxic impurity INRF-3 acid under accelerated conditions (25 °C).

The potential for the polymeric impurity to form in the drug product should be fully addressed and testing should be included in on-going stability studies.

In summary, there are concerns that on storage changes are observed in the dissolution profiles of batches stored under non-refrigerated conditions. The changes are considered to be related to cross linking of the gelatin but a comprehensive evaluation and discussion has not been presented and the information presented is limited. The potential impact of this change on product performance needs to be addressed fully as this may affect the clinical performance of the product. The proposal for Tier II testing could be accepted provided this is fully justified in relation to the clinical batches. Concerning the proposed dissolution specifications, it is stated that the differences in *in vitro* dissolution profiles up to 30 minutes, caused by differences in the capsule shell burst rate, are not considered biorelevant and that the specifications are based on the dissolution data of pivotal clinical and primary stability batches that are not presented. Therefore the dissolution specifications are not acceptable. This has been raised as a Major Objection.

3.3. Non clinical aspects

Pharmacology

Virological properties

Faldaprevir is an inhibitor of HCV replication that specifically targets the HCV NS3-NS4A serine protease. The protease activity of the NS3-NS4A heterodimer is essential for the viral replicative cycle and inhibitors of this activity reduce viral load in HCV infected patients. In-vitro potency assays against HCV GT-1a and -1b serine proteases gave a faldaprevir IC50 of 5.4 nM for both subtypes. In GT-1b replicon-containing S22.3 cells and in GT-1a replicon-containing 129-S.16 cells faldaprevir reduced intracellular HCV RNA levels. Dose-response inhibition curves resulted in an EC50 of 3.1 nM and 6.5 nM against GT-1b and 1a, respectively. Therefore faldaprevir is a potent inhibitor of GT-1 NS3 serine proteases.

The determination of the mechanism of inhibition and the inhibition constant (Ki) of faldaprevir against HCV GT-1a and -1b serine proteases using a steady-state velocity method revealed faldaprevir to be a competitive inhibitor with Ki values of 2.6 nM and 2.0 nM, respectively. Reversibility of inhibition of GT-1b serine protease was determined using a steady-state velocity method. The association and dissociation reactions were consistent with reversible inhibition. Data on the reversibility of the FDV inhibition on the HCV GT-1a serine protease should be provided (if available) or discussed by the applicant.

X-ray crystallography showed that faldaprevir binds in the active site of the GT-1b NS3 protease. Faldaprevir binds at the substrate binding pocket of the NS3 protease domain, providing evidence that this inhibitor exerts its antiviral activity against HCV by specific non-covalent, competitive binding at the substrate binding site.

An investigation using recombinant NS3 proteases showed that faldaprevir inhibited NS3 proteases of GT-2b, 2ac and 3a with IC_{50} values of 240 ± 150 nM, 290 ± 20 nM and 1300 ± 300 nM, respectively. Faldaprevir was found to inhibit the NS3 proteases of GT-4a, 5a and 6a with IC50 values of 9.0 ± 2.3 nM, 10 ± 2 nM and 17 ± 2 nM, respectively.

The faldaprevir metabolites M2a and M2b were both inhibitors of GT-1 NS3 proteases in biochemical assays. See the clinical section regarding the lack of relevance of this finding to overall clinical efficacy.

Faldaprevir is highly bound (>99%) to serum proteins. The evaluation of the effect of human serum proteins on activity showed that the inhibitory activity of faldaprevir against HCV RNA replication was progressively diminished, with an 8-fold higher EC50 value in the presence of 50% human serum (HS). The relationship between the percent HS and the change in EC50 value was not linear, and the effect of HS on the inhibitory activity appears to plateau between 25% and 50% HS.

However the analysis of the effect of HS on FDV antiviral activity was performed only with a hepatoma cell line containing a GT-1b replicon. The applicant should provide data describing the antiviral effect of FDV against a GT-1a replicon and discuss the relevance of individual HS components (i.e. albumin, lipoprotein, alpha-acid glycoprotein etc.) on antiviral activity. Moreover, the applicant should discuss the influence of HS proteins on the in-vivo activity and cytotoxicity of FDV.

The applicant hypothesised that efficacy may be determined primarily by the concentration of the drug in the liver rather than by antiviral activity in the presence of plasma proteins based on a PK/PD model that incorporates a liver partition coefficient-corrected inhibitory quotient for directly acting anti-hepatitis C virus agent.

In-vitro studies investigated the selection for resistance and characterisation of resistant variants. Faldaprevir resistant replicon clones were isolated and the resistance was mapped to mutations in the protease domain of the NS3 gene. The mutant replicons demonstrated reduced susceptibility to faldaprevir inhibition but they remained susceptible to inhibition by interferon-α. The resistance mutations that encode the amino acid substitution R155Q conferred a 60-fold reduction in sensitivity to faldaprevir. The A156V and A156T conferred 190- and 270-fold reductions, respectively. D168A and D168V conferred 690- and 1000-fold reductions in inhibition by faldaprevir.

The R155K and D168V mutants were selected in vitro in GT-1a and GT-1b subtypes. The applicant should discuss why D168V mutation was selected in vitro only with high concentrations of FDV in a GT-1a replicon. This result contrasted with what observed in vivo for GT-1a patients in whom only the mutation at position 155 was frequently selected. In addition the applicant should discuss why the R155K was selected in vitro only with low concentrations of FDV in the GT-1a replicon.

All NS3 site-directed mutants were also assessed in a transient transfection HCV replicon cell-based assay. The GT-1a NS3 R155K RAV reduced faldaprevir potency by 190-fold whereas the GT-1a NS3 D168V RAV reduced potency 810-fold. The major GT-1b RAV D168V reduced the activity of faldaprevir by 870-fold.

In a cross-resistance study susceptibility to faldaprevir was assessed for HCV containing the major boceprevir, telaprevir and macrocylcic NS3 protease inhibitor resistant mutants in transient cell culture replicon assays. NS3 D168V has not been reported to emerge with telaprevir or boceprevir treatment. HCV replicons expressing the D168V or a large panel of other D168 single amino acid substitutions remained fully sensitive to telaprevir or boceprevir but had reductions in faldaprevir activity over a

broad range. D168 variants also conferred substantial reductions in the in-vitro activity of the macrocyclic class of NS3/4A protease inhibitors, such as simeprevir. Faldaprevir maintained activity in vitro against other predominant single amino acid substitutions associated with resistance to telaprevir or boceprevir. Cross-resistance was not observed between faldaprevir and interferon-α or the NS5B polymerase inhibitors.

Ex-vivo analysis (i.e. NS3 cloned from patients) showed that R155K, R155Q and D168V were the major variants that emerged in >10% patients without SVR after treatment with FDV and PegIFN/RBV. Reduced susceptibility to FDV and simeprevir was observed for D168V but the same mutation did not confer resistance to TVR and BOC. R155K conferred a broad range of resistance to all PIs in GT-1a.

No cross resistance to FDV was observed for individual variants at positions V36 and T54 or for the A156S variant, which have been shown to be important in resistance to TVR and BOC. Nevertheless some NS3 variants from patients who did not achieve SVR showed a combined pattern of V36M+R155K mutations, which confers resistance to all PIs. The applicant should discuss the possibility that V36M, selected by TPV and BOC, might facilitate the subsequent emergence of R155K in GT-1a patients by reducing susceptibility to faldaprevir.

Faldaprevir and α-interferon demonstrated additive inhibition in cell culture. The applicant should specify the type of IFN alpha used to perform the in vitro combination studies and provide data (if available) on the efficacy of the combination in HCV GT-1a replicon assays.

Ribavirin has a very low therapeutic index in the replicon assay, making accurate combination studies difficult to perform. A study using ribavirin was assessed at the 50% and 75% levels of inhibition and the combination with faldaprevir was additive. The cytotoxicity of ribavirin was not enhanced by the presence of faldaprevir.

In vitro, faldaprevir had no effect on the antiviral potency of five different HIV-1 protease inhibitors as evaluated by in vitro model of HIV-1 replication. At sub-cytotoxic concentrations, HIV-1 protease inhibitors did not substantially affect the potency of faldaprevir against HCV RNA replication. The applicant should provide the information.

There are no data regarding the potential for an interaction between FDV and other anti-HIV compounds (e.g. NRTIs, NNRTIs). The applicant should provide data or justify its absence.

Hepatitis C virus does not infect non-human species, except for the chimpanzee. There are no widely used small animal disease models. Consequently there are no in-vivo pharmacodynamics studies.

Other issues

The applicant conducted some studies (non-GLP) which were termed secondary pharmacodynamic studies which were in fact safety pharmacology studies. Single doses were given in all studies.

There were no effects of oral doses of faldaprevir on behaviour, cardiovascular, respiratory, or renal parameters in rats up to 100 mg/kg. Faldaprevir caused a dose-dependent decrease in gastrointestinal transit in rats at 10, 30 and 100 mg/kg. The mechanism and significance of this finding was not addressed.

In safety pharmacology studies, faldaprevir had no effects on the CNS or respiratory functions.

Faldaprevir inhibited tail currents in hERG channels in a concentration-dependent manner with an estimated quarter maximal inhibitory concentration value of 10 µM. Faldaprevir had no effect on isolated guinea pig papillary muscle action potential configuration or contractile function at concentrations up to 10 µM. In rhesus monkeys equipped with telemetric devices, faldaprevir had no

effect at doses up to 250 mg/kg on blood pressure, heart rate or electrocardiographic parameters. Overall, the non-clinical data indicated a low faldaprevir-related cardiovascular risk.

Faldaprevir caused a dose-dependent decrease in gastrointestinal transit in rats at 10 mg/kg, 30 mg/kg and 100 mg/kg but the mechanism and clinical significance of this finding was not discussed. The significance of this finding should be discussed. Diarrhoea was observed as a very common AE in clinical studies.

Pharmacokinetics

The pharmacokinetics and metabolism of faldaprevir were studied in mice, rats, rabbits and monkeys and compared to human. These were the species used in toxicology studies. The oral bioavailability of faldaprevir was 29.1% (rat), 35.6% (dog), and 25.5% (monkey). The disposition of faldaprevir in these species was characterized by small to moderate volume of distribution, low to moderate clearance, and short half-life.

Plasma protein binding of ^{14}C-faldaprevir was high (99.6-99.8%) in mouse, rat, rabbit, beagle dog, rhesus monkey and human. The unbound fraction ranged from 0.2% to 0.4% across all species. There was no evidence of saturation of binding at 40 µg/mL in humans and 100 µg/mL in other species. Partitioning of faldaprevir into blood cells was low in all species.

In the rat radiolabeled faldaprevir was widely distributed to most tissues by 1 hour. Radioactivity was primarily associated with GI tract, liver, lung, kidney, and adrenal gland. Faldaprevir-derived radioactivity was not associated with the melanin-containing tissues in the eye or skin. Radioactivity was readily cleared from the tissues, and by 12 h post-dose, the concentrations of radioactivity in most tissues were below the LLOQ. Concentrations of radioactivity were below the LLOQ or at very low concentrations in the brain at all the time points, suggesting faldaprevir did not cross the blood:brain barrier. In pregnant Sprague Dawley rats faldaprevir-derived radioactivity was not observed in fetal tissue, indicating that drug derived radioactivity did not cross the placenta. In rats and mice faldaprevir concentrations in the liver were 42-fold and 22-fold higher, respectively, than plasma concentrations. Liver partitioning in humans was estimated to be a 35-fold enrichment in the liver compared to circulating plasma, using suspended cryopreserved hepatocytes. In-vitro studies with the human HepatoPac model estimated liver partitioning in humans to be 31.5- and 21.9-fold for 120 mg and 240 mg QD doses, respectively.

The metabolism of faldaprevir involved phase I metabolism (oxidation, dealkylation, and hydrolysis) and phase II conjugation with glucuronic acid and glucose in mice, rats, monkeys and humans. Six metabolites of faldaprevir were identified in plasma or excreta of mice, six in rats, ten in monkeys and seven in humans in the [14C] ADME studies. Faldaprevir was the main drug-related component found in human plasma, representing >97.9% of the drug-related material. Therefore, no metabolite is considered major (>10% of total drug-related material). In humans metabolism is a major clearance pathway of faldaprevir and the primary route of metabolism is oxidation by CYP3A (predominantly by CYP3A4 with a minor contribution from CYP3A5) in the liver, resulting in the formation of two hydroxylated metabolites - M2a and M2b - found at 21.6 and 19.4% of dose, respectively in faeces but not detected in plasma in the human [14C] ADME study.

Both M2a and M2b were present in monkeys. M2a and M2b had poor membrane permeability and were subject to efflux transport mediated by P-gp and BCRP in vitro. The applicant hypothesised that this could explain why they were not observed in plasma and were only found in faeces in the human [14C] ADME study. Once they are formed in the liver and intestine, they cannot pass the cell membrane readily and are likely to be immediately transported by P-gp and BCRP into bile and GI tract.

In-vitro studies also showed that M2a and M2b are substrates of hepatic uptake transporters, likely OATP. Thus, even if M2a and M2b permeate out of hepatocytes or enterocytes into the systemic circulation or portal vein flow, respectively, they can be then taken up by hepatic uptake transporters into the liver. It is expected that M2a and M2b are mainly formed in the liver but their levels are expected to be low in the liver based on the slow rates of formation observed in vitro and in vivo and the fact that they are good substrates of efflux transporters. Considering their expected low local exposure in the liver, the applicant considered that the contribution from M2a and M2b to the clinical efficacy of faldaprevir is limited.

In-vitro studies showed that glucuronidation was a relatively minor clearance pathway of faldaprevir. This may be mediated by multiple UGT isoforms so it is unlikely that faldaprevir exposure will be affected by drugs that are known to inhibit UGTs.

Faldaprevir is not an in-vitro inducer of the major human CYP450 isoforms. In-vitro studies showed that faldaprevir inhibited CYP2B6, CYP2C8, CYP2C9 and CYP3A and was a weak to moderate inactivator of CYP3A4.

In-vitro transporter studies indicated faldaprevir was a substrate of P-gp, MRP2 and OATP1B1 but not a substrate of BCRP, OATP1B3, OAT1, OAT3 or OCT2. At therapeutic doses (120 mg or 240 mg QD), faldaprevir may saturate intestinal P-gp. Thus, intestinal P-gp is not likely to limit absorption of faldaprevir. However, P-gp may play a role in the biliary excretion of faldaprevir. In-vitro hepatocyte studies also indicated that the uptake of faldaprevir into hepatocytes was mediated by passive permeability and active uptake through multiple transporters, including a rifamycin SV inhibitable process, likely OATP, and a sodium dependant transporter(s) that is not identified.

Faldaprevir is likely to inhibit P-gp, BCRP, OATP1B1 and OATP1B3 in the clinic based on in-vitro studies. In a clinical study in which digoxin was used as a probe P-gp substrate and faldaprevir was administered orally with a loading dose of 480 mg followed by 240 mg BID for 14 days the digoxin AUC0-∞ increased by 2.19-fold.

In vitro DDI interaction studies indicate a potential for FDV to interact with P-gp inhibitors at therapeutic concentrations. The Applicant did not take into consideration the potential for interaction between FDV, interferon alfa and ribavirin. The Applicant is requested to discuss this issue together with the clinical relevance of the effects on transporter system, in light of the clinical data generated.

The primary route of elimination of faldaprevir and its metabolites was through excretion into faeces in mouse, rat and monkey (84-100% of administered dose), with the exception that in monkey after oral dosing only 42% of administered dose was recovered in faecal samples, which was attributed to the high incidence of vomiting and diarrhoea. Urinary excretion of faldaprevir and its metabolites was negligible (<1.1% of administered dose) in mouse, rat and monkey. A high amount of radioactivity (18% of administered dose) recovered in monkey urine after oral dosing was attributed to contamination of urine with faeces. In a lacteal secretion study in the Sprague Dawley rat the faldaprevir-derived radioactivity was excreted into milk up to 8 h post-dose but was below the LLOQ at 24 h.

Toxicology

The calculated exposure multiples to clinical use achieved in the pivotal nonclinical safety studies were based on a maximum human dose of 240 mg with an associated AUC0-24h of 332000 ng·h/mL and Cmax of 20800 ng/mL.

The acute toxicity of faldaprevir assessed in rodent single dose studies was low with the ALD by the oral route of exposure being > 5000 mg/kg.

In a repeated dose study in mice, unexpected mortality and severe overt signs of toxicity occurred following the first dose of ≥ 550 mg/kg the cause of which is unknown. The applicant hypothesised that higher plasma exposure and unknown environmental factor(s) may have contributed to the mortality. The dose of 550 mg/kg corresponds to 2683 mg human equivalent dose based on body surface area conversion, approximately 11 x the 240 mg maximum recommended therapeutic dose. These findings did not occur in the other mouse studies. Consequently the acute mortality observed in this study may not be clinically relevant. Faldaprevir was generally well tolerated clinically in the single rising dose study up to 1200 mg.

In the repeated dose toxicity studies (up to 26 weeks in rats, up to 13 weeks in mice, and up to 39 weeks in rhesus monkeys), doses used were up to the MTD. The toxicokinetic studies showed that in all these studies and in the reproductive toxicity studies in which toxicokinetics had been conducted, with the exception of the 13-week mouse study, the systemic exposure in the test animals was a low multiple of, or even below that, of the clinical systemic exposure. This was the case whether the exposure multiples were considered as Cmax or AUC. The applicant should address this issue and discuss the predictive value and utility of the non-clinical studies in the light of this finding. The toxicokinetic studies also revealed a lack of dose proportionality. The mechanism was not fully explained. The toxicological significance and clinical relevance of this finding should be addressed.

There were an excessive number of deaths reported in the repeated dose toxicity studies in the mouse (16, 11 in two studies), rat (>15 in one study) and monkey (9 in one study). Some of these deaths were attributed to gavage errors. However, in several cases, deaths were unexplained and there has been inadequate discussion of the extensive mortalities across studies.

Hyperbilirubinaemia was consistently reported in the general toxicology studies in all species. There were several target organs of toxicity all of which appeared to be at least partially reversible. However, in view of the severe nature of some of the adverse treatment-related findings and a lack of knowledge of the mechanisms underlying these findings, several findings are raised as other concerns.

Hyperbilirubinaemia*:* In the general toxicology studies, reversible and dose-dependent increases in total bilirubin were observed, which were most pronounced in the monkey. In the repeat dose monkey studies up to 39 weeks increased total bilirubin occurred at ≥ 20 mg/kg/day which tended to peak at approximately 2 weeks (up to 11.7 mg/dL) and then declined by the study end. The applicant proposed that the transient nature suggest the possibility of an adaptive response. The increased total bilirubin was predominantly due to high indirect bilirubin values, consistent with unconjugated bilirubin. Increased bilirubin is not considered to be a result of liver damage as it was not always associated with an increase of liver enzymes and was not correlated to histopathological evidence of hepatotoxicity.

The applicant hypothesised that the mechanisms for the predominantly unconjugated hyperbilirubinaemia are likely to be inhibition of UGT1A1 and possibly also inhibition of bilirubin uptake into hepatocytes by faldaprevir. Jaundice and hyperbilirubinaemia (predominantly unconjugated) were observed in the clinical studies, and were reversible after the cessation of faldaprevir treatment.

Other clinical chemistry changes: Dose-dependent increases in liver enzyme activities (AST, ALT, ALP and SDH) were observed in the repeated dose studies in the rat and mouse. However no hepatocellular necrosis was observed in the rodents. Despite the pronounced increases in bilirubin in the monkey, liver enzyme activities were unaffected. Bile acids were increased in the 4 and 26 week monkey studies at 500 or 500/350 mg/kg/day. In-vitro studies suggested that inhibition of BSEP is possible at clinically relevant exposures. Therefore, the applicant hypothesised that the increase of bile acid in the monkey studies may be related to inhibition of BSEP. A slight increase in mean bile acid levels in humans was observed in Phase 3 studies, but the changes were not clinically significant. At the end of the recovery phase, all these changes were fully reversible.

Haematological changes*:* In the 4-week rat study there were increases in total WBC counts (up to 84%) and lymphocytes (up to 94%) at ≥ 125 mg/kg/day and neutrophils (up to 2.1 x) at 300 mg/kg/day. In the 13-week study there was an increase in neutrophil counts (58%) in males at 500 mg/kg/day. Dose-dependent increases in total WBC counts and neutrophils were also observed in the 4-week study in the CByB6F1 mice. These haematological changes were considered to be treatment-related. The applicant should discuss the clinical relevance of these findings.

Gastrointestinal tract: In the monkey, GI toxicities in the 26- and 39-week studies resulted in mortality/moribund status in the severe cases. In the 26-week study there was mucosal epithelial hyperchromasia in the ileum characterised by shortening of villi accompanied by lining with hyperchromatic high cuboidal epithelial cells (500/350 mg/kg/day) and mild to moderate gastritis in the stomach after (≥175 mg/kg/day). Treatment-related GI findings in animals that died or were sacrificed when moribund included mild to marked typhlitis, colitis and proctitis of the caecum, colon and rectum, respectively (500/350 mg/kg/day). In a 39-week study, acute inflammation/necrosis in the caecum, colon, rectum, stomach, jejunum and ileum were observed in two unscheduled-sacrifice males (80 and 250 mg/kg/day) and 1 female at 175 mg/kg/day, consistent with the GI effects observed in the 26-week study. GI toxicities were not present in the recovery animals in either study.

In the rat there were no effects in the gastrointestinal tract in the 4- or 26-week studies at dose levels up to 300 mg/kg/day. In the 13-week rat study macroscopic gastrointestinal tract dilatation with abnormal contents and microscopic vacuolation of small intestines and stomach erosion or ulceration occurred at ≥ 500 mg/kg/day. In CD-1 mice in the 13-week study vacuolation of enterocytes occurred in males at ≥ 300 mg/kg/day and females at ≥ 500 mg/kg/day but there was no microscopic cellular degeneration/necrosis. Minimal to slight vacuolation of the surface epithelium of the villi in the small intestines was present in a 4-week MTD study in CByB6F1 mice.

In addition to the severe adverse findings in the gastrointestinal tract including inflammation, necrosis, erosion and ulceration reported in all test animal species, faldaprevir also caused a dose dependent decrease in gastrointestinal transit in rats. There appears to be no information concerning the potential for any of these severe adverse treatment related findings to occur clinically. Therefore the clinical significance of these findings should be addressed.

Gallbladder: In the 26-week monkey study, faldaprevir-related gallbladder changes consisted of minimal to moderate mucosal hypertrophy of the gallbladder (≥ 175 mg/kg/day), minimal necrosis of gallbladder epithelium (500/350 mg/kg/day) and necrotizing cholecystitis (in one moribund sacrifice animal at 500/350 mg/kg/day). In the 39-week monkey study, mucosal hypertrophy of the gallbladder was a background finding and was exacerbated at ≥ 175 mg/kg/day. In the rat there were no findings in gallbladder (up to 1000 mg/kg/day) or CD-1 mice (up to 1000 mg/kg/day). In a 4-week MTD study in CByB6F1 mice, gallbladder mixed inflammation and mucosal hypertrophy/hyperplasia were observed at ≥250 mg/kg/day.

The applicant states that there were no signals for faldaprevir-related gallbladder adverse events in the clinical studies. However, in view of the severe adverse treatment related findings reported in the gall bladder in the repeated dose toxicity studies in all three test species, and that one cholecystitis event was observed in the clinical setting, it is difficult to draw a firm conclusion on the significance of these findings. The clinical significance of these findings should be addressed.

Pancreas*:* In the 13-week rat study, ductal inflammation or ulceration in the pancreas was present in 2 early decedants at 1000 mg/kg/day. Acinar cell vacuolation occurred in the 13-week rat study and 13 week mouse study, and generally limited to early decedants. The applicant hypothesised that since pancreatic acinar cell vacuolation can be a background finding and it was only observed in early decedants, the finding was likely secondary to the moribund conditions in the rodents. In the 26-week

monkey study, depletion of cytoplasmic granules in pancreatic exocrine cells was considered the result of decreased food consumption. Minimally increased apoptosis of acinar epithelial cells was observed in one 500/350 mg/kg/day female, which was considered exacerbated by treatment. The applicant states that there were no signals for faldaprevir-related pancreatic effects in the clinical studies.

Liver*:* Hepatocellular vacuolation was observed in the 13-week studies in CD-1 mice. Diffused vacuolation of hepatocytes was characterized by enlargement of hepatocytes by discrete round vacuoles that generally did not displace the nucleus and were most severe in the centrilobular areas. In a 4-week study in CByB6F1 mice the faldaprevir-related hepatocellular swelling was diffuse (panlobular) characterised by hydropic change variably accompanied by cytoplasmic vacuolation. The hepatocellular swelling in the CByB6F1 mice and CD-1 mice was similar and both were correlated to increased liver weight and accompanied by elevated liver enzyme activities (AST, ALT, ALP and SDH). Slight increase of ALT was observed in the rat studies without histopathology correlates.

In the 13-week rat study, liver eosinophilic globules were observed in the early decedants. Transmission electron microscopy of liver revealed that the mitochondria were of normal appearance and number ultra-structurally. Changes in the liver that were considered to be treatment related were the presence of an increased number of autophagic vacuoles and a decreased amount of rough endoplasmic reticulum (RER) in the cytoplasm of hepatocytes which did not appear to have resulted in hepatocellular necrosis by light microscopy. The applicant hypothesised that the ultra-structural changes in the liver may have been an adaptive response to marked food consumption and moribund conditions of the animals in the study. In the 2-year rat study, liver from males at 150 mg/kg/day had slightly increased incidence of cystic degeneration and centrilobular hepatocellular vauolation. There were no increases in liver enzyme activities or faldaprevir-related histopathological changes in the liver in the monkey. Since hepatocellular necrosis was not observed in the nonclinical studies and there was no drug-induced liver injury in the HCV patients in the clinical studies faldaprevir is not considered to be hepatotoxic.

The Applicant stated that the nonclinical liver findings are not considered adverse due to the lack of hepatocellular necrosis, moreover there was no drug-induced liver injury in HCV patients in the clinical studies. However, G3or G4 elevation of hepatic enzymes has been observed in patients treated with FDV when compared to placebo group, moreover two cases of hepatic failure occurred which led to the death of the patients after administration of FDV at 240 mg. The Applicant is asked to further clarify the clinical relevance of the liver toxicity in light of the clinical findings.

Ovary*:* Diminished corpora lutea occurred at ≥ 250 mg/kg/day in a 4-week study in CByB6F1 mice. Corpora lutea were typically absent (diagnosed as marked severity) except for few animals that had a reduced size and number of corpora lutea (diagnosed as moderate severity). There was no evidence of tissue injury. Ovarian follicles appeared to have developed normally. Therefore the ovarian effect was attributed to a disruption of ovarian cycling and not tissue injury. Reversibility was demonstrated for the same finding in faldaprevir-treated CD-1 mice. This effect was not observed in the other general toxicology studies. The sensitivity of the corpora lutea effect in the CByB6F1 mice is not correlated to faldaprevir exposure levels across the nonclinical species or strain. There was no faldaprevir-related effect in the ovaries in the 2-year carcinogenicity study in the CD-1 mice.

Hence the relevance of the ovarian finding in the CByB6F1 mice to humans is considered low due to the lack of species and/or strain concordance. The applicant hypothesised that the diminished corpora lutea in the CByB6F1 mice may be attributable to stress or may be secondary to other toxicities.

Adrenal: In the 4-week monkey study, lipid depletion in the adrenal glands was present at 500 mg/kg/day dose and was considered faldaprevir-related; however, in the 26-week monkey study a similar finding (diminished cytoplasmic vacuolation of the epithelial cells of the zona fasciculata) was

present in four males that were either sacrificed moribund or died accidentally and in this study the adrenal changes were considered stress-related. In the 13-week rat study, necrosis of the zona fasciculata and atrophy of the zona glomerulosa were present only in early decedants at ≥ 500 mg/kg/day. No adrenal changes were observed in the 26-week study or the carcinogenicity study in the rat. The applicant hypothesised that these results indicate that the adrenal is not a primary target organ of faldaprevir, and the adrenal effects were more likely due to stress or secondary to the moribund conditions. There appears to be no clinical information regarding potential effects of faldaprevir on the adrenal in humans. The clinical significance of these findings should be addressed.

Heart*:* There was no evidence of faldaprevir-related cardiotoxicity in the rat, mouse or monkey. Previous experience with other molecule of this therapeutic class has shown that some can cause swelling of mitochondria in cardiac myocytes, most notably in the non-human primate. Therefore, additional measures included echocardiography and electron microscopy of the heart. In the early 4-week monkey study, minimal, multifocal mitochondrial swelling with increased matrical lucency was found in 1/6 monkeys at 500 mg/kg/day. This finding was minimal and isolated to one animal. In the 26-week repeat dose study more animals were added to the high dose (n=18 vs 6) and higher systemic exposures were achieved. The evaluation of the hearts by ECG, echocardiography, light microscopy and transmission electron microscopy demonstrated that there were no treatment-related effects.

There was no evidence of cardiotoxicity in the 39-week monkey study as evaluated by ECG and light microscopy. In one of the 13-week studies in mice, exacerbation of epicardial inflammation at the heart base in males and females at ≥300 mg/kg/day was associated with an increase in incidence of thymic peripheral inflammation at 700 mg/kg/day. Based on the anatomic distribution, the change in the heart is not consistent with a drug-related cardiotoxicity. The distribution of this finding and the concurrence of peripheral thymic inflammation in several affected animals suggest a possible association with gavage mechanical trauma. The totality of the nonclinical safety data demonstrated that faldaprevir does not possess cardiotoxic potential.

The genotoxic potential of faldaprevir was assessed in a full package of studies. Faldaprevir is not genotoxic.

The carcinogenic potential of faldaprevir was evaluated in 2-year studies in CD-1 mice and Sprague Dawley rats. Dose levels were chosen based on MTD in the 13 week studies in mice and rats. Faldaprevir was not carcinogenic in either species. AUC exposures in the rat achieved 0.9 x and 1.1 x clinical exposures at 240 mg dose for the male and female, respectively. AUC exposures in the male and female mouse were estimated to be 3.5 x and 1.9 x clinical exposures at 240 mg dose, respectively.

No reproductive organ toxicity was observed in the general toxicology studies in the rat, CD-1 mouse or monkey. Diminished corpora lutea was observed in a non-pivotal 4-week MTD study in CByB6F1 mice. The finding was reversible. The clinical relevance is considered low due to the lack of species or strain concordance.

In the rat fertility study the NOAEL for fertility and early embryonic development was 500 mg/kg/day in the male and 1000 mg/kg/day in the female (1.3 x and 2.2 x respectively estimated AUC exposure multiple to 240 mg therapeutic dose), which were the highest doses tested. Faldaprevir had no effects on early embryonic development and was not teratogenic in rats or rabbits.

The NOAEL for embryo-fetal development in rats and rabbits was 1000 mg/kg/day (0.8 x AUC exposure multiple to 240 mg therapeutic dose) and 100 mg/kg/day (AUC exposure well below the clinical exposure at 240 mg dose), respectively; doses which were maternally toxic.

In the pre- and post-natal development study in the rat, 1000 mg/kg/day was not well tolerated by the dams. A maternal NOAEL was established at 150 mg/kg/day based on mortality, decreased absolute body weight and body weight gains, and decreased food consumption at 1000 mg/kg/day.

A NOAEL of 150 mg/kg/day (0.1 x AUC exposure multiple to 240 mg therapeutic dose) was established for pre- and post-natal development of the F1 offspring, based on increased mortality before PND 4, decreased body weight and an overall pattern of post-natal growth and development delay exhibited by the F1 males and females at 1000 mg/kg/day, a dose which caused maternal mortality.

The general toxicology of combinations of FDV with ribavirin or BI 207127 NA was evaluated in rats. No evaluation of sperm abnormalities was performed for the combination of FDV and ribavirin. Even though no effects on male or female fertility were reported, clinical data suggest an increased incidence of sperm abnormalities following the combination treatment of IFN alpha and ribavirin. Therefore the potential effects of FDV given in combination on sperm parameters should be discussed.

The tissue distribution and lacteal excretion of ^{14}C-faldaprevir-derived radioactivity was assessed in pregnant or lactating Sprague Dawley rats. The results showed that faldaprevir did not cross the placenta, but was excreted in maternal milk. The levels of faldaprevir in the milk were generally higher than levels observed in the maternal plasma in the rat. It is conceivable that high levels of faldaprevir in the milk resulted in significant exposure in the pups and contributed to the delay in post-natal growth and development. The significance of this finding should be further discussed.

Faldaprevir was shown to be non-irritating/non corrosive to the skin of rabbits and mildly irritating and non-corrosive to the eyes of rabbits.

Faldaprevir exhibits an absorption band in the spectral region of 290-700 nm with a maximum absorbance at 330 nm. Faldaprevir was distributed to the skin of the rat dosed orally, but there was no melanin binding in the skin or eyes. Faldaprevir was positive in a 3T3 cell Neutral Red Uptake Assay for phototoxicity potential. These results, together with cases of photosensitivity reactions observed in the Phase 2 clinical studies indicate a photosensitive/phototoxic potential of faldaprevir. Faldaprevir-related photosensitivity reactions were not observed in the Phase 3 trials, in which patients were advised to apply sun protection.

Two impurities specified above the qualification thresholds (0.15% for drug substance and 0.2% for drug product) have been qualified in the general toxicology studies. Proposed specifications for drug substance were set for both impurities. The proposed specification for drug product for one impurity was set. One impurity is not controlled in the drug product because it is not a degradation product.

The genotoxic potential of the impurities was tested in an Ames test and a test of chromosomal damage in mammalian cells *in vitro* (micronucleus test in CHO cells). Both were non-mutagenic in Ames tests. One impurity was negative in the in-vitro micronucleus assay. The *in vitro* micronucleus results were equivocal due to the statistically significant increase in micronucleated binucleated cells at single dose level for the non-activated 24-h exposure. The micronucleus assay was repeated to include additional concentrations. There was a statistically significant increase in micronuclei in this repeat study that was considered to be biologically irrelevant, however since the initial assay results showed a statistically significant positive response (5.5%) slightly above the historical range the overall assessment was concluded as equivocal. The potential clastogenicity should be unequivocally resolved.

All chemical structures stated to be reasonably expected to be present in drug substance or drug product were evaluated by in silico analysis and/or Ames. Genotoxic impurities are purged/removed by the synthesis process to below the conservative 1.5 μg/day TTC in the drug substance. INRF-3 acid is also a genotoxic degradant of the drug product. Considering the intended short term therapeutic use conditions for faldaprevir and the potential growth of INRF-3 acid during the product life, a

specification limit for drug product at release and through shelf life for a daily dose of 240 mg and maximum treatment duration of 12 weeks is proposed. The limit corresponds to the 1.5 μg/day TTC. The proposed limit during shelf-life translates to an intake approximately 2x the TTC. Given the conservative assumptions inherent in the TTC, especially that it assumes a cancer risk of <1 in 100000 due to lifetime exposure whereas the maximum daily treatment duration for faldaprevir is 12 weeks, i.e. a fraction of a lifetime, is considered justified. Establishing less-than-lifetime (LTL) limits for genotoxic impurities in pharmaceuticals has precedent in the establishment of the staged TTC limits for clinical development and it is consistent with EMA's document, "Q and A on the CHMP Guideline on the Limits of Genotoxic Impurities". This concept has been recently extended to marketed products with cumulative intakes of less than lifetime in the ICH M7 Step 2 Draft Consensus Guideline 2013.

There were no structural alerts for mutagenicity identified for the PD 1085 dimer representation. Hence, PD 1085 is not predicted to be genotoxic and therefore it was not tested in an Ames assay. It has to be considered endorsed, consistently with the Q and A on the CHMP Guideline on the Limits of Genotoxic Impurities, stating that “the absence of a structural alert based on a well-performed assessment (e.g. through application of commonly used QSAR assessment software such as DEREK or MCASE) will be sufficient to conclude that the impurity is of no concern with respect to genotoxicity and no further ‘qualification’ studies or justification will be required”. The Applicant is however requested to submit a risk assessment report of FDV potential genotoxic degradants which include the QSAR assessment of PD 1085, as it was not found in the dossier.

The general toxicology of combinations of faldaprevir with ribavirin or BI 207127 NA was evaluated in rats. Overall, the findings suggest that the co-administration of faldaprevir with ribavirin in the rat does not result in increased toxicity. The co-administration study with BI 207127 NA showed no new target organ toxicities compared to either faldaprevir or BI 207127 NA alone. The overall tolerability of co-administration was less compared to the administration of faldaprevir or BI 207127 NA alone and elevation of ALT was more pronounced in the co-administration group compared to faldaprevir group. However, elevated liver enzymes were not associated with any histopathology evidence of hepatotoxicity.

Concerning the ERA, the applicant is requested to provide a graphical presentation of results of the study of Gonsior, 2013, including fitted curves, and to update the ERA with the BCF values stated below. The results of the study on bioconcentration of faldaprevir in fish (test guideline OECD 305) are not sufficient. In particular, graphical presentations of results, namely uptake and depuration phase curves, showing data and the fitted models are missing. Furthermore, the derivation of BCF values is not acceptable. The applicant relates the BCF steady-state values to an interval which covers almost the whole uptake phase of the study (day 3 to 21). In contrast, it is concluded from the data that for both concentrations there have been no steady-state conditions after day 8. Therefore, the uncorrected BCFSS values at steady-state are calculated to be 250 and 110 (mean of samples of days 3 to 8), respectively (low and high concentration). Normalised to an average lipid content in fish of 5%, this corresponds to BCFSSL values of 347 (0,010 mg/L) and 153 (0,100 mg/L), respectively.

3.4. Clinical aspects

Pharmacokinetics

The doses described and the content of faldaprevir (BI 201335; presented as the sodium salt BI 201335 NA) in each dosage form refer to the amount of anhydrous form (free acid; designated BI 201335 ZW). With the exception of six studies (01, 02, 03, 06, 10 and 33) faldaprevir was administered as soft gelatin capsules (SGC 40 mg or 120 mg). The product intended for the market is

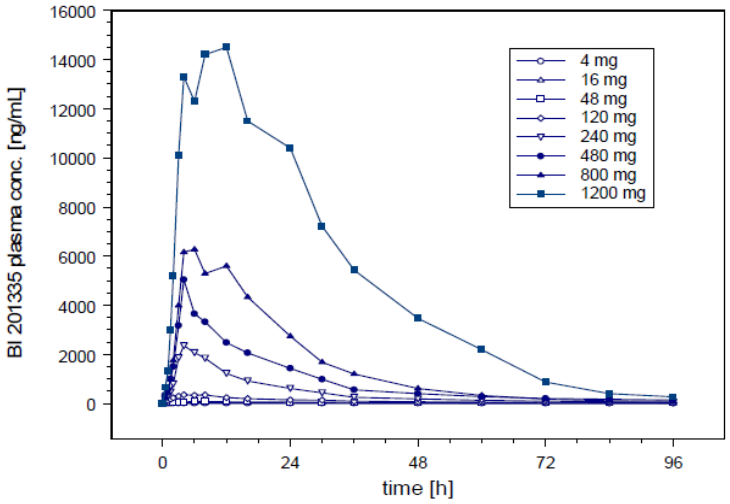
the liquid-filled immediate release 120 mg SGC. This dose form was used in the Phase 2 and 3 studies and most Phase 1 studies.

Plasma and urine concentrations of faldaprevir were determined using validated LC/MS/MS methods. In most studies assays were performed by Tandem Labs (Salt Lake City) with plasma LLOQ 2 ng/mL.

- **Bioavailability**

Absolute bioavailability has not been determined in man. The applicant has assumed it is at least ~ 40% based on study 33 in which M2a and M2b accounted for ~ 40% of the radioactivity recovered in faeces and almost all of the oral radiolabelled dose was recovered from faeces.

In **study 03** single doses (4-1200 mg) in oral solution were administered in the fasted state. The drug was very slowly absorbed at low doses (Tmax ~15 h at 4 mg) but Tmax was at 4 h at middle doses and 10 h at the highest dose. AUC and Cmax increased more than proportionately with dose. Mean Tmax, CL/F and t1/2 were dose dependent. The highest mean CL/F value was observed at 4 mg and the lowest at 1200 mg dose. The mean t1/2 and MRT in plasma also tended to decrease with increasing dose.



In **study 13** single doses from 40-480 mg BI 201335 NA (as multiples of 40 mg or 120 mg SGC) were administered to fasted Japanese male subjects. As in study 03, AUC and Cmax increased more than proportionately with dose. The Tmax decreased from 10 h and 6 h in the 40 mg and 80 mg groups, respectively, to 4 h at doses from 120-480 mg. Similarly, as in study 03 the terminal half-life decreased with increasing dose from 38.7 h (40 mg) to 16.4 h (480 mg) while CL/F decreased from 126 mL/min to 32.2 mL/min at respective doses. The GM Vz/F decreased with increasing dose from 423 L (40 mg) to 45.8 L (480 mg) and MRTpo decreased from 55.5 h to 22.7 h in the 240 mg treatment group and 22.9 h in the 480 mg treatment group.

In the metabolite profiling (mass-balance) **study 33** a single dose of 240 mg [^{14}C]-BI 201335 NA (labelled with 100 µCi [^{14}C]) was given as an oral solution to 8 healthy fasted male volunteers on Day 9 of dosing with 240 mg non-labelled drug once daily for 15 days following a loading dose of 480 mg on day 1. Dosing of non-labelled drug was with 120 mg SGCs. Data including the radiolabeled dose were obtained from 7 subjects. The Ctrough values showed that steady state was maintained from days 2-16.

Table 11.5.2.2: 1 Summary of pharmacokinetic parameters of total [^{14}C]-BI 201335 ZW related radioactivity and BI 201335 ZW following an oral administration of a planned 240 mg [^{14}C]-BI 201335 on Day 9

Parameter		[^{14}C]-BI 201335 ZW		Parameter	BI 201335 ZW
		Blood	Plasma		Plasma
$AUC_{0-\infty}$	Mean	51,900	92,100	$AUC_{\tau,ss}$	87,700
[ng Eq·h/mL]	%CV	32.7	35.4	[ng·h/mL]	32.0
	gMean	49,700	87,400		83,900
C_{max}	Mean	2,560	4,600	$C_{max,ss}$	7,960
[ng Eq/mL]	%CV	27.7	32.1	[ng/mL]	33.6
	gMean	2,490	4,410		7,600
t_{max}	Mean	4.58	3.72	$t_{max,ss}$	2.58
[h]	%CV	48.3	65.0	[h]	37.6
	gMean	4.09	3.16		2.45
$t_{1/2}$	Mean	19.1	23.3	$t_{1/2,ss}$	30.4
[h]	%CV	56.3	33.8	[h]	9.37
	gMean	17.1	22.3		30.3
MRT_{po}	Mean	27.0	28.7	$MRT_{po,ss}$	17.9
[h]	%CV	28.5	23.1	[h]	12.4
	gMean	26.2	28.1		17.8
CL/F	Mean	91.0	52.4	$CL/F_{,ss}$	54.2
[mL/min]	%CV	28.2	33.2	[mL/min]	31.2
	gMean	87.6	49.8		51.9
V_z/F	Mean	140	97.9	$V_z/F_{,ss}$	142
[L]	%CV	38.5	20.3	[L]	33.3
	gMean	129	96.3		136
C_{24}	Mean	--	1,070	$C_{min,ss}$	1,270
[ng Eq/mL]	%CV	--	32.7	[ng/mL]	53.8
	gMean	--	1,030		1,110

In blood the mean total [14C]-BI 201335 related radioactivity exposure was lower than in plasma with a slightly longer mean Tmax but slightly shorter terminal t1/2. While the mean blood MRTpo was similar to plasma the CL/F and Vz/F (140 L vs. 97.9 L) were higher.

On day 9 the steady state BI 201335 ZW plasma concentrations were much higher than the [14C]-BI 201335-related radioactivity in plasma over a 24 h dosing interval. The mean [14C]-radioactivity AUC0-∞ was 92,100 ng Eq·h/mL, which was slightly higher (5%) than the cold faldaprevir AUCτ,ss (87,700 ng·h/mL), whereas the t1/2 of radioactivity was approximately 20% lower than for faldaprevir.

- **Bioequivalence**

Study 10 compared the relative bioavailability in the fasted state of single doses of BI 201335 NA when administered as the SGC (40 mg or 120 mg sizes) and the PiB made up into oral solution. Dose groups received either 40 mg (14 subjects) or 240 mg (20 subjects) doses with each formulation.

- At the 40 mg dose the SGC was almost bioequivalent to PiB with the GMR AUC0-∞ at 92.2% (CI: 81.7%-104.1%) and GMR Cmax at 87.2% (CI: 78.7%-96.6%).
- In contrast, for the 240 mg dose the GMR AUC0-∞ was 70.5% (CI: 58.1-85.4%) and GMR Cmax was 59.5% (CI: 44.2%-80.1%) while Tmax was delayed with the SGC to 5.6 h vs. 3.6 h for the PiB. Three of the 20 subjects had particularly large reductions in exposure with SGCs vs. PiB but at this dose there were no important gender differences.

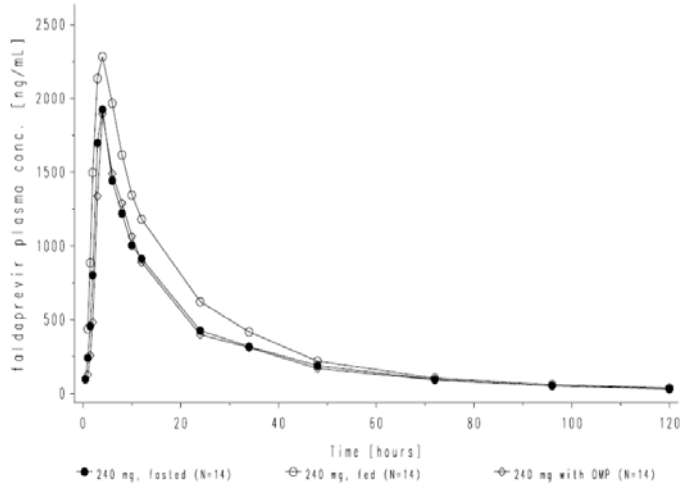
Study 53 compared the bioavailability of faldaprevir from the two SGC sizes (120 mg or 40 mg) used in various studies following single dose administrations 120 mg BI 201335 NA in 60 fasted Japanese male subjects. This was a replicative crossover study so that each subject was to receive 3 x 40 mg and 1 x 120 mg on each of two occasions. The GMRs and 90% CI fell within the BE criteria.

- **Influence of food**

In **study 03** the effect of a high fat breakfast was assessed on dosing with 480 mg BI 201335 ZW in oral solution. There was a slightly higher Cmax (108.89% [90% CI 82.31 - 144.06%]) and AUC0-∞ (113.56% [90% CI 92.70 - 139.12%]) on dosing with food while the Tmax was reduced from 6 h to 4 h.

Study 59 investigated the effect of food (high fat breakfast vs. fasted) and of increased gastric pH (40 mg omeprazole once daily; faldaprevir given on day 5 in fasted state) on the relative bioavailability of a single oral dose of 240 mg faldaprevir (as 2 x 120 mg SGC) in a three-way crossover design in healthy subjects. Plasma exposure to faldaprevir was slightly (~20%) higher in the fed vs. fasting state with or without omeprazole. Median Tmax was 3h under fed conditions (vs. 4 h fasted) but t1/2 was comparable (~30 h).

Faldaprevir parameter	Adjusted gMean ratio (Test/Reference) [%]	Two-sided 90% confidence interval		Intra-individual gCV [%]
		Lower limit [%]	Upper limit [%]	
Comparison faldaprevir fed (N=14) vs. faldaprevir fasted (N=14)				
$AUC_{0-\infty}$	120.4	102.1	141.9	23.2
AUC_{0-tz}	121.3	102.3	143.7	24.0
C_{max}	118.8	83.2	169.6	52.4
Comparison faldaprevir fasted with omeprazole (N=14) vs. faldaprevir fasted (N=14)				
$AUC_{0-\infty}$	94.3	76.2	116.8	30.8
AUC_{0-tz}	94.7	76.3	117.7	31.4
C_{max}	93.6	65.8	133.0	53.0



- **Distribution**

- In **study 033** the blood/plasma ratios of total radioactivity indicated minimal association of radioactivity with erythrocytes.
- In animals and in-vitro models faldaprevir was found to be 20- to 40-fold enriched in liver
- In HCV patients the GM (CV%) apparent volume of distribution (Vz/F,ss; assuming F is 40%) was 89.4 L (34.1%) and 36.1 L (17.9%), respectively, after multiple oral doses of 120 mg and 240 mg.
- Faldaprevir is > 99% bound to human plasma proteins. Protein binding is independent of concentration in the range 1 - 40 µg/mL. In **study 058** in renal impairment there was no difference in the fraction of free (unbound) faldaprevir for subjects with renal impairment

(0.10±0.06% mild, 0.10±0.03% moderate and 0.13±0.02% severe) vs. normal renal function (0.09±0.01%).

- **Excretion**

In **study 033** a mean of 98.7% of the radioactive dose was excreted in faeces and 0.113% was excreted in urine (mostly within 168 h) and recovery of the radio-labelled dose was > 98%.

Other than metabolism-mediated clearance, the applicant concludes that faldaprevir is mainly eliminated through biliary excretion.

- **Metabolism**

The metabolic turnover of faldaprevir *in vitro* was described as low using human liver microsomes (HLM), human intestinal microsomes and human hepatocytes and slow in HLM and human hepatocytes. The disappearance half-life was 193 min in HLM at a substrate concentration of 2 µM and was 355 min in human hepatocytes at a substrate concentration of 0.1 µM.

Using recombinant CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 it was concluded that CYP3A4 was responsible for approximately 76.5% of faldaprevir depletion with no major contributions (≤ 6%) from other CYPs evaluated. In addition, CYP3A4 was primarily responsible for the formation of M2a (93.1%) and M2b (97.4%). Due to low metabolic rates, the fraction of drug escaping first-pass gut and hepatic metabolism was estimated to be high (0.79-0.99 for 120 mg QD dosing and 0.87-0.99 for 240 mg QD dosing; the range reflects use of different models to estimate intrinsic clearance and organ clearance).

In **study 05** CL/Fss was estimated at 41.3 mL/min (0.6 mL/min/kg, based on 70 kg man) after 120 mg QD dosing and 12.1 mL/min (0.2 mL/min/kg) after 240 mg QD dosing. The applicant states that since bioavailability (F) is < 1, the actual clearance values will be lower and faldaprevir is considered to be a low clearance drug because CL/Fss values are <0.75-2.6% of hepatic blood flow in humans (1617 mL/min; FDA 2012).

In **study 033,** metabolite profiling was conducted at 3, 8 and 24 h post-dose. Faldaprevir accounted for 97.9% to 99.8% of plasma-derived radioactivity in plasma and it was the only drug-related component found in urine. In faeces unchanged faldaprevir was the most abundant drug-related component while M2a and M2b were the most abundant faecal metabolites, each accounting for ~20% of drug-related material.

Table 3.1.3: 1 Metabolite profile of [^{14}C] FDV in male human subjects at steady state following oral dosing

Mean Radioactivity Contributions of FDV and Metabolites in Human (n = 7)											
Compounds	**Plasma**						**Feces + Urine (96.1% of dose) [a]**				
	3 h		**8 h**		**24 h**		**Feces (96.0% dose) [a]**		**Urine (0.11% dose) [a]**		**Total**
	% [^{14}C] [b]	**ng eq/mL [c]**	**% [^{14}C] [b]**	**ng eq/mL [c]**	**% [^{14}C] [b]**	**ng eq/mL [c]**	**% [^{14}C] [b]**	**% dose [a]**	**% [^{14}C] [b]**	**% dose [a]**	**% dose [a]**
M11	-	-	-	-	-	-	0.5	0.5	-	-	0.5
M12	-	-	<0.1	<2.0	-	-	0.7	0.7	-	-	0.7
M2a	-	-	-	-	-	-	22.4	21.6	-	-	21.6
M2b	-	-	-	-	-	-	20.2	19.4	-	-	19.4
[M3+M13] [d,e]	-	-	-	-	-	-	1.7	1.6	-	-	1.6
FDV	99.7	3700	99.8	3070	97.9	1050	51.9	49.8	100	0.1	49.9
M14	-	-	-	-	-	-	1.3	1.2	-	-	1.2
Total	99.7	3700	<99.9	<3072	97.9	1050	98.7	94.8	100	0.1	94.9

[a] % of dosed radioactivity
[b] % of sample radioactivity.
[c] FDV free form equivalent concentration expressed as ng/mL.
[d] Authentic standards IN00075213 for M3 and IN00075136 for M13 were available.
[e] M3 and M13 co-eluted. Based on the comparison of MS response with standards, M3 and M13 accounted for approximately 1.5% and 0.1% dose, respectively

It was concluded that biotransformation of faldaprevir in humans consists of mono-oxidation and, to a lesser extent, amide and carbamate hydrolysis.

Oxidation via CYP3A results in the formation of the two major metabolites M2a and M2b although CYP3A5 can also contribute to formation of M2a in subjects with high CYP3A5 content. CYP3A4 and CYP3A5 are present in liver and intestine. Additional studies led the applicant to conclude that the liver predominates over intestine for formation of M2a and M2b. M2a and M2b have extremely low permeability through cell membranes so the amounts expected to diffuse into the circulation are low. Both metabolites can be readily taken up into hepatocytes from the circulation by uptake transporters, which is consistent with the negligible levels found in human plasma despite the fact that they represent approximately 40% of the administered dose in faeces. Both are good substrates of uptake transporters (likely OATPs) and efflux transporters (P-gp and BCRP).

Direct hydrolysis of faldaprevir yields M12, M3 and possibly M13. M11 could be formed through amide hydrolysis of M2a/M2b and/or oxidation of M3. The acyl glucuronide (BI 203279; formed in some species) was not measurable in this study and was present only at very low levels in human plasma obtained from the Phase I single dose study. The applicant pointed out that plasma concentrations of glucuronides may not reflect organ concentrations (e.g. liver) because they may be excreted efficiently through bile and not appear in the plasma.

- **Inter-conversion**

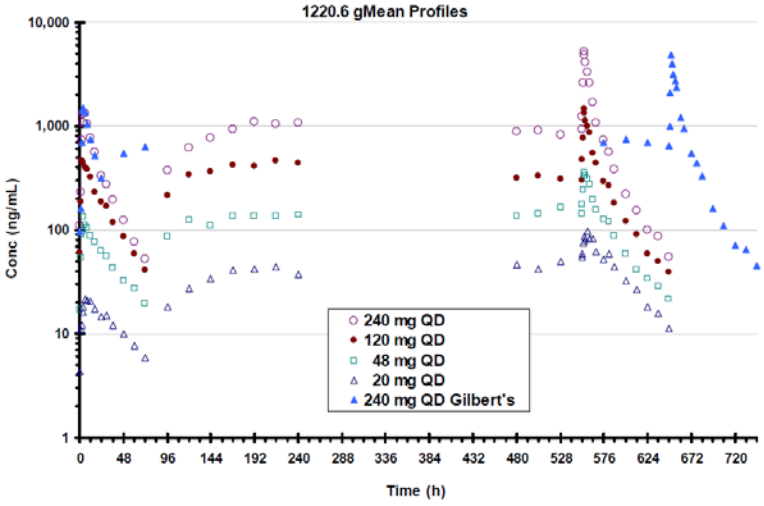
The sodium salt of faldaprevir is a single stereoisomer with 5 chiral centres. Module 3 states that the chiral centres are relatively stable with a very low risk of in-vitro epimerisation. The material used clinically comprises almost completely a single enantiomer. However, there is no discussion and there are no clinical data on the potential for in-vivo inter-conversion to occur.

- **Consequences of possible genetic polymorphism**

In **study 06** single (day 1) and multiple (days 4-24) daily doses of 20 mg, 48 mg, 120 mg and 240 mg BI 201335 NA (PiB given as an oral solution) were administered to four sequential groups of fasted

healthy male subjects without Gilbert's syndrome (GS) or UGT1A1 polymorphisms. A separate group of 9 male subjects was enrolled with Gilbert's syndrome (i.e. with reduced [~50%] bilirubin conjugation capacity due to impaired promotion of the gene encoding UGT1A1) of which 5 were homozygous for A(TA7)TAA (*28/*28) and 4 were heterozygous (*1/*28). These 9 subjects received 240 mg daily for 28 days.

AUC and Cmax of BI 201335 ZW increased in a greater than dose-proportional fashion after a single dose and at steady-state. The Tmax and t1/2 tended to be shorter at higher doses, while CL/F and Vz/F tended to decrease with increasing dose. Steady-state was achieved at ~6-7 days with accumulation ratios for AUC and Cmax about 2-fold and 3-fold, respectively. PK parameters for non-GS and GS subjects (GS) appeared to be similar after the first dose and slightly lower in GS subjects at steady state.



Single dose

Dose (mg)	$AUC_{0-\infty}$ [ng*h/mL]	$AUC_{\tau,1}$ [ng*h/mL]	C_{max} [ng/mL]	t_{max} [h]	$t_{1/2}$ [h]	CL/F [mL/min]
20 (N=6)	1,290	446	24.7	8.67	35.8	279
48 (N=6)	5,010	2,220	165	4.34	28.9	178
120 (N=6)	13,700	7,350	518	2.67	23.3	152
240 (N=5)	27,500	18,800	1,850	4.01	17.5	150
240 (GS, N=9)	--	19,400	2,130	3.89	--	--

Steady State

Dose (mg)	$AUC_{\tau,ss}$ [ng·h/mL]	$C_{max,ss}$ [ng/mL]	$t_{max,ss}$ [h]	$C_{min,ss}$ [ng/mL]	$t_{1/2,ss}$ [h]	$CL/F_{,ss}$ [mL/min]
20 (N=3)	1,750	99.3	5.33	52.5	30.9	188
48 (N=5)	5,600	400	3.80	147	30.1	161
120 (N=6)	17,000	1,700	2.17	314	24.9	130
240 (N=5)	53,800	5,680	2.20	765	22.3	84.3
240 (GS, N=8)	48,300	5,290	2.00	767	18.4	105

To understand the contribution of OATP1B1 to the disposition of faldaprevir the applicant evaluated exposures in HCV patients in study 05 with *SLCO1B1* genotypes. Two subjects with the *5/*15 genotype in the 240 mg QD dose group had higher exposure than the mean exposure of subjects with other genotypes. However, exposure in the two subjects with the *5/*15 genotype was still within the overall variability of faldaprevir exposure. No overall conclusion was drawn due to the limited number of subjects being homozygous or heterozygous *5 or *15 carriers but the data did not reveal a clear relationship between allelic variants of *SLCO1B1* and faldaprevir exposure.

- **Dose proportionality**

The faldaprevir AUC0-∞ and Cmax increased more than proportionately with dose. For example, in **study 13** on dosing with 40 mg and 120 mg SGC across a 12-fold range 40-480 mg the Cmax and AUC0-∞ increased about 139 times and 47 times, respectively, and the dose-normalised Cmax and AUC0-∞ increased about 12 times and 4 times, respectively. Dose proportionality was tested by using the power model. The point estimators and the 90% CI showed that AUC0-tz, AUC0-∞ and Cmax increased more than proportionately with dose.

- **Time dependency**

Faldaprevir steady-state is achieved only after ~5-7 days with accumulation ratios for AUC and Cmax about 2-fold and 3-fold, respectively.

- **Intra- and inter-individual variability**

There was moderate to high inter-subject variability observed. For example, in **study 10** regardless of oral formulation (SGC or PiB) the inter-subject variability was higher at the 240 mg vs. 40 mg dose level. At the 240 mg dose the CV% AUC0-inf was 54.6% for the SGC and 52.3% for PiB and CV% Cmax values were 68.4% and 62.8%, respectively. In **study 06** the inter-subject variability for AUC and Cmax on dosing with an oral solution in the fasted state was slightly higher for GS vs. non-GS subjects.

Dose (mg)		$AUC_{\tau,ss}$ [ng·h/mL]	$C_{max,ss}$ [ng/mL]	$t_{max,ss}$ [h]	$C_{min,ss}$ [ng/mL]	$t_{1/2,ss}$ [h]	$MRT_{po,ss}$ [h]	CL/F_{ss} [mL/min]	Vz/F_{ss} [L]
240 (N=5)	Mean	53,800	5,680	2.20	765	22.3	17.0	84.3	155
	CV%	40.8	38.0	20.2	39.3	19.8	13.2	46.9	39.3
	gMean	50,100	5,360	2.17	695	21.9	16.9	77.8	148
240 (Gilbert's, N=8)	Mean	48,300	5,290	2.00	767	18.4	16.3	105	171
	CV%	72.1	48.0	0	110	10.0	11.9	41.6	43.6
	gMean	41,200	4,890	2.00	555	18.3	16.2	94.5	150

In **study 59** inter-individual variability of AUC0-∞ and Cmax of faldaprevir showed GM CV% of 41.7 and 57.5% under fed conditions, 67.2 and 140% under fasted conditions and 63.4 and 122% under increased gastric pH conditions (with omeprazole).

Study 53 used a replicative cross over design and allowed for estimates of intra-subject as well as inter-subject variability. The degrees of intra-individual variability of Cmax for 40 mg x 3 capsules and 120 mg x 1 capsule were 32.2% and 39.2%, respectively. Those of AUC0-tz were 19.7% and 23.9%, respectively. The CV% values for each PK parameter were similar regardless of the formulation.

- **Pharmacokinetics in target population**

In the Phase 2 **study 02** in HCV-infected patients detailed PK sampling schedules were defined according to TN/TE status and viral load reductions on day 10.

- At day 14 plasma exposures on dosing TN patients with PiB increased supra-proportionally with dose but day 28 data indicated that there was no appreciable effect of adding PEG/RBV to faldaprevir at 120 mg or 240 mg QD.
- In contrast to the findings in **study 10**, the comparison between PiB (6 patients) and SGC (15 patients) showed that plasma exposure was slightly higher (35% for $AUC_{\tau,ss}$ and 15 % for Cmax,ss) with SGC on dosing with 240 mg QD. The applicant concluded that the two formulations provide similar exposures in HCV-infected patients.
- For TE patients receiving 240 mg as SGC QD the GM Tmax,ss, t1/2,ss and CL/Fss were similar between patients without cirrhosis and with compensated cirrhosis. With 240 mg SGC BID the

t1/2,ss was 14 h longer for patients with compensated cirrhosis and CL/F,ss was half that of patients without cirrhosis.

In **study 05** trough concentrations over 24 weeks showed that steady state was reached within one week and that PEG/RBV co-administration had no effect. Trough concentrations were 4-5-fold higher with 240 mg vs. 120 mg QD although CV% was 70% or more with once daily dosing vs. 20% for 240 mg BID dosing. There was also an intensive PK sub-study at week 10, which showed supra-dose proportionality. Faldaprevir GM trough concentrations were generally 25% higher in female vs. male patients treated with 120 mg QD but 60% higher for females vs. males who received 240 mg QD or BID. Trough concentrations were 40% higher for Asians (including Koreans) but 30% lower for blacks vs. whites. The applicant states that the higher overall exposure to faldaprevir in study 05 compared with study 02 reflected the greater proportion of female and Asian patients enrolled into study 05.

Healthy subjects vs. HCV-infected patients

At doses of 120 or 240 mg the faldaprevir $AUC_{\tau,ss}$ was ~2 to 4-fold higher in HCV-infected patients in study 02 than in healthy volunteers in study 06 regardless of race. The difference between healthy subjects and HCV-infected patients seemed to increase with dose up to 240 mg QD but there was little difference between subjects and patients for t1/2 values at each dose level. In contrast, dosing at 240 mg BID gave a GM $AUC_{0-\tau,ss}$ of 350,000 ng*h/mL in HCV-infected patients in study 02 compared to 314,000 ng/mL in healthy subjects in study 32 and 523,000 ng/mL in study 50.

The applicant discusses that the exposure difference between healthy and HCV patients could be partially explained by the difference in liver uptake and resultant change in volume of distribution between the two groups. Since the t1/2 appeared to be similar between healthy subjects and HCV patients the observed exposure difference seemed to be more related to the volume of distribution. The available literature suggests that chronic HCV infection may compromise the activity of transporters such as OATPs, resulting in less liver uptake of OATP substrates such as faldaprevir so that its plasma levels would be increased. However, other mechanisms such as alteration of efflux transporters or CYPs may also account for or at least contribute to this difference. As the uptake process is generally saturable at different dose levels for patients and healthy volunteers, it also may explain the rather more comparable AUCs observed on dosing healthy subjects and HCV-infected patients at 240 mg BID.

Table 3.1.1.2: 2 Comparison of steady-state exposure (gMean (gCV%)) to FDV in healthy volunteers (HV) and HCV patients at 120 mg and 240 mg

Study	Dose (mg)	N / Subject type	$AUC_{\tau,ss}$ [ng*h/mL]	$C_{max,ss}$ [ng/mL]	$C_{min,ss}$ [ng/mL]
1220.6	120 QD(PfOS)	6 / HV	16,000 (40.6)	1,550 (52.6)	310 (53.7)
	240 QD(PfOS)	5 / HV	50,100 (45.9)	5,360 (39.8)	695 (58.8)
1220.32*	240 BID (SGC)	23 / HV	314,000 (58.4)	36,800 (48.4)	16,300 (103)
1220.61	120 QD (SGC)	17/HV	29,900 (62.8)	2,780 (61.0)	512 (78.5)
1220.50	240 BID (SGC)	14/HV	523,000 (101)	50,400 (91.3)	40,000 (113)
1220.2	120 QD (PfOS)	7/HCV,TN	45,800 (85.4)	3,880 (82.8)	1,010 (97.9)
	120 QD (PfOS)	7/HCV,TE	43,400 (75.9)	4,170 (71.7)	863 (88.3)
	240 QD (PfOS)	6/HCV,TN	180,000 (42.0)	13,100 (38.2)	4,320 (42.3)
	240 QD (PfOS)	6/HCV.TE	164,000 (83.3)	15,400 (59.8)	3640 (105)
	240 QD (SGC)	15/HCV,TE	221,000 (82.2)	17,700 (81.7)	4,970 (124)
	240 BID (SGC)	15 /HCV,TE	350,000 (75.6)	32,200 (74.1)	25,500 (80.40
1220.5**	120 QD (SGC)	16/HCV, TN	48,400 (58.5)	3,640 (58.0)	1010 (80.8)
	240 QD (SGC)	12/HCV,TN	332,000 (57.7)	20,800 (47.8)	9,530 (69.4)

- **Population PK report**

The analysis was based on data collected from faldaprevir-treated patients in Phase 3 studies 07, 30 and 47. The factors most distinctly associated with faldaprevir exposure were dose, bilirubin, Japanese ethnicity, age, height and cirrhosis. Less influential but statistically significant factors were sex (higher in females), non-Japanese Asian ethnicity (higher vs. non-Asian), weight (higher at low weight) and UGT1A1*60 or *60*1 haplotype (paradoxically associated with lower exposure).

- *Dose* was the primary driver with ~ 5-fold increase in exposure associated with an increase in dose from 120 mg to 240 mg. Since faldaprevir was shown to be a substrate and inhibitor of P-gp and MRP2 efflux transporters and hepatic uptake transporters (OATP1B1, 1B3 and 2B1) at clinically relevant exposures the applicant concluded that disproportionate increases in plasma concentrations with dose reflect limiting intestinal efflux, primarily when intestinal concentrations are highest, and limiting hepatic uptake and subsequent metabolism and biliary excretion.
- *Japanese ethnicity* was associated with an approximate 2.6-fold increase in exposure independent of dose within the Asian race category that was not fully accounted for by body size. OATP expression and activity are reported to be lower in Japanese than Caucasian subjects.
- *Height* 150 cm was predicted to give 1.5 x plasma levels vs. the typical 170 cm patient while height 200 cm was predicted to give 0.61 x plasma levels.
- *Bilirubin* – Faldaprevir influences hepatic uptake of bilirubin via OATP1B1, inhibition of secondary metabolism via UGT1A1 and inhibition of efflux into bile via MRP2. Faldaprevir is a substrate for OATP1B1, 1B3, 2B1 and MRP2 so that bilirubin could competitively inhibit its hepatic clearance.

- *Cirrhosis* was associated with ~ 1.4 fold increase in exposure, which is not considered to be clinically relevant by the applicant.
- *Age* > 65 years was associated with a 2.5-fold increase in exposure regardless of dose vs. age < 40 years. The difference was < 1.3-fold for < 40 years vs. 40 to 65 years.
- *Gender* differences were largely driven by differences in body size. After adjusting for other significant covariates trough concentrations were 1.2-fold higher in female vs. typical male patients.
- *Renal impairment* was not a significant covariate after adjusting for age, gender and body size.
- UGT1A1*28 was not found to be a significant predictor of exposure but UGT1A1*60 homo- and heterozygous (*60*1) haplotype was. The *28 and *60 alleles are in linkage disequilibrium implying effects associated with one have a higher probability of being associated with the other. However, the fact that faldaprevir exposure was reduced in UGT1A1*60 SNP carriers is counter to the hypothesis that *28 and *60 carriers would be at risk for elevated bilirubin and indirectly, elevated faldaprevir. Nevertheless, this paradoxical finding was not considered to be clinically relevant as the predicted decrease in exposure was small.

- **Impaired renal function**

In **study 58** single doses of 480 mg faldaprevir (4 x 120 mg SGC fasted state) were administered to groups with normal renal function or mild, moderate or severe impairment based on eGFR [MDRD]. The results suggested that exposure to faldaprevir was higher in renal impairment but inter-subject variability was high and 90% CI were very broad. In the pooled analysis of Phase 3 studies, the GMR trough concentrations for the 60 to <90 mL/min/1.732 m2 group vs. ≥ 90 mL/min/1.732m2 group were 1.2 and 1.1 for doses of 120 and 240 mg, respectively. In the 30 to <59 mL/min/1.732m2 group GMRs were 1.1-fold (120 mg) and 1.2-fold (240 mg). Renal impairment was not found to be a significant covariate in the Phase 3 POP-PK models after adjusting for age, gender and body size and the applicant concluded that no dose adjustment is needed in patients with mild to severe renal impairment.

- **Impaired hepatic function**

In **study 02** in HCV-infected patients the steady state systemic exposure to faldaprevir was similar between 6 compensated cirrhotics (6 Child-Pugh A; GM $AUC_{T,ss}$ =243000 h*ng/mL, CV=75.8%) and 15 non-cirrhotics (GM $AUC_{T,ss}$= 221000 h*ng/mL, CV=82.2%) after multiple doses of 240 mg QD plus PEG/RBV. In the pooled analysis of Phase 3 the trough levels were 1.7- and 1.3-fold higher in cirrhotic (Child-Pugh A, N=47 at 120 mg; N=161 at 240 mg) compared to non-cirrhotic patients (N= 461 at 120 mg and N=910 at 240 mg). No studies were conducted in Child-Pugh B or Child-Pugh C patients. The applicant concluded that the increased exposure in cirrhotic patients is not clinically relevant with respect to AEs and no dose adjustment is required in patients with compensated cirrhosis.

- **Race**

In the pooled analyses of trough plasma levels from three Phase 3 studies (07, 30 and 47) the GMRs for steady state trough levels in Black vs. Caucasian patients were 0.95 (120 mg) and 0.8 (240 mg), indicating no differences. However, the steady state concentrations were 1.9-fold (120 mg group) and 2.3-fold (240 mg group) higher in Asian patients than in Caucasian patients. Japanese patients had higher exposures than other Asians while Asians living in Western countries had similar exposures as Caucasians although caution is needed since sample sizes are small.

Trough FDV concentration in Asian HCV patients from different regions based on pooled phase 3 analysis by dose

STAT	Asian (Global)	East Asian	Japanese	Korean	Taiwanese	Asian outside Asia	Caucasian	All patients
				120 mg				
N	101	96	50	28	18	5	362	509
gMean	2270	2310	2880	1810	1850	1560	1200	1360
gCV%	83.8	80.6	93.9	50.8	61.1	154	87.8	94.7
				240 mg				
N	212	205	158	30	17	7	770	1075
gMean	15600	15900	18300	10300	9330	8270	6750	7900
gCV%	116	117	98.4	68.9	384	62.0	99.0	117

East Asia =Japan + Korea + Taiwan.

In pooled phase 3 analysis, the trough ratios for Japanese vs. Caucasian were as 2.4 at 120 mg and 2.7 at 240 mg QD. These ratios were only slightly reduced after normalisation by weight (1.8 and 1.9, respectively), indicating that other factors must be involved in the ethnic differences. The applicant discussed that liver uptake of faldaprevir could partly explain differences between healthy subjects and HCV-infected patients as well as ethnic differences. The $t_{1/2}$ was similar for Caucasian and Japanese and the difference in clearance was probably due to the difference in Vdz/F. At 240 mg QD GM (CV%) $Vdz/F_{,ss}$ was 31.0 L (67.4%) in Japanese and 15.9 L (32.1%) in Caucasian patients. A decrease in liver uptake would result in a reduction of volume of distribution and hepatic clearance without an apparent difference in $t_{1/2}$. The available literature suggests that the activity or expression level of OATP is/are lower in Japanese vs. Caucasian, which is compatible with the difference in Vd_z/F and plasma exposures.

- **Weight**

In the pooled analysis of Phase 3 faldaprevir trough levels the GM values in patients < 50 kg were 1.7-fold (120 mg) and 2.2-fold (240 mg) higher vs. those weighing 50 kg to 80 kg. In patients weighing 80 kg to 100 kg, the trough levels were 30% lower compared to the 50 kg to 80 kg range at both dose levels. In patients > 100 kg the GM trough levels were 40 % (120 mg) or 50% (240 mg) lower than those in patients weighing 50 to 80 kg. The applicant concluded that no dose adjustment is required by body weight.

- **Elderly**

In the pooled analysis of Phase 3 studies, trough plasma concentrations were 1.5-fold (120 mg) or 2.1-fold (240 mg) higher in HCV patients aged > 65 years vs. 40 to 65 years. Plasma faldaprevir concentration was 30% lower in patients aged <40 years vs. 40 to 65 years. The population PK analysis gave close agreement with the observed values with a predicted exposure at age 21 years that was 0.67 times that at age 52 years. The age effect, especially at > 65 years, was related to the disproportionately high number of Asians, (particularly Japanese) in this age group, with a racial difference in trough exposures (see above).

	Age (years)	
	>65	40-65
N	60	886
% Female (N)	50.0 (30)	41.3 (366)
% Asian (N)	48.3 (29)	19.3 (171)
% Japanese (N)	43.3 (26)	14.2 (126)

	Race		
	Japanese	Asian	Caucasian
N	158	212	770
% Female (N)	47.5 (75)	46.2 (98)	40.9 (315)
% >65 (N)	16.5 (26)	13.7 (29)	3.77 (29)

The applicant considered that no dose adjustment according to age is needed.

- **Children**

There are no data at present.

- **Interactions**

Faldaprevir as a victim

- Faldaprevir exposure is likely to be affected by concomitant medications that inhibit or induce hepatic CYP3A. Since its metabolism is estimated to occur mainly in the liver, inhibition of CYP3A in the gut is not expected to change faldaprevir exposure.
- Faldaprevir glucuronide was not observed in plasma and excreta in the human [14C] ADME study and in-vitro studies indicated that glucuronidation was a relatively minor metabolic pathway that could be mediated by multiple UGT isoforms (UGT1A3, UGT1A4, and UGT1A8) so it is unlikely that faldaprevir exposure will be affected by drugs that inhibit UGTs.
- Faldaprevir is a substrate of P-gp, MRP2 and OATP1B1.
- At 120 mg QD it is likely that faldaprevir may saturate intestinal P-gp so that intestinal P-gp is not likely to limit the absorption of faldaprevir. However, P-gp may play a role in the biliary excretion of faldaprevir. It seems that multiple mechanisms are involved in the uptake of faldaprevir into hepatocytes, including passive permeability, a rifamycin SV inhibitable process (likely OATP), and a sodium-dependant transporter(s).
- Faldaprevir is not a substrate of BCRP, OATP1B3, OAT1, OAT3 or OCT2.

Faldaprevir as a perpetrator

- Faldaprevir inhibits CYP2B6, CYP2C8, CYP2C9, CYP3A and UGT1A1 and is a weak to moderate inactivator of CYP3A4.
- The applicant proposes that faldaprevir is unlikely to inhibit CYP2C8 when given at 120 mg QD but may weakly inhibit CYP2C8 when given at 240 mg QD.
- At 120 mg or 240 mg doses it is not expected that faldaprevir will inhibit CYP1A2, CYP2B6, CYP2C19 or CYP2D6.
- Faldaprevir can inhibit UGT1A1 when given at 120 mg QD.
- Faldaprevir may inhibit P-gp, BCRP, MRP2, OATP1B1 and OATP1B3 at therapeutic doses but is unlikely to inhibit OAT1, OAT3 or OCT2.

Co-administration with PEG/RBV

In the TN cohorts of **study 02** with PiB BI 201335 ZW the data obtained on Day 28 during combination therapy with PegIFN/RBV were similar to those on Day 14 during monotherapy for doses between 48 and 240 mg QD. In **study 014** using 120 mg SGC with dosing after breakfast plasma concentrations of RBV reached an almost steady state after 4 weeks with concentrations in the faldaprevir 240 mg QD group that were slightly lower than those in the placebo group.

UGT1A1 inhibition (faldaprevir + raltegravir)

In **study 65** 24 subjects (12 per gender) received raltegravir 400 mg BID with faldaprevir (240 mg BID on day 1 and then 240 mg QD) in the fed state except on the sampling days. Faldaprevir was not given alone in this study but the plasma levels at steady state were in keeping with expected values. AUCT,ss raltegravir increased from 4070 ng·h/mL to 11,100 ng·h/mL on co-administration and Cmax,ss increased from 1300 ng/mL to 3220 ng/mL. These increases were accompanied by decreases in raltegravir GM CL/Fss and Vz/Fss. Similar increases in GM AUCT,ss and Cmax,ss were observed for the metabolite raltegravir-glucuronide. From the data shown below the applicant concluded there was no clear effect by UGT1A1 genotype on baseline raltegravir PK but the effect of faldaprevir seemed largest in those carrying alleles indicative of a reduced UGT1A1 function.

Table 11.5.2.2: 3 Comparison of steady state raltegravir $C_{max,ss}$, $AUC_{\tau,ss}$, and $C_{12,ss}$ by UGT1A1 genotype after raltegravir alone and with faldaprevir

UGT1A1 genotype	Treatment		$C_{max,ss}$ [ng/mL]	$AUC_{\tau,ss}$ [ng·h/mL]	$C_{12,ss}$ [ng/mL]
*UGT1A1*1/*1* (N=7)	Raltegravir alone	gMean	1090	3730	37.5
		gCV [%]	149	111	49.7
	Raltegravir + faldaprevir	gMean	2420	9800	88.0
		gCV [%]	141	105	32.2
*UGT1A1*1/*28* (N=12)	Raltegravir alone	gMean	1530	4600	36.9
		gCV [%]	95.6	90.1	35.2
	Raltegravir + faldaprevir	gMean	3320	11 000	79.5
		gCV [%]	100	69.7	57.9
*UGT1A1*28/*28* (N=5)	Raltegravir alone	gMean	1130	3430	36.4
		gCV [%]	146	95.4	61.4
	Raltegravir + faldaprevir	gMean	4180	13 000	80.7
		gCV [%]	108	88.7	102

Inhibition of CYP2B6 and CYP3A4 by faldaprevir; effect of CYP3A induction on faldaprevir

Study 20 examined:

Group A The ability of 240 mg BID faldaprevir (days 7-19) to inhibit CYP2D6 based on PK efavirenz (EFV) after 50 mg alone on day 1 and with faldaprevir on day 14

Group B The effect of CYP3A4 induction by 600 mg QD efavirenz (evenings on days 10-18) on steady state PK faldaprevir (240 mg BID on days 3-18)

Effect of faldaprevir alone and in the presence of EFV on PK midazolam (MDZ; CYP3A4/5 substrate) after oral doses of 7.5 mg on days 1, 9 and 18

In both groups faldaprevir (SGC) was given in the fed state and with a first dose of 480 mg.

In Group A the PK parameters for efavirenz and 8-hydroxyefavirenz were not markedly affected by faldaprevir. The 90% CIs were 102-132% for EFV AUC and 91-123% for EFV Cmax. On Day 14 after administration of the 50 mg EFV dose the plasma concentrations of faldaprevir showed slight increases

in trough concentrations up until 96 h. The applicant stated this effect on faldaprevir may reflect transient inhibition of CYP3A4/5 by a single 50 mg dose of EFV.

In Group B PK faldaprevir showed lower exposures during co-administration with 600 mg QD EFV with 90% CI around GMs for AUC0-12,ss, Cmax,ss and C12,ss that were all below 84%. Midazolam exposure increased markedly when it was given with faldaprevir at steady-state, reflecting inhibition of CYP3A4/5. Co-administration with faldaprevir and EFV when each was at steady state on day 18 gave a substantial decrease in MDZ exposure, indicating that induction of CYP3A4 by EFV overcame inhibition by faldaprevir. The ratio of 1-hydroxyMDZ:MDZ was lower on co-administration with faldaprevir but higher when given with faldaprevir and EFV, consistent with net induction of CYP3A4/5

Inhibition of CYP isoenzymes and P-gp

Study 32 used a **probe drug cocktail** to evaluate the effects of faldaprevir (480 mg single dose and 240 mg BID to steady state; using SGC) as shown below.

Activity	Probe Drug[1]
CYP1A2	Caffeine
CYP2C9	Warfarin[2]
CYP2C19	Omeprazole
CYP2D6	Dextromethorphan
CYP3A4/5 (hepatic)	Midazolam (intravenous administration)
CYP3A4/5 (hepatic+intestinal)	Midazolam (oral administration)
P-glycoprotein	Digoxin

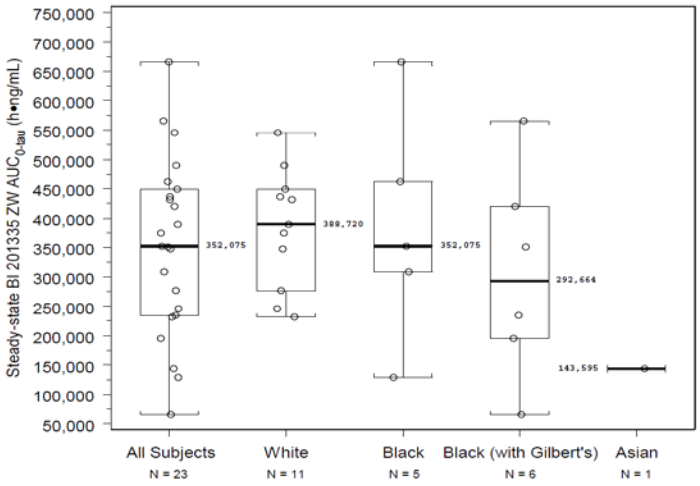
1 Probe drugs were administered orally unless indicated by other route (e.g., IV, intravenously)
2 Warfarin was co-administered with 10 mg Vitamin K orally, to mitigate possible effect of warfarin on coagulation

- There was no clinically relevant inhibition or induction of **CYP1A2** detected on co-administration of caffeine with faldaprevir at steady state.
- There was a 1.29-fold increase in S-warfarin AUC with 90% CI excluding 1 when it was given with steady state faldaprevir suggesting mild inhibition of **CYP2C9**.
- There were 1.58-fold and 1.54-fold increases in the AUCs of omeprazole and 5-OH-omeprazole (formed via **CYP2C19**), respectively, when omeprazole was given with steady state faldaprevir. This similar increase in omeprazole and its metabolite (with ratio unchanged) cannot be explained by inhibition of CYP2C19 and was thought to be consistent with faldaprevir inhibiting the CYP3A4/5-dependent minor pathway of omeprazole metabolism and CYP3A4/5-dependent 5-OH omeprazole metabolism. The applicant concluded that faldaprevir does not inhibit or induce CYP2C19. There were no significant differences in changes in ratios (Day 19 to Day 1) between CYP2C19 genotypes.
- There was no relevant inhibition or induction of **CYP2D6** detected on co-administration of dextromethorphan with faldaprevir at steady state. The extensive and intermediate metabolisers of CYP2D6 had 40% lesser effect of faldaprevir on the AUC ratios of dextromethorphan:dextrorphan vs. poor metabolisers.
- There was mild inhibition of hepatic **CYP3A4/5** (1.56-fold increase in AUC after IV MDZ) and moderate inhibition of hepatic and intestinal CYP3A4/5 (2.92-fold increase in AUC after oral MDZ) when given with steady state faldaprevir.

- A 2.19-fold increase in the digoxin AUC GMR was observed with steady state faldaprevir, suggestive of possible **P-glycoprotein** inhibition. The Cmax GMR was 2.05 also increased along with a substantial increase in t1/2 and decrease in clearance. This finding contrasted with in-vitro data showing that faldaprevir is a substrate of P-gp but had no effect on digoxin transport in two P-gp-expressing cell lines up to 20 µM. The applicant considered that the 480 mg loading dose followed by 240 mg BID would saturate intestinal P-gp so intestinal P-gp is not likely to limit faldaprevir absorption. The potential for inhibition of P-gp by faldaprevir at predicted intestinal concentrations cannot be assessed *in vitro* because of solubility. Since digoxin is also reported to be a substrate of other drug transporters (e.g. the OATP family) it remains unclear whether the increase in digoxin exposure was solely due to inhibition of P-gp by faldaprevir.

CYP genotypes and MDR1 genotypes were not informative in predicting changes in probe drug exposures when faldaprevir was administered. No genotype was associated with the steady-state accumulation of faldaprevir except that CYP2C19 wild type homozygotes had a 2-fold greater accumulation ratio for AUC faldaprevir vs. CYP2C19 heterozygotes.

At steady-state the faldaprevir AUC0-12h and Cmin were 22% and 33% lower for African Americans vs. whites. Further investigation showed that 6/11 African Americans had GS (e.g. homozygous for *28/*28 or *60/*60 UGT1A1). Steady-state faldaprevir median AUC0-12h for the 6 African Americans with GS was 25% lower vs. whites (N=11) and 17% lower vs. African Americans without GS (N=5).



Other DDI studies

In **study 49 darunavir plus ritonavir** (**DRV/r; 800/100 mg once daily**) was given alone and with 240 mg QD faldaprevir after a 480 mg loading dose.

- Co-administration increased the DRV AUCτ,ss and Cmax,ss by 15% and 28%, respectively, but the C24,ss decreased by 12%. The applicant concluded that faldaprevir has little additional effect on DRV plasma exposures in the presence of the strong CYP3A inhibitor ritonavir.
- Co-administration with faldaprevir at steady-state increased ritonavir AUCτ,ss by 37% while Cmax,ss increased 70% and C24,ss increased 39%.
- The faldaprevir GM AUCτ,ss and Cmax,ss were 115000 ng·h/mL and 8780 ng/mL, respectively. A comparison with study 06 indicated that co-administration with DRV/r increased AUCτ,ss 2.3-fold and increased Cmax,ss 1.6-fold (i.e. reaching values observed on dosing with 240 mg BID).

This was ascribed to CYP3A inhibition by ritonavir. On this basis, and taking into account the safety data obtained when dosing HCV-infected patients with 240 mg BID, the applicant recommended that the faldaprevir dose should be reduced to 120 mg QD when co-administered with DRV/r.

In **study 50 tenofovir disoproxil fumarate (TDF) 300 mg QD** was given alone and with faldaprevir 240 mg BID after a loading dose of 480 mg.

- The tenofovir (TFV) Tmax,ss and Cmax,ss values were not affected by co-administration but AUC0-24,ss and C24,ss increased by 22% and 47%, respectively, and the apparent oral clearance decreased vs. TDF alone. These changes were not considered to require TDF dose adjustment.
- The faldaprevir Tmax,ss was unaffected by co-administration but Cmax,ss, AUC0-12,ss and C12,ss decreased by 18%, 22% and 25%, respectively, whereas the apparent oral clearance increased vs. faldaprevir alone. These changes were not considered to require faldaprevir dose adjustment.
- Although there was no mechanistic reason to assess this combination the CSR states that unexpected effects of TDF on other drugs have been documented and also mentions that the biological base for the changes in TFV and faldaprevir PK observed on co-administration are unknown.

Study 56 assessed co-administration of faldaprevir (480 mg and then 240 mg QD with a **combined oral contraceptive (Microgynon; EE 30 µg and LNG 150 µg**). Exposures to EE and LNG were higher on co-administration with faldaprevir, with increases for both in AUCτ,ss, Cmax,ss and C24,ss. Tmax did not change substantially but values of t1/2,ss were longer (increasing by 3.0 h for EE and by 10.8 h for LNG). Statistical comparisons showed that none of the 90% CIs included 100%. The applicant ascribes the observed effects to inhibition of CYP3A and UGT1A1 by faldaprevir.

Relative bioavailability of EE and LNG in Period 2 compared with Period 1

Parameter	EE+LNG and faldaprevir (T)[1] Adj. gMean	EE+LNG (R)[2] Adj. gMean	gMean ratio T/R [%]	Intra-indiv gCV [%]	90% CI [%]
EE $AUC_{\tau,ss}$ [pg·h/mL]	1421	1008	141.0	8.1	133.8 to 148.5
EE $C_{max,ss}$ [pg/mL]	123.7	107.7	114.8	13.2	105.5 to 125.0
EE $C_{24,ss}$ [pg/mL]	32.72	19.09	171.4	10.5	160.2 to 183.3
LNG $AUC_{\tau,ss}$ [ng·h/mL]	117.0	83.28	140.5	4.6	136.4 to 144.8
LNG $C_{max,ss}$ [ng/mL]	8.721	7.565	115.3	6.1	110.8 to 119.9
LNG $C_{24,ss}$ [ng/mL]	3.737	2.429	153.9	8.2	146.0 to 162.1

[1]N=15
[2]N=16

Study 57 was conducted in subjects on stable dose addiction therapy (for at least 30 days pre-study) with the **opioids methadone or buprenorphine/naloxone** (Suboxone). Faldaprevir (480 mg loading dose and then 240 mg QD was given on days 2-9. Since methadone is metabolised by various CYP enzymes that include CYP3A4 and CYP2B6 and is a substrate for P-gp while buprenorphine is

metabolised by CYP3A4 and UGT1A1 the study examined the potential for faldaprevir to increase opioid exposures.

- Co-administration of faldaprevir and methadone resulted in < 20% increases in AUC0-24,ss, Cmax,ss or C24,ss for R-methadone or S-methadone with upper 90% CI for AUC ratios at 130% for each. There were no changes in OOWS or SOWS scores.
- Co-administration with Suboxone resulted in < 10% increases in AUC0-24,ss, Cmax,ss or C24,ss for buprenorphine and naloxone. For norbuprenorphine there were < 40% increases in these parameters but the upper 90% CI for AUC and Cmax ratios were ~190% but these changes did not result in changes in OOWS or SOWS scores.

Study 61 *Part 1* evaluated co-administration with **itraconazole** (inhibitor of CYP3A, P-gp and UGT1A1) on dosing with faldaprevir 120 mg BID loading dose and then 120 mg QD plus itraconazole 200 mg BID loading and then 200 mg QD.

- Plasma levels of itraconazole and 2-OH-itraconazole were measured only at 1.5 h before and after dosing on day 1. The post-dose plasma concentrations of itraconazole and the 2-OH metabolite reached 458 ng/mL (CV 57.5%) and 520 ng/mL (CV 35.4%), respectively, from which the CSR concludes that adequate itraconazole concentrations were achieved at the start of co-administration.
- Plasma exposures to faldaprevir were increased on co-administration with itraconazole in all subjects. Correspondingly the mean CL/Fss decreased by ~2-fold.

Table 2 Analysis of relative bioavailability of faldaprevir after multiple oral administration of faldaprevir alone or co-administration with mulitple doses of itraconazole

Pharmacokinetic parameter	Adjusted gMean ratio of test to reference treatment[1] [%][1]	90% CI of gMean ratio		Intra-individual gCV [%]
		Lower limit [%]	Upper limit [%]	
$AUC_{\tau,ss}$	198.6	182.4	216.1	14.2
$C_{max,ss}$	180.6	165.7	196.9	14.5

The CSR concludes that co-administration with itraconazole resulted in a larger fraction of the faldaprevir dose reaching the systemic circulation. Median Tmax,ss was comparable between treatments and the absorption slopes were similar, indicating that no substantial alteration in elimination kinetics occurred. The applicant concluded that the effect of itraconazole *was mainly confined to the bioavailability of faldaprevir and CYP3A4 inhibition and that relevant effects on disposition or elimination via inhibition of P-gp and UGT1A1 by itraconazole were not identified*.

Study 61 *Part 2* evaluated co-administration of faldaprevir (240 mg BID loading and 240 mg QD) with **atorvastatin (10 mg) and rosuvastatin (10 mg).**

- Co-administration increased atorvastatin AUC0-∞, AUC0-tz and Cmax by 9-fold, 13-fold and 33-fold, respectively. Mean CL/F was reduced from 12,100 mL/min to 1290 ml/min, t1/2 decreased from 10.8 h to 2.9 h and Vz/F decreased hugely from 11,300 L to 324 L.
- Ortho-OH-atorvastatin AUC0-∞ values were 171 ng·h/mL vs. 17.7 ng·h/mL while Cmax values were 32.4 ng/mL and 0.966 ng/mL for the test and reference treatments, respectively, with a ratio to parent drug ratio that was almost unchanged on co-administration. Para-hydroxyatorvastatin was measurable only on co-administration.

- Co-administration increased rosuvastatin AUC0-∞, AUC0,tz and Cmax by 15-fold, 17-fold and 33-fold for, respectively. Correspondingly the CL/F decreased from 6700 to 457 mL/min but t/12 was unchanged (15.6 vs. 14 h). The Vz/F decreased from 9050 L to 554 L. Plasma N-desmethylrosuvastatin AUC0-∞ values were 28.5 ng·h/mL and 3.61 ng·h/mL and Cmax values were 6.10 ng/mL and 0.494 ng/mL, respectively, but t1/2 was not affected. The ratio for metabolite vs. parent drug was 2-fold higher during monotherapy.
- On co-administration with atorvastatin the faldaprevir $AUC_{T,ss}$ and $C_{max,ss}$ values were 145,000 ng·h/mL (34.3%) and 12,900 ng/mL (27.8%), respectively and on co-administration with rosuvastatin the respective values were very similar at 136,000 ng·h/mL (43.9%) and 12,200 ng/mL (36.8%).

The applicant concluded that:

- Inhibition of OATP1B1/1B3-mediated hepatic uptake of the statins and their metabolites was the major contributor to the increases in plasma exposures and reductions in Vd on co-administration.
- The effect on atorvastatin in part reflected CYP3A inhibition by faldaprevir and inhibition of P-gp likely contributed to effects on parent drug and ortho-OH-atorvastatin.
- Some effect of CYP2C9 inhibition on rosuvastatin (<10% is metabolised) cannot be excluded but the high plasma levels on co-administration could have simply saturated the N-demethylation pathway, leading to the change in parent:metabolite ratio.
- Inhibition of BCRP by faldaprevir could have contributed to the overall effect.

CHMP's comment on pharmacokinetics

Drug and formulation

There are 5 chiral centres but Module 3 indicates that almost all of the material presented for clinical use consists of the sodium salt of a single enantiomer. In-vitro data suggest that chiral centres are relatively stable but there is no discussion of or data on the potential for in-vivo inter-conversion to occur.

Features of the pharmacokinetics

The absolute bioavailability of faldaprevir is not known which somewhat limits a full understanding of its pharmacokinetics. The applicant points out that in the mass balance study almost all the oral radioactive dose was recovered in faeces and the two major metabolites together accounted for about 40% of the radioactivity. On this basis it has been proposed that absolute bioavailability (F) is at least 40%.

At 120 mg and 240 mg doses Tmax is at 3-4 h. Cmax and AUC are higher with food (90% CI for AUCs exceed 1.00 with upper limits ~140%). Although faldaprevir was to be given without regard to food in Phase 3 studies, and this advice is proposed for the SmPC, in reality it was likely almost always given in the fed state because it was given with the morning dose of ribavirin, which is administered with food.

There was up to a ~4-fold increase in AUC and up to ~5-fold increase in trough concentrations between 120 mg and 240 mg doses in healthy subjects and in HCV-infected patients but this marked non-linearity does not appear to be mechanistically well understood. The applicant has attributed it to saturation and/or inhibition of clearance processes in the gut and liver. It is hypothesized that the tissue binding and/or observed enrichment of faldaprevir in hepatocytes observed *in vitro* impacts on faldaprevir PK. At lower doses (4 mg) it is presumed that faldaprevir is taken up from plasma into deep

tissue compartments (i.e. liver or other tissues) and subsequently gradually released back into the plasma during the elimination process. This gradual release may account for the long Tmax and t1/2. As the oral dose increases the uptake process (or tissue binding) would be gradually saturated so that more faldaprevir remains in the plasma, leading to a supra-proportional increase in plasma concentration with increasing dose along with shorter Tmax and t1/2 values. However, the applicant states that other processes such as saturation of transporters (i.e. P-gp) may also potentially contribute to the observed PK profiles.

At doses of 120 or 240 mg QD, the exposures ($AUC_{T,ss}$) to faldaprevir were ~ 3-fold higher in HCV-infected patients in study 02 than in healthy volunteers in study 06 regardless of race but these somewhat higher exposures in HCV patients were not evident on dosing with 240 mg BID. In both populations the fact that half-life decreased with dose indicates a larger effect on volume of distribution than on clearance. The applicant attributes this to faldaprevir being a substrate and inhibitor of OATP1B1, which is suggested to be compromised in HCV-infected patients.

The applicant proposes that the exposure difference between healthy and HCV patients could be partially explained by the difference in liver uptake and resultant change in volume of distribution between the two groups. Since t1/2 was similar between healthy subjects and HCV patients the observed exposure difference was thought to be more related to the volume of distribution. The available literature suggests that chronic HCV infection may compromise the activity of transporters such as OATPs, resulting in less liver uptake of OATP substrates such as faldaprevir so that its plasma levels would be increased. However, the applicant states that other mechanisms, such as alteration of efflux transporters or CYPs, may also account for, or at least contribute to, this difference. As the uptake process is generally saturable at different dose levels for patients and healthy volunteers, it also may explain the rather more comparable AUCs observed on dosing healthy subjects and HCV-infected patients at 240 mg BID.

Inter-subject variability increased with increasing dose of faldaprevir while intra-subject variability was lower. There is a need to discuss how this finding relates to the hypotheses described above.

In the POPPK model dose was used as a covariate on Ka and F and bilirubin as a covariate on CL/F. There do not appear to be any in-vitro or in-vivo data to support the inhibition of faldaprevir clearance by bilirubin and, as expected, it has been shown to be highly correlated to drug concentrations so it is hard to separate from an intrinsic effect of drug. The applicant has stated that other than metabolism-mediated clearance, faldaprevir is mainly eliminated through biliary excretion. It is also stated that faldaprevir has high membrane permeability and it is a substrate of liver uptake transporters OATP and another sodium-dependant transporter(s) as well as the efflux transporters (P-gp and MRP2). It is proposed that these features help explain the possible enrichment of faldaprevir in the liver and the significant biliary excretion.

The POPPK model was built on plasma concentrations obtained during the three placebo-controlled Phase 3 studies but these data do not provide definition of the PK profile and show high variability so they support only a limited understanding of parameters other than the steady state trough concentrations. It could be useful to use all PK data in a POPPK analysis (i.e. including the Phase I and 2 data rather than just the Phase 3 data) over the extended dose range to allow an improved understanding of the pharmacokinetics and a more robust model.

Metabolic fate and elimination

In the mass balance study it is acceptable that metabolite profiling in plasma was limited to 3, 8 and 24 h since radioactivity was predominantly associated with unchanged drug and the drug and radioactivity half-lives were similar.

The plasma exposure to unstable acyl glucuronide metabolites may have been under-estimated. Recognising this, the applicant provided in-vitro estimates of the expected amounts (16-19%) but these may be significant under-estimates as F is not known. Nevertheless, the applicant has determined that a number of UGTs (1A3, 1A4 and 1A8) contribute to metabolism and therefore it is accepted that interactions with UGT inhibitors are unlikely. Regarding the possible reactivity of these acyl glucuronides the applicant has shown that they are relatively stable and states that they are not circulating in significant amounts. However, since the samples were not treated to stabilise possible conjugates the applicant should provide more data on possible acyl glucuronide concentrations in stabilised plasma or in-vitro data that demonstrates good stability of conjugates in plasma.

The metabolites M2a and M2b may also be under-estimated and may contribute > 25% to the clearance. However, in-vitro studies identified CYP 3A4 to be the enzyme predominantly responsible and an itraconazole interaction study showed only a 2-fold increase in exposure.

Although the total clearance of this compound is low, it is not possible to agree with the applicant that faldaprevir is a low clearance compound as protein binding is high and clearance of unbound drug (CL/fu), which is the important parameter, will be much higher.

Covariates affecting pharmacokinetics

A number of covariates have been identified as affecting pharmacokinetics but the applicant has dismissed them as not being clinically significant such that no dose adjustment is proposed regardless of whether the recommended daily dose is 120 mg or 240 mg. The following issues require further discussion and justification taking into account also the safety and efficacy observed in the various subsets:

- In the pooled Phase 3 studies, trough plasma faldaprevir concentrations were ~ 1.9 to 2.3-fold higher in Asians vs. Caucasians or Blacks but the simulations suggested up to an 8.5-fold increase in exposure (i.e. in an extreme individual). If the applicant's explanation is correct then this higher plasma exposure does not mean necessarily higher liver concentrations. The higher efficacy in Asians cannot be ascribed to PK since there was also a major HCV genotype factor (i.e. most had GT1b).
- In Phase 3 studies, trough faldaprevir concentrations were ~ 1.6-fold higher in females vs. males.
- Across the studies 5% (120 patients) were aged at least 65 years but none was > 75 years. In the pooled analysis of Phase 3 studies, trough plasma faldaprevir concentrations were 1.5-fold (120 mg) or 2.1-fold (240 mg) higher for those aged > 65 years vs. 40-65 years and 30% lower in those < 40 years vs. 40-65 years. The comparison between patients aged < 40 years and > 65 years showed that advancing age is associated with a 2.5-fold increase in exposure regardless of dose. The effect of age should be reported for sub-categories (in this case 65-< 70 and ≥ 70 years).
- Study 58 showed 1.8-fold and 1.7-fold increases in AUC in those with moderate or severe renal impairment despite the fact that < 0.1% of an oral dose is recovered in urine. Renal impairment was not found to be a significant covariate after adjusting for age, gender and body size in the POPPK analyses (this is often the case and appears to be due to differences in the methodology). The applicant acknowledges that renal impairment can affect uptake and efflux transporters as well as metabolic enzymes in the liver and gut and proposes that effects on OATP1B1 and P-gp explain the higher plasma exposures in moderate or severe renal impairment.

  In Phase 3 trials 907 and 46 patients had mild (eGFR 60-89 mL/min/1.73 m2) or moderate (eGFR 50-59 mL/min/1.73 m2) renal impairment at baseline. The trough GMRs vs. controls were 1.2 for mild and 1.1 for moderate renal impairment at 120 mg and 1.1 and 1.2, respectively, for the 240 mg dose. Furthermore, 60% and 40 % of the patients with CrCL 30 to < 60 mL/min in the 120 mg

and 240 mg dose groups, respectively, had body weight < 50 kg vs. <1% of those with normal renal function. These data suggest that low CrCL values, particularly in 30 to < 60 mL/min group, were partially driven by low body weight. When normalised by body weight, the trough exposure difference between patients with mild or moderate renal impairment vs. patients with normal renal function based on CrCL was diminished. In contrast, the trough exposure difference between renal function groups based on eGFR assessment was much less influenced by body weight.

However, the SmPC states that no dose adjustment is needed in severe renal impairment and there are no data to support this.

- In study 32 faldaprevir AUC0-12h and Cmin were 22% and 33% lower for African Americans vs. whites. For the 6/11 African Americans who had GS (e.g. homozygous for *28/*28 or *60/*60 UGT1A1) the steady-state AUC0-12h was 25% lower vs. whites and 17% lower vs. African Americans without GS. In the POPPK analysis the statistically significant factors included UGT1A1*60 or *60*1 haplotype (paradoxically associated with lower exposure). It is stated that for UGT1A1A 68% had a possibly reduced activity compared to 7% for UGT1A1B while for UGT1A1C 39% and 10.5% had a possibly reduced or reduced activity, respectively, compared to 51% and 22% for UGT1A1P. However, in study 06 the faldaprevir PK parameters for non-GS and GS subjects appeared to be similar after the first dose and only slightly lower in GS subjects at steady state. These findings require further consideration for safety and efficacy, including the efficacy data in blacks.
- Study 05 attempted to further understand the possible contribution of OAT1B1 to faldaprevir PK. Two subjects with the *5/*15 *SLCO1B1* genotype in the 240 mg QD dose group had higher exposure than the mean exposure of subjects with other genotypes but no overall conclusion can be drawn due to the limited number of subjects being homozygous or heterozygous *5 or *15 carriers. The applicant should discuss how this matter might be explored further in light of the results of the DDI studies and the proposals that have been regarding the influence of OAT1B1 on faldaprevir exposure.
- In study 32 CYP2C19 wild type homozygotes had a 2-fold greater accumulation ratio for AUC faldaprevir vs. CYP2C19 heterozygotes. The applicant should consider the safety implications of this finding when the higher dose is used.

Drug-drug interactions

The applicant conducted a range of in-vitro and in-vivo studies to evaluate the potential for drug interactions to occur. Calculations are provided based on in-vitro data and the basic model and compared with in-vivo data, where available. As this compound is highly protein bound it is recommended to set unbound fraction (fu) to 0.01. Thus, target concentrations to test for inhibition would be ~2 and 12 µM, based on plasma Cmax values after 120 mg and 240 mg, respectively. The applicant should review the sufficiency of the studies based on setting fu to 0.01.

A number of in-vivo studies have been performed including one cocktail study, at the higher dose of 240 mg BID. In the SmPC the applicant proposes contraindicating use of faldaprevir at either dose with strong CYP3A inducers (but efavirenz [EFV] is not listed) and with all HMG-CoA reductase inhibitors. At the 240 mg dose only co-administration of faldaprevir with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events are also contraindicated. At the 120 mg dose such co-administrations are advised with caution. The rationale for the distinctions between the two doses requires further explanation and justification.

The ability of faldaprevir 240 mg BID to inhibit UGT1A1 was demonstrated by the effect on raltegravir (400 mg BID) plasma concentrations. Despite the magnitude of the effect the draft SmPC does not suggest any dose adjustment even for those with reduced UGT1A1 activity. The safety data for patients who received these agents in study 19 require review before accepting that the increment in raltegravir exposures (especially for those with reduced UGT1A1 activity) has no clinical importance.

Co-administration with EFV indicated that CYP3A induction reduced faldaprevir plasma concentrations. In addition, induction of CYP3A by EFV overcame inhibition by faldaprevir based on the effect on midazolam. Study 19 showed lower efficacy when these agents were co-administered to HCV/HIV co-infected patients even though 240 mg QD faldaprevir was used. The SmPC advice regarding use with EFV is not appropriate and it should advise avoidance of co-administration.

The interaction with IV and PO midazolam demonstrated the ability of faldaprevir to inhibit CYP3A in liver and gut. In the cocktail study there was no relevant effect of faldaprevir on AUC or Cmax of dextromethorphan (based on GMRs and 90% CI) but the ratio dextromethorphan:dextrorphan was reduced on co-administration. This should be discussed.

Co-administration with digoxin may not be entirely due to an ability of faldaprevir to inhibit P-gp but, whatever the mechanisms, monitoring of digoxin levels has been advised in the SmPC.

Inhibition of CYP2C8 and BCRP has not been studied in vivo but faldaprevir shows strong inhibition of these enzymes (Kiu = 3.45 µM for CYP 2C8 and BCRP IC50= 0.05 µM) and therefore a specific in-vivo study should be performed. As a possible alternative, a well-constructed PBPK model which incorporates all the in-vitro data and which shows accurate prediction of the available in-vivo interaction data may be acceptable in lieu of clinical data. This model could also be used to model interactions for once daily dosing of 120 and 240 mg.

In study 49 faldaprevir had little additional effect on DRV plasma exposures in the presence of the strong CYP3A inhibitor ritonavir. However, co-administration with faldaprevir increased ritonavir $AUC_{T,ss}$ by 37% while $C_{max,ss}$ increased 70% and $C_{24,ss}$ increased 39%. The implications for this finding when faldaprevir is given with other PI/r combinations require discussion.

Co-administration with a COC indicated that faldaprevir will not impact on contraceptive efficacy. However, the possible long-term effects of the higher than usual plasma concentrations of EE and LNG should be discussed.

In general, study 57 showed higher exposures to faldaprevir in subjects taking methadone or Suboxone compared to monotherapy in study 06. The applicant considered that the comparison is likely confounded by the different populations (male and female opiate maintenance vs. male healthy subjects) and formulations (capsule vs. oral solution) but these potential confounders require further explanation and exploration.

While it is agreed that faldaprevir should not be co-administered with any statin (this is contraindicated at either faldaprevir dose) this fact could be expected to severely limit the utility of faldaprevir in the general HCV-infected population.

In the draft SmPC the applicant has placed the results of the cocktail study in section 5.2 and not mentioned some of the drugs (e.g. itraconazole, which doubles faldaprevir AUC) in 4.5. There is a table of presumed interactions and then a table of the results of DDI studies. While it is agreed that section 4.5 should carefully describe instances where there are and are not clinical data, all of the information should be in one table. If there are different implications according to the dose of faldaprevir then this should be highlighted in the table and text. This table should include the cocktail study results that imply no clinical significant interaction will occur and/or these findings could be described in the text of section 4.5.

Pharmacodynamics

- **Primary pharmacology**

o Faldaprevir is a competitive inhibitor of HCV genotype (GT) 1a and 1b serine proteases and it is a reversible inhibitor of GT 1b serine protease. Ki values of 2.6 nM and 2.0 nM were reported from steady-state velocity analyses using the NS3-NS4 protein of GT 1a and 1b, respectively. In a validated surrogate cell-based assay faldaprevir inhibited HCV RNA replication of GT1a and GTlb with mean EC50 values of 6.5 nM and 3.1 nM, respectively.

o Data from a fluorogenic assay with purified full-length NS3/4A heterodimer protease showed inhibition of enzymes from GT 4a, 5a, and 6a with IC50 values of 9.0 ± 2.3 nM, 10 ± 2 nM and 17 ± 2 nM, respectively.

o Activity against GT 2 and 3 NS3/NS4A serine proteases was considerably less than that against the GT 1 enzyme in a radiometric assay. For GT 2b, 2ac and 3a the IC50 values derived from the assay were 240 ± 150 nM, 290 ± 20 nM and 1300 ± 300 nM respectively.

o The EC50 value of FDV increased 8-fold in the presence of 50% human serum.

IC50 values of > 30 µM were obtained against **human serine protease** (leukocyte elastase and cysteine protease cathepsin B). Against a panel containing 36 human proteases no inhibition was observed except against the unrelated aspartyl protease cathepsin D (IC50 = 30.3 µM), hepatic acyl CoA-cholesterol acyltransferase (IC50 = 2.4 µM) and the phosphatase PP2B (IC50 = 9.17 µM). These IC50 values are well above the cellular IC50 for faldaprevir observed in in-vitro efficacy models (3.5 nM - 5 nM).

The two major metabolites of faldaprevir in man (M2a and M2b) are pharmacologically active (2- to 4-fold more potent than faldaprevir in GT 1a and 1b NS3 protease inhibition assays. Thus they could potentially contribute to the clinical efficacy of faldaprevir in the liver. However, considering their expected low local exposure in the liver, the applicant concluded that any contribution from M2a and M2b to clinical efficacy would be limited.

In a combination study with **ribavirin** there was an additive antiviral effect. The cytotoxicity of ribavirin was not enhanced by faldaprevir.

In GT 1b **mutations encoding key amino acid substitutions** were found independently at position R155, A156 or D168 of the NS3 protease. R155Q conferred a 68-fold reduction in sensitivity to faldaprevir, A156V and A156T conferred 190 and 270-fold reductions while D168A and D168V conferred 690- and 1000-fold reductions, respectively. Faldaprevir inhibited NS3/4A protease GT 1b resistant mutants A156T and D168V with IC50 values of 760 ± 160 nM and 1100 ± 210 nM, respectively, which compare with 3.3 (± 0.9 nM) for wild types.

There was in-vitro selection of R155K mutants in the GT1a but not in the GT1b replicon system, which was consistent with the differences in the resistance profile observed during short term monotherapy. The R155K mutant had a similar effect on the susceptibility of the GT 1a and 1b replicons with 350- and 360-fold shifts in the EC50, respectively. The applicant stated that the R155K mutant did not emerge during selection in GT 1b replicons because the codon would require two nucleotide changes, whereas the corresponding codon in GT1a replicons only requires 1 nucleotide change.

Drug sensitivity assays revealed that:

(i) R155 variants resulted in a broad range of cross-resistance to all PIs and

(ii) Variants at position D168 exhibited cross-resistance to faldaprevir and the macrocyclic class of PIs such as simeprevir but not to the covalent inhibitors telaprevir (TVR) and boceprevir (BOC).

For **NS3/4A variants reported to be resistant to other PIs**:

(i) There was no cross resistance to faldaprevir for individual variants at V36 and T54 and the A156S variant, which have been shown to be important in conferring resistance to TVR and BOC.

(ii) The natural variants at Q80, which confer resistance to the macrocyclic inhibitor simeprevir, remain susceptible to faldaprevir.

iii) The A156T variant showed cross-resistance between faldaprevir and the ketoamide inhibitors TVR and BOC.

iv) R155 substitutions reduced sensitivity to all compounds, albeit GT1b R155Q only had an EC50 fold change with faldaprevir in the in-vitro assay.

v) D168 substitutions reduced sensitivity to both faldaprevir and SMV while I/V170T conferred a 5-fold EC50 change for FDV and 1.4-fold for SMV.

The potential for **drug-drug interactions between HCV and HIV protease inhibitors** was evaluated *in vitro* using an HIV-1 viral replication assay. The antiviral activity of five different HIV-1 protease inhibitors in the presence of fixed doses of faldaprevir (2.5 and 5µM) was evaluated. These concentrations represent approximately 50 and 100% of the Cmax value achieved with the 120 mg QD dose of faldaprevir in TN patients. Both concentrations of faldaprevir had no effect on the antiviral activity of the HIV-1 protease inhibitors tested (amprenavir, atazanavir, lopinavir, ritonavir and darunavir).

The antiviral activity of faldaprevir in the presence of five different HIV-1 protease inhibitors (amprenavir, atazanavir, lopinavir, ritonavir and darunavir) was tested. At sub-cytotoxic concentrations *in vitro* (10 µM or less), the HIV-1 protease inhibitors did not substantially affect the activity of faldaprevir against HCV. The maximum change in EC50 observed was only a 0.4-fold decrease. Hence there was no evidence that any of the HIV protease inhibitors reduced the antiviral activity of faldaprevir in any experiment and no synergistic cytotoxicity was observed.

In the first part of study 02 96 patients with HCV genotype 1 (1A, 1B or mixed 1A/1B only) and ≥ 100,000 IU/ml at screening were enrolled. TN cohorts (I to IV) received faldaprevir or placebo monotherapy for 14 days. Patients with <1 log10 VL decrease on day 10 discontinued faldaprevir at day 14 while all others added PEG/RBV from day 15-28. The HCV sub-genotype was GT1 non-A/B for 4/34, 1A for 12/34 and 1B for 18/34. TE patients (without cirrhosis VI-X or with compensated cirrhosis XI-XII) received faldaprevir and PEG/RBV for 28 days as shown in the table.

Cohort	Dosing schedule	Formulation
VI	48 mg QD	PiB
VII	120 mg QD	PiB
VIII	240 mg QD	PiB
IX	480 mg QD (240 mg BID)	SGC
X	240 mg QD	SGC
XI	240 mg QD	SGC
XII	480 mg QD (240 mg BID)	SGC

- Virologic response (VR; ≥ 2 log10 reduction in plasma HCV RNA level from baseline any time up to Day 14 for TN or Day 28 for TE) occurred in 25/26 TN who received faldaprevir and none who received placebo. All 49 TE patients displayed VR. In general, decreases in VL were greater for patients treated with higher doses of faldaprevir.
- During monotherapy 4 TN patients had a RVR. All TN cohorts showed a significant rebound of VL after the maximum decrease was reached but the smallest rebound was seen for Cohort IV. After adding PEG/IFN at Day 14 the VL decreased until the end of treatment (Day 28).
- For TE patients without cirrhosis 12/49 had RVR (BLLD at Day 28). Combination treatment produced a rapid decrease in HCV RNA levels. VL levels at the end of treatment were not noticeably between the different cohorts with no difference between 240 mg QD PiB and 240 mg QD SCG.
- For TE patients with compensated cirrhosis 5/13 had a RVR and no patient showed breakthrough during treatment. Both Cohorts showed a rapid decrease in HCV RNA (~ 3.5 log10 within 2 days).

- **Secondary pharmacology**

The TQT **study 16** evaluated single doses of 480 mg and 1200 mg faldaprevir, placebo and moxifloxacin 400 mg administered in the fasting state in a 4-way crossover design. The safety (but not ECGs) of 1200 mg faldaprevir (6) vs. placebo (2) was assessed in female subjects before enrolling 28 male and 20 female subjects into the crossover part, in which the 480 mg dose gave broadly comparable exposures by gender (AUC0-24: females 73900 ng·hr/mL, males 65300 ng·hr/mL; Cmax: 6360 ng/mL vs. 5900 ng/mL). The analysis QTcI for moxifloxacin vs. placebo yielded a mean QTcI prolongation of 15.1 ms (90% CI: 13.07, 17.16), which confirmed assay sensitivity. For both genders, the absence of a clinically relevant increase in QTcI following dosing of 480 mg and 1200 mg faldaprevir was confirmed and there was no relationship between exposure to faldaprevir and prolongation of QTcI.

- **Relationship between plasma concentration and effect**

In the first part of **study 02** the TN patient group demonstrated a clear concentration- and time-dependent reduction in HCV VL. Overall, the TE group demonstrated little concentration dependency, as indicated by small absolute values for the slope, but a notable decrease in VL up to Day 6, as indicated by the minimum intercept of -3.96 calculated for this treatment day. In **study 014** no statistically significant correlation was observed between faldaprevir PK parameters and VL reduction but there was a significant correlation between $C_{max,ss}$ and $AUC_{\tau,ss}$ and increase in total bilirubin from baseline to day 29.

Phase 3 SVR12

All patients who received at least one dose of faldaprevir and provided at least two quantifiable trough values were analysed for SVR12 exposure-response using logistic regression. All analyses were adjusted for race as Asians predominantly carry GT1b for which response rates are higher. There were no significant exposure-response relationships identified among GT1a-infected patients. For HCV GT1b, a significant exposure-response relationship was identified for the TE Partial Responders ($p = 0.0169$) such that SVR12 decreased from 73% in Q1 to 33% in Q4. Given these unexpected results observed with GT1b Partial Responders it cannot be ruled out that results falling in the upper quartiles of exposure with 240 mg could have been confounded with tolerability issues leading to inconsistent adherence.

Phase 3 AEs of interest

There were 521 patients treated with 120 mg QD and 837 with 240 mg QD in the placebo-controlled studies 07, 30 and 47.

- Adverse skin reactions (Grade 2 DAIDS) were adjudicated by an independent committee and showed no significant relationship to faldaprevir. There was a higher rate of skin AEs in Asians but this effect is likely not due to the increased exposure observed in Japanese vs. non-Japanese patients.
- Rates for GI AEs increased with increasing dose of faldaprevir, increased slightly with increasing duration of 240 mg QD and increased significantly with increasing faldaprevir plasma concentrations.
- The incidence of bilirubin-associated AEs increased with faldaprevir dose (120 mg vs. 240 mg), duration of 240 mg QD treatment (12 weeks vs. 24 weeks) and increasing plasma concentration. These results were expected, due primarily to increases in indirect bilirubin and are consistent with competition between bilirubin and faldaprevir for common clearance pathways.

- **Genetic differences in PD response**

Nearly all patients enrolled into the Phase 3 placebo-controlled studies had IL28B genotype documented. SVR rates were lower in subjects with the C/T and T/T genotypes compared to those with the C/C genotype, particularly in TN patients. Among TN and TE patients of any IL28B genotype higher SVR rates occurred with faldaprevir vs. placebo.

CHMP's comment on pharmacodynamics

The two major metabolites of faldaprevir in man (M2a and M2b) were 2- to 4-fold more active than faldaprevir in HCV Genotype 1a and 1b NS3 protease inhibition assays. The applicant states that they will likely achieve low concentrations in the liver so they would make a limited contribution to clinical efficacy. However, the applicant should discuss any circumstances in which intra-hepatic metabolite levels could increase such that they could play a significant therapeutic role.

While there were no significant exposure-response relationships identified for HCV GT1a-infected patients there were inverse relationships observed for GT1b in TN and TE Partial Responders. The applicant states that this could reflect lower adherence at the higher dose and/or AEs but the data to support his are not shown. The applicant should investigate further.

The investigation of the virological properties of faldaprevir has been comprehensive and has taken into account ongoing developments.

Although faldaprevir was 2-fold more active against GT1b vs. GT1a *in vitro* the mean EC50 values were still in the single digit nM range. There was a lower SVR12 rate for GT1a vs. GT1b when faldaprevir was added to PEG/RBV but the difference between genotypes was less than observed for PEG/RBV alone. In study 02 faldaprevir monotherapy was given to TN and TE patients with known GT1a or GT1b status. Protocol-defined VR was observed in 25/26 TN patients, all 49 TE patients without cirrhosis and all 13 TE patients with compensated cirrhosis but the magnitude of effect on VL according to GT1a or GT1b and rebound rates by sub-genotype are not shown. These data should be provided and discussed along with details of the HCV associated with rebound.

Specific GT1a and 1b NS3 RAVs have been identified as being associated with major reductions in susceptibility to faldaprevir. Thus far the D168V variant has been found to confer the greatest reduction in susceptibility in GT1a and GT1b. The R155K RAV emerged only in GT1a and increased EC50 ~350-fold. RAVs at R155 or D168 were present at baseline in 0.8% (18/2259) of Phase 3

patients with results so it is not possible to determine their possible effect on treatment outcomes. Similarly, no single baseline NS3/4A polymorphism was associated with a reduction in SVR in an analysis across all treatment groups.

Nevertheless, the T344I baseline polymorphism was highly represented in GT-1b and was associated with a reduction in the RVR and SVR12 rate in all clinical studies. The influence of T344I polymorphism on the antiviral activity of faldaprevir should be further investigated.

The predominant treatment-emergent NS3 amino acid substitutions associated with lack of SVR12 in Phase 3 included the GT1a NS3 R155K substitution, which also emerges with telaprevir or boceprevir treatment, and the GT1b D168V RAV. The latter has not been reported to emerge with telaprevir or boceprevir treatment and HCV replicons expressing this variant are fully sensitive to telaprevir or boceprevir. However, D168V variants are cross-resistant to macrocyclic NS3/4A protease inhibitors such as simeprevir.

The dose of faldaprevir had little effect on the frequency of emergence of R155 or D168 variants in GT-1a TN patients. The frequency of R155 variants was slightly greater in GT-1b TN patients receiving the 120 mg dose vs. the 240 mg dose. The possible clinical relevance of these findings requires discussion.

The R155Q mutation, alone or in combination with D168V, was detected in a pooled analysis of post-baseline virus populations in GT-1b patients. Data from SDM studies and clinical NS3 variants carrying the R155Q + D168V combination showed a significant effect on the EC50 (FC) and replicative capacity of such mutants in comparison with those carrying R155Q alone. The applicant should discuss the potential clinical relevance of these findings.

Faldaprevir maintained activity *in vitro* against other predominant single amino acid substitutions associated with resistance to telaprevir or boceprevir (NS3 mutants V36A/L/M, T54A/S, V55A, A156S, I/V170A). HCV replicons expressing faldaprevir-associated resistance substitutions remained fully sensitive to interferon-alfa and ribavirin, as well as other direct-acting antivirals with different mechanisms of action, such as NS5B polymerase inhibitors. No clear evidence of treatment-emergent substitutions in the NS3 helicase domain or NS4A coding regions was observed in samples from patients who did not achieve SVR12.

In Phase 2 the largest difference in RVR was observed in TE patients with GT-1a containing NS3 Q80K but this was not observed in the Phase 3 studies, thus suggesting that Q80K did not significantly reduce SVR in TN or TE patients. Furthermore there was a discrepancy with regard to the effect of Q80K on susceptibility to faldaprevir between *in vitro* and *in vivo* studies. The applicant should further address these discrepancies.

Among 477 samples from patients without SVR in the Phase 3 placebo-controlled studies there were 304 with R155 RAVs and 193 with D168 RAVs. In the LOCF 78.3% had R155 RAVs, whereas only 51.3% had D168 RAVs one year after virological failure. The estimated time to outgrowth of wild type virus in 50% of cases and loss of GT1a R155 substitutions was 280 days and loss of GT1b D168 substitutions was 145 days. As stated by the applicant, lack of detection of a substitution based on a population-based assay does not necessarily indicate the substitution has declined to the pre-treatment level. The long-term clinical impact of the emergence or persistence of detectable faldaprevir resistance-associated substitutions is unknown. No data are available regarding faldaprevir efficacy among patients who were previously exposed to a HCV direct acting antiviral, or who previously failed treatment with a regimen containing faldaprevir.

The TQT study in healthy subjects achieved plasma Cmax and AUC values after the 1200 mg dose that were considerably lower than those observed in the HCV-infected patients at the recommended doses.

The applicant should discuss the relevance and adequacy of the data from this TQT study to use in HCV-infected patients.

Clinical efficacy

All completed CSRs involved co-administration of faldaprevir (as 120 mg SGC) with **Peg-IFN alfa 2a (Pegasys) and ribavirin (Copegus).** Oral dosing was recommended to be with food.

Dose response studies

Subsequent to **studies 02 and 014** two Phase 2 studies (**05 and 40**) were conducted to evaluate doses and durations of faldaprevir when co-administered with PEG/RBV as shown in the table.

Study 05 5 Interim analyses	HCV GT1 24 weeks plus 24 or 48 weeks of PEG/RBV +/- 3-day lead-in with PEG/RBV	Multi-centre, randomised, DB, PC	FDV SGC 120 mg and 240 mg QD Pegasys + Copegus	TN 120 mg QD with lead-in: 240 mg QD with/without lead-in TE 240 mg QD with/without lead-in 240 mg BID with lead-in	HCV GT1 (1a, 1b or mixed 1a/1b)
Study 40	12 vs. 24 wks FDV + 24 or 48 wks PEG/RBV	Multi-centre, randomised, OL	FDV 240 mg QD Pegasys + Copegus	FDV 240 mg QD for 12 w FDV 240 mg QD for 24 w	HCV GT1 TN only

Study 05

Four of the six faldaprevir groups had a 3-day lead-in with PEG/RBV. At Week 24 TN patients in the 240 mg QD groups and TE patients in the 240 mg QD group with lead-in who had HCV < LLOQ at Week 4 and < LLD up to Week 20 were re-randomised stop all treatment at week 24 or continue with another 24 weeks PEG/RBV (total 48 weeks).

TN patients had higher SVR24 rates with faldaprevir vs. placebo with no apparent difference by dose and no benefit from lead in at the 240 mg QD dose level. An eRVR (BLQ at Week 4 and BLD at Week 12) was achieved in 15.5% in the placebo group vs. 80.9 – 90.8% in the faldaprevir groups. Within the 240 mg QD groups according to lead in the response rates were similar for 24 and 48 weeks PEG/RBV. Also, for 240 mg without lead in there was no benefit for 48 vs. 24 weeks PEG/RBV. Relapse rates were highest for placebo (15.5%) and lowest for 120 mg QD (7.2%). In 240 mg dose groups relapses occurred more often in those who stopped at week 24.

- For 189 GT1A patients the highest SVR24 rate was 82.4% in the 240 mg QD – LI group.
- For 253 GT1B patients the highest SVR24 rate was 86.0% in the 120 mg QD+LI group.
- SVR24 rates for the faldaprevir groups were 100%, 90.0% and 100% in patients with IL28 CC vs. 78.6%, 81.5% and 74.3%, respectively, for all others.

In TE patients the SVR rates were from 28% to 41% (latter for 240 mg QD without lead in) and were highest for prior partial responders/breakthrough subsets. SVR rates were better in those who received

RGT for 48 weeks PEG/RBV vs. those who had RGT that stopped at week 24 (72.4% vs. 43.3%) and relapse rates were 20.7% vs. 56.7%, respectively.

- For 147 with GT1A the highest SVR24 (38%) and lowest relapse rate (9.5%) occurred in the 240 mg QD-LI group.
- For 136 with GT1B the highest SVR24 occurred with 240 mg QD regardless of lead in (46%).

Study 40

TN GT1 patients without eRVR (BLQ week 4 and BLLD week 8) received PEG/RBV for 48 weeks. For the primary endpoint week 28 RVR (W28RVR = viral load BLLD) there was no difference between 12 and 24 weeks faldaprevir treatment (81% and 85%). Response rates were slightly higher for GT1B vs. GT1A and slightly lower for those with the highest viral loads at baseline. Rates decreased with increasing age and were lower for men vs. women but numbers are relatively small. An eRVR occurred in 70% and 83% in 12 and 24-week faldaprevir groups and these subjects stopped PEG/RBV at week 24.

Main studies

Study 30 STARTVERSO 1	FDV 240 mg 12w or 120 mg for 12 or 24 w (RGT) with PegIFN/RBV vs. PegIFN/RBV	Multi-centre, randomised, stratified, DB, PC	FDV SGC 120 mg or 240 mg (loading dose of 240 mg or 480 mg) Pegasys + Copegus	120 mg: 259 240 mg: 261 placebo: 132	HCV GT1 TN
Study 47 STARTVERSO 2	FDV 240 mg 12w or 120 mg 24 w with PegIFN/RBV vs. PegIFN/RBV	Multi-centre, randomised, DB, stratified, PC	FDV SGC 120 mg or 240 mg (loading dose 240 mg or 480 mg) Pegasys + Copegus	PEG/RBV:132 120 mg: 262 240 mg: 263	HCV GT1 TN
Study 07 STARTVERSO 3	FDV 240 mg 12 or 24 wks plus PegIFN/RBV 24 to 48 wks vs. historical PegIFN/RBV	Multi-national, randomised, DB, PC	FDV SGC 480 mg on day 1 and then 240 mg QD Pegasys + Copegus	<u>Relapsers:</u> 240-12w: 99 240-24w: 102 Placebo: 49 <u>Partial:</u> 240-12w: 57 240-24w: 55 Placebo: 29 <u>Null:</u> 240-12w: 145 240-24w: 141	HCV GT1 previous partial responders or relapsers on/after PegIFN/RBV
Study 19 STARTVERSO 4	FDV 240 mg or 120 mg QD + PegIFN/RBV in HCV/HIV co-infected: HCV-TN or relapsers and HIV-TN or on HAART	Multi-national, randomized, stratified, OL	FDV SGC 120 mg or 240 mg with loading dose of 480 mg or 240 mg Pegasys + Copegus	120 mg + pegIFN/RBV: 123 240 mg + pegIFN/RBV: 185	HCV GT 1 TN and TE pts (relapsers) co-infected with HIV-1

<u>Quantification of HCV RNA</u>

The Roche COBAS TaqMan HCV/HPS assay version 2.0 was used in central clinical laboratories. Specimens with results < LLOQ are reported *<25 IU/mL, HCV RNA detected* and those < LLOD are reported *No HCV RNA detected*.

HCV genotype subtype identification of screening plasma samples

This was performed by the central laboratories using the TRUGENE 5'NC HCV Genotyping assay for Phase 2 and the VERSANT HCV Genotype version 2.0 (LiPA) assay for Phase 3 studies. However, NS3/4A sequencing was subsequently available for the majority of patients in all Phase 2 and 3 studies and these results were used in the analyses by genotype.

HCV genotyping and NS3 phenotyping assays

These were applied to the baseline samples and were conducted by Boehringer Ingelheim (Canada) for Phase 2 and by Janssen Diagnostics BVBA for Phase 3. The HCV NS3/4A population sequences were used for phylogenetic analysis to retrospectively assign HCV genotype and subtype for each patient and in the resistance analyses.

The four Phase 3 studies were multicentre and multinational. The data in the current CSRs derive from 2011-2013 and all studies were ongoing at the time of submission (e.g. not all patients had completed the SVR24 visit). Placebo group failures were offered rollover into study 48 to receive faldaprevir.

Patients

- Studies 30 and 47 enrolled only TN patients.
- Study 07 enrolled patients who had failed on PEG/RBV into three cohorts defined as follows:
  - Null response: Lack of EVR (defined as ≥2 log10 drop from baseline at Week 12
  - Partial Response (Partial Responder and Breakthrough): Had an EVR but did not achieve HCV RNA undetectable at the end of treatment (based on an assay considered sensitive at the time of treatment)
  - Prior Relapse: Undetectable HCV RNA (based on an assay as above) at the end of treatment but HCV RNA detectable within 24 weeks post-treatment
- Study 19 enrolled PEG/RBV TN patients and TE relapsers who were co-infected with HIV-1 and were ARV-naïve or were on stable HAART with < 40 copies/mL and ≥ 200 cells/mm3.
- All patients were to have HCV RNA ≥1,000 IU/mL at screening and had a liver biopsy within 3 years or Fibroscan within 6 months prior to randomisation. There were numerous exclusions based on concomitant diseases and laboratory criteria, some of which were related to the need to co-administer PEG/RBV.

Treatments

Studies 30 and 47 compared faldaprevir (120 mg or 240 mg QD after loading doses of 240 mg or 480 mg, respectively, on day 1) with placebo, each added to PEG/RBV. Both studies tested 240 mg QD for 12 weeks and 120 mg for 24 weeks. Study 30 allowed 12 weeks at 120 mg QD using RGT. In both studies patients in the 240 mg group and those in the 120 mg group in study 30 who stopped faldaprevir at 12 weeks based on the RGT criteria continued with placebo to 24 weeks. The first daily dose of RBV was to be taken with food before faldaprevir so effectively dosing of faldaprevir was in the fed state although the applicant states that dosing was without regard to food. In both studies PEG/RBV was given for 48 weeks except for faldaprevir patients with ETS who received 24 weeks.

In study 07 treatment was assigned by cohort (see further below).

In study 19 TN or TE relapsers were initially randomised to:

- Faldaprevir 120 mg^ QD (loading dose 240 mg on day1) for 24 weeks. ^ Patients taking DRV/r or ATV/r received this dose
- Faldaprevir 240 mg* QD (loading dose 480 mg on day 1) for 12 weeks; this group underwent a second randomisation to stop at week 12 (240-12w) or continue for 24 weeks (240-24w). * Patients taking EFV received this dose

PEG/RBV was given for 24 or 48 weeks if ETS or 48 weeks if no ETS.

Primary endpoint

In all Phase 3 studies this was SVR12 = < 25 IU/mL (undetected) at 12 weeks after the originally planned treatment duration. For example, in study 30 the SVR12 for patients on a 24-week treatment schedule was assessed at Week 36 and for those on a 48-week schedule it was assessed at Week 60, regardless of the actual date of the treatment completion. SVR12 was assessed based on HCV RNA result at least 8 weeks (to allow an appropriate visit window) after the originally planned treatment duration.

Secondary endpoints were:

- SVR24 = < 25IU/mL (undetected) at 24 weeks after the originally planned treatment duration.
- Early treatment success (ETS) = < 25 IU/mL at week 4 (detected or undetected) and <25 IU/mL (undetected) at Week 8.
- ALT and AST normalisation at EOT and post-treatment
- RVR = <25 IU/mL(detected or undetected) at Week 4
- cEVR = <25 IU/mL (undetected) at Week 12
- W24VR) = <25 IU/mL (undetected) at Week 24
- ETR = <25 IU/mL (undetected) at the end of all therapy
- Time to achieving < 25 IU/mL (undetected)
- Time to rebound from nadir (lowest HCV RNA level on treatment)
- Time to rebound from < 25 IU/mL (undetected)
- Progression of liver disease following EOT

Randomisation was performed using IVRS.

Studies 30 and 47 used 1:2:2 for P:120 mg:240 mg with stratification by GT1a/1b/non-1a or b and by race (Black/Asian/other).

In study 07 randomisation of Null Responders and Partial Responders/Relapsers was handled separately.

In study 19 there were three randomisations, each stratified by HCV genotype subtype:

Day 1 - Randomisation (1:1) to 120 mg or 240 mg faldaprevir with PEG/RBV for 12 weeks

Week 12 - Randomisation (1:1) of patients in the 240 mg group to stop faldaprevir or continue to Week 24

Week 24 - Randomisation of all patients with ETS to stop PEG/RBV or continue to Week 48; those without ETS received 48 weeks.

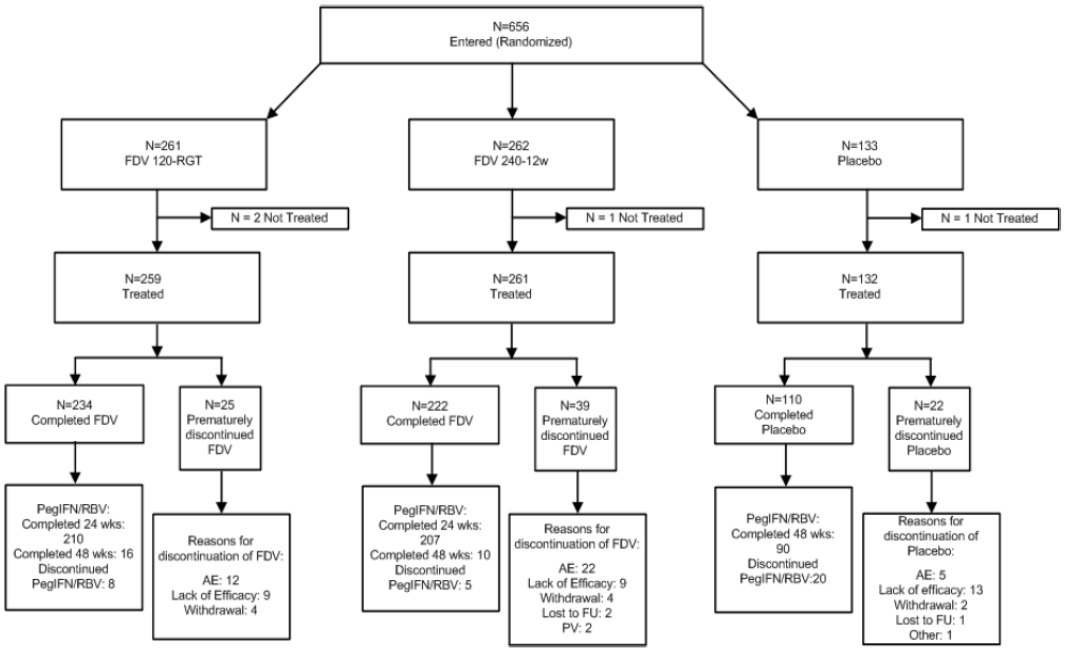
Studies 30, 47 and 07 were double-blind. In the PEG/RBV RGT groups the investigators were informed by IVRS at Week 24 whether this was to be stopped. Study 19 was open label.

A single DMC monitored safety in all four studies but it seems they also reviewed unblinded efficacy data.

Results in TN patients

Study 30

Patient disposition was as follows:



Using the protocol-defined criteria for RGT the majority of patients in the 120 mg RGT group (87.3%) was eligible to stop faldaprevir at 12 weeks and the majority in both faldaprevir groups (~80%) was eligible to stop PEG/RBV at 24 weeks.

In the primary analysis both faldaprevir treatments were superior to PEG/RBV alone. There was no difference overall between the 120-RGT and 240-12w faldaprevir groups.

Table 11.4.1.1.1: 1 Comparisons of SVR12 rates across treatment groups, adjusted for race and genotype – FAS

	FDV 120-RGT		FDV 240-12w		Placebo	
	N	(%)	N	(%)	N	(%)
Number of Patients	259	(100.0)	261	(100.0)	132	(100.0)
Number (%) of patients with response	204	(78.8)	210	(80.5)	69	(52.3)
95% Confidence interval [%]		(73.8,83.7)		(75.6,85.3)		(43.8,60.8)
Comparison vs Placebo						
Estimate[1]	26.7		28.6			
95% Confidence interval[1]		(17.1,36.3)		(19.0,38.2)		
p-value[2]	<0.0001		<0.0001			
Comparison vs FDV 240-12w						
Estimate[1]	-1.8					
95% Confidence interval[1]		(-8.7,5.1)				

[1] Adjusted for Genotype and Race using Koch's method, with continuity correction
[2] Based on Cochran Mantel-Haentzel methods, adjusted for Genotype and Race

The sensitivity analyses were consistent with the primary analysis. A sensitivity analysis adjusting for IL28B instead of race showed nearly identical results to the primary analysis adjusting for race. SVR12 rates by important sub-groups were as follows:

Table 11.4.1.1.2: 1 Summary of SVR12 rates by subgroups and treatment – FAS

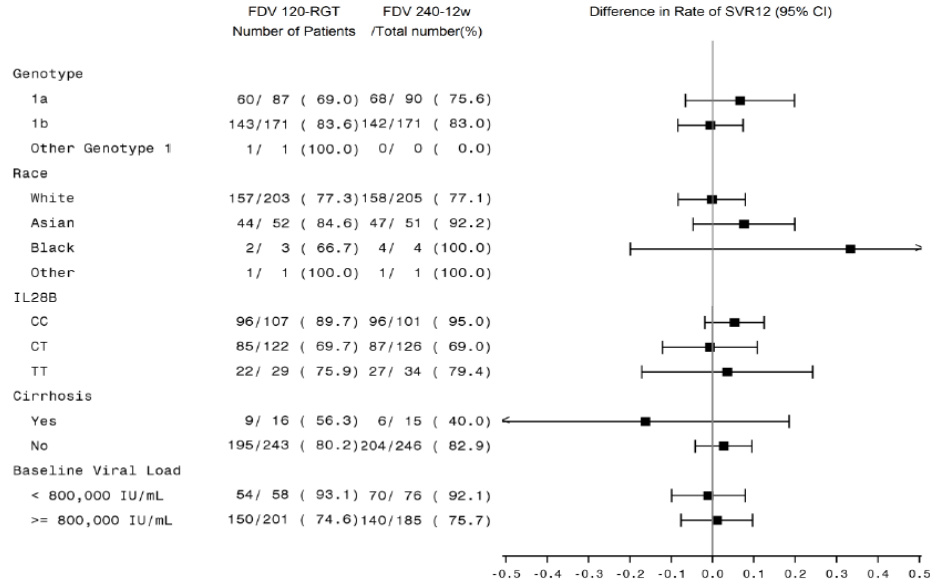
	FDV 120-RGT			FDV 240-12w			Placebo		
	N[1]	n[2]	(%)	N[1]	n[2]	(%)	N[1]	n[2]	(%)
GT 1 subtype									
1a	87	60	69.0	90	68	75.6	45	16	35.6
1b	171	143	83.6	171	142	83.0	86	52	60.5
Other genotype 1	1	1	100	0	0	0.0	1	1	100
Race									
Asian	52	44	84.6	51	47	92.2	27	18	66.7
Other	1	1	100	1	1	100	0	0	0.0
Black	3	2	66.7	4	4	100	2	2	100
White	203	157	77.3	205	158	77.1	103	49	47.6
IL-28B									
CC	107	96	89.7	101	96	95.0	46	29	63.0
CT	122	85	69.7	126	87	69.0	68	35	51.5
TT	29	22	75.9	34	27	79.4	18	5	27.8
Cirrhosis									
Yes	16	9	56.3	15	6	40.0	8	3	37.5
No	243	195	80.2	246	204	82.9	124	66	53.2
Baseline VL									
< 800,000 IU/mL	58	54	93.1	76	70	92.1	31	23	74.2
>= 800,000 IU/mL	201	150	74.6	185	140	75.7	101	46	45.5

Each of HCV GT-1 subtype, race, IL28B, cirrhosis and baseline viral load had a significant impact on achieving SVR12 in at least one treatment group but high baseline viral load appeared to be the only significant negative predictor of achieving SVR12 across all treatment groups.

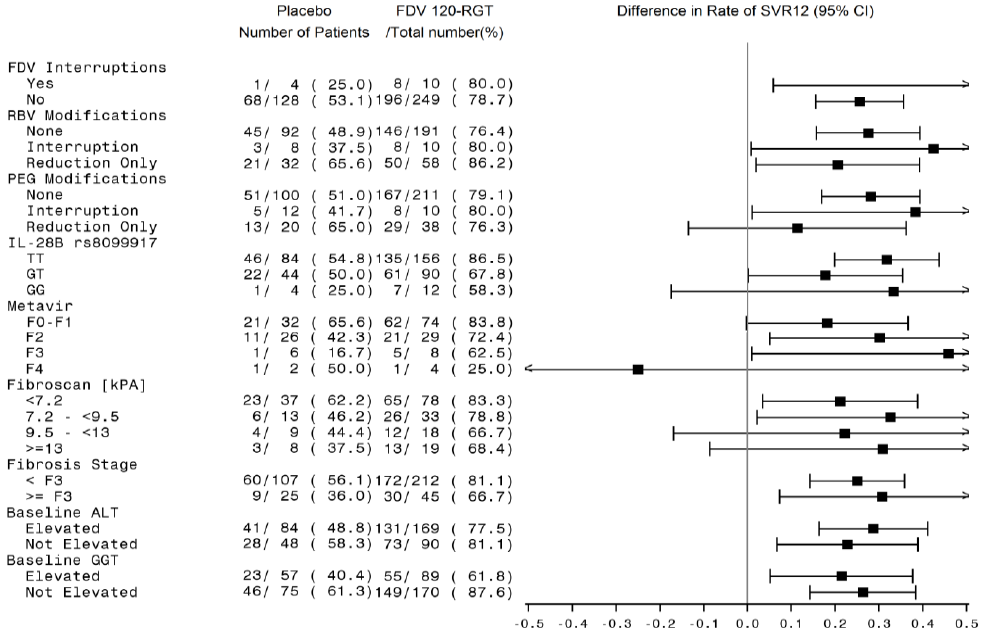
- IL28B CC gave a significantly better chance of achieving SVR12 in both faldaprevir groups
- HCV GT-1a subtype gave a significantly lower SVR12 rate with 120-RGT (69%) but not with FDV 240-12w (75.6%) vs. GT1b (83%) although both doses showed large differences vs. placebo.

In the logistic regression analyses GT-1 subtype, IL28B, baseline VL, age and baseline GGT were retained in the stepwise model as being significantly associated with achieving SVR12, after adjusting for other factors in the model.

The diagram compares SVR12 rates between the 120-RGT and 240-12w groups by several factors.



Faldaprevir was associated with higher SVR12 rates vs. placebo in other subgroups. The figure shows the comparison for 120-RGT and placebo. The figure that compares 240-12w vs. placebo is broadly similar whereas the comparison between doses showed that all 95% CI included zero.



Among patients with SVR12 who had been assessed for SVR24 (N = 437) only 3 had experienced a relapse, giving a PPV of 99.3%. There were few on-treatment virological failures in the faldaprevir groups. In all treatment groups, the most frequently reported reason for not achieving SVR12 was relapse, with a higher rate in the placebo group.

ETS was achieved by 87.3% in the 120-RGT group and 89.3% in the FDV 240-12w group but in only 22.0% in the placebo group.

- Most (>85%) of the patients who achieved ETS also achieved SVR12.

- The SVR12 rates for patients who achieved ETS were 85.8% and 89.3% in the 120-RGT and 240 12w groups but SVR12 rates for those not achieving ETS were 30.3% and 7.1%, respectively.
- For patients without ETS the SVR12 rates were 10/33 for 120-RGT and 2/28 for 240-12w but for PEG/RBV alone, in line with a slower response, the SVR12 rate was 41.7% (43/103).

The findings for other virological response endpoints showed a consistent benefit for adding faldaprevir to PEG/RBV with no appreciable difference between dose groups. RVR and cEVR showed high PPVs (at least 83%). The W24VR and ETR showed the least difference between faldaprevir and placebo groups.

Table 11.4.1.3.1: 1 Rapid viral response (RVR), complete early viral response (cEVR), Week 24 viral response (W24VR), and end-of-treatment response (ETR) – FAS

	FDV 120-RGT		FDV 240-12w		Placebo	
	N	(%)	N	(%)	N	(%)
Number of Patients	259	(100.0)	261	(100.0)	132	(100.0)
RVR	236	(91.1)	243	(93.1)	29	(22.0)
cEVR	233	(90.0)	236	(90.4)	60	(45.5)
W24VR	230	(88.8)	235	(90.0)	95	(72.0)
ETR	238	(91.9)	240	(92.0)	97	(73.5)

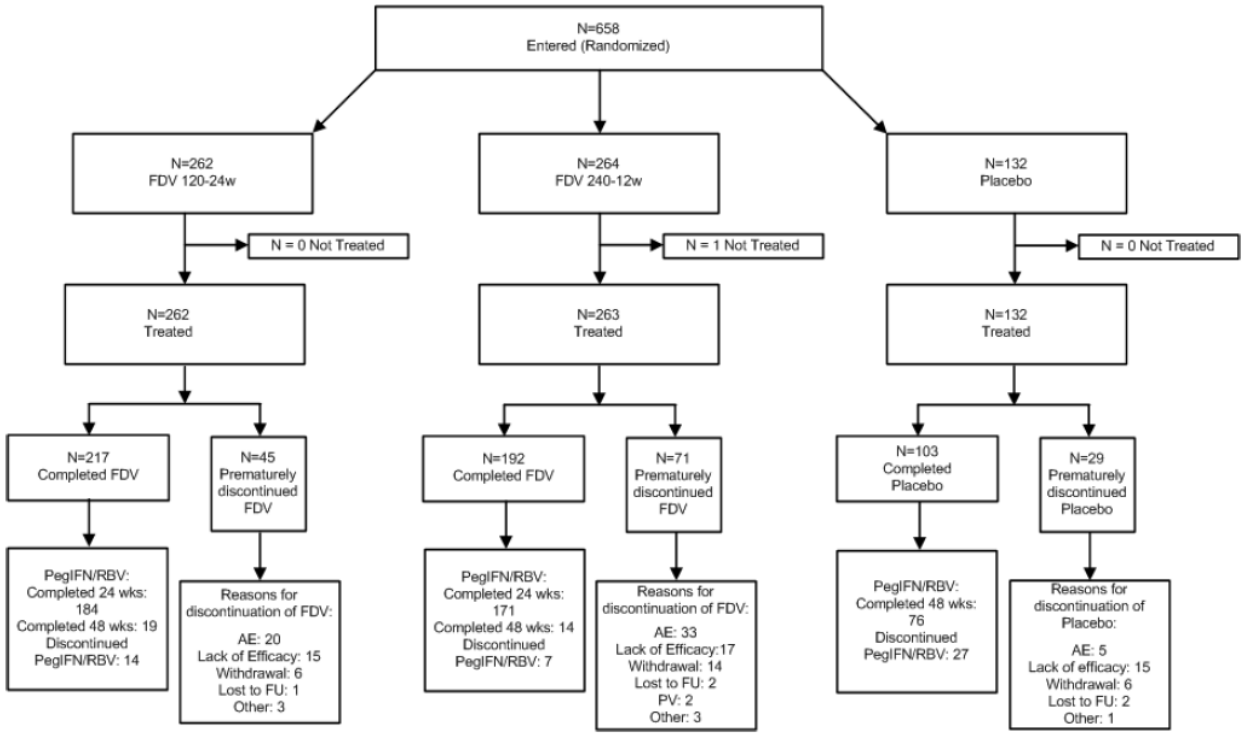
All treatment groups included a background therapy of PegIFN/RBV.

Achievement of undetected HCV RNA was rapid and similar for the two faldaprevir groups. Treatment with faldaprevir, GT-1b subtype virus, IL28B CC genotype, non-cirrhotic status and baseline VL < 800,000 IU/mL all showed a significant positive association with shorter time to achieving HCV RNA undetected and a significant negative association with rebound.

Similar rates of breakthrough were observed during the first 12 weeks of treatment (2.7% for 120-RGT, 2.3% for 240-12w and 1.5% in the placebo group). Slightly more GT-1a subtype patients had a breakthrough on faldaprevir during the first 12 weeks (5.7% for 120 mg and 3.3% for 240 mg) compared with GT-1b subtype patients (1.2% and 1.8%, respectively).

Study 47

Patient disposition was as follows:



Using the protocol-defined criteria for RGT the majority of patients in both faldaprevir groups (~80%) achieved ETS and so they were eligible to stop PEG/RBV at 24 weeks.

The critical baseline features of the HCV infections and other demographic characteristics were generally well balanced between the randomisation groups. However, only 6 Asians had GT1a while 123 had GT1b.

In the primary analysis both faldaprevir treatments were superior to PEG/RBV alone. There was a suggestion of a slightly better SVR12 rate for 120-24w vs. 240-12w faldaprevir.

Table 11.4.1.1.1: 1 Comparisons of SVR12 rates across treatment arms, adjusted for race and genotype – FAS

	FDV 120-24w		FDV 240-12w		Placebo	
	N	(%)	N	(%)	N	(%)
Number of Patients	262	(100.0)	263	(100.0)	132	(100.0)
Number (%) of patients with response	178	(67.9)	168	(63.9)	62	(47.0)
95% Confidence interval [%]	(62.3,73.6)		(58.1,69.7)		(38.5,55.5)	
Comparison vs Placebo [%]						
Estimate[1]	20.7		17.0			
95% Confidence interval[1]	(10.7,30.6)		(6.9,27.0)			
p-value[2]	<0.0001		0.0010			
Comparison vs FDV 240-12w [%]						
Estimate[1]	3.8					
95% Confidence interval[1]	(-4.0,11.6)					

1 Adjusted for Genotype and Race using Koch's method, with continuity correction

2 Based on Cochran Mantel-Haentzel methods, adjusted for Genotype and Race

The number that discontinued faldaprevir and all study medication before week 8 was much higher in the 240-12w group (17; 15 also discontinued PEG/RBV) and only one went on to SVR12, which is stated in the CSR to be the main factor driving the lower SVR12 with the higher faldaprevir dose.

Table 11.4.1.1.1: 3 Timing of discontinuation and achievement of SVR12 for patients that discontinued while HCV RNA was undetected – FAS

	FDV 120-24w (N= 262)			FDV 240-12w (N= 263)			Placebo (N= 132)		
	N[1]	n[2]	%	N[1]	n[2]	%	N[1]	n[2]	%
Discontinuation of FDV/PBO[3]									
< Week 4	1	0	0.0	6	0	0.0	1	0	0.0
Week 4 - < Week 8	1	0	0.0	11	1	9.1	0	0	N/A
Discontinuation of all study drug[4]									
< Week 4	1	0	0.0	5	0	0.0	0	0	N/A
Week 4 - < Week 8	1	0	0.0	10	0	0.0	1	0	0.0

The sensitivity analyses were consistent with the primary analysis. A sensitivity analysis adjusting for IL28B instead of race showed nearly identical results to the primary analysis adjusting for race.

Among patients with SVR12 who had been assessed for SVR24 (N = 357) only 6 had experienced a relapse, giving a PPV of 98.3%.

SVR rates by important sub-groups are summarised in the table below.

- Race was a significant predictor of achieving SVR12 across all treatment groups. The highest rates in the faldaprevir groups were observed in Asians and the lowest in Blacks. No Asian patient in the faldaprevir groups had an on-treatment virological failure. The reason for the lower SVR12 rates among Asians with 240-12w vs. 120-24w is the 11.8% discontinuation rate from the 240-12w group while HCV RNA was undetected.
- The overall failure rate for Blacks was similar between faldaprevir dose groups but there were more relapsers in the 120-24w group (27.3% vs. 8.6%) and more patients discontinued while HCV RNA was undetected in the 240-12w group (17% vs. 3%) whereas the on-treatment failure rates were comparable (8/33 for 120-24w and 9/35 for 240-12w).
- IL28B CC patients had a significantly better chance of achieving SVR12 compared to non-CC patients in all treatment groups.

Table 11.4.1.1.2: 1 Summary of SVR12 rates by subgroups and treatment – FAS

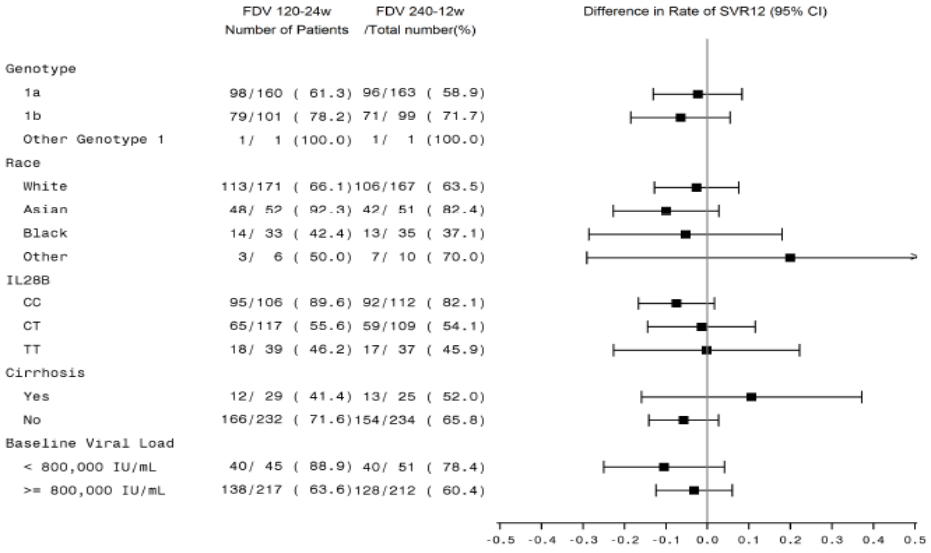
	FDV 120-24w			FDV 240-12w			Placebo		
	N[1]	n[2]	(%)	N[1]	n[2]	(%)	N[1]	n[2]	(%)
GT 1 subtype									
1A	160	98	61.3	163	96	58.9	80	37	46.3
1B	101	79	78.2	99	71	71.7	52	25	48.1
Race									
Asian	52	48	92.3	51	42	82.4	26	13	50.0
Black	33	14	42.4	35	13	37.1	17	4	23.5
White	171	113	66.1	167	106	63.5	85	44	51.8
Other	6	3	50.0	10	7	70.0	4	1	25.0
IL-28B									
CC	106	95	89.6	112	92	82.1	48	34	70.8
CT	117	65	55.6	109	59	54.1	58	20	34.5
TT	39	18	46.2	37	17	45.9	25	7	28.0
Cirrhosis									
No	232	166	71.6	234	154	65.8	109	53	48.6
Yes	29	12	41.4	25	13	52.0	22	9	40.9
Baseline VL									
< 800,000 IU/mL	45	40	88.9	51	40	78.4	24	16	66.7
>= 800,000 IU/mL	217	138	63.6	212	128	60.4	108	46	42.6

- Cirrhotic patients had lower SVR12 rates vs. non-cirrhotic patients but the effect was greatest in the faldaprevir (and especially 120-24w) groups.
- HCV GT-1a subtype virus resulted in significantly lower SVR12 rates vs. GT1b in the faldaprevir groups but the differences were not significant after adjusting for race and were driven by the predominance of GT1b in Asians and GT1a in Blacks.

In the planned logistic regression analyses:

- In addition to treatment, GT-1 subtype, IL28B, race and cirrhosis as well as the baseline VL, BMI and GGT values were retained in the stepwise model as being significantly associated with achieving SVR12, after adjusting for other factors in the model.
- All of these factors were also significant in the individual logistic regressions except BMI.

The diagram compares SVR12 rates for the two faldaprevir groups according to several factors.



There were relatively low rates of on-treatment virological failures in the faldaprevir groups. In all treatment groups, the most frequently reported reason for not achieving SVR12 was relapse, with a higher rate in the 120-24w group.

Rates of on-treatment failure and relapse also differed between GT1a and GT1b in the faldaprevir groups.

Table 11.4.1.1.2: 4 Summary of reasons for not achieving the primary endpoint of SVR12 by GT-1 subtype – FAS, FDV groups

	FDV 120-24w				FDV 240-12w			
	GT-1a		GT-1b		GT-1a		GT-1b	
	N	(%)	N	(%)	N	(%)	N	(%)
Number of patients	160	(100.0)	101	(100.0)	163	(100.0)	99	(100.0)
SVR Yes	98	(61.3)	79	(78.2)	96	(58.9)	71	(71.7)
SVR No	62	(38.8)	22	(21.8)	67	(41.1)	28	(28.3)
Resp: FDV BT	4	(2.5)	1	(1.0)	1	(0.6)	0	(0.0)
Resp: PR BT	1	(0.6)	1	(1.0)	9	(5.5)	0	(0.0)
Resp: Relapse	27	(16.9)	11	(10.9)	16	(9.8)	5	(5.1)
Resp: D/C Nadir	8	(5.0)	5	(5.0)	16	(9.8)	13	(13.1)
Resp: Other	2	(1.3)	0	(0.0)	4	(2.5)	1	(1.0)
No Resp: Null	2	(1.3)	1	(1.0)	1	(0.6)	0	(0.0)
No Resp: FDV BT	9	(5.6)	1	(1.0)	6	(3.7)	3	(3.0)
No Resp: PR BT	1	(0.6)	0	(0.0)	3	(1.8)	0	(0.0)
No Resp: Partial Resp	3	(1.9)	1	(1.0)	1	(0.6)	1	(1.0)
No Resp: D/C Nadir	3	(1.9)	1	(1.0)	6	(3.7)	3	(3.0)
No Resp: Other	1	(0.6)	0	(0.0)	4	(2.5)	2	(2.0)
No Vl	1	(0.6)	1	(1.0)	0	(0.0)	0	(0.0)

ETS was achieved by 80.2% in the 120-24w group and 79.1% in the 240-12w group but in only 15.9% in the placebo group. Most (80% and 76.9% in the faldaprevir groups) who achieved ETS also achieved SVR12. For patients without ETS the SVR12 rates were 10/52 (19%) for 120-24w and 8/55 (14%) for 240-12w but only 17/52 and 9/55 completed the assigned treatment, of which 9/17 and 8/9 achieved SVR12. For PEG/RBV alone, in line with a slower response, the SVR12 rate was 42% (47/111).

- Most (83.7%; 79.6% for GT-1a but 88.8% for GT-1b) of the 355 faldaprevir patients who achieved ETS and completed all study medication at Week 24 had undetected HCV RNA at Week 4. Among those with HCV RNA undetected at Week 4 the SVR12 rates were 88.8% for GT-1a and 94.1% for GT-1b. Also, SVR12 rates were 90.2% for 120-24w and 92.4% for 240-12w.
- Numbers with < 25 IU/mL (detected) at Week 4 were small but these patients had lower SVR12 rates (46.6%) vs. those with HCV RNA undetected. There was a larger difference in this respect for the GT1a infections (39% detected vs. 88.8% undetected) than for GT1b infections (64.7% vs. 94.1%).

Table 11.4.1.2.2: 3 Summary of achievement of ETS by baseline factors and treatment – FAS

	FDV 120-24w		FDV 240-12w		Placebo	
	n/N	(%)	n/N	(%)	n/N	(%)
GT subtype						
1A	117/160	73.1	122/163	74.8	15/80	18.8
1B	92/101	91.1	85/99	85.9	6/52	11.5
Race						
Asian	50/52	96.2	47/51	92.2	4/26	15.4
Black	23/33	69.7	20/35	57.1	3/17	17.6
Other	137/177	77.4	141/177	79.7	14/89	15.7
IL28B						
CC	96/106	90.6	98/112	87.5	15/48	31.3
Non-CC	114/156	73.1	107/146	73.3	6/83	7.2
Cirrhosis						
Yes	23/29	79.3	16/25	64.0	5/22	22.7
No	187/232	80.6	190/234	81.2	16/109	14.7
Baseline VL (IU/mL)						
<800,000	42/45	93.3	44/51	86.3	10/24	41.7
≥800,000	168/217	77.4	164/212	77.4	11/108	10.2

Achievement of undetected HCV RNA was rapid and similar for the two faldaprevir groups. Treatment with faldaprevir, GT-1b subtype virus, IL28B CC genotype, non-Black/African American race and baseline VL < 800,000 IU/mL all showed a significant positive association with shorter time to achieving HCV RNA undetected. These same factors plus non-cirrhotic status showed a significant negative association with rebound.

Similar rates of breakthrough were observed during the first 12 weeks of treatment (3.1% 120-24w and 3.8% 240-12w) with slightly more with GT1a having breakthrough (3.8% and 4.3%) than GT1b (2% and 3%) in respective dose groups. In addition, 3.8% had a breakthrough while on PEG/RBV alone in the 240-12w group vs. 2.7% in the 120-24w group and all of these cases were GT1a infections.

Of the patients with ETR 19.9% 120-24w, 13.8% 240-12w and 21.6% placebo group patients subsequently experienced a relapse. Many occurred during the first follow-up assessment 4 weeks after stopping treatment (23/40, 8/25 and 8/16, respectively) and all except 7 relapses occurred by 12 weeks post-treatment.

TN patients in studies 30 and 47

Regression analyses further explored the differences in results between the two studies, which were ascribed in CSRs mainly to differences in characteristics of the patient populations and HCV factors, with an additional component of patient adherence and/or management for the 240 mg QD dose groups.

For the 120 mg dose and prior to adding any variables in the model, study was significantly associated with SVR12 (Step 0 p-value = 0.0306). The study effect gradually disappeared as more variables were added to the model, with a negligible study effect after accounting for baseline GGT, baseline HCV RNA, age, fibrosis stage and GT-1 subtype.

Step	Variable entered	Chi Sq	P-value	Study p-value
0				0.0306
1	IL28B	47.6846	< 0.0001	0.0273
2	BL GGT	26.7103	< 0.0001	0.1315
3	BL HCV RNA	15.9465	< 0.0001	0.1646
4	Age	12.8488	0.0003	0.3921
5	Fibrosis Stage	8.4686	0.0036	0.5180
6	GT-1 subtype	6.5212	0.0107	0.9588
7	FDV interruptions	5.0926	0.0240	0.9952

For the 240 mg dose and prior to adding any variables in the model, study was again significantly associated with SVR12 (Step 0 p-value<0.0001).

Step	Variable entered	Chi Sq	P-value	Study p-value
0				< 0.0001
1	IL28B	39.6860	< 0.0001	< 0.0001
2	BL HCV RNA	23.5387	< 0.0001	< 0.0001
3	Study	16.4784	< 0.0001	< 0.0001
4	BL Platelet Count	9.9873	0.0016	< 0.0001
5	Fibrosis Stage	5.7244	0.0167	< 0.0001
6	Race	6.2813	0.0433	0.0009
7	Age	4.1955	0.0405	0.0030

However, unlike the results for 120 mg, study remained significantly associated with response, regardless of the adjustments for baseline predictors. In fact, at Step 3, study entered the model as the most significant factor, and remained significant throughout the forward selection procedure, indicating that there was not a combination of factors that sufficiently explained the differences between SVR12 rates.

After excluding patients who did not achieve SVR12 due to discontinuation while HCV RNA was at nadir or for other reasons (i.e. non-virological reasons for no SVR12) study was borderline significant (p-value = 0.0720 at Step 0) and then gradually became non-significant as more factors were added to the model. Specifically, the addition of fibrosis stage, baseline HCV RNA and GT-1 subtype appear to sufficiently explain the higher failure rates observed with 240 mg in study 47 vs. 30.

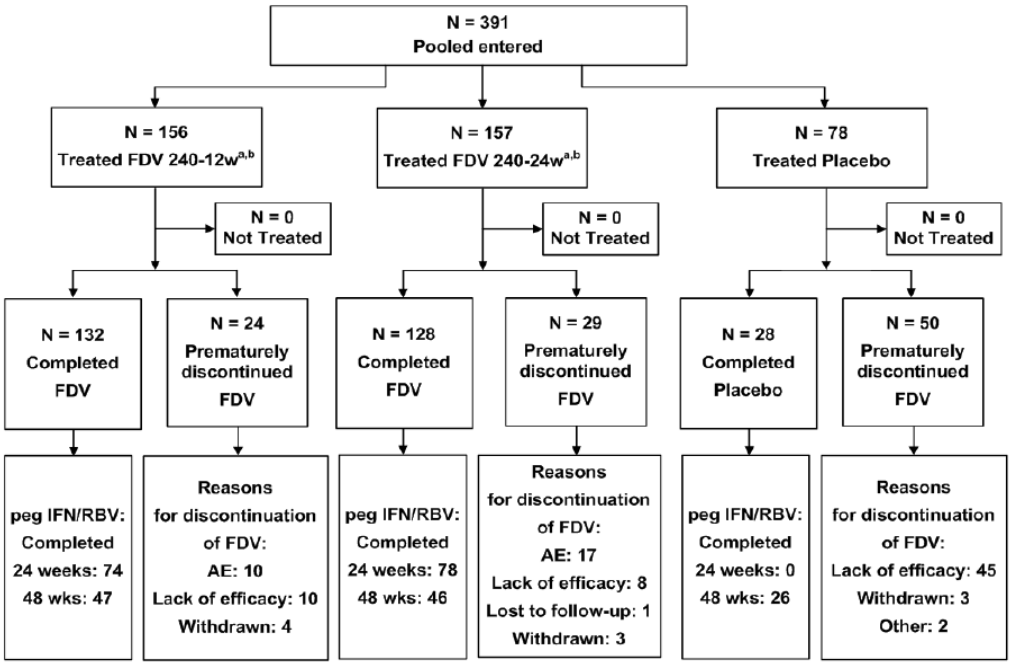
Step	Variable entered	Chi Sq	P-value	Study p-value
0				0.0720
1	IL28B	39.6860	< 0.0001	0.0172
2	BL HCV RNA	23.5387	< 0.0001	0.1287
3	Fibrosis Stage	16.4784	< 0.0001	0.1480
4	GT-1 subtype	9.9873	0.0016	0.4393
5	BL Platelet Count	5.7244	0.0167	0.4222

The baseline HCV RNA, fibrosis stage and GT-1 subtype are known factors affecting response. These were observed at a higher rate in study 47 compared to 30. These data and the difference in rate of discontinuation while at nadir, especially at the 240mg dose, were considered to explain the different efficacy results in the two studies in TN patients. However, pooling of the studies for the purpose of addressing specific questions regarding dose and duration was considered to be supported by logistic regression which showed that the study by treatment interaction was non-significant.

Results in TE patients

Study 07

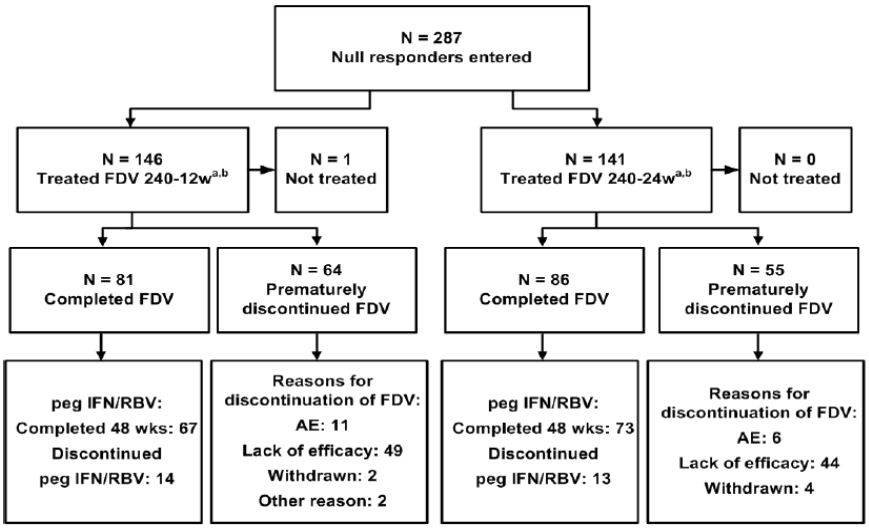
There were 391 relapsers (250 Cohort 1) and partial responders (141 Cohort 2) randomised and disposition was similar between these Cohorts except that rates for discontinuing faldaprevir due to lack of efficacy were higher for the partial responders (240-12w 12.3% vs. 3.0%; 240-24w 7.3% vs. 3.9%).



Most of the relapsers were White (79.2%) and almost all of the 17.2% Asians were Japanese. In the HCV GT-1a subtype nearly all patient were White (94.0%) but in the HCV GT-1b subtype 66.4% were White and 29.9% were Asian. Similarly, 79.4% of the partial responders were White and all of the 16.3% Asians were Japanese. Nearly all with GT1a were White (95.4%) but among the GT1b infections 65.8% were White and 30.3% Asians.

There were 287 null responders randomised into Cohort 3 and 286 were treated. Premature discontinuation rates were comparable between the two faldaprevir regimens and were higher than observed in Cohorts 1 and 2 (240-12w: 44.1% vs. 19.3% and 13.1%, respectively; 240-24w: 39.0% vs. 23.6%, and 15.7%, respectively). Most discontinuations from Cohort 3 were due to lack of efficacy (240-12w: 33.8% vs. 12.3% and 3.0% in Cohorts 1 and 2; 240-24w: 31.2% vs. 7.3% and 3.9%, respectively).

Most of these null responders were White (74.5%) and all of the 20.3% Asians were Japanese. Nearly all with GT-1a were White (92.6%) but for the GT-1b cases 58% were White and 38.7% were Asian.



Within each Cohort the major HCV-specific baseline characteristics were balanced across the three treatment groups.

For the pooled and individual Cohorts 1 and 2 there were marked and statistically significant differences in SVR12 rates between each of the faldaprevir groups vs. placebo. There were no apparent differences between the SVR12 rates for the faldaprevir regimens within Cohort 1. The SVR12 rates in Cohort 2 were lower than for Cohort 1 in all three treatment groups and the rate was lower for 24 weeks vs. 12 weeks faldaprevir.

Table 11.4.1.1.1: 1 Comparisons of SVR12 rates across treatment groups, adjusted for HCV GT1 subtype and response to previous treatment, relapsers and partial responders – FAS

Cohort	Treatment groups	FDV 240-12w N (%)		FDV 240-24w N (%)		Placebo N (%)	
Relapsers + Partial responders	Number of patients	156	(100.0)	157	(100.0)	78	(100.0)
	Patients with SVR12	102	(65.4)	97	(61.8)	8	(10.3)
	Comparison vs Placebo						
	Difference [1]	54.7		50.9			
	95% Confidence interval[1]	(57.9, 72.9)		(54.2, 69.4)			
	p-value[2]	< 0.0001		< 0.0001			
	Comparison vs FDV 240-24w						
	Difference [1]	4.0					
	95% Confidence interval[1]	(-6.4, 14.4)					
Relapsers	Number of patients	99	(100.0)	102	(100.0)	49	(100.0)
	Patients with SVR12	69	(69.7)	71	(69.6)	7	(14.3)
	Comparison vs Placebo						
	Difference[3]	55.1		55.0			
	95% Confidence interval[3]	(41.5, 68.7)		(41.4, 68.5)			
	p-value[4]	< 0.0001		< 0.0001			
	Comparison vs FDV 240-24w						
	Difference[3]	0.3					
	95% Confidence interval[3]	(-12.3, 12.9)					
Partial responders	Number of patients	57	(100.0)	55	(100.0)	29	(100.0)
	Patients with SVR12	33	(57.9)	26	(47.3)	1	(3.4)
	Comparison vs Placebo						
	Difference[3]	54.0		43.9			
	95% Confidence interval[3]	(38.4, 69.7)		(28.2, 59.7)			
	p-value[4]	< 0.0001		< 0.0001			
	Comparison vs FDV 240-24w						
	Difference[3]	10.8					
	95% Confidence interval[3]	(-7.4, 29.0)					

1 Estimation adjusted for GT1 subtype and response to previous treatment using Koch's method, with continuity correction
2 Based on Cochran-Mantel-Haenszel methods, adjusted for genotype and response to previous treatment
3 Estimation adjusted for GT1 subtype using Koch's method, with continuity correction
4 Based on Cochran-Mantel-Haenszel methods, adjusted for genotype

In Cohort 3 (null responders) SVR12 rates were the same in the faldaprevir groups (33%). The lower limits of the 95% CIs around these rates were above the pre-defined historical rate (20%) and the applicant concluded that addition of faldaprevir gave increased antiviral activity vs. PEG/IFN in null responders.

Table 11.4.1.1.1: 2 Summary of SVR12 rates across treatment groups, null responders – FAS

Treatment groups	FDV 240-12w N (%)	FDV 240-24w N (%)
Number of patients	145 (100.0)	141 (100.0)
Patients with SVR12	40 (33.1)	46 (32.6)
95% Confidence interval	(25.4, 40.8)	(24.9, 40.4)
p-value[1]	< 0.0001	0.0002
Comparison vs FDV 240-24w		
Difference[2]	-0.5	
95% Confidence interval[2]	(-11.3, 10.2)	

[1] Each p-value corresponds to a two-sided test against the historical rate of 20%

[2] Estimation adjusted for GT1 subtype using Koch's method, with continuity correction

For relapsers and partial responders who were treated with faldaprevir most of the patients who did not achieve SVR12 had a relapse. In contrast, the most common reason for failure to achieve SVR12 in the placebo group was *Null by Week 4*. Specifically 16/49 (32.7%) placebo patients in Cohort 1 and 14/29 (48.3%) in Cohort 2 did not achieve 2 log10 drop by Week 4 and stopped due to lack of efficacy.

Among null responders the most common reason for not achieving SVR12 was breakthrough.

The results of the primary analysis were supported by sensitivity analyses. An additional sensitivity analysis adjusted for IL28B in addition to HCV GT1 subtype gave results for Cohorts 1 and 2 that were similar to those of the primary analysis.

At the time of the data cut-off and across the three cohorts there were 563 patients with SVR12 = Yes and SVR24 assessed. There were seven relapses by SVR24 (PPV = 96.3%) including 4 in the 240-12w group and 3 in the 240-24w group. These seven patients were all prior relapsers (i.e. in Cohort 1).

In the subgroup analyses for relapsers (Cohort 1) and partial responders (Cohort 2) the SVR12 rates were at least 30% higher for faldaprevir vs. placebo and were mostly comparable between faldaprevir regimens. Exceptions in Cohort 1 were noted in Asian patients (94.1% 240-12w, 75.0% 240-24w) and those aged < 40 years (66.7% vs. 85.7%).

Table 11.4.1.1.2: 1 Summary of SVR12 rates by subgroups and treatment, relapsers – FAS

	FDV 240-12w			FDV 240-24w			Placebo		
	N[1]	n[2]	(%)	N[1]	n[2]	(%)	N[1]	n[2]	(%)
GT 1 subtype									
1A	46	28	60.9	46	29	63.0	24	3	12.5
1B	53	41	77.4	56	42	75.0	25	4	16.0
Race									
Asian	17	16	94.1	20	15	75.0	6	0	0.0
Black	4	1	25.0	3	0	0.0	0	0	0.0
White	78	52	66.7	78	55	70.5	42	7	16.7
Other	0	0	0.0	1	1	100.0	1	0	0.0
IL28B									
CC	32	28	87.5	28	24	85.7	12	1	8.3
CT	56	35	62.5	63	39	61.9	34	5	14.7
TT	11	6	54.5	10	7	70.0	2	1	50.0
Cirrhosis									
Yes	13	9	69.2	11	6	54.5	6	1	16.7
No	85	59	69.4	91	65	71.4	42	5	11.9
Baseline VL (IU/mL)									
< 800,000	20	16	80.0	22	19	86.4	13	4	30.8
≥ 800,000	79	53	67.1	80	52	65.0	36	3	8.3

In Cohort 2 there were some exceptions that concerned large differences between faldaprevir regimens, including Asian patients (90% vs. 28.6%), cirrhotics (40% vs. 18.8%) and those aged 40-55 years (72.4% vs. 46.2%) but in each instance the denominators are small.

Table 11.4.1.1.2: 2 Summary of SVR12 rates by subgroups and treatment, partial responders – FAS

	FDV 240-12w			FDV 240-24w			Placebo		
	N[1]	n[2]	(%)	N[1]	n[2]	(%)	N[1]	n[2]	(%)
GT 1 subtype									
1A	25	13	52.0	26	15	57.7	14	0	0.0
1B	32	20	62.5	29	11	37.9	15	1	6.7
Race									
Asian	10	9	90.0	7	2	28.6	6	0	0.0
Black	3	0	0.0	1	0	0.0	1	0	0.0
White	44	24	54.5	46	24	52.2	22	1	4.5
Other	0	0	0.0	1	0	0.0	0	0	0.0
IL28B									
CC	5	5	100.0	9	5	55.6	5	0	0.0
CT	45	25	55.6	34	15	44.1	19	1	5.3
TT	7	3	42.9	12	6	50.0	5	0	0.0
Cirrhosis									
Yes	10	4	40.0	16	3	18.8	7	0	0.0
No	47	29	61.7	39	23	59.0	20	1	5.0
Baseline VL (IU/mL)									
< 800,000	7	4	57.1	8	4	50.0	6	0	0.0
≥ 800,000	50	29	58.0	47	22	46.8	23	1	4.3

In null responders the 240-12w group had numerically higher SVR12 rates in GT-1a and IL28B CC patients, whereas the FDV 240-24w group had numerically higher SVR12 rates in Asians, those aged < 40 years and cirrhotic patients but all denominators were rather small.

Table 11.4.1.1.2: 3 Summary of SVR12 rates by subgroups and treatment, null responders – FAS

	FDV 240-12w			FDV 240-24w		
	N[1]	n[2]	(%)	N[1]	n[2]	(%)
GT 1 subtype						
1A	66	17	25.8	69	15	21.7
1B	78	30	38.5	72	31	43.1
Race						
Asian	29	9	31.0	29	15	51.7
Black	4	2	50.0	8	1	12.5
White	109	36	33.0	104	30	28.8
Other	3	1	33.3	0	0	0.0
IL28B						
CC	8	5	62.5	10	5	50.0
CT	100	34	34.0	99	36	36.4
TT	35	9	25.7	32	5	15.6
Cirrhosis						
Yes	40	5	12.5	40	7	17.5
No	105	43	41.0	101	39	38.6
Baseline VL (IU/mL)						
< 800,000	15	6	40.0	15	5	33.3
≥ 800,000	130	42	32.3	126	41	32.5

HCV GT-1 subtype, previous response to treatment, IL28B, cirrhosis and baseline viral load had a significant impact on achieving SVR12 in at least one treatment group. In the logistic regression analyses, in addition to treatment, HCV GT-1 subtype and IL28B:

- *Relapsers and partial responders* - the factors retained in the stepwise model were race, cirrhosis, baseline VL and baseline GGT. Response to previous treatment was no longer significant after adjusting for baseline GGT category.
- *Null responders* - Only cirrhosis was retained in the stepwise model.
- In subgroups by genotype, IL28B, cirrhosis and baseline VL the reasons for not achieving SVR12 were consistent with those in the primary analysis of efficacy.

- In the logistic regression models including country by treatment and centre by treatment none of these interactions was significant in the models. The number of patients (in particular within centre) was not adequate to make any meaningful conclusions on any interactions.

In Cohort 1 ETS was achieved by 85.9% in the 240-12w group and 87.3% in the 240-24w group but in only 4.1% of placebo patients. Most (>75%) faldaprevir patients with ETS also achieved SVR12.

Of the 152 faldaprevir patients who were eligible for RGT based on ETS and completed 24 weeks 120/152 (78.9%) achieved SVR12. Patients who were < 25 IU/mL detected at Week 4 had lower SVR12 rates (37.5%).

In Cohort 2 ETS was achieved by 66.7% in the 240-12w group and 78.2% in the 240-24w group but in only one (3.4%) placebo patient. There were 28/57 (73.7%) patients in the 240-12w group who achieved ETS and also achieved SVR12 compared to 24/55 (55.8%) in the FDV 240-24w group.

In Cohort 3 null responders, ETS was achieved by 157/286 patients (58.6% and 51.1% per group) and 89/157 (56.7%) also achieved SVR12.

The time to <25 IU/mL (undetected) was similarly short for the faldaprevir groups and much more rapid than for placebo patients. In Cohort 1 treatment with faldaprevir, having IL28B CC genotype and baseline VL < 800,000 IU/mL were significantly associated with shorter time to undetected HCV RNA. In Cohort 2 treatment with faldaprevir and IL28B CC genotype were significantly associated with shorter time to undetected. In Cohort 3 having GT-1b virus and not having cirrhosis were the significant factors associated with shorter time to achieving undetected HCV RNA.

- In Cohorts 1 and 2 there were very few on-treatment virological failures. In null responders, more virological failures were noted, consistent with the proportion of failures due to breakthrough.
- Time to rebound from nadir was associated with the same factors that predicted shorter time to achieving undetected HCV RNA but with the addition of race in relapsers, cirrhosis in partial responders, and IL28B in null responders.
- Time to rebound from HCV RNA <25 IU/mL was also associated with these same variables with the addition of variable HCV GT-1 subtype in relapsers.

Most of the cases with relapse after ETR occurred by 4 weeks after stopping treatment and almost all had occurred by 12 weeks after stopping treatment such that no relapses occurred after week 12 post-treatment in Cohorts 2 and 3 and there were only 7 such cases in Cohort 1.

Results in HCV/HIV co-infected patients (TN and TE)

Study 19

There were 308 patients randomised and treated in this study. At the time of the data cut-off for the interim analysis (CSR is dated July 2013) 70.5% were evaluable for the primary endpoint but higher proportions were evaluable for SVR4 (83.8%) and ETR (87.7%). Demographic and baseline characteristics were mostly balanced across the treatment groups. Most patients were male (80.5%) and White (83.1%). Female and Black or African American patients were more likely to have GT-1b virus than GT-1a. The 120 mg group had higher proportions with IL-28B CC (38.2% vs. 28.6%) and fibrosis stage (38.2% vs. 23.2%) than the 240 mg group.

HIV baseline characteristics were balanced across treatment groups and only 11 patients were not taking ARV. Most patients (46.4%) were taking raltegravir (RAL)-based ARV. The most frequent NRTI combination used was emtricitabine + tenofovir. Few patients changed their regimen during the study.

Most patients were adherent to assigned treatment (received ≥80% to <120% of faldaprevir) with rates at least 94% in each group and overall.

For the total 217 evaluable for SVR12, 67.7% (95% CI: 61.5%, 74.0%) achieved SVR12. Based on a lower bound 95% CI > 40%, the applicant concluded that efficacy was significantly higher than PEG/RBV. The lower bound of the 95% CI in each treatment group also exceeded the pre-defined limit based on historical data for PEG/RBV in co-infected patients.

Table 11.4.1.1: 1 SVR12 rates overall and across treatment arms – FAS

	FDV 120-24w N (%)	FDV 240-12w N (%)	FDV 240-24w N (%)	FDV 240-T [0] N (%)	Total N (%)
Number of Patients	123	84	86	185	308
Number of evaluable Patients	83 (100.0)	60 (100.0)	65 (100.0)	134 (100.0)	217 (100.0)
Number (%) of patients with response	53 (63.9)	45 (75.0)	48 (73.8)	94 (70.1)	147 (67.7)
95% Confidence interval [%]	(53.5,74.2)	(64.0,86.0)	(63.2,84.5)	(62.4,77.9)	(61.5,74.0)
p-value[1]					<0.0001

[0]Includes additional patients in the 240mg treatment group that discontinued prior to Week 12
[1]Corresponding to a two-sided test against the historical rate 0.4, i.e., H_0: SVR12 rate = 0.4 vs. Ha: SVR12 rate ≠ 0.4.

Overall, 166/217 (76.5%) achieved ETS and 143/166 (86.1%) achieved SVR12. The overall SVR12 rate was slightly higher for the ETS patients randomised to continue PEG/RBV for 48 weeks (44/48; 91.7%), with rates within the 120-24w and 240-T groups of 12/12 (100%) and 32/36 (88.9%), respectively.

Only 4/51 evaluable patients (7.8%) who did not have ETS achieved SVR12. These 4 patients without ETS had reached Week 24 without discontinuation (No ETS - to continue PEG/RBV for 48 weeks).

Because the current SVR12 data are incomplete a K-M analysis of time to rebound from <25 IU/ml (not detected) was performed to estimate the SVR12 rate for all patients in the FAS. The survival estimate for time to failure at 12 weeks post-treatment was used as the estimate for SVR12. K-M survival estimates were calculated for each of the 9 distinct FDV dose and ETS randomisation categories with an overall survival estimate calculated based on a weighted average of these estimates. Based on this analysis the overall estimate of SVR12 was 84.3% (95% CI: 80.0%, 88.5%).

In this interim analysis there were some notable differences between SVR12 rates but in many instances denominators were relatively small.

Faldaprevir plasma exposure was expected to increase on co-administration of PI/r regimens and to decrease when given with EFV. However, within the 120-24w group the response rates tended to be lower in those on a PI/r-based vs. RAL-based regimen. In the 240 mg groups SVR12 rates were lower for those taking EFV vs. RAL.

Relapse occurred in 17/217 (7.8%) patients evaluable for SVR12 and 15/17 occurred in GT1a patients. Adding up on-treatment failures indicated that breakthrough was the most frequent reason for not achieving SVR12. All but 1 failure while on faldaprevir and one on PEG/RBV occurred in IL-28B Non-CC patients. Also 10/12 relapses in the FDV 240-T group occurred in patients taking an EFV regimen. However, there was considerable overlap between the relapse patients with GT-1a and those taking EFV in the 240-T group.

There were 142 patients with data on SVR12 and SVR24 at the data cut-off. Among these 72 had SVR12 (50.7%) and 69 had SVR24 (48.6%). Hence three patients had SVR12 but did not have SVR24

(95.8% PPV). Overall > 80% achieved RVR, cEVR and W24VR. Rates were comparable between the 120-24w and the 240-T group as well as between the 240-12w and 240-24w groups.

Table 11.4.1.3: 1 Rapid viral response (RVR), complete early viral response (cEVR), and Week 24 viral response (W24VR – FAS

	FDV 120-24w		FDV 240-12w		FDV 240-24w		FDV 240-T [0]		Total	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Number of Patients	123	(100.0)	84	(100.0)	86	(100.0)	185	(100.0)	308	(100.0)
RVR	97	(78.9)	72	(85.7)	76	(88.4)	157	(84.9)	254	(82.5)
ETS	95	(77.2)	70	(83.3)	73	(84.9)	150	(81.1)	245	(79.5)
cEVR	101	(82.1)	75	(89.3)	77	(89.5)	157	(84.9)	258	(83.8)
W24VR	96	(78.0)	72	(85.7)	78	(90.7)	152	(82.2)	248	(80.5)

IL28B CC genotype and having baseline VL <800,000 IU/mL were significantly associated with shorter time to achieving HCV RNA undetected. Having GT-1b subtype virus and not being of Black/African American race were marginally significant. There was also a shorter time to HCV RNA undetected for the 240 mg (without EFV) vs. 240 mg (with EFV) subgroups.

Resistance analyses across the Phase 2 and 3 studies

Resistance monitoring of clinical isolates included all baseline samples and select post-baseline samples from non-SVR patients with sufficient viral load in the Phase 2 and 3 clinical efficacy studies. In the absence of approved, standard assays for genotyping and phenotyping of variant NS3/4A proteases the applicant developed in-house techniques.

NS3/4A population sequencing was performed for the majority of GT1a and GT1b baseline samples (99%; 3239/3269 with NS3 protease domain sequence) to identify amino acid polymorphisms and examine the relationship of baseline sequence to virological response. Post-baseline NS3/4A sequences (1068 patients with NS3 protease domain sequence that included 77.8% [672/864] of non-SVR12 patients were analysed to identify mutations in NS3/4A that emerged in treated patients who experienced virological failure and to evaluate the persistence of resistance-associated mutations (RAMs) in the post-treatment follow-up period.

Baseline Analysis

NS3/4A population sequencing of baseline isolates reflected the natural heterogeneity of HCV quasispecies with the rates of conservation of wild-type reference amino acid generally similar to sequences assembled from public databases. The major treatment-emergent variants associated with resistance to FDV are detected at NS3 codons 155 and 168. R155 and D168 amino acids were highly conserved (>99% of population sequences with wild-type) in both GT1a and GT1b clinical baseline isolates and rare pre-existing variants did not necessarily preclude patients from achieving a virological response.

Phenotypic analysis of NS3 proteases from baseline clinical isolates in study 02 showed that faldaprevir EC50 values were similar for both GT1a and GT1b baseline isolates. A minor change in faldaprevir susceptibility was noted for one GT1b baseline isolate encoding an NS3 V170T substitution. GT1b V170T is a rare baseline substitution at this highly polymorphic position, and though associated with a 5.2-fold shift in faldaprevir EC50 and lower initial viral load decline, was not associated with virological breakthrough during faldaprevir monotherapy with the 20 mg dose. The patient with baseline V170T did achieve a virological response after switching to faldaprevir plus PEG/RBV. Thus, V170T represents a rare polymorphism that does not preclude a response to faldaprevir.

Among all NS3 amino acids analysed with available phenotypic data from clinical isolates in study 02 only GT1a isolates with a Q80K were significantly ($p < 0.001$) associated with reduced in-vitro susceptibility to faldaprevir but there was only a 2-fold difference relative to isolates without Q80K. Q80K was a common GT1a polymorphism (30.4% of GT1a in Phase 3) but was rarely detected in GT1b baseline clinical isolates.

The analysis of baseline NS3/4A amino acid polymorphisms and response is confounded by small sample sizes, baseline IL28B genotype and degree of liver cirrhosis among other factors. In Phases 2 and 3 no amino acid position in the NS3 protease domain, including Q80K, was found to be significantly associated with a reduced SVR rate in TN or TE patients although initial Phase 2 data suggested a relationship existed.

Phase 2 and 3 analyses of the region beyond the NS3 protease domain did not identify non-consensus baseline NS4A variants associated with reduced SVR. GT1a F418Y and GT1b T344I variants were the only variants in the NS3 helicase domain identified that were associated with reduced response.

However, the reduced SVR among patients in the placebo group with these variants, the enrichment of T344I in pre-treatment samples from TE patients, and the lack of predominant emergent variants detected at NS3 418 or NS3 344, suggest that these amino acid sites in the NS3 helicase domain may be related to a differential response to PEG/RBV rather than to faldaprevir or represent T-cell epitopes subject to mutation escape.

In summary, no single NS3 protease domain or non-consensus NS4A polymorphism was associated with a significant ($p< 0.05$) reduction in SVR in a pooled analysis across all treatment groups.

Emergence Analysis

Major NS3 R155 and D168 RAVs

The predominant resistance associated variants (RAVs) that emerged in patients who did not achieve SVR were detected at NS3 codons 155 and/or 168. RAVs at these positions emerged at a high frequency in non-SVR patients in Phase 3 with up to 91.3% of GT1a with R155 substitutions and 79% of GT1b with D168 variants so that very few non-SVR patients lacked R155 or D168 RAVs: 4% (13/321) of GT1a and 15.5% of (31/200) GT1b.

NS3 R155K and NS3 D168V were the most frequently detected RAVs in >10% of non-SVR GT1a and GT1b patients, respectively. Other variants that emerged in >10% of non-SVR GT1b patients included R155K and R155Q. Also, D168V was detected in 8.4% of GT1a non-SVR patients.

D168 variants were more heterogeneous (V/A/N/T/E/I/H/L/F/K/P/Y) than R155 substitutions (K/Q/T/S/G/C). In a small number of patients, dual R155+D168 RAVs emerged (R155Q+D168V/N or R155K+D168E) in the same clinical isolate. D168 variants conferred a larger reduction in FDV susceptibility than R155 variants in *in vitro* phenotyping assays. Clinical isolates with R155K showed a reduced susceptibility to FDV that ranged from 130- to 520-fold compared to the 1100- to 2800-fold reductions conferred by D168V clinical isolates.

R155G/R and R155C/R were detected once each and in patients who did not achieve SVR in the "other" category of failure. These substitutions were only observed as mixtures and the predominant variant at failure could not be confirmed. D168 substitutions I, F, L, K or P in Phase 3 were only detected in the presence of more predominant D168 substitutions (V, N, and/or T) within the same clinical isolate. Since F, L, K, and P represent unconfirmed individual D168 substitutions that have been inferred from population sequence analysis and degeneracy in codon usage, their biological relevance has not been substantiated.

Most cases of breakthrough showed the emergence of RAVs at NS3 R155 or D168 (> 99% of faldaprevir breakthroughs and > 94% of PR breakthroughs in Phase 3). R155 and D168 RAVs were more frequently detected in GT1a relapsers compared to GT1b relapsers, which reflects the longer post-treatment persistence of the major GT1a R155 variants relative to the major GT1b D168 variants. In Phase 3 more GT1b relapsers lacked detectable R155 and D168 RAVs and encoded wild-type (14.9%, 10/97) compared to GT1a relapsers [only 2% (2/101) lacking R155 and D168 RAVs]. The other types of failures largely included patients that prematurely discontinued treatment or were lost to follow-up and were associated with a lower frequency of detectable R155 and D168 RAVs with 11.7% of GT1a and 22.1% of GT1b with available sequence in Phase 3 studies encoding wild type at these positions. In an analysis of all non-SVR patients, there was no substantial difference in the frequency or amino acid substitutions detected at R155 or D168 between TN or TE patients nor was there a substantial difference between patients who received 120 mg or 240 mg.

Analysis of low-frequency, minor emerging NS3/4A variants

The techniques used in population sequencing differed between Phase 2 and Phase 3 in that Phase 2 used a lower threshold for variant identification. As a result, more amino acid mixtures and minor variants are reported in Phase 2 baseline and emergent analyses than in Phase3.

Also, since Phase 2 analyses employed a more sensitive process for the detection of variants, a higher threshold of ≥3 emergent minor variants was used for analysis, compared to a threshold of >1 minor variant in Phase 3. Only one variant, NS3 S61L, emerged at a low frequency and only with D168 substitutions in both Phase 2 and 3 failures and may represent an unknown polymorphism, a compensatory mutation, or substitution that influences susceptibility in GT1b infected patients.

Although the pre-clinical resistance profile included variants at NS3 codon 156 in GT1b in addition to 155 and 168, A156 RAVs alone were not observed with failures in Phase 2 or 3. In the in-vitro selection studies A156 variants were only selected at lower faldaprevir concentrations and were not detected at 10-fold higher concentrations.

In Phase 2 a relapse on day 204 (follow-up week 4) encoded R155K variants and only in a subsequent visit (follow-up week 28) was A156A/T mixture detected alone. Another relapse in Phase 2 was associated with D168E RAVs at the SVR12 time point and only at the later SVR24 time point was an A156A/T mixture detected with D168E (patient 11701).

In Phase 3 two A156 variants emerged but only as A156A/G mixtures. One breakthrough virus encoded D168V variants at week 8 and only at the week 24 visit was an A156A/G mixture detected with D168V RAVs. A second patient experienced breakthrough at week 24 at which time D168 RAVs were detected with A156A/G mixtures. Though A156 variants have been shown to reduce susceptibility up to 230-fold (e.g. A156T), a predominant A156 variant did not emerge during treatment and A156 mixtures were only detected with the predominant D168 RAVs associated with failure.

An NS3 Q80K variant only emerged once in Phase 2 in a GT1a relapse and was detected with a predominant R155K. In Phase 3, Q80K/Q mixtures were detected in one breakthrough and one in the "other" category of failure. The GT1a breakthrough occurred at week 18 with R155K detected at week 24; only at the subsequent planned end of treatment visit was a Q80K/Q mixture detected with R155K. The "other" GT1a failure occurred at week 18 with predominant R155K RAVs and a mixture of Q80K/Q. There was also one GT1b placebo-treated patient with an emergent Q80K variant. Therefore, there was a low frequency at which Q80K variants emerged in faldaprevir-treated patients and they were Q80K/Q mixtures with predominant R155 or D168 RAVs.

Emergent NS3 V170T was detected together with D168E in the relapse sample for one GT1b patient in Phase 2. In Phase 3 V170T variants emerged in only one GT1b patient as a V170I/T mixture with

D168E/D at a follow-up week 24 visit which was subsequent to detection of R155K in the relapse sample at follow-up week 4. Thus, V170T emerged at a low frequency, only in relapses, and only with predominant D168 RAVs.

Overall, there was no correlation between the faldaprevir breakthrough rate and PK parameters reflecting the low numbers of breakthroughs. Similarly, there was no apparent correlation between plasma concentrations and failure and the rate of the emergence of R155 or D168 and other variant strains.

Persistence Analysis

Persistence of R155 and D168 RAVs in Phase 2 clonal sequence analysis first indicated longer persistence of R155K variants compared to D168V. The estimated time to when 50% of all non-SVR patients have wild-type virus with concomitant loss of R155 or D168 RAVs was similar between Phase 2 and 3 Kaplan-Meier analyses, showing a median time to loss of R155 variants of 280 days, which was longer than the median time to loss of 145 days for D168 variants. One year after failure with an R155 or D168 RAV, R155 variants were still detected in 78.3% of patients while D168 variants were detected in 51.3%. Sequencing of additional follow-up samples from the Phase 3 studies is ongoing.

Other analyses across studies

Response-Guided Therapy (RGT) was not successful for TE partial and null responders in study 05. In Phase 3 RGT was tested in TN and TE relapsers. The ETS rates were similar for TN (83.9%) and TE relapsers (86.6%) but the relapse rate for TE relapsers was higher (22.0% vs. 12.8%), resulting in a lower SVR12 rate for patients who met the criteria for stopping treatment at Week 24 (75.3% for TE relapsers compared to 83.2% for TN patients).

Table 3.2.1.5.4: 4 ETS, corresponding SVR12 rates and relapse rates overall and by Week 4 HCV RNA (undetected vs. detected) – TN pooled and TE relapsers

		TN		TE Relapsers		TN+ TE Relapsers	
Week 4 HCV RNA		N	(%)	N	(%)	N	(%)
	Number of patients	1045	(100.0)	201	(100.0)	1246	(100.0)
Overall	Number of patients [1]	877	(83.9)	174	(86.6)	1051	(84.3)
	SVR12 = Yes [3]	730	(83.2)	131	(75.3)	861	(81.9)
	N (%) with ETR [2]	775	(88.4)	150	(86.2)	925	(88.0)
	Relapse rate [3]	99	(12.8)	33	(22.0)	132	(14.3)
Undetected	Number of patients [1]	737	(70.5)	145	(72.1)	882	(70.8)
	SVR12 = Yes [3]	648	(87.9)	122	(84.1)	770	(87.3)
	N (%) with ETR [2]	653	(88.6)	129	(89.0)	782	(88.7)
	Relapse rate [3]	57	(8.7)	21	(16.3)	78	(10.0)
Detected	Number of patients [1]	140	(13.4)	29	(14.4)	169	(13.6)
	SVR12 = Yes [3]	82	(58.6)	9	(31.0)	91	(53.8)
	N (%) with ETR [2]	122	(87.1)	21	(72.4)	143	(84.6)
	Relapse rate [3]	42	(34.4)	12	(57.1)	54	(37.8)

In both populations, the proportion achieving ETS with HCV RNA not detected at Week 4 was >70% with a smaller proportion (13.6%) being <25 IU/mL, detected. Among the patients who were <25 IU/mL (detected) at Week 4, the combined relapse rate was 37.8% compared to 10% for patients who were undetected at Week 4, with a higher relapse rate in TE relapsers compared to TN patients.

For those with HCV RNA detected at Week 4 the question remains whether there would have been benefit from longer treatment with PEG/RBV. Data to address this come from studies 05 and 19 in

which there was re-randomisation at Week 24 to stop or continue PEG/RBV among those who had met RGT criteria. These included the same Week 4 criterion as in Phase 3. For patients who were undetected at Week 4, the results are clear that an extra 24 weeks of PEG/RBV is not needed. For the patients who were <25 IU/mL (detected) at Week 4 there are only small numbers but the data suggest a marginal benefit, if any, of extending PEG/RBV to 48 weeks. On this basis the applicant states that it is hard to justify extending treatment for all patients who are <25 IU/mL (detected) at Week 4.

Table 3.2.1.5.4: 5 SVR rates for patients who met RGT criteria [1] by achievement of undetected HCV RNA at Week 4 and re-randomization in SILEN-C1 and 1220.19

		1220.5 (SILEN-C1)		1220.19	
Week 4		PR24	PR48	PR24	PR48
< 25 IU/mL (detected)	N	22	22	28	14
	SVR [2] N	15	18	20	11
	SVR [2] %	68.2%	81.8%	71.4%	78.6%
< 25 IU/mL (undetected)	N	83	85	77	65
	SVR [2] N	77	82	72	64
	SVR [2] %	92.8%	96.5%	93.5%	98.5%

[1] RGT criteria in 1220.5 was < 25 IU/mL (detected or undetected) at Week 4 and undetected at Weeks 12-20 and <25 IU/mL (detected or undetected) at Week 4 and undetected at Week 8 in 1220.19. All patients in these studies who achieved these criteria were re-randomized at Week 24 to stop (PR24 group) or continue (PR48 group) PegIFN/RBV

[2] SVR24 for patients in 1220.5, SVR12 for patients in 1220.19 (interim, based on May 29 snapshot updated results)

A post-hoc assessment of the Phase 3 study concordance between Week 8 (ETS) or Week 12 (ETS12) showed that applying ETS or ETS12 led to nearly identical SVR12 rates. There were 55/1045 patients with discordant ETS vs. ETS12 yielding a very high concordance rate of 94.7%.

Table 3.2.1.5.4: 6 ETS, ETS12 and concordances of the 2 RGT definitions in pooled TN trials and TE relapsers

		FDV 120-Total	FDV 240-12w	FDV Total
Number of patients		521	524	1045
ETS achieved	N (%)	436 (83.7)	441 (84.2)	877 (83.9)
	SVR12 N (%)	362 (83.0)	368 (83.4)	730 (83.2)
ETS12 achieved	N (%)	435 (83.5)	433 (82.6)	868 (83.1)
	SVR12 N (%)	362 (83.2)	371 (85.7)	733 (84.4)
Concordance [1]	% (n/N)	94.8 (494/521)	94.7 (496/524)	94.7 (990/1045)
PPV ETS vs ETS12	% (n/N)	96.8 (422/436)	95.9 (423/441)	96.4 (845/877)
NPV ETS vs ETS12	% (n/N)	84.7 (72/85)	88.0 (73/83)	86.3 (145/168)

CHMP's comment on efficacy

Posology and duration of therapy

The three placebo-controlled Phase 3 studies clearly point to the advantage of adding faldaprevir to PEG/RBV in chronic HCV due to GT1 viruses. The most important issues for discussion are the derivation of the faldaprevir dose regimen recommendations and the futility criteria.

As an overall comment, it is not logical that a different dose of faldaprevir was studied and is proposed in the SmPC according to PEG/RBV TN or TE status. This critical matter requires further discussion by the applicant. The fact that patients have or have not been previously exposed to PEG/RBV would not *per se* have any impact on the antiviral activity of faldaprevir. The overall efficacy of faldaprevir plus PEG/RBV may well differ according to prior exposure to PEG/RBV but this would be due to factors

impacting on the efficacy of PEG/RBV and not faldaprevir. There are some factors that could impact on the efficacy of faldaprevir itself but these are not linked to prior exposure to PEG/RBV. Prior exposure to another HCV protease inhibitor might affect antiviral activity if this had selected for mutations conferring reduced susceptibility to faldaprevir but no such patients were enrolled into the studies in this dossier. Other factors that may affect antiviral activity include the plasma and intrahepatic concentrations of faldaprevir and its two active metabolites as well as HCV sub-genotype (GT1a or GT1b).

There are several pieces of data and issues to consider regarding the efficacy of faldaprevir and the dose regimens proposed by the applicant.

- In the **monotherapy** study (02) it was clear that the lowest dose in TN cohorts had an initial and short term effect on viral load but the rebound was least with the highest dose. There was a relationship between dose, plasma exposure and effect on viral load. The TE patients all received PEG/RBV and effects on viral load were not dose or exposure-related but the lowest dose was associated with some breakthroughs. Thus it was appropriate to evaluate 120 mg and 240 mg QD doses further.
- **Study 05** showed that TN patients had higher SVR24 rates with 24 weeks faldaprevir vs. placebo with no apparent difference between 120 mg QD and 240 mg QD and no benefit from lead-in at the 240 mg QD dose level.
- The CSRs for the Phase 3 studies in mono-infected suggest that small numbers had not reached the 12 weeks post-therapy time point yet they had not been withdrawn earlier for any reason since the numbers do not add up to the total treated. The applicant should confirm whether the final outcomes are currently incomplete. In study **19** it is quite clear that the data are incomplete. The applicant should update all SVR12 rates (as necessary) at the time of answering the LOQ.
- The Phase 3 data in **TN patients** are not entirely straightforward with regard to supporting 120 mg QD for 12 weeks. When considering the following it should be noted that the primary analyses were adjusted for GT-1a and GT-1b and race and that an additional adjustment for IL28B had no important effect on the results.
- In study 30 66% of HCV were GT-1b while ~25% of patients were Asian and predominantly Japanese. Using the protocol-defined criteria for RGT the majority in the 120 mg RGT group (87.3%) was eligible to stop faldaprevir at 12 weeks and the majority in both faldaprevir groups (~80%) was eligible to stop PEG/RBV at 24 weeks. The primary and sensitivity analyses showed that 120 mg, mostly for 12 weeks due to the high ETS rates, was as good as 240 mg for 12 weeks.
- In faldaprevir and placebo groups SVR12 rates (and ETS rates) were lower for GT-1a vs. GT-1b, for whites vs. Asians, for cirrhotics vs. non-cirrhotics, for IL28B non-CC vs. CT or TT and for those with the highest baseline VL. Within the various subgroups the faldaprevir regimens mostly gave comparable SVR12 rates although 120-RGT gave slightly lower SVR12 for GT-1a and for Asians. The overall and GT-1a rates of breakthrough during the first 12 weeks of treatment were slightly higher for 120-RGT vs. 240-12w.
- In study 47 60% of HCV were GT-1a while ~19% of patients were Asians (Korean and Taiwanese rather than Japanese) but 123/129 Asians had GT-1b. The 120 mg for 12 weeks regimen was not studied and no RGT was applied to faldaprevir. Reflecting the difference in percentages with GT-1a vs. GT-1b and other baseline differences between study populations the overall SVR12 rates were lower than in study 30 in all treatment groups.

The comparison of the 120-24w or 240-12w groups, 80% of whom were eligible for 24 weeks PEG/RBV, indicated that they gave broadly comparable SVR12 rates. However, 120-24 gave slightly higher SVR12 rates than 240-12 for GT-1b infections and, hence, for Asians. In addition, 120-24 appeared to be slightly better than 240-12 in most other subgroups. Nevertheless, for GT-1a and for IL28B non-CC there did not seem to be an advantage for a longer duration of therapy.

- In summary, the applicant's proposed standard dose regimen in TN patients of 120 mg QD faldaprevir for 12 weeks ***regardless of ETS*** plus 24 weeks PEG/RBV to be extended only if ETS is not achieved was not actually studied. A regimen of 120 mg for 12 weeks for those ***with ETS*** was evaluated in only one Phase 3 study in which two-thirds of patients had GT-1b. The dossier lacks a direct comparison between 120 mg QD for 12 weeks vs. 120 mg for 24 weeks. Nevertheless, addition of faldaprevir consistently achieved superiority over placebo and the applicant's rationale for recommending a standard regimen of 120 mg for 12 weeks in the TN population is acceptable.

- In study 07 **TE patients who were prior relapsers** did not receive the 120 mg QD dose. Only the 240 mg QD dose was evaluated for 12 or 24 weeks. ETS was achieved by 86-87% in the two faldaprevir groups so the majority of patients received only 24 weeks PEG/RBV.

  Within the TE relapsers cohort the SVR12 rates were the same for 12 or 24 weeks 240 mg QD faldaprevir and very clearly distinguishable from placebo. The 95% CI were -12.3, 12.9 but the study was not powered for showing non-inferiority between faldaprevir regimens within this cohort. The SVR12 rates were higher for GT-1b and Asians. The actual data support 240 mg for 12 weeks plus PEG/RBV for 24 or 48 weeks according to ETS.

  However, there are also limited data up to June 2013 in HCV/HIV co-infected patients who were TE relapsers showing that virological responses with 120-24w were similar to those observed with 240 mg. On this basis, and taking into account all the other evidence suggesting no important advantage for prolonging faldaprevir from 12 to 24 weeks, the applicant proposes treating TE relapsers exactly as for TN patients.

- Study 07 in **TE patients who were partial or null responders** evaluated 240 mg QD for 12 weeks plus a fixed PEG/RBV duration of 48 weeks in each of these Cohorts.

  In the **partial responders** the benefit of faldaprevir over placebo was very clear and the SVR12 rates suggested no advantage for 24 weeks vs. 12 weeks faldaprevir. In the **null responders** there was again no difference between faldaprevir groups but the actual rates were lower (33%) compared with the other cohorts (> 50%). Although there was no placebo group it can be accepted that these SVR12 rates would be superior to re-treatment with PEG/RBV alone. The subgroup analyses involve too small numbers for conclusions to be drawn.

  Therefore the data from study 07 support 240 mg QD for 12 weeks for any PEG/RBV TE patients and they support use of 48 weeks PEG/RBV except that prior relapsers with ETS could have 24 weeks. However, based on virological considerations, it remains possible that 120 mg QD for 12 or 24 weeks would be similarly efficacious. It is also possible that the duration of PEG/RBV could be shortened according to ETS in all TE patients rather than just the TE relapsers. Unfortunately there are no data and the applicant has provided no argumentation on scientific grounds to consider these alternatives.

- The Phase 3 data in **HIV/HCV co-infected** patients represent outcomes in a mixture of TN and TE patients who were prior relapsers and a range of different regimens due to the adjustments allowed in the amended protocol. The 120 mg QD for 12 weeks regimen was not studied, the 120-24w regimen was added by protocol amendment and many in this group received DRV/r or ATV/r.

The use of EFV had a negative effect on plasma levels and efficacy in the 240 mg group. In addition to these issues the data up to June 2013 are still incomplete.

The 120 mg dose was added by amendment and was mandated for those taking DRV/r or ATV/r because the DDI study showed that DRV/r increased plasma exposures to faldaprevir. The total 120 mg group had higher proportions with IL-28B CC (38.2% vs. 28.6%) and fibrosis stage F3 or higher (38.2% vs. 23.2%) than the 240 mg group. In the 120 mg group 43.9% were taking DRV/r and 9.8% were taking ATV/r but response rates tended to be lower in those on a PI/r-based vs. RAL-based regimen. This occurred despite the fact that plasma exposure to faldaprevir was higher for patients taking DRV/r (GM trough 2010 ng/mL) compared to those treated with 120 mg faldaprevir in conjunction with raltegravir (GM trough 1390 ng/mL).

In principle, it is rational to apply the same dose recommendations to the co-infected patients as finally determined for the mono-infected TN and the TE subsets in the absence of co-administered medications with implications for dose adjustment. However, the available data raise several other issues regarding how to dose the co-infected based on their HIV regimen. In this regard the data from study 019 are very difficult to interpret over and above accepting the conclusion that, although there was no placebo group, the available data do support a conclusion that addition of faldaprevir to PEG/RBV is beneficial. Related to this are concerns regarding the recommendation to use 240 mg EFV in HCV/HIV co-infected patients because the SVR12 rates appear to be very low in this subset and it is doubtful that EFV should be used during faldaprevir therapy.

- The SVR12 rates in mono-infected patients with **compensated cirrhosis** were lower when adjusted for other baseline predictors. In HCV mono-infected TN and TE patients with cirrhosis the applicant states that there was little or no evidence to support use of 240 mg vs. 120 mg or 24 weeks vs. 12 weeks but the data in individual studies (although small numbers) do not necessarily support this conclusion and the total data have not been pulled together to ascertain the overall picture. Despite this conclusion the applicant proposes in the SmPC that TN or TE patients with [compensated] cirrhosis may benefit from a total of 48 weeks PEG/RBV. There is a need to further substantiate the dose recommendations for these subsets.

Futility

The recommendations made in the SmPC do not reflect the rules that were applied during the Phase 2/3 studies. However, in the summary of efficacy the applicant provided a justification for the very simple futility rules that have been suggested. The rules suggested from the retrospective analyses in TN and TE patients are not very convincing and require further consideration.

Other issues - factors affecting efficacy

In-vitro data showed that faldaprevir inhibited HCV RNA replication of GT1b and la with mean EC50 values of 3.1 nM and 6.5 nM, respectively. The efficacy of faldaprevir against GT1a was consistently lower than for GT1b and lower in whites vs. Asians. The same pattern applied to the placebo group in study 30 but not in study 47 although rates were always lower than for faldaprevir.

The POPPK analysis was conducted to evaluate predictors of systemic FDV exposure in TN and TE patients in the placebo-controlled Phase 3 studies. The 240 mg dose gives supra-dose proportional exposure with an apparent increase in bioavailability of 84% over 120 mg. Apparent clearance is inversely related to total bilirubin concentration which is generally higher for 240 mg than for 120 mg. The increased bioavailability and decreased clearance with the 240 mg dose contribute to a model predicted 6.2-fold increase in trough concentration over the 120 mg dose. Nevertheless, the clinical efficacy in TN patients does not suggest an advantage for the 240 mg dose.

Other than the dose, factors associated with faldaprevir exposure in these Phase 3 studies included Japanese ethnicity, bilirubin and body size (height being the most sensitive predictor). The Company reports that none of these factors was associated with significant differences in faldaprevir efficacy, from which the applicant concludes that prospective dose adjustment based on these factors is not needed. Overall, the assessor agrees that the data do not point clearly towards a dose adjustment schema based on patient or HCV characteristics. Also, although faldaprevir efficacy was lower in some sub-groups than others it was consistently better than placebo.

To summarise – recommendations in need of more justification are in red text:

Treatment-Naïve and Prior Relapser Patients*			
HCV RNA	**Faldaprevir 120 mg, peginterferon alfa and ribavirin**	**Peginterferon alfa and ribavirin**	**Total treatment duration**
<25 IU/mL at Week 4, and <25 IU/mL target not detected at Week 12	12 weeks	Additional 12 weeks	24 weeks
≥25 IU/mL at Week 4 or detected at Week 12	12 weeks	Additional 36 weeks	48 weeks
Partial and Null Responder Patients **			
	Faldaprevir 240 mg, peginterferon alfa and ribavirin	**Peginterferon alfa and ribavirin**	**Total treatment duration**
All Patients	12 weeks	Additional 36 weeks	48 weeks

*On the first day of treatment patients receive a single loading dose of 240 mg
** On the first day of treatment patients receive a single loading dose of 480 mg

Treatment Futility Rules: All Patients

HCV RNA	***Action***
Week 4 or Week 12: Greater than 100 IU/mL	***Discontinue Faldaprevir and peginterferon and ribavirin***
Week 24: Detectable	*Discontinue peginterferon and ribavirin*

Patients with cirrhosis (treatment-naïve or experienced) may benefit from a total of 48 weeks treatment duration of peginterferon alfa and ribavirin (see section 5.2, *Clinical efficacy and safety*).

HIV/HCV co-infected patients on an efavirenz-based antiretroviral regimen should take the 240 mg dose of Faldaprevir Boehringer Ingelheim (see section 4.5).

Clinical Safety

The safety data are reported up to February/March 2013. A total of 3819 subjects and HCV-infected patients were treated with faldaprevir or placebo in Phases 1-3 of which 3355 were exposed to faldaprevir and > 70% received at least 12 weeks of treatment. Also, ≥ 85% of the 1358 HCV-infected patients treated with faldaprevir in the three placebo-controlled Phase 3 studies received ≥ 12 weeks.

Adverse events

Healthy subjects

Gastrointestinal disorders (52.9%) were the most frequently reported AEs and nausea (31.5%), diarrhoea (29.7%), vomiting (16.4%) and abdominal pain upper (5.5%) were the most frequently gastrointestinal events for faldaprevir-treated subjects while jaundice occurred in 7.5% and hyperbilirubinaemia in 1.8%. Skin and subcutaneous tissue disorders were reported in 7.9% with faldaprevir and 5.1% with placebo. Additional AEs reported more frequently with faldaprevir than with placebo included headache (23.8% vs. 15.4%), fatigue (5.3% vs. 0%), ocular icterus (7.5% vs. 0%) and decreased appetite (3.6% vs. 0%).

In **study 03** marked hyperbilirubinaemia (>3.0 mg/dL) was reported as an AE in 2 subjects in the 480 mg group and 5 subjects in the 1200 mg group. These subjects had elevated unconjugated bilirubin due to inhibition of UGT1A1 by faldaprevir and genotyping showed a polymorphism in the UGT1A1 gene in 6/7 subjects. Some degree of elevated unconjugated bilirubin was observed in 2 subjects at 120 mg, 3 at 240 mg, 4 at 480 mg, all at 800 mg and 1200 mg doses and all who received 480 mg with food.

Phase 2 studies 05 and 40

Almost all patients (848/873; 97.1%) reported at least one AE but those treated with faldaprevir had a greater frequency of severe AEs, primarily with BID dosing. AEs reported in a higher proportion treated with faldaprevir 240 mg vs. placebo included nausea (47.4% vs. 19.7%), pruritus (35.9% vs. 16.9%), diarrhoea (30.4% vs. 18.3%), rash (25.4% vs. 16.9%), vomiting (19.8% vs. 5.6%) and jaundice (19.6% vs. 1.4%). AEs reported in a higher proportion treated with 120 mg vs. placebo included nausea (30.1% vs. 19.7%), pruritus (33.2% vs. 16.9%), dry skin (20.1% vs. 14.1%) and arthralgia (12.2% vs. 7.0%).

Phase 3 studies in patients with HCV mono-infection

Almost all patients reported AEs during the double-blind phase (97.6% to 98.7% faldaprevir and 96.2% PEG/RBV only) and there were no clinically relevant differences in AE profiles between TN and TE patients. AEs within the GI disorders and skin and subcutaneous tissue disorders SOCs were reported more frequently with faldaprevir at either dose vs. placebo and the rates increased with dose and duration of therapy. Skin and subcutaneous tissue disorders were reported by 61.4% in the placebo group vs. 68.7% and 70.3% treated with faldaprevir 120 mg or 240-12w. Other AEs reported at higher rates with increasing dose (120-Total vs. 240-12 w and 240-Total) included pruritus (29.2% vs. 33.1 % and 34.1%), dry skin (12.5% vs. 16.3% and 16.6%), jaundice (4.4% vs. 14.9% and 15.3%), hyperbilirubinaemia (2.3% vs. 7.4% and 7.3%) and ocular icterus (1.7% vs. 4.6% and 4.4%). Frequently reported AEs such as fatigue, pyrexia, headache, insomnia and anaemia were reported in a similar proportion in the faldaprevir and placebo groups, reflecting their association with PEG/RBV.

Faldaprevir patients had a higher frequency of Grade 3 or 4 AEs compared with the placebo group (~22% vs. 15.5%) but rates were similar by faldaprevir dose and duration. For example, 10.2% to 11.1% of faldaprevir patients had DAIDS Grade 3-4 blood and lymphatic disorders compared with 7.6% in the placebo group. Neutropenia (5.8%), anaemia (3.6%) and thrombocytopenia (1.5%) were the most frequently reported DAIDS Grade 3-4 AEs within this SOC.

Grade 4 AEs were infrequent (3.4%) and were reported in a higher proportion of faldaprevir-treated patients (3.1% to 5.1%) vs. the placebo group (1.5%) and the rates tended to increase with increasing dose and treatment duration.

AEs reported in a higher proportion (≥5%) in the 120-Total group **vs. placebo (PC Phase 3 studies)**

	FDV 120-Total		FDV 240-12w		FDV 240-24w		FDV 240-Total		Placebo	
System organ class / Preferred term	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
Number of subjects	521	(100.0)	680	(100.0)	157	(100.0)	837	(100.0)	342	(100.0)
Total with adverse events	511	(98.1)	664	(97.6)	155	(98.7)	819	(97.8)	329	(96.2)
Nausea	172	(33.0)	326	(47.9)	88	(56.1)	414	(49.5)	88	(25.7)
Rash	163	(31.3)	213	(31.3)	43	(27.4)	256	(30.6)	82	(24.0)
Diarrhoea	125	(24.0)	204	(30.0)	58	(36.9)	262	(31.3)	50	(14.6)
Vomiting	68	(13.1)	168	(24.7)	47	(29.9)	215	(25.7)	22	(6.4)
Additional AEs reported in a higher proportion (≥5%) in the 240-12w group **vs. placebo (PC Phase 3 studies)**										
Jaundice	23	(4.4)	101	(14.9)	27	(17.2)	128	(15.3)	2	(0.6)
Hyperbilirubinaemia	12	(2.3)	50	(7.4)	11	(7.0)	61	(7.3)	1	(0.3)

Treatment-related AEs that reported in a higher proportion treated with 240 mg compared with placebo included nausea (47.6% vs. 22.8%), rash (28.9% vs. 21.9%), diarrhoea (25.7% vs. 9.1%), vomiting (24.0% vs. 5.0%), jaundice (14.9% vs. 0.6%) and hyperbilirubinaemia (7.2% vs. 0.3%). For treatment-related AEs with 120 mg vs. placebo rates were nausea (29.9% vs. 22.8%), rash (28.8% vs. 21.9%), diarrhoea (18.6%% vs. 9.1%) and vomiting (10.2% vs. 5.0%). Other treatment-related AEs of note included photosensitivity reactions, which were reported infrequently across all treatment groups (1.6%). Treatment-related hepatic failure was reported in 2 (0.3%) patients treated with 240 mg for 12 weeks

Some observations of special interest included the following:

There was a much lower incidence of **photosensitivity reactions** in Phase 3 (1.7%) vs. Phase 2 studies (8.9%), which likely reflects the implementation of sun protection measures in Phase 3, giving rates by dose group which were 0.2% for 120 mg, 2.7% for 240 mg and 1.5% for placebo.

In the TN patients **rash** was observed in 31.4% on placebo, 37.8% treated with 120 mg QD and 42.9% treated with 240 mg QD. Among TE patients the rates were lower for placebo (25.6%) and for faldaprevir (32-34% per regimen). Rates of at least DAIDS Grade 2 rash were ~ 4-7% while ≤ 1.0% experienced DAIDS Grade 3 events. The Kaplan-Meier curves showed a relatively linear increase in cumulative numbers experiencing onset of rash until about Week 12, after which there were few additional events.

Patients from the Asian region had the highest rash rates regardless of treatment with 51.4% for faldaprevir and 44.8% for placebo while rates for DAIDS Grade 2 or higher rashes were 10.8% vs. 7.7%. The faldaprevir attributable risk was about 9% in Asians and 8% in Whites, suggesting a strong contribution of PEG/RBV to the higher rate of rash in Asians as well as Whites. Rates of rash appeared to increase with increasing age but did not differ by gender in the faldaprevir and placebo groups. There was no clear relationship between plasma concentration of faldaprevir and rash, although the highest quartile tended to have a higher proportion with rashes. While Asians tended to have more rash events than non-Asians, logistic regression analysis indicated that this effect was likely not due to the increased exposure observed in Asian patients relative to non-Asian patients.

The incidence of **GI AEs** increased with faldaprevir dose (120 mg 58.0%, 240-12w 68.2%) and slightly with duration of 240 mg QD (68.2% 12w and 71.3% 24w). Rates of Grade 3 or 4 GI AEs were low but also increased with faldaprevir dose and duration. Based on the Kaplan-Meier estimates of time to first GI events most GI events had first onset within the first 2 weeks of treatment in all treatment groups

but the hazard ratio was significantly greater ($p \leq 0.05$) for all dose regimens of faldaprevir vs. placebo (HRs were 1.37, 1.90 and 2.09 for 120, 240-12w and 240-24w, respectively, vs. placebo).

Overall, 22.8% of patients had AEs associated with **anaemia** during the double-blind treatment period but the rate was generally comparable across treatments (24.4% at 120 mg, 22.6% 240-12w, 21.0% 240-24w and 22.8% for placebo). It was concluded that anaemia was associated with PEG/RBV and was not significantly exacerbated by addition of faldaprevir. Based on the Kaplan-Meier estimates, the majority of the anaemia events were first reported between Week 8 and Week 16. There was no significant difference ($p \geq 0.5$) in the risk of developing anaemia for faldaprevir vs. placebo (hazard ratios from 0.86 to 1.00).

Bilirubin-associated AEs occurred in 9.4% to 29.9% treated with faldaprevir vs. 2% in the placebo group. The majority were due to increases in indirect bilirubin. The incidence and intensity of these AEs increased with dose (120 mg vs. 240 mg) and duration of 240 mg treatment (12 vs. 24 weeks). For example, DAIDS Grade 3 or Grade 4 bilirubin-associated AEs occurred in 1.3% at 120 mg group vs. 6.4% at 240-24w and 0% with placebo and Grade 4 rates were 1.2% and 1.9% for 240-12w and 240-24w, respectively. Based on the Kaplan-Meier estimates, the majority first experienced bilirubin-associated events within the first 2 weeks of treatment. The hazard ratios for bilirubin-associated events were 4.71, 14.84 and 16.28 for 120 mg, 240-12w and FDV 240-24w, respectively.

HCV/HIV co-infected patients

Overall, 97.7% of patients reported AEs and the AE profile was generally consistent with that observed in the HCV mono-infected patients treated with faldaprevir in Phase 3 studies. The most frequently reported AEs included nausea (37.3%), fatigue (34.1%), diarrhoea (26.9%), headache (24.4%), asthenia (23.1%), decreased appetite (21.4%), anaemia (18.8%), insomnia (18.5%), pyrexia (18.2%), rash (17.9%), pruritus (17.2%), vomiting (17.2%) and neutropenia (15.9%). AEs that tended to increase with increasing dose (120-24w vs. 240 mg-24w) included nausea (27.6% vs. 41.9%), vomiting (9.8% vs. 24.4%), pruritus (15.4% vs. 19.8%) and dry skin (13.8% vs. 20.9%). Jaundice was reported in 8.4% overall and increased with dose and duration (120-24w: 5.7%, 240-12w: 9.5%, and 240-24w: 11.6%).

The majority of AEs were DAIDS Grade 1 or 2 in intensity (38.6% and 40.6% vs. Grade 3 and 4 rates of 15.3% and 3.2%, respectively). The SOCs with the highest frequency of DAIDS Grade 3-4 AEs included blood and lymphatic disorders (6.5%), general disorders and administrative site conditions (3.2%) and gastrointestinal disorders (2.6%). Neutropenia (5.2%) was the only DAIDS Grade 3-4 AE that was reported in ≥5% of patients but there did not appear to be a relationship between dose and frequency of neutropenia. Patients treated with 120-24w had the highest incidence of DAIDS Grade 3-4 AEs (19.5%) compared with 15.5% at 240-12 w and 16.3% at 240-24w. It is not clear if an assignment to this regimen based on use of DRV/r or ATV/r impacted the rate of DAIDS Grade 3-4 AEs.

Serious adverse events and deaths

Deaths

There were 18 deaths among HCV-infected patients (3 in Phase 2 and 16 in Phase 3) treated with assigned study therapy. There was no pattern with regards to demographics, risk factors or AEs among patients who died. Most (14/18) patients who died had fatal AEs that were not attributed to study drug.

Hepatic failure leading to death was reported in 2 (0.3%) patients treated with 240 mg for 12 weeks (see deaths above). These SAEs were deemed to be drug-related by the investigator. One TN male aged 50 years was assigned to 240 mg for 12 weeks but died at week 4 on therapy due to hepatic failure that the investigator considered to be related to pegIFN. The patient was morbidly obese and had evidence of liver cirrhosis based on fibroscan/biopsy at baseline. The other had no evidence of liver cirrhosis based on fibroscan/biopsy performed at baseline but was found to have liver cirrhosis based on biopsy upon hospitalisation. This patient had a history of alcohol abuse (many years of heavy drinking according to the examining physician) that ended approximately 6 months before the patient died.

Three others had onset of fatal events within 30 days of the last dose of faldaprevir. These deaths included an accidental overdose with methadone, tramadol and alprazolam, multiple injuries following a fall in patient (who had treatment-related anaemia) and spontaneous bacterial peritonitis leading to fatal sepsis. The fourth death reported by an investigator as treatment-related included a patient who died due to SJS but at 5 months after discontinuation of faldaprevir due to DRESS

SAEs

In the Phase 2 studies (05 and 40) 3.9% in the faldaprevir 120 mg group reported SAEs compared to 2.8% in the placebo group but the rates were higher with 240 mg QD (8.7%) and 240 mg BID for 24 weeks (18.8%). There were no individual SAEs reported in ≥1.0% of patients treated with 120 mg or 240 mg with the sole exception of anaemia (1.3% for 120 mg). Anaemia (4.3%) and vomiting (2.9%) were the only SAEs reported in more than one patient in the 240-24w BID group.

HCV mono-infected patients in Phase 3 reported SAEs at rates of 7.5% and 8.4% in the faldaprevir 120 mg and 240 mg groups compared with 5.0% for placebo. There were no SOCs with a frequency of SAEs that exceeded 1.2% of patients. Overall, the frequency of SAEs generally showed a modest increase with increasing dose (120 mg vs. 240 mg) and duration of FDV (240 mg for 12 vs. 24 weeks). Thrombocytopenia and vomiting were the only individual SAEs reported in ≥1.0% of patients in any treatment group. Serious thrombocytopenia occurred in five faldaprevir patients (1 at 120 mg, 1 at 240-12w and 3 at 240-24w) and no placebo patients.

There were 32 HCV/HIV co-infected patients (10.4%) who reported SAEs during faldaprevir treatment with rates of 13.8% for 120-24w but 6.0% and 5.8% for 240-12w and 240-24w. Pyrexia (1.3%) and abdominal pain (1.0%) were the only individual SAEs reported in ≥1.0% of patients. Serious rash maculo-papular was reported for 2 (1.6%) patients treated with 120-24w. One patient treated with 240 mg experienced fatal drug rash with eosinophilia and systemic symptoms deemed to be possibly related to faldaprevir (see above and below).

In the four Phase 3 studies and in two ongoing Phase 3 studies the rash adjudication committee (RAC) identified one patient with DRESS, 2 with probable and 2 with possible DRESS. The patient with DRESS was diagnosed post-treatment, subsequently developed SJS and died 4 months after completing study treatment. The four patients with probable or possible DRESS were receiving faldaprevir at the time of onset (120 mg QD n=1; 240 mg QD n=3). The estimated risk of DRESS for faldaprevir was 4/2202 (0.18% [95% CI 0.05% to 0.46%]) but was zero for placebo (i.e. 0/342 [upper 95% CI 0.88%]).

Laboratory findings

In the placebo-controlled Phase 3 studies

The trends for mean change from baseline, last value on treatment and worst value on treatment in faldaprevir and placebo groups were toward decreases in haemoglobin, WBC, neutrophils and platelets. AST, ALT and GGT also decreased in all treatment groups but the difference was greater in the faldaprevir groups. Total bilirubin increased in all faldaprevir groups (0.6 mg/dL at 120 mg, 2.0 mg/dL

and 1.8 mg/dL for 240-12w and 240-24w, respectively) vs. no change for placebo, mostly due to increases in indirect bilirubin (0.5 mg/dL, 1.5 mg/dL, 1.4 mg/dL in faldaprevir groups). The GGT, bilirubin (total and indirect) and bile acids were all lower at the end of the entire treatment vs. end of faldaprevir, indicating reversibility after cessation of treatment.

The greatest frequency of shifts to Grade 3 or 4 were for bilirubin and were similar with 240-12w (37.2% Grade 3 and 9.4% Grade 4) and 240-24w (40.0% Grade 3 and 8.3% Grade 4) vs. 0% for placebo (see below).

Criteria for severe DILI were met by one patient in study 07 who had a spike in AST (more than 10 x ULN) and ALT (more than 5 x ULN) and elevated total bilirubin and direct total bilirubin at Day 62. On repeat testing 17 days later the hepatic enzymes had declined spontaneously. These laboratory tests returned to baseline while the patient remained on treatment. The course for this patient does not fit the expected course of DILI.

Two patients in the Phase 2 studies met the pre-defined criteria for potential severe liver injury. Both were treated with faldaprevir 240 mg for 24 weeks (one QD and one BID) in study 05 and were identified as having met the laboratory criteria for a potential DILI case but they did not meet the direct/total bilirubin ratio > 0.5 using normalised values and the abnormalities occurred at different time points and resolved even though the patients continued treatment with faldaprevir.

Number (%) with shifts in laboratory values from normal at baseline to DAIDS Grade 3 or 4 during active treatment in pivotal, placebo-controlled Phase III studies

Laboratory Parameter/ DAIDS Grade Shift	FDV 120-Total (N = 521) N (%)	FDV 240-12w (N = 825) N (%)	FDV 240-24w (N = 298) N (%)	FDV 240-Total (N = 1123) N (%)	Placebo N = 342 N (%)
ALT					
Grade 3	4 (1.8)	0	0	0	0
Grade 4	0	0	0	0	0
AST					
Grade 3	0	2 (0.4)	1 (0.6)	3 (0.5)	0
Grade 4	0	0	0	0	0
Total bilirubin					
Grade 3	50 (10.0)	296 (37.2)	116 (40.0)	412 (38.0)	0
Grade 4	3 (0.6)	75 (9.4)	24 (8.3)	99 (9.1)	0
Haemoglobin					
Grade 3	45 (8.7)	56 (6.8)	20 (6.8)	76 (6.8)	17 (5.0)
Grade 4	5 (1.0)	4 (0.5)	0	4 (0.4)	0
Platelet count					
Grade 3	4 (0.8)	9 (1.3)	3 (1.2)	12 (1.2)	2 (0.7)
Grade 4	1 (0.2)	1 (0.1)	0	1 (0.1)	0
Lymphocytes, absolute count					
Grade 3	78 (15.1)	109 (13.3)	38 (13.0)	147 (13.3)	26 (7.7)
Grade 4	15 (2.9)	41 (5.0)	24 (8.2)	65 (5.9)	8 (2.4)
WBC					
Grade 3	35 (6.8)	35 (4.3)	14 (4.8)	49 (4.4)	11 (3.2)
Grade 4	0	1 (0.1)	2 (0.7)	3 (0.3)	0
Neutrophils, absolute count					
Grade 3	80 (15.6)	80 (9.9)	26 (8.9)	106 (9.6)	49 (14.5)
Grade 4	24 (4.7)	22 (2.7)	7 (2.4)	29 (2.6)	7 (2.1)

Data represent shift to worst value on treatment

One subject in study 57 had been on addiction management therapy (buprenorphine/naloxone) for 5 years and had an increase in transaminases after 7 doses of faldaprevir resulting in discontinuation of treatment. This patient met Hy's law for potential for severe DILI with respect to elevation in ALT, AST and bilirubin in the absence of an alternate explanation except that the rise in bilirubin was an expected effect of faldaprevir. All laboratory results normalised after discontinuation of study drug.

In the HCV/HIV co-infected patients there were no shifts in ALT and AST values to Grade 3 or 4 in the 240-12w group and no shifts to Grade 4 in any group. Total bilirubin values were Grade 3 in 10.7% at 120-24w and 17.9% at 240 mg. Shifts to Grade 4 bilirubin values were infrequent. There were few shifts to Grade 3 or 4 in haemoglobin values or WBC counts and the most pronounced shifts were seen in absolute neutrophil counts which were to Grade 3 in approximately 11% at both faldaprevir doses. Similar shifts in platelet counts were seen in the 120-24w and 240 mg groups.

Increases in total and indirect bilirubin in patients on ATV (all in the 120-24w group) were similar to the values in all patients. These 12 patients had total bilirubin values Grade 0-2 at baseline but reached Grade 3 in 6 and Grade 4 in one patient during treatment. Mean total bilirubin levels increased from baseline to Week 2 and decreased gradually to the end of treatment with faldaprevir, returning to

baseline post-treatment. The increase in mean total bilirubin was due primarily to an increase in mean indirect bilirubin. No patient met the criteria for the potential for severe drug-induced liver injury.

Safety in special populations

AE patterns across age groups were generally consistent with those observed for the overall population, with faldaprevir-treated patients reporting a higher frequency of AEs compared with the placebo group. A higher proportion of females reported Grade 3 and 4 AEs (24.2% vs. 18.6%) and SAEs (9.3% vs. 6.5%). Jaundice was reported in 7.6% with normal renal function, 10.5% with mild impairment and 13.0% with moderate impairment while hyperbilirubinaemia was reported in 5.7%, 4.2% and 1.9%, respectively. Both were reported more frequently with faldaprevir and increased with increasing dose.

In the placebo-controlled Phase 3 studies a higher proportion of Asian patients reported Grade 3 and 4 AEs (31.3% vs. 18.6% vs. 17.8%) and SAEs (8.9% vs. 7.4% vs. 7.6%) compared with whites or Blacks/African Americans, respectively.

- Gastrointestinal disorders were reported more frequently for Asians (75.2%) compared with whites (68.7%) or Black or African Americans (59.3%). Asian patients treated with 240-24w reported the highest frequency of nausea, diarrhoea and vomiting (67.9%, 48.2%, and 37.5%, respectively) compared with whites (52.6%, 33.8%, and 26.3%, respectively) or Blacks or African Americans (33.3%, 16.7%, and 16.7%, respectively).
- A higher proportion of Asians reported skin and cutaneous tissue disorders (81.7%) compared with whites (66.0%) and Blacks or African Americans (55.9%). Asians treated with 240-12w had the highest frequency of rash (47.5%) compared to whites (27.0%) and Blacks or African Americans (20.0%). In the placebo group rash was reported in 40%, 20% and 20.0% in respective racial groups.
- A higher proportion of Asians reported anaemia (29.8%) compared with whites (15.2%) or Blacks or African Americans (24.6%). In the placebo group the rate for Asians was 35.4%.
- The incidence of pyrexia (38.9% vs. 14.8%) was approximately twice that in Asians compared with whites, respectively.
- Hyperbilirubinaemia was reported more frequently for Asians (13.8%) compared with whites (2.4%) or Blacks or African Americans (4.2%).

When looked at by region skin and cutaneous tissue disorders were reported more often by patients in Asia (82.4%) compared with Europe (60.1%) and North America (73.2%). Pruritus and rash rates in Asia were 42.7% and 46.3%, respectively, compared with Europe (31.6% and 18.5%) and North America (28.7% and 35.3%). However, rash and pruritus were reported in a comparable proportion of patients in the placebo and faldaprevir groups in Asia.

Anaemia was reported in a higher proportion of patients in Asia (29.8%) vs. Europe (14.1%) and North America (19.0%) but within Asia anaemia was reported in a higher proportion in the placebo vs. faldaprevir dose groups. Patients in Asia reported a higher incidence of hyperbilirubinaemia (14.6% vs. 2.0% in Europe and 3.3% in North America). Rates of pyrexia increased with increasing dose and duration of faldaprevir in Asia (34.3% - 49.1% for faldaprevir vs. placebo: 36.2%) but pyrexia was generally reported in comparable proportions across all doses, including placebo, in Europe and North America.

Patients with cirrhosis tended to have a higher frequency of Grade 3 or 4 AEs (26.7% vs. 20.2%), discontinuations due to AEs (10.5% vs. 6.9%) and SAEs (11.2% vs. 7.2%). Also 3 (1.2%) cirrhotic and 3 (0.2%) non-cirrhotic patients had fatal SAEs. A similar trend was seen in patients who received

placebo. The overall AE patterns across treatment groups were comparable between cirrhotic and non-cirrhotic patients and were generally consistent with those observed for the overall patient population.

Discontinuation due to AES

In the Phase 2 studies 05 and 40 discontinuations due to AEs occurred in 5.2% treated with 120 mg QD and 6.7% treated with 240 mg QD but the rate was 23.2% in those assigned to 240-24w BID vs. 1.4% in the placebo group. Individual AEs that most often led to discontinuation of faldaprevir were rash, nausea and vomiting.

In the HCV mono-infected patients in Phase 3 studies discontinuation of faldaprevir/placebo due to AEs occurred in 6.3% in the 120 mg QD group, 9.7% in the 240 mg group and 3.2% in the placebo group. The most common AEs leading to discontinuation (>1% but < 2%) were nausea, vomiting, thrombocytopenia and fatigue.

In the HCV/HIV co-infected patients discontinuations due to AEs were reported in 25 (8.1%) patients, including 10 (8.1%) treated with 120 mg for 24 weeks and 5 (5.8%) treated with 240 mg for 24 weeks with no discontinuations due to AEs in the 240-12w group. Fatigue (1.6%), nausea (1.3%), vomiting (1.3%), asthenia (1.0%), headache (1.0%) and rash (1.0%) were the only AEs that led to discontinuation in ≥1.0% of patients.

Pharmacovigilance system

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

Risk management plan

Please see the PRAC report.

CHMP's comment on safety

The total numbers exposed to faldaprevir are at least sufficient to describe uncommon AEs with reasonable precision.

In healthy subjects the comparisons of faldaprevir (n=495) with placebo (n=39) indicated that it was particularly associated with gastrointestinal AEs (especially nausea, vomiting and diarrhoea), decreased appetite, headache, fatigue and visible jaundice. Each 120 mg SGC contains 260.57 mg of polyoxyl 35 castor oil and 39.6 mg sorbitol, which could predispose to diarrhoea. The applicant should compare the Phase 1 diarrhoea rates between the PiB and SGC by dose level to assess whether at least part of the problem could relate to the formulation.

In Phase 1 studies increases in bilirubin occurred at 120 mg while marked hyperbilirubinaemia tended to occur mostly at doses above 240 mg. In study 06 Grade 3 elevated total bilirubin occurred in 2 in the 240 mg non-GS group vs. 5 in the 240 mg GS group. As the faldaprevir dose increased in non-GS subjects the change from baseline in total bilirubin increased and correlated well with trough concentrations.

The Phase 2 data demonstrated that the 240 mg QD dose was generally associated with higher rates of AEs, including some specific AEs, vs. the 120 mg dose. Dose-related AE rates were particularly apparent for gastrointestinal disorders, skin and subcutaneous tissue disorders and hepatobiliary disorders.

Two of the four Phase 3 studies allow for further evaluation of the possible additive effects of faldaprevir on AEs vs. PEG/RBV alone. While the HCV/HIV co-infected population had no control group the general features of the safety profile were compatible with the HCV mono-infected population, including the differences in rates by dose and the effect of prolonged duration. Some observations include the following:

Rates of gastrointestinal disorders were higher with faldaprevir and increased with dose and with duration.

Higher rates of rash occurred when faldaprevir was added to PEG/RBV but the difference between the 120 mg and 240 mg QD groups was not large, rates were slightly lower for the TE patients and the types of rashes seemed similar between faldaprevir and placebo groups. Asians had higher rates of rash vs. other racial groups in faldaprevir and placebo groups but the rates were higher with faldaprevir vs. placebo despite the fact that the applicant's analysis failed to detect a significant relationship between plasma concentrations and rash. This matter remains to be addressed despite the applicant's reported logistic regression analysis that apparently indicated that the higher rate of rash in Asians was likely not due to the increased plasma exposures.

While applicant has provided a detailed summary of rashes, there is no discussion regarding any possible cases that could represent hypersensitivity reactions or other AEs that could reflect hypersensitivity to faldaprevir. Such an analysis should be provided.

It cannot be dismissed that there is a risk of DRESS associated with addition of faldaprevir to PEG/RBV although the actual rates was <0.5.

Following the institution of appropriate advice, the rates of photosensitivity were much lower in Phase 3 studies but still slightly higher with 240 mg vs. 120 mg QD. Hence appropriate advice in the SmPC and PL seems to be essential for routine use.

As expected there was a clear faldaprevir dose-related effect on rates of hyperbilirubinaemia (mainly indirect), jaundice and ocular icterus, including Grade 3-4 events, and in most cases onset was early during treatment, which fits with the mechanism. In study 109 very few patients took atazanavir (ATV) with faldaprevir and it appears that addition of 120 mg QD did not worsen the indirect hyperbilirubinaemia in these cases. It could be assumed then that ATV already exerted near to maximal inhibition of UGT1A1 so co-administration had no additive effect. However, raltegravir also inhibits UGT1A1 to some (lesser) extent and the applicant should compare the bilirubin data between those who received faldaprevir with ATV or raltegravir or neither of these agents.

In study 06 9/39 subjects had GS of which 5 were homozygous for A(TA7)TAA allele (*28/*28) while 4 were heterozygous *1/*28. The faldaprevir plasma levels were not markedly different between GS and non-GS groups but they are not shown separately for the two GS sub-groups. Also, the safety profile (albeit based on small numbers) did not show marked differences between non-GS and GS subjects except for ocular icterus. The applicant should separate the PK and safety data between the two GS sub-groups and discuss any observations made. In addition, the applicant should clarify whether the reports of ocular icterus in GS subjects represent new onset or worsening of the condition.

It may also be relevant to consider the effect of faldaprevir on bilirubin levels in light of available relevant information for ATV and raltegravir in persons with <50% UGT1A1 activity. Based on the available evidence as summarised in a 2013 publication, homozygosity of the UGT1A1*28 allele does not strongly predict the incidence of severe hyperbilirubinaemia observed in association with ATV. Thus, until large, prospective trials demonstrate otherwise, UGT1A1*28 testing is not considered useful for clinical decision-making when initiating ATV treatment in HIV-infected patients. Raltegravir is a weak inhibitor of UGT1A1 *in vitro* but was found to be associated with elevated bilirubin even though

this was not predicted initially from typical plasma levels. Plasma concentrations of raltegravir are modestly higher in individuals with the UGT1A1*28/*28 genotype vs. the UGT1A1*1/*1 genotype but no dose adjustment is considered necessary for individuals with the UGT1A1*28/*28 genotype.

Experience with other drugs associated with this effect (particularly atazanavir) suggests that the issue is manageable when it is well-recognised and anticipated by physicians and patients. Nevertheless, careful monitoring is needed to identify patients in whom hyperbilirubinaemia does not occur in isolation (i.e. there are other laboratory abnormalities that could represent a more serious pathological process, including severe DILI).

It is not possible to confirm or dismiss the role of faldaprevir in the cases of hepatic failure, including the two fatal cases. The fact that there may have been pre-existing liver disease additional to HCV but patients must have met the inclusion criteria actually enhances the concern. There were no shifts from normal to Grade 3 or 4 LFT abnormalities with PEG/RBV alone but there were some cases with faldaprevir. Further details of these cases should be supplied, including displays of consecutive values over time, AEs (of any type) and virological responses in those who continued treatment. At present the applicant seems to dismiss the cases of potential DILI but it is particularly of concern that one patient met Hy's law and it is not agreed that the case is dismissed because the rise in bilirubin *was an expected effect of faldaprevir*.

Total rates for AEs associated with anaemia were not higher with faldaprevir vs. PEG/RBV alone in TN patients but in TE patients the rates were 23.6% and 20.8% for faldaprevir doses vs. 14.1% for placebo. The applicant ascribes the difference to early discontinuation in the placebo group, especially by week 4, while the majority of anaemia-associated events had onset between weeks 8 and 16. However, rates for Grades 2-4 anaemia and thrombocytopenia were higher with faldaprevir, only faldaprevir patients discontinued due to such events and all 5 cases of serious thrombocytopenia occurred in faldaprevir-treated patients. In light of the issues observed with other NS3/4A inhibitors this feature is very important to note and, although the data suggest that the additive risk for faldaprevir would not be a major objection to approval, these findings need to be adequately reflected in the SmPC.

In addition to the rates of rash noted above, Asian patients reported higher rates of several other AEs (gastrointestinal, skin, anaemia, pyrexia and hyperbilirubinaemia), including some for which there was a dose and likely exposure-related relationship. Also, a higher proportion of Asians reported Grade 3/4 AEs (31.3% vs. 18.6% vs. 17.8%) and SAEs (8.9% vs. 7.4% vs. 7.6%) compared with whites or Blacks/African Americans, respectively. The applicant should explore the available PK data for these Asian patients with severe or serious AEs vs. other Asian patients and non-Asian patients.

As noted in the comment on PK, plasma raltegravir levels were increased considerably on co-administration with faldaprevir. There is a need to present and discuss the safety data specific to those who received faldaprevir with raltegravir in study 019.

Faldaprevir was associated with a slightly higher incidence of serious infections and infestations, which was unexpected. This observation requires further investigation.

The applicant estimated that the frequency of DRESS was 0.18% (95% confidence interval: 0.05%, 0.46%) based on 4/2202 patients identified by the Rash Adjudication Committee (RAC) as having definite, probable or possible DRESS. The RAC identified three additional cases where a DRESS could not be excluded. As a worst case scenario, the risk of DRESS associated with faldaprevir is likely close to that observed for telaprevir (0.4%). The applicant should add a suitable warning to section 4.4 of the SmPC.

Finally, gastrointestinal AEs, rashes and haematological abnormalities feature among AEs leading to discontinuation of faldaprevir. Discontinuation due to hyperbilirubinaemia-associated events or elevated transaminases occurred on occasion but rates were low. It is difficult to make clear comparisons with placebo for discontinuations due to AEs because of discontinuation rates based on virological results.

In summary, there are several issues to be addressed and it will be essential that the SmPC and PL adequately and accurately reflect the safety profile but there are no safety issues identified thus far that would preclude approval.

See the PRAC report regarding the RMP.

4. Orphan medicinal products

N/A

5. Benefit risk assessment

Benefits

Beneficial effects

The three placebo-controlled Phase 3 studies clearly point to the advantage of adding faldaprevir to PEG/RBV in chronic HCV infection due to GT-1 viruses.

Uncertainty in the knowledge about the beneficial effects

The most important issue is the derivation of the dose regimen recommendations proposed in the applicant's draft SmPC. From the Phase 2 data it was logical that the applicant evaluated both 120 mg and 240 mg QD and for 12 or 24 weeks in Phase 3 but the 120 mg dose was not assessed in TE patients. Based on virological considerations it is not logical that different doses and regimens of faldaprevir were studied and are proposed in the SmPC according to PEG/RBV TN or TE status. In contrast, based on prior experience and the characteristics that pre-dispose to lack of virological response to PEG/RBV alone, it is plausible that different durations of PEG/RBV could be needed in different patient subgroups.

In addition to this important issue the applicant does not always recommend the regimens that were actually studied. The 120 mg for 12 weeks regimen was studied in TN patients but only in one treatment arm in one study and only in the subset (albeit the majority) who met the ETS criteria. In addition, in the one study in which it was evaluated two-thirds of patients had GT-1b HCV infection, which was strongly associated with higher SVR12 rates vs. GT1a. Nevertheless, the totality of data points to the adequacy of this regimen in the TN.

Acceptance of this regimen for the TN raises the question as to why the 120 mg QD was not even evaluated in the TE patients (other than in a few relapsers in study 19). However, while it is illogical to recommend a higher dose for the TE at the same time there are no or inadequate data to confirm the sufficiency of 120 mg QD for 12 weeks in any TE subset, including the relapsers in whom the applicant wishes to suggest this dose based on very few TE relapsers in study 19. In addition, there is no clear scientific reason to recommend a different dose in HCV/HIV co-infected patients but at present there are concerns that doses recommended to be used with different ART regimens may not be entirely appropriate.

Whereas the applicant does recommend the tested regimen for TE partial and null responders and the data demonstrate the efficacy of faldaprevir 240 mg QD for 12 weeks, it is quite possible that 120 mg would suffice and it cannot be ruled out that less than 48 weeks PEG/RBV could be used in those with ETS.

There are also several questions posed about the suitability of the recommended dose regimens in different subsets and related questions on unexplained features of the pharmacokinetics of faldaprevir.

The recommendations made in the SmPC regarding treatment futility do not reflect the rules that were applied during the Phase 2/3 studies. The rules suggested from the applicant's retrospective analyses in TN and TE patients are not very convincing and require further justification.

Therefore while the efficacy of faldaprevir is accepted the dose recommendations and the futility criteria are in need of further consideration and justification.

Risks

Unfavourable effects

Currently there are sufficient concerns about the starting materials and the changes observed in the dissolution profiles of batches stored under non-refrigerated conditions to support Major Objections on Quality grounds. The changes in dissolution on storage are considered to be related to cross linking of the gelatin. The potential impact of this change on product performance needs to be addressed fully as this may affect the clinical performance of the product.

Addition of faldaprevir to PEG/RBV is particularly associated with gastrointestinal AEs, cutaneous AEs, general malaise symptoms and hyperbilirubinaemia. There are also effects on RBC, WBC and platelets and on transaminases over and above those observed with REG/RBV. Several of these AEs, including the effect on bilirubin, are dose-related and some also show higher rates when treatment with faldaprevir is extended from 12 to 24 weeks. However, only 12 weeks is recommended in the SmPC.

There are some racial differences, including higher rates of rash and several other AEs in Asians, in whom plasma exposures also tend to be higher. Nevertheless, the applicant's reported logistic regression analysis apparently indicated that the higher rate of rash in Asians was likely not due to the increased plasma exposures.

It cannot be dismissed that there is a risk of DRESS associated with addition of faldaprevir to PEG/RBV although the actual rates was <0.5.

It is not possible to confirm or dismiss the role of faldaprevir in the cases of hepatic failure, including the two fatal cases. The fact that there may have been pre-existing liver disease additional to HCV but must have met the inclusion criteria actually enhances the concern. There were no shifts in transaminases from normal to Grade 3 or 4 with PEG/RBV alone but there were some cases with faldaprevir.

Rates for Grades 2-4 anaemia and thrombocytopenia were higher with faldaprevir, only faldaprevir patients discontinued due to such events and all 5 cases of serious thrombocytopenia occurred in faldaprevir-treated patients. In light of the issues observed with other NS3/4A inhibitors this feature is very important to note.

Uncertainty in the knowledge about the unfavourable effects

There are several issues regarding safety, including AEs in sub-groups, requiring further exploration and comment. The real risk of hepatotoxicity and negative effects on blood cells cannot be discerned with confidence pre-licensure.

Balance

Importance of favourable and unfavourable effects

Faldaprevir is efficacious but its use, especially at the 240 mg dose, is associated with higher rates of several AEs compared to PEG/RBV alone. Despite this fact there are no major concerns regarding clinical safety based on current evidence although a careful RMP is needed. If the dose regimens can be further substantiated after taking into account the LOQ on PK, PD and efficacy, and if no additional safety issues are apparent from the responses then the clinical favourable effects likely outweigh the unfavourable effects. However, there are Major Objections on Quality at present.

Benefit-risk balance

Due to the Major Objections on Quality it is not possible to conclude that the favourable effects outweigh the unfavourable effects.

5.1. Conclusions

The overall B/R of faldaprevir is negative at present due to the Major Objections on Quality grounds.

The below table summarises the favourable and unfavourable effects of faldaprevir.

Effect		Description	Units	FDV 120 mg	FDV 240 mg	Plcbo / Hist Ctrl	Uncertainties / Strength of evidence	References
Favourable effects	SVR12 = plasma HCV RNA <25 IU/mL undetected at 12 weeks after the originally planned treatment duration.	Pts wit5h SVR12	%	78.8[1] 67.9[2]	80.5[1] 63.9[2] Rlps:12W: 69.7[3.1] 24W:69.6[3.1] Prtl12W:57.9[3.2] 24W:47.3[3.2] Null12W:33.1[3.3] 24W:32.6[3.3]	52.3[1] 47[2] 14.3[3.1] 3.4[3.2]	Significant differences with Plcb/Interim analysis for co-infected: results in line with mono-infected. Optimal posology not established/ the proposed RGT for the duration of PEG/RBV, and the stopping rules to assess treatment futility need further discussion/ AEs are dose and time dependent	**[1]StartVerso1**. **[2]StartVerso2.** FDV 120 mg QD (plus PegIFN/RBV for 12 or 24 weeks, depending on ETS. Patients with ETS received this treatment for 12 weeks and subsequently PegIFN/RBV alone up to Week 24; patients without ETS received this treatment for 24 weeks and subsequently PegIFN/RBV alone up to Week 48 FDV 240 mg QD plus PegIFN/RBV for 12 weeks, followed by PegIFN/RBV up to Week 24. Patients with ETS stopped all study medication at Week 24; patients without ETS subsequently received PegIFN/RBV alone up to Week 48 Placebo QD plus PegIFN/RBV for 24 weeks, followed by PegIFN/RBV alone up to Week 48 **[3.1] StartVerso3- Relapsers.** **[3.2]StartVerso3-PRTLresponders.** **[3.3]StartVerso3- Null Responders.** FDV 240-12w: FDV, 240 mg once daily combined with PegIFN/RBV for 12 weeks, followed by placebo once daily combined with PegIFN/RBV for 12 weeks FDV 240-24w: FDV, 240 mg once daily combined with PegIFN/RBV for 24 weeks Placebo: Placebo once daily combined with PegIFN/RBV for 24 weeks followed by PegIFN/RBV for 24 weeks
	SVR24 = plasma HCV RNA <25 IU/mL undetected at 24 weeks after the originally planned treatment duration.	Pts with SVR24.	%	77.9[1] 65.2[2]	18.5[1] 60.6[2] 12W:55[3.1/3.2] 12W:15.2[3.3] 24W:53[3.1/3.2] 24W:14[3.3]	43.1[1] 35.5[2] 2[3.1/3.2]		
	ETS = defined as plasma HCV RNA level <25 IU/mL (detected or undetected) at Week 4 and HCV RNA <25 IU/mL, undetected at Week 8.	Pts with ETS	%	87.3[1] 80.2[2]	89.3[1] 79.1[2] Rlps 12W:85.9[3.1] 24W:87.3[3.1] Prtl 12W:66.7[3.2] 24W:78.2[3.2] Null12W:58.6[3.3] 24W:51.1[3.3]	22.0[1] 15.9[2] 4.1[3.1] 3.4[3.2]		
	YES ETS, YES SVR12	Positive predictive value of ETS	%	85.8[1] 80.0[2]	89.3[1] 76.9[2] Rlps12W:75.3[3.1] 24W:75.3[3.1] Prtl12w:73.[3.2] 24W:55.8[3.2] Null12W:55.3[3.3] 24W:58.3[3.3]	89.3[1] 71.4[2] 50[3.1] 0[3.2]		

	No ETS, YES SVR12	Negative predictive value of ETS	%	30.3[1] 19.2[2]	7.1[1] 14.5[2] Rlps12W:35.[3.1] 24W:30.8[3.1] PrtI12w:26.3[3.2] 24W:16.7[3.2] Null12W 1.7[3.3] 24W:5.8[3.3]	41.7[1] 42.3[2] 12.8[3.1] 3.6[3.2]		[3.3] Historical Ctrl
Unfavourable effects	**Effects: Grade 3 or higher AEs**	**Description**	**Units**	**FDV [1,2] 120 mg**	**FDV[1,2,3] 240 mg**	**Plcbo[1,2,3]**	**Uncertainties / Strength of evidence**	
	Blood and lymphatic system disorders (neutropenia, anemia, thrombocytopenia		n (%)	58 (11.1)	87 (10.4)	26 (7.6)	safety issues the relevance of which on B/R balance is not at present fully elucidated 2 cirrhotic pts treated with FDV 240 mg, died due to hepatic failure. slightly superior incidence of serious infections and infestations, which was not expected giving the general toxicity profile of the drug	
	Hepatobiliary disorders (Jaundice and hyperbilirubinemia)		n (%)	4 (0.8)	31 (0.7)	0 (0.0)		
	Serious infections and infestations		n (%)	6 (1.1)	12 (1.4)			
	GI disorders		n (%)	8 (1.5)	21 (2.5)	2 (0.6)		
	DRESS		n (%)	1(0.14)	3(0.20)	0 (0.0)	4 cases of probable/possible DRESS in FDV-pts and in none of PBO-pts	
	Rash		n (%)	197(37.8)	324(38.7)	103(30.1)		