EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Assessment report

INCIVO

telaprevir

Procedure No.: EMEA/H/C/002313/

Note

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

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July 2011
EMA/CHMP/475470/2011
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

INCIVO

International non-proprietary name: **telaprevir**

Procedure No. **EMEA/H/C/002313**

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Product information

Name of the medicinal product:	INCIVO
Applicant:	Janssen-Cilag International N.V. Turnhoutseweg 30 BE-2340 Beerse Belgium
Active substance:	telaprevir
International Nonproprietary Name/Common Name:	telaprevir
Pharmaco-therapeutic group (ATC Code):	Protease inhibitors (J05AE)
Therapeutic indication(s):	INCIVO, in combination with peginterferon alfa and ribavirin, is indicated for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease (including cirrhosis): - who are treatment-naïve; - who have previously been treated with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin, including relapsers, partial responders and null responders (see sections 4.4 and 5.1).
Pharmaceutical form:	Film-coated tablet
Strength:	375 mg
Route of administration:	Oral use
Packaging:	bottle (HDPE)
Package size:	168 (4 x 42) tablets

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List of abbreviations

AAG	alpha 1-acid glycoprotein
ADME	absorption, distribution, metabolism, and excretion
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BCS	Biopharmaceutics Classification System
BMI	body mass index
CHC	chronic hepatitis C
CI	confidence interval
CPA	Child-Pugh A
CPB	Child-Pugh B
CPC	Child-Pugh C
CrCl	creatinine clearance
CSR	clinical study report
CTP	clinical trial protocol
CYP	cytochrome P450
DBP	diastolic blood pressure
DDI	drug-drug interaction
ECG	electrocardiogram
DEP	dermatology expert panel
EPO	erythropoietin
eRVR	extended rapid virologic response
ESA	erythropoiesis-stimulating agent
ESI	event of special interest
EVR	early virologic response
FA	full analysis
FTC	emtricitabine
FU	follow-up
GGT	gamma-glutamyl transferase
HAART	highly-active antiretroviral therapy
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HSA	human serum albumin
IFN	interferon
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LDH	lactate dehydrogenase
LDL l	ow-density lipoprotein LLOQ lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NA	not applicable
NIH	National Institutes of Health
Pbo	placebo
Pbo/PR	placebo, peginterferon alfa, and ribavirin
Peg-IFN	pegylated interferon
Peg-IFN-alfa-2a	peginterferon alfa-2a (Pegasys)
Peg-IFN-alfa-2b	peginterferon alfa-2b (PegIntron)
P-gp	P-glycoprotein
PR	pegylated interferon alfa and ribavirin
PT	prothrombin time
PTT	partial thromboplastin time
q8h	every 8 hours
q12h	every 12 hours
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate according to Fridericia
RBC r	ed blood cell
RBV	ribavirin
RVR	rapid virologic response
SAE	serious adverse event

SAP	statistical analysis plan
SCS	summary of clinical safety
SD	standard deviation
SSC	special search category
SVR	sustained virologic response
TDF	tenofovir disoproxil fumarate
t.i.d.	tris in die, three times per day
TPGS	d-alpha-tocopheryl polyethylene glycol-1000 succinate
T/PR	telaprevir, peginterferon alfa, and ribavirin
V/F	volume of distribution
WBC	white blood cell
WT	wild-type

Definitions of Terms

EVR (early virologic response)	≥2-log10 decrease in HCV RNA at Week 12 of treatment compared to baseline HCV RNA level
RVR (rapid virologic response)	Undetectable HCV RNA at Week 4 of treatment
eRVR (extended RVR)	Undetectable HCV RNA at Weeks 4 and 12 of treatment
Prior treatment failure	Subjects who previously received Peg-IFN/RBV, but who did not achieve SVR
Prior relapser	Subject who had undetectable HCV RNA at the end of prior treatment followed by detectable HCV RNA
Prior nonresponders:	Subjects who never had undetectable HCV RNA during prior treatment. This includes prior partial responders and prior null responders
- Prior partial responder -	Subject who had ≥2-log10 decrease in HCV RNA at Week 12 of prior treatment compared to baseline HCV RNA level, but who never achieved undetectable HCV RNA levels during prior treatment
- Prior null responder -	Subject who had <2-log10 decrease in HCV RNA at Week 12 of prior treatment compared to baseline HCV RNA level during prior treatment and never achieved undetectable HCV RNA levels during prior treatment
Relapse	Undetectable HCV RNA at the end of treatment followed by detectable HCV RNA during follow-up
SVR (sustained virologic response)	Undetectable HCV RNA 24 weeks after the last planned dose of treatment
Viral breakthrough (Phase 3 studies)	Undetectable HCV RNA followed by >100 IU/mL HCV RNA during treatment, or, for subjects who did not have undetectable HCV RNA, >1-log10 increase in HCV RNA over nadir during treatment
On-treatment virologic failure:	Discontinued due to meeting a virologic stopping rule and/or having detectable HCV RNA at the end of treatment with viral breakthrough

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Janssen-Cilag International N.V. submitted on 16 December 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for INCIVO, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 March 2010.

The applicant applied for the following indication:

INCIVO, in combination with peginterferon alfa and ribavirin, is indicated for the treatment of

genotype 1 chronic hepatitis C in adult patients with compensated liver disease (including cirrhosis):

- who are treatment-naïve;
- who have previously been treated with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin, including relapsers, partial responders and null responders (see section 5.1).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/127/2008 on the agreement of a paediatric investigation plan (PIP).

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

Information relating to orphan market exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.

New Active substance status

The applicant requested the active substance telaprevir contained in the above medicinal product to be considered as a new active substance in itself.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 27 April 2007. The Scientific Advice pertained to insert quality aspects of the dossier.

Licensing status

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

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

1.2. Manufacturers

Manufacturer(s) responsible for batch release

Janssen-Cilag S.p.A.
Via C. Janssen
IT-04010 Borgo San Michele
Latina
Italy

1.3. Steps taken for the assessment of the product

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

Rapporteur: **Tomas Salmonson** Co-Rapporteur: **Philippe Lechat**

- The application was received by the EMA on 16 December 2010.
- Accelerated Assessment procedure was agreed-upon by CHMP on 18 November 2010.
- The procedure started on 19 January 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 April 2011. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 20 April 2011. In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 19 May 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 May 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 June 2011.
- The summary report of the GCP inspection carried out at the following sites: Vertex Pharmaceuticals Incorporated; Cedars-Sinai Medical Center; Reddy, K. Rajender, Hospital of the University of Pennsylvania between 07 and 16 June 2011 was issued on 1 July 2011.
- The Rapporteur's circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 4 July 2011.
- During the meeting on 18-21 July 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to INCIVO on 21 July 2011.

2. Scientific discussion

2.1. Introduction

Hepatitis C virus (HCV) is the most common infectious cause of chronic liver disease in Europe, and is globally second only to Hepatitis B virus. Worldwide, approximately 3% of the population is estimated to be infected, corresponding to around 200 million people at risk of developing serious liver related morbidity. In Europe, where the vast majority of CHC cases are reported among patients with past blood transfusion (before 1991) or with a history of intravenous drug use, the prevalence varies by geographic region, from about 0.5% in the Northern countries to 2% and higher in the Mediterranean countries and in Eastern Europe. HCV of genotype (GT) 1 is the predominant genotype globally as well as in most European regions. In Europe and in the US, approximately 30% of HIV-infected patients are co-infected with HCV, ranging up to 50% in some regions.

Around 60-80% of those infected with HCV become chronic carriers. Studies in patients who acquired CHC by blood transfusion prior to the availability of HCV-screening indicate that after 20 years of infection, around 20–30% will have progressed to cirrhosis, 5–10% will have end stage liver disease and 4–8% will have died of liver-related causes. In patients with cirrhosis, the 5-year risk of hepatic decompensation is approximately 15-20% and the risk of hepatocellular carcinoma 10%.

The general aim of therapy is to achieve sustained viral response (SVR), presently defined as the absence of detectable virus 24 weeks after the planned end of therapy. This ends the progression of HCV-related hepatic injury. Despite SVR however, the risk of cirrhosis-related complications, including hepatocellular carcinoma, still remains in patients that have developed significant liver injury due to the infection.

Over approximately 15 years, HCV therapy has evolved from the use of a standard (non-pegylated) interferon alone, via combination therapy with a standard interferon + ribavirin, to the combination of a pegylated interferon and ribavirin. For GT 1 virus, SVR rates in treatment naive patients with GT1 virus with 48 weeks of standard interferon therapy were approximately 10 percent, whereas with combination therapy of an unpegylated interferon and ribavirin for 48 weeks, SVR rates were about 30-35%. With pegIFN 2a or 2b and ribavirin bi-therapy for 48 weeks, the standard of care prior to the approval of the first directly acting antivirals, response rates in GT1 or 4 have been approximately 40-50% in the pivotal trials. Lower SVR rates, however, are seen in some sub-populations such as those with HCV/HIV co-infection. In contrast, around 70-85% of treatment naive patients infected with HCV GT 2 and 3 achieve SVR after a 6-month treatment course with pegIFN and ribavirin. Telaprevir has primarily been developed for use with PegIFN and ribavirin in patients with GT1, though preliminary studies in other genotypes have been performed.

Type of application and aspects on development

The applicant was granted accelerated procedure by the CHMP 2010-11-18.

No specific concern was raised to initiate a GCP inspection; however, a routine GCP inspection was conducted in June 2011.

In summary, the inspection findings indicate that the study is conducted in accordance with international regulations and that the results presented in the clinical study report is correctly presented.

2.2. Quality aspects

2.2.1. Introduction

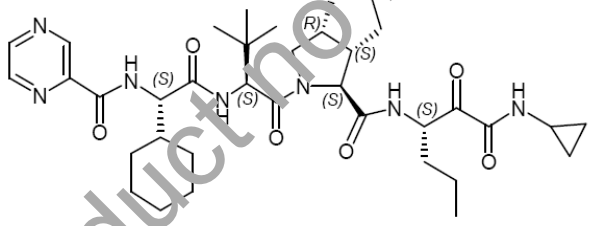
INCIVO is presented as film-coated tablets containing 375 mg of telaprevir as the active substance. The tablets are yellow, caplet shaped, of approximately 20 mm in length and marked with "T375" on one side.

Excipients used in the preparation of INCIVO are well known excipients, commonly used in solid oral dosage preparations, such as hypromellose acetate succinate, anhydrous calcium hydrogen phosphate, microcrystalline cellulose, anhydrous colloidal silica, sodium lauryl sulphate, croscarmellose sodium and sodium stearyl fumarate (present in the tablet core) and polyvinyl alcohol, macrogol, talc, titanium dioxide (E171), iron oxide yellow (E172) (present in the tablet film-coat).

The tablets are packed in high density polyethylene (HDPE) bottles fitted with polypropylene (PP) child resistant closure and induction seal liner. A desiccant is added to each bottle.

2.2.2. Active substance

Telaprevir (INN) is chemically designated as (1*S*,3a*R*,6a*S*)-2-[(2*S*)-2-[[(2*S*)-2-cyclohexyl-2-[(2-pyrazinylcarbonyl)amino]acetyl]amino]-3,3-dimethylbutanoyl]-*N*-[(1*S*)-1-[(cyclopropylamino)(oxo)acetyl]butyl]octahydrocyclopenta[c]pyrrole-1-carboxamide (Chemical name), and has the following structure:



Telaprevir is white to slightly yellow solid. The substance is more soluble in organic than in aqueous solvents. It is slightly soluble in ethanol, freely soluble in dichloromethane and practically insoluble in water. The partition coefficient is found to be pH independent and it is consistent with the low aqueous solubility of the substance, hence the hydrophobic nature of telaprevir. The substance is not hygroscopic. Telaprevir possesses six chiral centres and is optically active.

Telaprevir primarily exists in a single stable, non-solvated crystalline form (Form A). Solvates and polymorphic forms of telaprevir also exist. Sufficient evidence was provided to demonstrate that the Form A is obtained by the utilised manufacturing process.

Manufacture

Telaprevir can be manufactured according to two commercial processes: Process 1 or Process 2, from the same starting materials. Both processes are relatively complex, convergent route. The manufacturing process was changed at a late stage of development to minimise levels of a potentially genotoxic reagent. Batch analysis data showed that the changed process produces cleaner substance and that the changes have no further impact on the quality control of the telaprevir.

In general, sufficient information regarding the manufacturing process, materials, critical steps and intermediates, process validation and manufacturing process development have been provided. The

synthesis and process parameters have been well characterised and described. The classification of key starting materials was justified by the fact that these compounds constitute important structural fragments, are isolated and well-characterised, have well-defined impurity profiles and are stable.

During the evaluation, one of the proposed starting materials was redefined to an earlier compound in the synthesis. The initially proposed compound was too complex to be accepted as a starting material in the synthesis of the active substance. After the re-classification, supportive information to control the quality of the starting materials was provided and considered suitable. The applicant also demonstrated that the stereoisomeric purity of the active substance could be appropriately controlled. In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommended to finalise and provide additional validation reports for analytical methods used to control the starting materials.

Confirmation of the chemical structure of telaprevir was provided by elemental analysis (confirmation of the determined elementary composition by evaluation of C, H and N content), spectroscopic methods as UV, IR, ^{1}H-NMR, ^{13}C-NMR as well as by mass spectral (MS) analysis. The IR, NMR and MS spectrum assignations were consistent with the declared chemical structure.

Also, the potential for polymorphism has been investigated to identify polymorphic forms of telaprevir. Screening was conducted using more than 70 solvents and a broad range of crystallization methods. No other new crystalline forms of telaprevir were derived directly from the screening experiments.

The substance was characterised by termogravimetric analysis (TGA), differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD). Results affirmed that Form A is the thermodynamically stable crystalline form. Moreover, it is the only solid form observed in the manufacture of the active substance.

Potential impurities have been well discussed in relation to their origin (raw material, manufacturing process and degradation products) and potential carry-over into the final drug substance. It has been demonstrated in a satisfactory manner that the stereochemical purity of the active substance is assured by the combination of the controlled chemistry and QC testing of the starting materials. The possibility of genotoxic impurities was also considered during the development. Impurities with a potential structural alert have been identified and are controlled by appropriate specification limits.

Specification

The active substance specification includes tests for appearance, identification (FT-IR and HPLC), assay (HPLC), chromatographic purity (HPLC), water content (Karl Fisher), residual reagent, heavy metals and residue on ignition.

A detailed description for all analytical methods was provided. Complete method validation data was provided for the non compendial (*in-house*) analytical methods. Appropriate HPLC method (reversed-phase HPLC method with UV detection) is used for assay, chromatographic purity and identification. The method was appropriately validated.

Tests for residual solvents are not included in the specification for the active substance. Although various organic solvents are used during the manufacturing process, their presence in telaprevir raises no safety concerns with regard to the finished product. Residual solvents are controlled with a head space GC-FID method during the manufacturing process of film-coated tablets. Therefore the presence of residual solvents was considered a non critical quality attribute for the active substance.

Particle size was not considered a critical quality attribute of the active substance as telaprevir is dissolved during the manufacturing process of film-coated tablets. Therefore no test on particle size determination was included in the specification.

In general specification limits and analytical methods proposed are suitable to control the quality of the active substance.

Batch analysis results for telaprevir have been presented. All batches were manufactured by the proposed commercial manufacturer according to the proposed processes. All batches showed the same impurity profile. It can be concluded that the batch analysis results indicate that the processes are reproducible and under control.

Stability

Stability studies were performed according to ICH requirements. Stability studies of telaprevir were conducted on 3 primary stability batches that were manufactured according to both processes: Process 1 and Process 2. Twenty four months long term (25°C/60% RH) and intermediate (30°C/75% RH) stability data and 6 months accelerated (40°C/ 75% RH) stability data were presented. The active substance batches used in the stability studies were packaged in the proposed packaging system.

Forced degradation studies were also performed in order to further characterise the active substance. A stress stability study in solution allowed the main degradation pathway to be determined. The effect of acid, base, oxidative agents and light was also tested. Furthermore, this study was also initiated to confirm the stability-indicating properties of the HPLC purity method.

The stress in solution study showed that telaprevir was not stable in alkaline, acidic or oxidative solutions. In the aqueous solution, the active substance was stable with a slight increase of some degradation products, though still within the specification limits. Very limited light degradation in the solid drug substance was observed. In general the proposed degradation pathways were analysed and well presented in the dossier. All major degradation compounds were separated and no relevant degradation compounds were found to co-elute with the active substance. This proved that the HPLC purity method is stability-indicating.

Stability results generated for telaprevir, manufactured in accordance to Process 1 and Process 2, demonstrated that there were no observed differences between two manufacturing processes. Based on the available stability data, telaprevir showed to be a stable when packaged in the proposed container closure system.

2.2.3. Finished medicinal product

Pharmaceutical development

The aim of the pharmaceutical development was to obtain a solid, oral dosage form that would deliver the required dose of the active substance.

Telaprevir has very low aqueous solubility, irrespective of the pH, and hence poor bioavailability. The development of the product focused on the improvement of the bioavailability by converting the crystalline substance to a stabilized, amorphous form using appropriate excipients. Spray drying was chosen as the processing step to produce amorphous telaprevir. The spray-dried dispersion (SDD) was introduced to stabilise the amorphous form of the active substance with the help of hypromellose acetate succinate (HPMCAS). The excipients were selected to assure rapid disintegration and

dissolution, and acceptable manufacturability. Mixture stability studies were conducted to investigate the compatibilities of telaprevir with excipients and solvents. The studies concluded that core tablet excipients are compatible with telaprevir formulated as an amorphous dispersion when water content is appropriately controlled.

Various formulations were considered and studied during development phase. Bridging studies have been performed between the tablets used throughout the development program. The addition of the film coat showed not significant difference on dissolution and *in-vivo* performance of the drug product. The applicant has described the optimisation and development of the product clearly and in sufficient details.

The manufacturing process development has been well documented. The development program consisted of in process characterisation studies to support the robustness of the process. Choice of the process was considered justified and the critical process parameters and process equipment were generally satisfactorily identified. It has been shown that the manufacturing process was robust.

It can be concluded that the formulation development of the product was satisfactorily described. The key critical parameters were identified and successfully evaluated. The formulation choice and optimisation were considered acceptable.

Adventitious agents

None of the excipients used in the product are of animal origin. Magnesium stearate, used in the formulation, is of vegetal origin.

Manufacture of the product

The manufacturing process is sufficiently described as well as a process flow diagram provided. The film-coated tablets are manufactured from a SDD of the active substance. The SDD is manufactured using a solvent based spray-drying followed by secondary drying to remove residual solvents. The SDD is blended with the tabletting excipients and the final blend is compressed into tablets which are then film-coated.

The spray drying mixture preparation was considered to be a critical step of the manufacturing process. Although spray-drying mixture preparation was characterized, the CHMP recommended the applicant to perform a study demonstrating suitable physical characterization and stability during the proposed holding time for the final spray-drying mixture, using 2 commercial scale batches. Furthermore, the CHMP recommended re-evaluation of the holding time of the SDD using 2 additional commercial scale batches.

The SDD technology, has been used in the past years for the manufacture of pharmaceutical products, and could be considered a standard manufacturing process. Batch results of full scale commercial batches of the telaprevir SDD intermediate showed the capability of the process with results well within proposed specifications. Validation of the telaprevir SDD intermediate and film-coated tablets, as part of general GMP, will be performed prior to launch of the product. The process validation protocol of the manufacturing process of the SDD and the film-coated tablet was provided. This was considered acceptable.

Product specification

Separate specifications were presented for the finished product and for the SDD.

The SDD specification includes tests for appearance, identity (HPLC), assay (HPLC), chromatographic purity (HPLC), residual solvents (GC), crystallinity (XRD), particle size (laser diffraction), bulk density and water content (Karl Fisher).

The drug product specifications include tests for appearance, identity (IR and HPLC), chromatographic purity (HPLC), uniformity of dosage units (mass variation), dissolution, water content (Karl Fisher), assay (HPLC) and microbiological purity.

The proposed specifications were justified based on the batch and stability results and are generally adequate for assuring the product quality and therefore were accepted.

A detailed description for all analytical methods was provided. Full method validation data was provided for the non compendial (in-house) analytical methods.

The Applicant has submitted batch analyses data. Batch analysis results demonstrated compliance with the proposed specifications and confirmed consistency and uniformity of the product. The results were consistent from batch to batch and proved that the product can be manufactured reproducibly according to the agreed specifications.

Stability of the product

Three primary batches of the film-coated tablets were placed on stability under ICH conditions, and results were available up to 24 months. In addition, supportive stability data was presented, including: data on 3 clinical batches of 375 mg core tablets, stability data used to define a chemical stability mathematical model, and stability data on a lot of film-coated tablets manufactured with SDD at the end of shelf-life.

Furthermore, 3 primary and 3 full scale batches of the SDD intermediate have been included in the stability testing program. One end-to-end stability study was performed for a batch of the SDD stored for 12 months. This batch was used in the manufacturing of one batch of film-coated tablets that was placed on stability for 24 months. The second end-to-end stability study has been initiated and is pending. Two commercial scale batches of the SDD were stored for 7 months and then used to manufacture a full-scale commercial batch of film-coated tablets.

The applicant has demonstrated, on development-scale batches, that finished product (coated or uncoated) manufactured with stressed SDD maintains its physicochemical properties. In view of the data provided the CHMP recommended to conduct additional end-to–end stability studies over 24 months under ICH conditions, using 2 pilot scale batches of telaprevir 375 mg film-coated tablets produced with the SDD stored for 12 months at the intended storage condition.

The overall stability data showed that INCIVO was stable under all tested conditions. The results generated during the stability studies support the proposed shelf life and storage conditions as defined in the SmPC.

With regard to the ongoing stability program, the CHMP recommended to further investigate the possible carry-over of an impurity in order to verify that the agreed specification limit was appropriate, and if necessary to introduce relevant amendments to the dossier.

<u>In-use stability</u>

The in-use stability study was also conducted on one batch of the product. The bottles were regularly opened and tablets were removed during one week at long-term and intermediate storage conditions. The data thus generated allowed the conclusion that the drug product has an acceptable stability profile after multiple openings of the bottle during one week.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The information provided about the active substance, telaprevir, was of acceptable quality. Although the manufacturing process is a relatively complex, convergent route with 5 key starting materials, in general sufficient information regarding the manufacturing process, materials, critical steps and intermediates, process validation and manufacturing process development have been provided. The synthesis and process parameters have been well characterised and described. The classification of key starting materials was justified by the fact that these compounds constitute important structural fragments, are isolated and well-characterised, have well-defined impurity profiles and are stable.

Specification limits and analytical methods are suitable to control the quality of the active substance.

A retest period was supported by satisfactory stability studies which show that the active substance is stable.

The finished product is an immediate release film-coated tablet containing 375 mg of telaprevir. The composition of the finished product has been described, and all excipients have been fully characterised.

The development pharmaceutics has been satisfactorily described. The excipients are well established and used in acceptable quantities. Their function has been satisfactorily described.

The formulation is considered satisfactorily justified.

The method of manufacture is considered standard and has been satisfactorily described, including hold times and in-process tests. The data shows consistent manufacture and is considered sufficient for this manufacturing process. A satisfactory validation protocol has been provided.

The proposed specifications were justified based on the batch and stability results, and are in general adequate for assuring the product quality and therefore were accepted.

The stability program is considered satisfactory. The batches placed on stability are considered representative of the product to be marketed. The results generated during the stability studies support the proposed shelf life and storage conditions as defined in the SmPC.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The active substance (telaprevir) and the finished product (film-coated tablets 375 mg) have been appropriately characterised and generally satisfactory documentation has been provided. The results indicate that telaprevir as well as the film-coated tablets can be reproducibly manufactured. Therefore the product should have a satisfactory and uniform performance in the clinic.

2.2.6. Recommendations for future quality development

In the context of the obligation of the applicants to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- To finalise and provide additional analytical validation reports used to control the starting materials.
- To perform a study demonstrating the suitable physical characterization and stability during the proposed holding time for the final spray drying mixture suspension (2 commercial scale batches).

- To conduct additional end-to–end stability studies over 24 months under ICH conditions, using 2 pilot scale batches of telaprevir 375 mg film-coated tablets produced with spray dried dispersion (SDD) stored for 12 months at the intended storage condition.
- To re-evaluate the holding time of the spray dried mixture using 2 additional SDD batches, and if necessary to introduce relevant amendments to the dossier.
- To further investigate the possible carry-over of a related substance, in order to verify that the agreed specification limit is appropriate, and if necessary to introduce relevant amendments to the dossier.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical testing of telaprevir consisted of a standard programme of pharmacology and toxicology studies. Scientific advice, both from national agencies as well as from central authorities, relating to non-clinical aspects has been provided during the course of drug development.

Several formulations were used during the non clinical development of telaprevir. Indeed, telaprevir drug substance (free base) has a very low solubility in water (< 0.01 µg/mL). In the perspective of its development for oral administration, amorphous SDDs of telaprevir with stabilizing polymers were developed to maintain the compound in amorphous form and ensure adequate bioavailability.

Early in the nonclinical program, polyvinylpyrrolidone (PVP) SDD formulations were employed; however, issues of physical stability resulted in the evolution to an optimized hydroxypropyl methylcellulose acetate succinate (HPMCAS) SDD formulation which exhibited greater physical stability, and when coadministered with vitamin E d-α-tocopheryl polyethylene glycol-1000 succinate (TPGS) improved solubility and bioavailability.

Multiple animal studies were carried out to optimize the oral formulation of Telaprevir used in nonclinical studies.

The optimized HMPCAS SDD formulation (49.5% Telaprevir, 49.5% HPMCAS, 1% SLS) suspended in an aqueous vehicle (1% HPMCAS, 10% Vitamin E-TPGS, 0.01% Simethicone) was used for oral administration in Pivotal Nonclinical Studies, including toxicity studies supporting clinical development.

All pivotal toxicity studies, including the safety pharmacology studies were performed in accordance with GLP principles.

EMA scientific advice was sought on the non clinical aspects, including carcinogenicity studies and the issue of combination toxicity studies.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Pharmacology

Primary pharmacodynamic studies

Telaprevir is a potent slow-binding inhibitor of the active site of the HCVNS3/4A protease with a maximal potency (Ki*) of 7-10 nM. The *R*-diastereomer or epimer of telaprevir, VRT-127394, is nearly 30-fold less potent than telaprevir.

The IC_{50} of telaprevir in HCV replicon cells was determined to be 0.35 µM (wild type subtype 1b replicon), which when compared to the CC_{50} of 83 µM in the same assay, resulted in an in vitro selectivity index (CC_{50}/IC_{50}) of 234. An infectious virus HCV replication assay was used to determine that telaprevir is able to inhibit viral replication using genotype 1a virus from human serum (IC_{50}= 0.28 µM=0.19 ug/mL).

Telaprevir inhibits genotype 2 HCV NS3 serine protease with similar potency to genotype 1a or 1b HCV proteases while its activity against genotype 3 and 4 HCV proteases is reduced.

Phenotypic studies (enzymatic and replicon-based) were performed to characterize substitutions identified in the HCV NS3 protease domain that were observed after treatment failure in clinical studies of telaprevir. A lower-level of resistance to telaprevir (3- to 25-fold increase in IC_{50} from wild-type) was conferred by single substitutions at V36A/M, T54A/S, R155K/T, and A156S. A higher-level of resistance to telaprevir (>25-fold increase in IC_{50} from wild-type) was conferred by A156T/V and the double substitution variant V36M+R155K. The in vitro replication capacity of all telaprevir-resistant variants was lower than that of wild-type in the replicon system.

While there is cross resistance with other NS3/4A protease inhibitors, telaprevir-resistant variants remained fully sensitive to interferon-α, ribavirin, and representative HCV nucleoside and non-nucleoside polymerase inhibitors.

The effect of telaprevir and interferon-α was additive or moderately synergistic in reduction of HCV RNA in replicon cells in vitro, and there was no significant increase in cytotoxicity by the combined treatment. Data obtained also indicate an additive effect of telaprevir and ribavirin.

Telaprevir was shown to be selective for HCV NS3 protease as compared to four human serine proteases, and induced a less than 10% inhibition at 10 µM in assays for kallikrein, thrombin, Factor Xa, and plasmin.

The in vivo effect of telaprevir was studied in SCID mice infected with replication defective adenovirus expressing wild type HCV protease SEAP constructs. Data from in vitro studies supporting a protease dependent release of secreted alkaline phosphatase (SEAP) was presented. In vivo telaprevir was shown to inhibit HCV protease–dependent SEAP secretion from the liver with an ED50 of <0.3 mg/kg. The concentration of telaprevir was found to be 6 to 16–fold higher in the liver compared to the concentration in plasma.

The SmPC adequately reflects the available information.

Secondary pharmacodynamic studies

In addition to possible effects on other proteases mentioned above, the selectivity of telaprevir was also investigated in a panel of radio-ligand binding assays (~60 targets including GPCRs, ion channels and transporters). Screening performed at 10µM did not reveal any significant effects (no inhibition or stimulation larger than 50% was detected). The largest effect seen was a 43% stimulation of the androgen receptor. Telaprevir was also investigated in a HIV-1 protease assay and was estimated to have an IC50 > 10 µM, which was also supported by results from an assay measuring the effect on replication of HIV-1 in MT4-LTR-EGFP cells, in which telaprevir had an IC50 of 15.3 µM. However, it should be noted that this was similar to the and CC50 value, 16 µM, in MT4 cells. When the HBV antiviral activity of telaprevir was investigated in vitro in HBV transfected HepG2 cells the IC50 was again estimated to be higher than 10 µM.

Safety pharmacology programme

Safety pharmacology studies were performed to investigate the effects of telaprevir on cardiovascular, central nervous and respiratory system. These studies were performed with telaprevir drug substance and/or SDD formulations, which are the formulations used in the pivotal nonclinical toxicity studies and in the clinical studies.

Central Nervous System

Neurological effects of telaprevir were investigated in rat after oral administration at doses of 100, 300 and 1000 mg/kg. Neither VRT-108720 nor VX-950 produced any behavioural (Irwin Test) or physiological changes when compared to vehicle treated animals in two separate studies. VRT-108720 (mixture of telaprevir (S-diastereomer) and VRT-127394 (R-diastereomer)) and VX-950 did not show any statistically significant effect on spontaneous locomotor activity.

Cardiovascular system

The possible effects of telaprevir on the cardiovascular system were addressed both in vitro and in vivo. In whole cell patch clamping studies using hERG transfected HEK293 cells, VRT 111950 (research grade telaprevir) gave a dose dependent inhibition of hERG (at 37˚C) but did not reach a 50% inhibition at 100µM (the highest concentration tested). VRT-108720 gave a dose dependent inhibition of hERG (at 37˚C) with an IC25 estimated to 12.2 µM and IC50 101 µM. Telaprevir in the form of VX-950 was also investigated, but at room temperature, and was found to give a concentration-dependent and significant inhibition of tail current at 30 and 80 µM (estimated IC25 was 55µM). However, a 50% inhibition was not achieved. In addition, exposure of dog Purkinje fibres to VX-950 (up to 50 µM) or VRT-108720 (up to 100 µM) did not cause any significant prolongation of the action potential. However, it should be noted that the solubility of telaprevir in water is less than 15 nM. The actual concentrations achieved in these in vitro experiments are not known, but are likely to be much less than what is stated as the concentrations used.

Telaprevir given orally (25, 75, and 250 mg/kg), using a spray-dried dispersion/mixture containing 49.5% VX-950, 49.5% HPMC-AS and 1% SLS, to conscious beagle dogs fed approximately 2 h prior to dosing to maximize exposure (see Pharmacokinetics below) did not elicit any noticeable changes in cardiovascular parameters (analysed by telemetry). At the highest dose Cmax for VX-950 was determined to be 17.6 µg/mL and AUC 243 µg•h/mL, and for VX-127394 the Cmax was determined to be 8.96 µg/mL and AUC 155 µg•h/mL. The ratio between VX-950 and VX-127394 was thus 66:34 and 61:39 for Cmax and AUC, respectively.

Respiratory system

Telaprevir at doses up to 1000 mg/kg, either as VRT-108720 or as a spray-dried mixture containing 49.5% VX-950, 49.5% povidone USP K30, methylene chloride (149 ppm), and 1% SLS in 1% (w/v) HPMC was also shown not to elicit any noticeable changes in respiratory parameters in rat relative to placebo treated controls.

2.3.3. Pharmacokinetics

The pharmacokinetics and toxicokinetics of Telaprevir and its epimer VRT-127394 were investigated in mice, rats, rabbits and dogs after single intravenous and single or repeated oral administration. The solubility of crystalline telaprevir is low and oral bioavailability was optimized via the use of amorphous SDD formulations and stabilizing polymers, to increase physical stability of the formulations. The analytical method used was validated for quantitation of both telaprevir and VRT-127394

simultaneously and methods were validated for plasma (mouse, rat, rabbit, dog, human) and liver homogenate (rat and dog). Oral PK parameters for VRT-127394 were similar to those observed for telaprevir. The relative percent systemic exposure of VRT-127394 compared to the combined telaprevir and VRT-127394 total exposure ranged from 4% to 23% in mice, 17% to 34% in rats, from 17% to 31% in dogs, and from approximately 29% after a single 750 mg telaprevir dose to 37% after multiple telaprevir doses in humans. Telaprevir was rapidly absorbed and exhibited a moderate (20 mL/min; dog), to moderately high (50 mL/min; rat and dog) and high (120 mL/min; rabbit) clearance, a relatively short half-life (0.8 to 1.5 h), and a moderate volume of distribution at steady state (1.3 in dog to 2.7 in rat, L/kg). Dose-proportional, less than dose-proportional as well as larger than dose proportional increases in systemic exposure (Cmax and AUC) were seen, but generally the exposure to telaprevir did not increase with increasing dose at the highest dose levels used. Systemic exposures (Cmax and AUC) to VRT-127394 were also variable depending on dose level.

A clear food effect was detected in dogs with a 1.5- to 4.0-fold increase in exposures observed as compared to fasted conditions. Under fasted conditions, systemic exposures (Cmax and AUC0-∞) increased in a less than dose-proportional manner with increases in dose ranging from 25 to 250 mg/kg, resulting in an apparent oral bioavailability of 43% to 67% at the highest dose.

Telaprevir (14C-labelled) was moderately bound to plasma proteins in the concentration range 0.1-20 µM; mouse (63%-71%), rat (82%-86%), dog (62%-67%) and in human plasma (59%-76%). Concentration-dependent decrease in binding was evident in mouse and human plasma but not in rat or dog plasma. Protein binding to human serum albumin (HSA) and α1 acid glycoprotein (AAG) was low to moderate and was dependent upon telaprevir concentration and protein concentration. Data indicated that both proteins may be involved in binding of telaprevir.

Highest exposure was seen in the liver, intestine and pancreas after administration of 14C-telaprevir to rats (small intestine>liver>large intestine>pancreas>stomach>kidneys). Distribution to the brain, fat, lymphatic tissues, muscle, and testes was considered to be low. After 168 h post-dose elimination of radioactivity was almost complete in all organs with the exception of brown fat where measurable amounts remained after 168 hours. No binding to melanin was indicated when distribution in Sprague-Dawley and Long Evans rats was compared. Prolonged half life (>70 h) of radioactivity both after intravenous and oral administration, as compared to telaprevir and VRT127394, was detected. The radioactivity was shown to elute in the void volume at later time points and is thus likely to represent small and polar metabolites (although not identified).

Steady-state liver exposures to telaprevir and VRT-127394 were also evaluated in repeat dose toxicity studies conducted in rats and dogs. The liver to orbital plasma AUC0-8h ratio of telaprevir ranged from 14 to 65 and the corresponding ratio for VRT-127394 ranged from 35 to 129 in the 28-day and 13-week toxicity studies in rats, while in the 6-month toxicity study, this ratio ranged from 3.7 to 9.4 for telaprevir and from 4.8 to 18 for VRT-127394. In dogs the liver to jugular plasma AUC1-8h or AUC2-8h ratio for telaprevir ranged from 1.6 to 6.3 and for VRT-127394 from 2.4 to 8.2 in the 28-day and 13-week toxicity studies, and from 0.56 to 1.4 for telaprevir and from 0.4 to 0.9 for VRT-127394 on terminal sacrifice days 183 and 274 in the 9-month study.

Placenta transfer of telaprevir and fetal exposure to telaprevir and VRT-127394 established in mouse and rat. Fetal plasma and whole fetus exposures to telaprevir represented 6.8% and 21% of the maternal plasma exposure in mouse and 4.7% and 7.6% in the rat.

Telaprevir undergoes extensive metabolism via epimerisation, oxidation, reduction, and hydrolysis and multiple metabolites were observed. CYP3A was identified as the major isoform responsible for telaprevir metabolism across all species investigated (rat, dog and human). In addition non-CYP-mediated metabolism (amide hydrolysis) was observed. The major metabolites of telaprevir identified in vitro from preparations from all species evaluated were VRT-127394 (epimer of telaprevir) and M1

(hydroxylation of the cyclohexyl-glycine or pyrazinoic acid moieties). Steady state metabolite profiling identified VRT-127394, pyrazinoic acid (PZA) and M3 isomer as the predominant metabolites in plasma from rats, dogs, and humans. Minor qualitative sex differences were observed in the metabolism of 14C-telaprevir in vitro in incubations with microsomal and S9 fractions from all species.

Dose-dependent increases in CYP3A1/2 and CYP2E1 activities were observed in liver of rats (both sexes) after 13 weeks of treatment, whereas CYP2B activity was inhibited in female rats only. (After 28 days of treatment with telaprevir no changes in CYP activity was seen, except for a decreased CYP3A activity in female rats.) In both male and female dogs significant dose-dependent declines in liver microsomal CYP3A12 and CYP2E1 activities were observed concomitant with a decline in total CYP content.

When administered orally 14C-telaprevir was mainly excreted via feces as unchanged compound. Biliary clearance was likely the major route of elimination of absorbed compound, whereas renal clearance was limited. Telaprevir was excreted in the milk of lactating rats.

Toxicology

Single dose studies

Single-dose oral toxicity studies were conducted in mice and rats. Telaprevir was administered once orally by gavage as an aqueous suspension of PVP SDD formulation (PVP suspension 2) up to the maximum feasible dose established at 50 mg/g. Findings from these studies suggest that the acute oral toxicity of Telaprevir is low.

Repeat-dose studies

The repeat-dose toxicity program for Telaprevir is extensive. Several different formulations have been used during development . In studies VX-950-001 and VX-950-TX-002 a PVP suspension was used which resulted in a skewed PK due to stability issues. Therefore, the applicant performed new toxicity studies with an optimized clinically relevant HPMCAS formulation (VX-950-TX-016, FXU0003, VX-950-TX-020, VX-950-TX-014, VX-950-TX-017 and VX-950-TX-021). In this section only pivotal studies using the relevant formulation are presented.

The repeat-dose toxicity program presented by the applicant holds eight relevant studies conducted under GLP with the clinically relevant formulation. Four studies have been conducted in rat over eight weeks to nine months with doses ranging from 1 to 1000 mg/kg/day. Toxicokinetic data generated during these studies do not give rise to any exposure margins to humans in terms of AUC_{last}. On the contrary, rats dosed 1000 mg/kg/day for three months do only reach 53% and 29% of the clinical exposure in females and males, respectively. The remaining studies were conducted in dogs over eight weeks to one year, with doses ranging from 15 to 500 mg/kg/day. In some of these studies the toxicokinetic data show small exposure margins to humans in terms of AUC_{last} (2.7/3.5 times the human exposure in male and female dogs, respectively, after 28 days of dosing with 300 mg/kg/day). Both rat and dog is considered as relevant species to use in toxicity testing.

The toxicity findings from the presented studies are;

Clinical signs

In rats excessive or increased salivation and red material around the mouth was observed in the three month study in the ≥300 and ≥100 mg/kg/day groups. In dogs abnormal stool was generally observed. In dogs administered ≥150 mg/kg/day most animals showed general signs of toxicity including thinness, decreased activity, inappetence and vomiting.

Haematology/Coagulation

Data from both species show Telaprevir toxicity on the haematological/coagulation system. These findings include lowering of erythrocytic parameters (rat), higher levels of activated partial thromboplastin times (rat), increase in lymphocyte/monocyte numbers (rat, dog), anaemia (dog) and lower eosinophil counts (dog). In the long term studies all haematological parameters were normalized after recovery. The potential mechanisms of the anemia/erythrocytic effects noted in nonclinical and clinical studies were addressed by an *in vitro* study on human erythrocytes which showed that Telaprevir have no effects on red blood cells osmotic fragility at 80 µM. The Applicant has not investigated other causes of haematological toxicity, particularly an impact on progenitor cells.

Serum chemistry

AST and/or ALT elevations was observed in most studies on both species (ALT up to 7.8-fold increase and AST up to 6.2-fold increase in rats dosed 300 mg/kg/day). In addition, both species show increase in cholesterol, (+22.2% in rat dosed 300 mg/kg/day and >65% in dogs dosed 100 mg/kg/day), decrease in albumin (>25% in dog dosed ≥150mg/kg/day). In rat all chemical parameters, but the increase in ALT, was normalised after recovery.

Organ/Body weights

In rat increased spleen weights (up to +28.6% in males dosed ≥300 mg/kg/day), increased thyroid/parathyroid weights (up to +33.7% in males dosed 1000 mg/kg/day), increased liver weights (+32.8% to +42.9% in females dosed 1000 mg/kg/day), decreased testicular weights (up to 32.1% in males dosed ≥300 mg/kg/day). In dogs a non-statistical significant-dose dependent increase in liver weight was noted. In the one year dog study epididymides, heart, lung, and pituitary gland weights relative to brain weight were significantly increased for males administered 100 mg/kg/day compared to placebo controls. In general administration of Telaprevir induced a decreased mean body weight.

Histopathology

In rat and dog the histopathological findings in the liver was similar and not all of these findings was fully resolved after recovery. In rat males microscopic findings in the testis was also generally observed. These findings include bilateral degeneration of the germinal epithelium, bilaterally exfoliated germ cells, bilateral hypospermia, and/or bilateral aspermia. Findings in the testis were not observed in dogs and were fully resolved after recovery.

Effects on the vascular system in dogs were consistent with those observed in Beagle Pain Syndrome (Idiopathic Canine Polyarteritis), and in more severe cases animals presented with clinical signs of poor or ill health consistent with this syndrome. Microscopic findings were generally minimal to mild in nature and were observed in multiple tissues, particularly the coronary artery, a known target tissue for vasculitis in Beagle dogs. Many other microscopic findings noted in dogs were considered secondary effects to diffuse vasculitis noted in these animals. Drug induced vasculitis in Beagle dogs has been observed previously with marketed products including endothelin antagonists and phosphodiesterase inhibitors, with no correlate in humans. These effects are considered species-specific, and no signs of vasculitis were observed in biopsies taken from subjects presenting with rash in clinical studies with telaprevir.

Some of the toxic signals observed in the non-clinical program have also been observed in the clinical trials. These include increased cholesterol and haematological effects. The clinical data do not show an increase in ALT/AST related treatment-emergent laboratory abnormalities. The findings of testicular toxicity in rats prompted the measurement of reproductive hormone levels in the clinic. Levels of serum inhibin B, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) were assessed in

male subjects during the telaprevir dosing period. In each study, inhibin B, FSH, and LH levels, as well as changes from baseline, were similar between the telaprevir and placebo treatment groups. There was no indication of any effect of telaprevir on human testes in these studies, nor have there been any reports in any telaprevir clinical study suggestive of testicular toxicity.

The issue of combination toxicity studies was addressed during a CHMP scientific advice in which the CHMP agreed with the applicant in that no such studies werenecessary. In accordance with this advice the applicant has presented an acceptable justification for the waiving of preclinical combination toxicity studies.

Genotoxicity

Telaprevir was concluded to be negative for mutagenic and clastogenic potential when evaluated in the definitive ICH S2B battery of GLP-compliant genotoxicity studies. The R-diastereomer of telaprevir, VRT-127394, was also found to be negative for mutagenic potential when evaluated in a GLP-compliant bacterial reverse mutation study.

Positive genotoxic signals were detected during early development using experimental batches. This issue was addressed in advice given by the CHMP. The CHMP concluded that no further testing was necessary and that the applicant should ensure that the clinically relevant material is adequately tested. The data presented are deemed as sufficient in this regard.

Carcinogenicity studies

Since the duration of treatment is limited to 12 weeks and no concern for carcinogenicity have been observed during toxicity testing, carcinogenicity studies for Telaprevir were deemed unnecessary. This is further supported by the extant guideline (CPMP/ICH/140/95) and given CHMP scientific advice. However, if the duration of treatment were to be increased, the need for carcinogenicity studies would need to be re-evaluated.

Fertility, early embryonic development, embryo-foetal development and pre/postnatal development.

Telaprevir had no effects on mating performance and fertility in male and female rats; however, slight increases in pre-implantation loss (first cohabitation) and/or an increase in non-viable conspectuses (first and second cohabitation) were noted at the paternal high dose of 300 mg/kg/day. Satellite males administered this dose and incorporated in the design to characterize the nature, timing and severity of the effects of telaprevir on the male reproductive organs, presented with macroscopic testicular findings consistent with those observed in the repeat-dose toxicity studies in rats which correlated to effects in sperm evaluation endpoints and to reversible treatment-related microscopic findings in these organs.

The presented data show that Telaprevir readily cross the placenta in both rat and mouse giving high foetal: maternal exposure (19-50%). The data also show that telaprevir has no teratogenic potential in rat or mouse. Peri- and post-natal developmental evaluations suggest that telaprevir has no effects on natural delivery in rats but may have adverse effects on the growth of offspring as evidenced by body weight effects pre- and post-weaning (up to an 11% decrease); however, no effects on development, behaviour, and Caesarean-sectioning or litter parameters were noted in the offspring. The dosing of the animals does not result in any margins to human exposure. This issue has been raised in conjunction to the repeat-dose toxicity section.

Local tolerance

Available data demonstrate that telaprevir is a non-irritant from both the dermal and ocular perspectives. Telaprevir does not absorb UV irradiation or visible light between 290 and 700 nm and does not show any obvious distribution to skin and eye or binding to melanin. Telepravir is therefore considered not to have any significant phototoxic potential.

Antigenicity

On the basis of a positive result for skin sensitizing potential associated with the regulatory starting material VRT-126032 recognized strong structural similarity of this material to the M11 metebolite VRT-841125) of telaprevir, and incidence of rash observed clinically, it was postulated that antigenicity associated with M11 may play a role in the etiology of rash observed in clinical studies evaluating telaprevir VRT-841125 was initially found to be negative for skin sensitizing potential in an LLNA and was later demonstrated positive for skin sensitizing potential in a follow-on Guinea pig maximization test. Given that M11 is not a predominant circulating metabolite in humans and the nature of the rash observed in clinical studies with telaprevir, it is unlikely that the observed potential for skin sensitivity relates to the etiology of the observed rash, but these results show that a telaprevir metabolite can act as an antigen in a delayed-type hypersensitivity reaction.

Studies on impurities, degradation products and the M5 metabolite

The applicant has performed a series of studies to address potential genotoxicity and repeat-dose toxicity associated with organic process impurities related to telaprevir drug. *In vivo* data show that Telaprevir spiked with several impurities and degradants do not result in additional toxicity when compared to Telaprevir alone. The data indicate that the two process impurities TEMPO and VRT-836871 have genotoxic properties. For this reason the applicant has added two washing steps in the manufacturing process of telaprevir to reduce the level of VRT-836871 impurity below the threshold for toxicological concern and implemented manufacturing controls to bring the level of TEMPO and TEMPOH as low as reasonably practicable (ALARP). Batch data presented in the quality AR show that the contamination for TEMPO/TEMPOH is 0.2-0.7 ppm and for VRT-836871 the LT is 0.2 ppm.

Other studies

Data from the effect study on human erythrocytes show that telaprevir has no appreciable effects on red blood cell osmotic fragility at the concentration evaluated. Results from an exploratory secondary pharmacodynamic screening study evaluating binding affinity of research grade telaprevir (VRT-111950) for a range of receptors and ion channels showed an apparent species-specific binding displacement for the rat testosterone receptor. Investigational studies were performed to confirm rat testosterone binding with telaprevir and VRT-127394 and to determine the potential for effects mediated by a similar mechanism to occur in dog and human. Consistent with the potential association with the observed rat testicular toxicity, effects previously noted with the rat testosterone receptor were confirmed, whereas no appreciable binding was reported for either the dog or human androgen receptor binding assays. The relevance of this finding could potentially account for the testis toxicity observed in rat, but not in dog.

2.3.4. Ecotoxicity/environmental risk assessment

The worst-case $PEC_{SURFACE\ WATER}$ of telaprevir at the point of discharge of sewage effluent to surface water (11.25 $\mu g.L^{-1}$) assumes that the parent substance is not metabolised and is excreted from the body unchanged. PEC/PNEC ratios for surface water, microorganisms and ground calculated using this worst-case value confirmed that telaprevir does not present a potential risk to the aquatic environment. The PEC/PNEC ratio for telaprevir for the larval stages of Chironomus riparius tested at concentrations

up to its limit of aqueous solubility confirmed the absence of risk and in a fish bioconcentration test where the highest steady-state BCF was 2x, telaprevir showed very little tendency to concentrate in the tissues of the rainbow trout. Assessments based on estimated worst case levels of telaprevir therefore confirmed that based on the studies conducted it does not present a risk in the environment.

Table 1. Summary of main study results

Phase IIb Studies					
Substance (INN/Invented Name): Telaprevir (VX-950)					
CAS-number (if available): 402957-28-2					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …	4.00			Potential PBT (N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	4.00			not B
	BCF	0.29			not B
Persistence	DT50 or ready biodegradability	10.9/12.8			P/not P
Toxicity	NOEC or CMR				T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)		11.25 µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 or …	K_{oc} =60 (Arrow), 505 (Elmton), 36.2 (Evesham), 258 (Wasop), 119 (Sewage sludge)			List all values
Ready Biodegradability Test	OECD 301	The mean cumulative carbon dioxide production by mixtures containing telaprevir was negligible			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 9.7 $DT_{50, sediment}$ = 11.1 $DT_{50, whole\ system}$ = 10.9/12.8 % shifting to sediment =			Not required if readily biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae Growth Inhibition Test/*Species*	OECD 201	NOEC	2.36	mg/L	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	2.85	mg/L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	1.32	mg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	1000	mg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			for all 4 soils
Soil Micro organisms:	OECD 216	%effect		mg/	

Nitrogen Transformation Test				kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/ kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/ kg	
Collembola, Reproduction Test	ISO 11267	NOEC		mg/ kg	
Sediment dwelling organism		NOEC	1048	mg/ kg	*Chironomus riparius*

2.3.5. Discussion on non-clinical aspects

Pharmacology

Telaprevir has been shown to be a specific, reversible, tight and slow binding inhibitor of the HCV NS3•4A serine protease with a similar sub-micromolar IC50 for HCV genotype 1a and 1b. However, it should be noted that due to the plasma concentrations reached clinically the specificity of telaprevir seen in vitro might not be relevant for the human situation. All telaprevir resistant variants analysed remained fully sensitive to IFN-α and ribavirin and the NS5B nucleoside and non-nucleoside inhibitors tested and were also found to have a decreased replication capacity as compared to the wild type. The effect of telaprevir and interferon-α, and telaprevir and ribavirin, was found to be at least additive in replicon cells in vitro.

No safety pharmacology issues were identified. However, the exposure levels achieved in these studies are uncertain and only a ~2.5 time exposure margin was reached in the telemetry study in dogs where actual measurements were performed. In addition, due to the low aqueous solubility of telaprevir (<15 nM) the concentrations reached in the studies performed in vitro on hERG transfected cells and Purkinje fibres are likely to have been lower than the stated concentrations used. It should thus be pointed out that no definite conclusions can be made based on the lack of non-clinical findings in the safety pharmacology studies performed with telaprevir. However, since higher exposures are not likely to be possible to obtain, neither in vivo nor in vitro, the lack of identified exposure margins can only be further addressed clinically. It may also be noted that clinical investigations include studies regarding possible cardiovascular effects, which continue to be evaluated, and have so far not indicated any other safety pharmacology issues.

Pharmacokinetics

The pharmacokinetics and toxicokinetics of telaprevir and its epimer VRT-127394 were investigated in mice, rats, rabbits and dogs. A rapid clearance of telaprevir was detected in rabbit and sufficient systemic exposure was not reached in this species (mouse was therefore selected as the second species for embryo-fetal development evaluations). Metabolic investigations revealed an extensive metabolism and formation of numerous metabolites via epimerisation, oxidation, reduction and hydrolysis. No human specific metabolite of telaprevir has been identified and all three major human plasma metabolites were present in the species used in non-clinical studies. Some uncertainty remains due to both qualitative and quantitative differences but these differences of minor metabolites between species and between in vitro and in vivo are not considered to have any significant impact on the evaluation of the general safety of telaprevir or on the assessment of genotoxicity.

The solubility of crystalline telaprevir is low and a large number of studies were carried out to optimize the oral formulation of telaprevir to be used in non-clinical studies and later also to optimize and monitor the bioavailability of tablet formulations used for clinical studies. An optimized amorphous sprayed dried dispersion formulation was used for oral administration in pivotal nonclinical studies and

a clear food effect was detected in dogs with a 1.5- to 4-fold increase in exposures under fed as compared to fasted conditions. It was not possible to reach any exposure margins in the safety studies performed and a maximum exposure of approximately 2 times that seen in the clinic could only be achieved. As judged from the efforts made by the applicant to optimize the oral formulations used it may be concluded that higher exposures are not likely possible to obtain in animal studies and thus that this potential issue most likely cannot be resolved. A rapid clearance of telaprevir was detected in rabbit and the applicant concludes that a sufficient systemic exposure was not reached in this species. These results also support the selection of mouse for the embryo-fetal development evaluations, which is endorsed. However, the possibility to use repeated intra venous administration to achieve higher exposure was not evaluated.

Telaprevir was found to be excreted in the milk of lactating rats.

Toxicology

Telaprevir has toxic effects mainly to the liver and on the hematological system. Most of the toxic signals are resolved after recovery. The signal of testis toxicity, observed in rat, was addressed in the clinic as well as in dedicated non-clinical studies. The studies presented by the applicant are deemed as sufficient in terms of species and length. However, the dosing of the animals does not generate exposure margins to humans (no margin to human exposure in the rat studies and only a two times human exposure is reached in the long-term dog study). The exposure levels are also influenced by feeding status of the animals. Exposure levels has been maximised by the use of a SDD and a twice daily dosing regimen. Maximum feasible doses have been used in the pivotal studies and the influence by the feeding status of the animals as well as the possible influence of gastro-intestinal toxicity observed on exposure levels have also been addressed in an acceptable manner. The ratio animal AUC/human AUC for the rat at the highest dose in the 6 month study is well below unity and the ratio for the pregnant mouse and the dog in the 9-month study is ~2. Overall, reasonable efforts seem to have been made to increase exposure in non-clinical studies and it should be noted that in spite of the relatively low exposures obtained, target organs (liver and the hematological system) were identified. However, some uncertainty remains and the full toxicological profile of telaprevir may not have been possible to identify.

Telaprevir is to be used in combination with interferon alpha and ribavirin. Both peginterferon and ribavirin are potent drugs accompanied with known specific toxicity. Overall, the toxicity program/data presented by the applicant is deemed as sufficient for assessment of Telaprevir related toxicity.

2.3.6. Conclusion on the non-clinical aspects

The non-clinical program adequately supports the marketing authorisation application for INCIVO. The toxicity profile of INCIVO is sufficiently characterised by the non-clinical data submitted. The statements in section 5.3 of the SmPC pertaining to non clinical data are appropriate.

2.4. Clinical aspects

2.4.1. Introduction

The CHMP granted an accelerated assessment for telaprevir on 18 November 2010.

The recommended indication is:

INCIVO, in combination with peginterferon alfa and ribavirin, is indicated for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease (including cirrhosis):

- who are treatment-naïve;
- who have previously been treated with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin, including relapsers, partial responders and null responders (see sections 4.4 and 5.1).

EMA scientific advice was sought (with follow up) on the clinical aspects. There have been no important deviations from the advice given on clinical development, which would have ramifications on the present assessment.

GCP

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

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

- Tabular overview of clinical studies

Table 2. Tabular overview of clinical studies

Phase 1 Single-Dose Studies in Healthy Subjects		N_{TOT} (N_{TPV})
VX03-950-001	Randomized, double-blind, placebo-controlled, single-dose escalation study	35 (33)
VX05-950-002	Randomized, open-label, 2-sequence, 2-period, single-dose crossover food effect study	16 (16)
VX05-950-003	Randomized, open-label, single-dose, crossover bioavailability and DDI study with ketoconazole and low-dose ritonavir	35 (35) 36 (36)
VX05-950-004	Randomized, open-label, single-dose, crossover bioavailability study	
VX06-950-005	Nonrandomized, open-label, mass-balance study	6 (6)
VX06-950-010	Randomized, open-label, single-dose, crossover bioequivalence study	115 (115)
VX07-950-017	Randomized, open-label, single dose escalation study	20 (20)
VX-950-TiDP24-C121	Randomized, open-label, single-dose, 5-way crossover food effect study	30 (30)
VX-950-TiDP24-C130	Randomized, open-label, single-dose, crossover DDI study with esomeprazole	24 (24)
VX06-950-006	Nonrandomized, open-label study in healthy subjects and in subjects with mild hepatic impairment	20(20) 10(10)
VX06-950-012		
VX-950-TiDP24-C132	Nonrandomized, open-label study in subjects with moderate or severe hepatic impairment Nonrandomized, open-label study in subjects with severe renal impairment as compared to subjects with normal renal function	24(24)

Phase 1 Multiple-Dose Studies in Healthy Subjects		
VX04-950-101 Part A[a]	Randomized, double-blind, placebo-controlled, dose-escalation study	24 (18)
VX06-950-007	Nonrandomized, open-label DDI study with oral contraceptive	24 (24)
VX06-950-009	Randomized, open-label, parallel-group DDI study with ritonavir	48 (48)
VX06-950-011	Nonrandomized, open-label, single sequence DDI study with midazolam and digoxin	24 (23)
VX07-950-016	Nonrandomized, open-label, single sequence DDI study with rifampin and efavirenz [EFV]	44 (44)
VX-950-TiDP24-C122	Randomized, open-label, 2-way crossover DDI study with ritonavir-boosted lopinavir [LPV/rtv] and atazanavir [ATV/rtv]	41 (37)
VX07-950-018	Nonrandomized, open-label DDI study with amlodipine and atorvastatin	21 (21)
VX-950-TiDP24-C123	Randomized, open-label, 3-way crossover DDI study with tenofovir disoproxil fumarate [TDF]	18 (18)
VX07-950-019	Nonrandomized, open-label, crossover DDI study with zolpidem and alprazolam	40 (40)
VX-950-TiDP24-C124	Randomized, open-label, 2-way crossover DDI study with ritonavir-boosted darunavir [DRV/rtv] and fosamprenavir [fAPV/rtv]	40 (3[illegible])
VX-950-TiDP24-C134	Randomized, open-label, crossover DDI study with EFV and TDF	2[illegible] (20)
VX-950-TiDP24-C135	Nonrandomized, open-label, single sequence DDI study with methadone	[illegible] (18)
VX-950-TiDP24-C133	Randomized, open-label, crossover DDI study with escitalopram	16 (14)
VX-09-950-021	Nonrandomized, open-label DDI study with cyclosporine and tacrolimus	30(28)
VX06-950-008	Randomized, placebo-controlled, 4-way crossover thorough QT study	89(84)
VX-950-TiDP24-C136	Randomized, double-blind, double-dummy, placebo-and active-controlled, 4-period crossover thorough QT study	44(43)
Phase 1b/2a Studies in Subjects with Chronic Hepatitis C		
VX04-950-101 Part B[a]	Randomized, double-blind, placebo-controlled, dose-escalation study	34 (28)
VX05-950-102	Nonrandomized, single-arm, open-label study	12 (12)
VX05-950-103	Randomized, placebo-controlled parallel-group study	20 (16)
VX-950-TiDP24-C209	Randomized, partially-blinded, multiple-dose study in treatment-naïve subjects with genotype 2 and 3 hepatitis C Randomized, partially blinded, multiple-dose study in treatment-naïve subjects with genotype 4 hepatitis C	49 (31) 24 (16)
Phase 2 Studies in Subjects with Chronic Hepatitis C		
VX05-950-104	Randomized, double-blind, placebo-controlled, parallel-group study in treatment-naïve subjects with genotype 1 hepatitis C	250 (175)
VX05-950-104EU	Randomized, partially double-blind, partially placebo-controlled, parallel-group study in treatment-naïve subjects with genotype 1 hepatitis C	323 (241)
VX06-950-106	Randomized, stratified, partially placebo-controlled, partially double-blind study in subjects with genotype 1 hepatitis C who have not achieved SVR with prior interferon based therapy	453 (339)
VX06-950-107	Nonrandomized, single arm, open-label study in subjects who received and failed Peg-IFN/RBV in the control groups of Studies 105, 104, or 104EU	117 (117)
VX-950-TiDP24-C208	Randomized, open-label study in treatment-naïve subjects with genotype 1 hepatitis C	161 (161)
Phase 3 Studies in Subjects with Chronic Hepatitis C		
VX07-950-108	Randomized, double-blind, placebo-controlled, parallel-group study in treatment-naïve subjects with genotype 1 hepatitis C	1088 (727)
VX08-950-111	Randomized, open-label study in treatment naïve subjects with genotype 1 hepatitis C	540 (540) 662
VX-950-TiDP24-C216	Randomized, double-blind, placebo-controlled study in subjects with genotype 1 hepatitis C who failed prior treatment with Peg-IFN/RBV	(530)
Ongoing Phase 2-3 Studies in Subjects with Chronic Hepatitis C		
VX08-950-110	Phase 2a, randomized, double-blind, placebo-controlled, parallel-group study in HCV/HIV-1 coinfected subjects	68 (42) planned 400 (0) planned
VX08-950-112	Nonrandomized, 3-year virology noninterventional follow-up study Phase 3,	120 (120)
VX-950-TiDP24-C219	nonrandomized, single-arm, open-label rollover study	planned
Taste-Profiling Studies		
VX06-950-013	Open-label, single-dose study	3 (3)
VX07-950-015	Open-label, multiple-dose study	4 (4)
Studies Conducted in Japan by Mitsubishi Tanabe Pharma Company		
G060-A1, G060-A3	Phase 1, randomized, placebo-controlled, double-blind, single-dose study Phase 1,	32 (24) 10 (10)
G060-A4, G060-A5	nonrandomized, open-label, multiple-dose study Phase 1, randomized, open-label, single-	18 (18) 20 (20)
G060-A6, G060-A7	dose, crossover study Phase 1, randomized, open-label, multiple-dose, parallel-group study	189 (126) 15
G060-A8 (ongoing at the cut-off date of 16 July 2010) G060-A9	Phase 3, randomized, open-label, multiple-dose, parallel-group study Phase 2, nonrandomized, open-label, multiple-dose study Phase 3, nonrandomized, open-label, multiple-dose study Phase 3, nonrandomized, open-label, multiple-dose study	(15) 100 (100) planned 32 (32)

[a]Study 101 consisted of Part A in healthy subjects and Part B in subjects infected with hepatitis C. N_{TOT}: total number of subjects; N_{TPV}: number of subjects who received telaprevir (at least one dose)

Clinical Pharmacology studies in healthy subjects were performed to understand the dose-proportionality (Studies 001, 017), food-effect (Studies 002, C121), bioavailability from different formulations (Studies 003, 004, 010), absorption/distribution/metabolism/excretion (ADME Study 005), effect of hepatic impairment (Studies 006, 012), and the effect of renal impairment (Study C132).

Several studies were conducted to examine the DDI potential of telaprevir as a substrate, and as an inhibitor, of CYP3A and P-gp, using both model drugs and drugs that are commonly prescribed to subjects with HCV. Because HCV co-infection is relatively common in subjects with human immunodeficiency virus (HIV), studies were conducted to examine the potential DDIs between telaprevir and commonly used HIV medications that might interact with telaprevir (i.e., ritonavir-boosted HIV protease inhibitors, tenofovir disoproxil fumarate, and efavirenz). Data were collected from 4 Phase 2 studies (104, 104EU, 106, C208) and 3 Phase 3 studies (108, 111, C216) to assess the effects of subject demographic characteristics and other covariates on telaprevir PK and to characterize the exposure-response (efficacy and safety) relationships. The effect of telaprevir on the QT interval has also been studied (Studies 008, C136).

Telaprevir is converted to an inactive (considering antiviral effect) diastereoisomer VRT-127394 which is present in plasma (about half the exposure of telaprevir (1:3 of total exposure). To minimize conversion ex vivo, formic acid is added to plasma and plasma samples are kept on ice. Both forms have been measured by LC-MS-MS in studies performed until 2009.

Standard statistical methods have been used. Non-compartmental data analysis for intense sampling scheme and population analysis utilizing nonlinear mixed effects modeling for sparse sampling data was applied.

Early clinical studies used an aqueous suspension of an amorphous spray-dried dispersion of Telaprevir. Subsequently 250-mg and 375-mg tablets were developed. The registration studies used an uncoated 375-mg tablet. The commercial tablet contains a non-functional film-coating. The uncoated and film-coated 375-mg tablets were shown to have similar relative bioavailability in fed subjects. No relevant differences in bioavailability are expected.

Absorption

Information regarding absorption characterization of telaprevir was obtained from in vitro investigations and also from the mass-balance study (Study 005), and other formal clinical PK studies.

In vitro studies performed with human Caco-2 cells suggested a high intestinal permeability of telaprevir. The observed permeability index is slightly lower than that observed with highly permeable drugs such pindolol. In presence of P-gp inhibitors, the permeability index is sharply enhanced (approximately 10 folds) demonstrating that telaprevir is a substrate of P-gp. Therefore, telaprevir absorption may be affected by other substrates or inhibitors/inducers of P-gp. Although in vitro studies did not demonstrate that telaprevir is an inhibitor of P-gp, a subsequent clinical study showed a DDI with digoxin, suggesting that telaprevir may inhibit/saturate P-gp in the gut.

After oral administration of 14C-telaprevir (with a different formulation than the spray-dried dispersion used in the pivotal studies), the median total recovery of administered dose was 91% (range: 86.9%; 93.9%). The median percent of the administered dose recovered in the feces was 82%, while approximately 9% of the administered dose was recovered in expired air and 1% in urine. The contribution of unchanged 14C -telaprevir and VRT-127394 towards total radioactivity recovered in feces was 31.8% and 18.7%, respectively. From this study it is not possible to distinguish non-absorbed drug from biliary excreted but in a worst case about 50% of the dose is not absorbed. Further, in this particular study the systemic exposure was unexpectedly low; hence absorbtion data for telaprevir in this study should be interpreted with caution.

In healthy volunteers as well as in patients treated with the 375 mg tablets, detectable plasma levels were observed approximately 1 hour after administration. The rate of absorption of telaprevir appears to be relatively slow; the peak plasma concentrations are reached in a median t_{max} of 4-5 hours after administration, likely caused by the limited solubility of telaprevir.

Bioavailability

Telaprievir is practically insoluble in aqueous media. Therefore, that drug has not been given as an intravenous infusion to humans. Consequently, there is no estimate of absolute bioavailability in humans.

Influence of food

The effect of food on the PK of Telaprevir was assessed in numerous studies. Among these studies, study C121 is most relevant, as the influence of different type of foods on the BA of the 375 mg tablet were tested using an appropriate design. This was an open-label, randomized, 5-way crossover study in 30 healthy male and female subjects between 18 and 55 years of age. Complete PK profiles up to 24 hours post-dose were assessed after single-dose administration of 750-mg telaprevir with a standard breakfast, under fasted conditions, with a high-fat breakfast, a low-calorie/high protein breakfast, and a low-calorie/low-fat breakfast. Twenty-eight subjects completed the study.

Compared to a standard breakfast (approximately 533 kcal, 189 kcal fat), telaprevir exposure (expressed as Cmax, AUCtlast, and AUC∞) decreased by 73% to 83% when telaprevir was administered under fasting conditions; 25% to 26% when telaprevir was administered after a low-calorie, high-protein breakfast (approximately 260 kcal, 81 kcal fat); and 38% to 39% when telaprevir was administered after a low-calorie, low-fat breakfast (approximately 249 kcal, 32 kcal fat). Increasing the meal to 928 kcal and increasing the fat content above that of a standard meal (to approximately 504 kcal fat) had no effect on Cmax and resulted in a 19% to 20% increase in AUC.

Telaprevir will be recommended for dosing at 750 mg q8h with food. In the Phase 2 and 3 studies, subjects were advised to consume a meal or snack within 30 minutes prior to intake of telaprevir, which was to be taken with approximately 240 mL (8 ounces) of water. The nutrient content of meals and snacks was to be consistent with a regular diet (not a low-fat meal). Efficacy and safety data were obtained from Phase 2 and Phase 3 studies with these dosing recommendations.

Distribution

The mean (SD) apparent volume of distribution V/F of telaprevir in healthy subjects is approximately 377 (177) L suggesting a large volume of distribution with penetration of telaprevir into tissues beyond the systemic circulation. V/F (point estimate [bootstrap 95% CI]) of telaprevir was estimated from population PK analyses of Phase 2 and Phase 3 studies to be 252 (204,273) L, with inter-individual variability on V/F estimated to be 72.2%

Telaprevir is moderately (59-76%) bound to plasma proteins, both albumin and alpha acid glycoprotein, with a mild concentration-dependency.

Individual whole blood to plasma ratio at each measurable time point in the mass-balance study ranged between 0.58 and 1.42 suggesting that telaprevir can distribute into red blood cells.

Elimination

Telaprevir is predominantly eliminated in the faeces with minimal renal excretion. Following administration of a single oral dose of 750 mg 14C-telaprevir in healthy subjects, the median recovery of the administered radioactive dose was approximately 82% in faeces, 9% in exhaled air, and 1% in urine. Apparent clearance (CL/F) of telaprevir was estimated from population PK analyses of Phase 2 and Phase 3 studies to be 32.4 L/hr, with inter-individual variability estimated to be 27.2%.

Telaprevir is extensively metabolized in the liver via hydrolysis, oxidation, and reduction. Telaprevir is metabolised by CYP3A4. Other enzymes may be involved. A prolonged half-life of radioactivity was

observed in the mass-balance study; the structure responsible for the prolonged half-life has not been identified. The exposure of telaprevir and metabolites in the mass balance study was low, preventing adequate determination of the metabolites in plasma. Telaprevir and its diastereomer contributed to a small part of the total radioactivity in plasma. After repeated oral administration of telaprevir in combination with Peg-IFN/ RBV in subjects with Hepatitis C, the main metabolites of telaprevir in plasma were VRT-127394 (R-diastereomer of telaprevir, 30-fold less active), pyrazinoic acid (not active from an antiviral perspective, but this is also an active metabolite of the antimycobacterial drug pyrazinamide - see further safety assessment) and VRT-0922061 (M3 isomer metabolite, reduction at the α-ketoamide bond of telaprevir, not active).

Dose proportionality and time dependency

In a single-dose study in healthy subjects, telaprevir AUC increased more than dose proportionately for doses ranging from 375 mg to 1875 mg. However, in a multiple-dose study, telaprevir 1875 mg q8h only resulted in a 40% higher AUC compared to 750 mg q8h. The reason for the discrepancy between single and multiple doses is unknown.

When telaprevir was dosed as 750 mg q8h, steady-state was reached by 3 to 7 days with an accumulation ratio (ratio of the AUC at steady-state to the AUC after the first dose) of approximately 2.2. After a single dose, the mean half-life was approximately 4 hours. At steady-state, the effective half-life was approximately 9 to 11 hours.

Pharmacokinetics in the target population

A comparison of telaprevir exposure and the elimination half-life in healthy subjects and patients showed similar results after single- or multiple-dose administration of telaprevir monotherapy.

During co-administration with Peg-IFN, telaprevir exposure was approximately 30% higher compared to telaprevir monotherapy, while RBV co-administration had no effect on telaprevir exposure. Telaprevir did not affect the exposure of Peg-IFN or RBV. Similar telaprevir exposures were observed in combination with either PegIntron/Rebetol or Pegasys/Copegus.

Following multiple doses of telaprevir (750 mg q8h) in combination of Peg IFN and RBV in treatment-naïve subjects with genotype 1 CHC, mean (SD) Cmax was 3510 (1280) ng/mL, Cmin was 2030 (930) ng/mL, and AUC8h was 22300 (8690) ng.h/mL In a substudy in study 108 (N=41) with intense sampling.

Special populations

Impaired renal function

Study C132 was a Phase 1, open-label study in both healthy (non-CHC) subjects and subjects with severe renal impairment (defined as CrCL <30 mL/min). A single-dose (750-mg) PK of telaprevir in subjects with severe renal impairment (n = 12) was compared to that in healthy control subjects (n = 12).

Severe renal impairment (CrCL <30 mL/min) in non-CHC subjects was associated with modest increases in telaprevir exposure: 10% increased Cmax and 21% increased AUC∞ after single-dose administration. As such no dose adjustment is necessary for telaprevir in subjects with mild, moderate, or severe renal impairment. However, RBV is either contraindicated (Rebetol) or reserved for use only when essential (Copegus) in subjects with creatinine clearance <50 mL/min. Telaprevir has not been studied in subjects with end-stage renal disease (ESRD) or on hemodialysis. It is not known whether telaprevir is dialyzable by peritoneal or hemodialysis; however, based on a plasma protein binding of 59% to76%, dialysis may increase the clearance of telaprevir.

Impaired hepatic function

The pharmacokinetics of single and multiple doses (750 mg q8h for 6 days) of telaprevir was investigated in 10 subjects with mild hepatic impairment defined as Child-Pugh A (without HCV infection) and 10 healthy subjects (VX06-950-006). Subjects with mild hepatic impairment had reduced Cmax (10%) and AUC (15%) after multiple doses administration.

Another study (012) was planned to further investigate the effect of hepatic impairment in subjects with moderate (Child Pugh B, score 7-9) and severe (Child-Pugh C) hepatic impairment (without HCV infection) in comparison with the PK data from the healthy subjects in previous study. Ten subjects (Child-Pugh B) received a single 750 mg dose of telaprevir on Day 1 and multiple doses (750 mg q8h) on Day 2 to Day 5 with a final dose of 750 mg in the morning of Day 6. The study was discontinued and no subjects with severe hepatic impairment (Child-Pugh C , score >10) were enrolled.

Exposure was approximately 46% lower in subjects with moderate hepatic impairment (Child-Pugh B, score 7-9) compared to healthy subjects. Of note, Peg-IFN is contraindicated in patients with severe hepatic dysfunction or decompensated cirrhosis of the liver. In addition, RBV is contraindicated in patients with hepatic impairment (Child-Pugh B or C). Telaprevir is not recommended for subjects with moderate or severe hepatic impairment.

Demographic characteristics

A pooled population PK analysis conducted on the Phase 2 and 3 studies (104, 104EU, 106, C208, 108, 111, and C216) indicated that subject's age (up to 70 years of age), sex, race (estimated as Caucasian or other) and fibrosis category had no clinically relevant impact on the clearance and, therefore, on average steady state exposure of telaprevir. Subject's weight had an effect on the clearance of telaprevir but is considered to have no clinically relevant impact on the safety or efficacy of a telaprevir-containing regimen.

The applicant provided additional analyses treating blacks as a separate group, which had no clinically relevant impact on the clearance and, therefore, on average steady state exposure of telaprevir.

No PK investigations were performed in paediatric population. Telaprevir is not indicated in patients under 18 as no clinical efficacy/safety data are available.

Interactions

Drug-drug interactions

Telaprevir is a competitive inhibitor of CYP3A in vitro. VRT-127394 also inhibited CYP3A in vitro with lower Ki values than telaprevir. Inhibition of CYP3A4 by telaprevir was both concentration and time dependent suggesting time or metabolism dependent inhibition. No or weak inhibition by telaprevir and VRT-127394 (diastereomer) of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1 and CYP2D6 isozymes was observed in vitro.

In vitro induction study results (CYP2C, CYP3A, or CYP1A) are inconclusive due to inhibition and no mRNA levels were assessed. Some of the interaction studies suggest that induction may occur in vivo.

Because telaprevir is both a substrate and inhibitor of CYP3A there is a potential for drug-drug interactions between telaprevir and substrates, inducers, and inhibitors of CYP3A.

Rifampicin reduces plasma concentrations of telaprevir by approximately 92%, concomitant administration of rifampin and telaprevir is contraindicated. In addition, herbal preparations containing St John's wort, as well as enzyme-inducing anticonvulsants are contraindicated during treatment with telaprevir.

Co-administration of potent inhibitors of CYP3A (ketoconazole or ritonavir) and telaprevir resulted in approximately 60% to 100% increased exposure to telaprevir in single-dose studies. Administration of ketoconazole after repeated doses of telaprevir appeared to affect exposure less and the inhibitory effect on telaprevir CL/F was very limited at steady state. These results suggest that co-administration of a potent CYP3A inhibitor may have limited impact on the exposure to telaprevir, possibly due to the fact that telaprevir itself is already an inhibitor of CYP3A or, alternatively, because there are other important elimination pathways. Metabolism by other enzymes will be further investigated.

When telaprevir was co-administered with HIV protease inhibitors, exposure to telaprevir was reduced. This was most pronounced for lopinavir/rtv (54%) and darunavir/rtv (35%). Atazanavir exhibited the least effect (20% reduction).

Co-administration with efavirenz decreased telaprevir exposure with 26%, with a somewhat larger effect on Cmin (47%). An increased dose of telaprevir (1125 mg q8h) in combination with efavirenz resulted in 18% lower AUC and 25% lower Cmin as compared to 750 mg q8h telaprevir alone.

Telaprevir is a potent inhibitor of CYP3A in vivo (8-fold increase of orally administered midazolam) and therefore contraindicated when combined with active substances that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. Co-administration may increase their plasma concentration and may lead to serious and/or life threatening adverse reactions such as cardiac arrhythmia (i.e., amiodarone, astemizole, bepridil, cisapride, pimozide, quinidine, terfenadine) or peripheral vasospasm or ischaemia (i.e., dihydroergotamine, ergonovine, ergotamine, methylergonovine), or myopathy, including rhabdomylosis (i.e., lovastatin, simvastatin and atorvastatin), or prolonged or increased sedation or respiratory depression (i.e., orally administered midazolam and triazolam), or hypotension or cardiac arrhythmia (i.e., alfuzosin and sildenafil for treatment of pulmonary arterial hypertension).

As a safety precaution, because of the potential for pharmacokinetic and/or pharmacodynamic interactions that may increase the risk of QT interval prolongation telaprevir must not be administered concurrently with Class Ia or III anti-arrhythmics. Other Class I anti-arrhythmics should only be co-administered with caution and ECG monitoring. Telaprevir must also not be administered with other drugs that may induce QT prolongation or Torsades de Pointes, and which are metabolized by CYP3A, unless an assessment of the benefit/risk justifies its use.

Outcomes of a clinical drug-drug interaction study with digoxin, which showed increased digoxin plasma concentrations (AUC increased by 85%) upon co-administration with telaprevir but no or very limited effect on renal clearance of digoxin, indicate that telaprevir may inhibit or saturate P-gp at relatively high local concentrations in the gut, while significant systemic P-gp inhibition by telaprevir is unlikely.

Interaction studies with commonly administered drugs were performed. Reduced ethinyl estradiol exposure (AUC) (28%) and slightly reduced norgestrel levels (11%) were observed. Also, reduced zolpidem (47%), methadone (about 30%), escitalopram (35%), fosamprenavir (47%), darunavir (40%) and efavirenz (7%) exposure was found. The mechanism suggested by the applicant is enzyme induction or displacement of protein binding.

Increased exposure to midazolam (IV 240% and 796% oral), alprazolam (35%), amlodipine (179%), atorvastatin (688%), cyclosporine (364%), tacrolimus (about 70-fold) on co-administration with telaprevir is likely attributable to CYP3A inhibition and P-gp inhibition. Tenofovir exposure was increased by 30%.

Due to the expected magnitude (studied or predicted) of DDIs with telaprevir, and the subsequent potential for serious adverse events or loss of efficacy, recommendations concerning co-administration

of a number of drugs are included in section 4.5 in the SmPC. Furthermore the applicant will further characterise the interaction profile of telaprevir post authoristion as reflected in the RMP.

The exposure obtained in the thorough QT study (C136) was similar to exposure observed in the Phase 3 studies (no exposure margin) and no data on supratherapeutic exposure is available.

Pharmacokinetics using human biomaterials

In vitro metabolism of telaprevir in recombinant Supersomes of CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 were studied. Some disappearance was observed for CYP2C19 and CYP2D6 but the largest disappearance occurred with CYP3A4. Data on CYP2C8 is lacking and will be further studied. In vitro interaction data and protein binding data is described above. Metabolism by non-CYP enzymes will be further studied.

2.4.2. Pharmacodynamics

For mechanism of action, primary and secondary pharmacology see nonclinical section.

PKPD

PK/PD data has been provided by the applicant from the phase 2b studies. Due to a high correlation between Cmin, Cmax and AUC no single parameter was identified as most predictive. With increasing Cmin within the range of exposures seen at the recommended dose (approximately 1500-3500 ng/mL), an increased rate of RVR (a surrogate for SVR) was seen. In treatment-experienced patients (driven by prior non-responders) increasing Cmin is also associated with a decreased risk of virological breakthrough. Thus it appears that the selected dose yields exposures that are on the steep part of the exposure response curve, at least in patients with relatively low interferon response. Anemia is an exposure dependent side effect of telaprevir, whereas within the exposure range reached, no clear relation of exposure and severe rash emerged.

PD interactions with, e.g., methadone are further addressed the clinical safety section. Concerning genetic differences in PD response (IL28B), see the Clinical efficacy section.

2.4.3. Discussion on clinical pharmacology

An ambitious clinical pharmacology program has been performed with telaprevir. No issues of major concern have been identified. A number of other concerns have been identified. Some issues will need to be addressed post authorisation.

It appears that the range of exposures reached is on the steep part of the exposure response curve (utility curves), indicating that any decrease in exposure may be associated with lower virological efficacy, and particularly so in prior non-responders. The applicant was requested to define what increase and decrease in exposure is considered acceptable from a safety and efficacy perspective. Since no supra therapeutic exposure has been observed an upper limit cannot be defined. The applicant provided additional PKPD analyses which clearly indicate that the exposure margins for telaprevir in poor interferon responders is absent and any decrease in exposure may lead to decreased efficacy; It is noted that the effect of carbamazepine, phenytoin and phenobarbital on telaprevir exposure has not been studied. Based on known effects of carbamazepine and phenytoin on midazolam exposure, these agents are contraindicated and additional general warning has been included for mild and moderate inducers in section 4.5.

The effect of food on absorption of telaprevir is extensive. Further information on risk of reduced efficacy if taken without food was requested to be included in section 4.2.

Given the presented data on mass balance and metabolism the applicant was requested to further discuss the main elimination pathways of telaprevir and discuss whether there are any human specific metabolites or pharmacologically active metabolites that have not been identified. Due to the position of the labelling it is possible that it is included in endogenous structures (not identified) giving raise to the observed prolonged half-life of the radioactivity in plasma. Metabolism by CYP2C8 and other enzymes than CYP450 will be further explored.

The reasons for the lack of dose proportionality at multiple doses are unclear. Based on single dose data the accumulation at repeated dosing is larger than expected indicating autoinhibition. Multiple dose data with higher doses show a less than proportional increase. Given that higher doses may be warranted for co-administration with inducers, the applicant was requested to further discuss the mechanism and discuss whether solubility may be an issue. The discrepancy between single and multiple doses remains unclear but solubility issues is a possible explanation as concentration in the gut widely exceeds the solubility of the drug (also at single doses).

In study -101 it appears that the C_{trough} levels were first increasing but later decreased to a new steady state level, indicating autoinduction. A similar pattern was observed when telaprevir was administered with Peg-IFN in study -103, though possibly with a lower tendency of decreased levels over time. The applicant was requested to further discuss whether the interaction pattern observed when telaprevir is administered as single agents in the interaction studies, would likely be similar when telaprevir is given in combination with Peg-IFN and ribavirin. The applicant argued that the interaction pattern is likely to be similar also when peginterferon and ribavirin are co-administered with telaprevir, despite the increased exposure to telaprevir. Also, the applicant stated that peginterferon has not been shown to have any significant effects on CYP metabolism (its impact on telaprevir exposure might be mediated by p-gp inhibition). Though the effects on peginterferon on CYP activity is not fully clarified, it is agreed that any such effects are not expected to be large.

Although the effect on the gestagen component when co-administered with telaprevir was limited, a conservative approach with respect to hormonal contraceptives is taken given the co-administration with ribavirin.

Further in vitro studies exploring interaction potential with UGTs will be provided. An interaction study with raltegravir has been performed but no study report has been submitted. Preliminary data suggests no clinically relevant interaction, but a final assessment of the data will be done at submission.

A study with buprenorphin/naloxone has been performed. Preliminary data suggests that no dose adjustments will be required; however a final assessment will be done when the data are submitted.

For sensitive substrates for CYP3A inhibition such as midazolam, inhibition is clearly dominating at repeated dosing with telaprevir. Regarding substrates for other elimination pathways, decreased exposure has been observed, possibly explained by CYP induction for some substrates, and possible protein binding displacement for others. The mechanisms will be further investigated by the applicant, particularly regarding the reduced exposure to HIV protease inhibitors.

In vitro data on other transport proteins than P-gp is lacking. It will be further investigated whether telaprevir is a substrate and or inhibitor of transport proteins. Inhibitory potential should also be investigated for VRT-127394.

The mechanism for reduced exposure in hepatic impairment will be further investigated to evaluate the possible use of telaprevir as novel agent in regime without Peg-IFN in this group of patients.

2.4.4. Conclusions on clinical pharmacology

Overall the clinical pharmacology aspects of telaprevir have been sufficiently characterised and meet the requirements to support the application.

2.5. Clinical efficacy

Initial studies of telaprevir in subjects with chronic hepatitis C were designed to assess viral kinetics and antiviral responses with telaprevir alone or in combination with Peg-IFN, with or without RBV. The duration of telaprevir treatment in these studies was short (2 to 4 weeks), and the study designs did not include SVR as an endpoint. These studies include the -101, -103 and -102, covering dose-ranging monotherapy, a comparison of short term monotherapy and the combination of telaprevir with peginterferon alfa-2a, and a 4 week study of telaprevir in combination with peginterferon and ribavirin.

Eight studies were conducted to evaluate efficacy (SVR) of treatment with a telaprevir-based regimen in subjects with genotype 1 chronic hepatitis C: 5 studies in treatment-naïve subjects (never received treatment for chronic hepatitis C) and 3 studies in treatment-failure subjects (did not have SVR after Peg-IFN/RBV treatment for chronic hepatitis C). A listing of these studies is provided in table 3 below.

A total of 3594 subjects with genotype 1 HCV (2362 treatment-naïve and 1232 treatment failure subjects) were treated in these 8 completed efficacy studies in the Phase 2 and 3 clinical development program, and 2830 of these subjects received at least 1 dose of telaprevir.

Table 3. Overview of Studies That Evaluated Efficacy (SVR)

Study Module 5 location	Study Phase Type of Control Blind[a]	Number of Subjects[b]	Treatment Groups[c] (N per Group)	Efficacy Endpoint
Treatment-naïve genotype 1 HCV population				
104 Module 5.3.5.1 VX05-950-104	Phase 2 Randomized Placebo-controlled Blinded	250	T12/PR24 (79) T12/PR48 (7[illegible]) T12/PR12[illegible] Pbo/PR4[illegible] (75)	SVR 24 weeks after last dose
104EU Module 5.3.5.1 VX05-950-104EU	Phase 2 Randomized Placebo-controlled Blinded	323	T12/P[illegible]24 (81) T12/PR[illegible] (82) T12/P12 (78) Pbo/PR48 (82)	SVR 24 weeks after last dose
C208 Module 5.3.5.2 VX-950-TiDP24-C208	Phase 2 Randomized Uncontrolled Open-label	161	T12(q8h)/P(2a)R[d] (40) T12(q8h)/P(2b)R[d] (42) T12(q12h)/P(2a)R[d] (40) T12(q12h)/P(2b)R[d] (39)	SVR 24 weeks after last dose
108 Module 5.3.5.1 VX07-950-108	Phase 3 Randomized Placebo-controlled Blinded	[illegible]88	T8/PR[d] (364) T12/PR[d] (363) Pbo/PR48 (361)	SVR 24 weeks after last planned dose
111 Module 5.3.5.1 VX08-950-111	Phase 3 Randomized Active-controlled Open-label	540	T12/PR[d] (540)	SVR 24 weeks after last planned dose
Treatment-failure genotype 1 HCV population				
106 Module 5.3.5.1 VX06-950-106	Phase 2 Randomized Placebo-controlled Blinded	453	T12/PR24 (115) T24/PR48 (113) T24/P24 (111) Pbo/PR48 (114)	SVR 24 weeks after last dose
107 Module 5.3.5.1 VX06-950-107	Phase 2 Not randomized Uncontrolled Open-label	117	T12/PR[d] (117)	SVR 24 weeks after last dose
216 Module 5.3.5.1 VX-950-TiDP24-C216	Phase 3 Randomized Placebo-controlled Blinded	662	T12/PR48[e] (266) T12(DS)/PR48[e] (264) Pbo/PR48 (132)	SVR 24 weeks after last planned dose

[a] In placebo-controlled studies, telaprevir-matching placebo was administered to maintain double-blinding.
[b] Total number of subjects with hepatitis C who received at least 1 dose of study drug
[c] T: telaprevir; P: Peg-IFN-alfa-2a; R: RBV; Pbo: placebo; Tx/P(R)y: telaprevir for x weeks in combination with Peg-IFN (and RBV) for y weeks; P(2a): Peg-IFN-alfa-2a; P(2b): Peg-IFN-alfa-2b; q8h: every 8 hours; q12h: every 12 hours
[d] The total duration of Peg-IFN and RBV treatment was 24 or 48 weeks, based on subject's individual on-treatment virologic response.
[e] In both telaprevir groups, subjects received 12 weeks of telaprevir in combination with 48 weeks of Peg-IFN and RBV. In the T12(DS)/PR48 group, telaprevir treatment had delayed start (DS), i.e., telaprevir treatment started after 4 weeks of treatment with Peg-IFN and RBV.

In addition to the studies listed in Table 3, a 3-year follow-up study is ongoing in subjects with genotype 1 chronic hepatitis C treated with telaprevir from selected Phase 2 and Phase 3 studies (Study 112).

Furthermore, there were 2 Phase 2 viral kinetic studies conducted in subjects with HCV genotypes 2 and 3, and genotype 4, respectively. A Phase 2 study in subjects co-infected with HCV and human immunodeficiency virus is ongoing. As the studies on other genotypes than 1, and in patients with HIV co-infection, are not relevant to the present labelling claims of the applicant, they are not further discussed in this assessment.

Summary of Main Efficacy Results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections). The Phase III studies are discussed in detail hereafter.

Table 4. Summary of Efficacy for trial VX07-950-108

<table>
<tr><td colspan="3">Title: A Phase 3 Study of 2 Dose Regimens of Telaprevir in Combination With Peginterferon Alfa-2a (Pegasys) and Ribavirin (Copegus®) in Treatment-Naïve Subjects with Genotype 1 Chronic Hepatitis C</td></tr>
<tr><td>Study identifier</td><td colspan="2">VX07-950-108</td></tr>
<tr><td>Design</td><td colspan="2">Randomized, double-blind, placebo-controlled, parallel-group, multicenter study, conducted in treatment-naïve subjects with genotype 1 chronic HCV infection.</td></tr>
<tr><td></td><td>Duration of main phase:
Duration of run-in phase:
Duration of extension phase:</td><td>72 weeks
not applicable
not applicable</td></tr>
<tr><td>Hypothesis</td><td colspan="2">Superiority of each telaprevir arm over PR</td></tr>
<tr><td>Treatment groups</td><td>T8/PR</td><td>365 randomised
<table><tr><td>Telaprevir 750 mg q8h</td><td>Telaprevir matching placebo</td><td>Peg-IFN-alfa-2a and RBV Dosing Period</td></tr><tr><td>Day 1 through Week 8</td><td>Weeks 9 through 12</td><td>Day 1 through Week 24–with eRVR
Day 1 through Week 48–without eRVR</td></tr></table></td></tr>
</table>

<table>
<tr><td></td><td>T12/PR</td><td colspan="2"><table><tr><td>Telaprevir 750 mg q8h</td><td>Telaprevir matching placebo</td><td>Peg-IFN-alfa-2a and RBV Dosing Period</td></tr><tr><td>Day 1 through Week 12</td><td>NA</td><td>Day 1 through Week 24–with eRVR
Day 1 through Week 48–without eRVR</td></tr></table>
365 randomised</td></tr>
<tr><td></td><td>Pbo/PR48</td><td colspan="2"><table><tr><td>Telaprevir 750 mg q8h</td><td>Telaprevir matching placebo</td><td>Peg-IFN-alfa-2a and RBV Dosing Period</td></tr><tr><td>NA</td><td>Day 1 through Week 12</td><td>Day 1 through Week 48</td></tr></table>
365 randomised</td></tr>
<tr><td>Endpoints and definitions</td><td>Primary endpoint</td><td>$SVR24_{planned}$</td><td>Defined as having undetectable plasma HCV RNA levels 24 weeks after the last planned dose of study medication</td></tr>
<tr><td></td><td>Key Secondary endpoint</td><td>SVR Week 72</td><td>Proportion of subjects who have SVR at Week 72 (i.e., 24 weeks after last planned dose for subjects with a planned treatment duration of 48 weeks, and 48 weeks after last planned dose for subjects with a planned treatment duration of 24 weeks)</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td>Database lock</td><td colspan="3">10 May 2010</td></tr>
<tr><td colspan="4">Results and analysis</td></tr>
<tr><td>Analysis description</td><td colspan="3">Primary analysis</td></tr>
<tr><td>Analysis population and time point description</td><td colspan="3">Intent to treat (full analysis set)
24 weeks after the last planned dose of study treatment</td></tr>
<tr><td>Descriptive statistics and estimate variability</td><td>Treatment group</td><td>T8/PR</td><td>T12/PR</td><td>Pbo/PR48</td></tr>
<tr><td></td><td>Number of subjects</td><td>364</td><td>363</td><td>361</td></tr>
<tr><td></td><td>$SVR24_{planned}$ (<statistic>)</td><td>68.7%
$P<0.0001$</td><td>74.7%
$P<0.0001$</td><td>43.8%</td></tr>
<tr><td></td><td>95% CI</td><td>(63.6%, 73.4%)</td><td>(69.9%, 79.1%)</td><td>(38.6%, 49.1%)</td></tr>
<tr><td></td><td>SVR Week 72 (<statistic>)</td><td>66.8%
$P<0.0001$</td><td>73.0%
$P<0.0001$</td><td>43.8%</td></tr>
<tr><td></td><td>95% CI</td><td>(61.7%, 71.6%)</td><td>(68.1%, 77.5%)</td><td>(38.6%, 49.1%)</td></tr>
<tr><td>Effect estimate per comparison</td><td>$SVR24_{planned}$</td><td>Comparison groups</td><td colspan="2">T8/PR versus Pbo/PR48</td></tr>
<tr><td></td><td></td><td>Difference in SVR</td><td colspan="2">24.9%</td></tr>
</table>

		95% CI	(17.9%, 31.9%)
		P-value	*P*<0.0001
	$SVR24_{planned}$	Comparison groups	T12/PR versus Pbo/PR48
		Difference in SVR	30.9%
		95% CI	(24.1%, 37.7%)
		P-value	*P*<0.0001
	SVR Week 72	Comparison groups	T8/PR versus Pbo/PR48
		Difference in SVR	23.0%
		95% CI	(15.9%, 30.1%)
		P-value	*P*<0.0001
	SVR Week 72	Comparison groups	T12/PR versus Pbo/PR48
		Difference in SVR	29.2%
		95% CI	(22.4%, 36.1%)
		P-value	*P*<0.0001
Notes	Statistical analyses were pre-specified according to statistical analysis plan		
Analysis description	**Secondary analysis** The percentages of subjects with RVR (undetectable HCV RNA at week 4) were 66.5% in the T8/PR group, 67.8% in the T12/PR group, and 9.4% in the Pbo/PR48 group. The percentages of subjects with eRVR (undetectable HCV RNA at weeks 4 and 12) were 56.9% in the T8/PR group, 58.4% in the T12/PR group, and 8.0% in the Pbo/PR48		

Table 5. Summary of Efficacy for trial VX-950-TiDP24-C216

Title: A randomized, double-blind, placebo-controlled, Phase III trial of 2 regimens of telaprevir (with and without delayed start) combined with pegylated interferon alfa-2a (Pegasys) and ribavirin (Copegus®) in subjects with chronic genotype 1 hepatitis C infection who failed prior pegylated interferon plus ribavirin treatment.		
Study identifier	VX-950-TiDP24-C216	
Design	Randomized, double-blind, placebo-controlled Phase 3 study with telaprevir in subjects with genotype 1 chronic hepatitis C infection who failed prior treatment with pegylated interferon (Peg- IFN; Peg-IFN-alfa-2a or Peg-IFN-alfa-2b) plus ribavirin (RBV).	
	Duration of main phase:	72 weeks
	Duration of run-in phase:	not applicable
	Duration of extension phase:	not applicable
Hypothesis	Superiority of each telaprevir arm over PR	

Treatment groups	T12/PR48		telaprevir 750 mg q8h from Day 1 through Week 12; placebo q8h from Week 13 through Week 16; Peg-IFN-alfa-2a 180 µg/week from Day 1 through Week 48; RBV 1000 or 1200 mg/day (twice daily regimen). 266 randomised
	T12(DS)/PR48		placebo q8h from Day 1 through Week 4; telaprevir 750 mg q8h from Week 5 through Week 16; Peg-IFN-alfa-2a 180 µg/week from Day 1 through Week 48; RBV 1000 or 1200 mg/day (twice daily regimen). 264 randomised
	Pbo/PR48		placebo q8h from Day 1 through Week 16; Peg-IFN-alfa-2a 180 µg/week from Day 1 through Week 48; RBV 1000 or 1200 mg/day (twice daily regimen). 133 randomised
Endpoints and definitions	Primary endpoint	$SVR24_{planned}$	defined as having undetectable plasma HCV RNA levels 24 weeks after the last planned dose of study medication
Database lock	16 August 2010		

Results and analysis

Analysis description	**Primary analysis**			
Analysis population and time point description	Intent to treat (full analysis set) Week 72			
Descriptive statistics and estimate variability	Treatment group	T12/PR48	T12(DS)/PR48	Pbo/PR48
	Prior relapsers			
	Number of subjects	145	141	68
	$SVR24_{planned}$	83.4%	87.9%	23.5%
	95% CI	(76.4%, 89.1%)	(81.4%, 92.2%)	(14.1%, 35.4%)
	Prior non-responders			
	Number of subjects	121	123	64
	$SVR24_{planned}$	41.3%	41.5%	9.4%
	95% CI	(32.4%, 50.6%)	(32.7%, 50.7%)	(3.5%, 19.3%)
	Secondary			
	Prior null-responders			

	Number of subjects	72	75	37
	$SVR24_{planned}$	29.2%	33.3%	5.4%
	95% CI	(19.0%, 41.1%)	(22.9%, 45.2%)	(0.7%, 18.2%)
	Prior Partial Responders			
	Number of subjects	49	48	27
	$SVR24_{planned}$	59.2%	54.2%	14.8%
	95% CI	(44.2%, 73.0%)	(39.2%, 68.6%)	(4.2%, 33.7%)
Effect estimate per comparison	SVR prior relapsers	Comparison groups	T12/PR48 vs Pbo/PR48	T12(DS)/PR48 vs Pbo/PR48
		Difference	60.5%	64.9%
		95% CI	(48.8%, 72.2%)	(53.5%, 76.2%)
		P-value	P<0.001	P<0.001
	SVR prior non responders	Comparison groups	T12/PR48 vs Pbo/PR48	T12(DS)/PR48 vs Pbo/PR48
		Difference	35.0%	35.3%
		95% CI	(22.9%, 47.0%)	(23.4%, 47.3%)
		P-value	P<0.001	P<0.001
	Secondary			
	SVR prior null responders	Comparison groups	T12/PR48 vs Pbo/PR48	T12(DS)/PR48 vs Pbo/PR48
		Difference	24.7%	29.0%
		95% CI	(11.6%, 37.7%)	(15.8%, 42.2%)
		P-value	P<0.001	P<0.001
	SVR prior partial responders	Comparison groups	T12/PR48 vs Pbo/PR48	T12(DS)/PR48 vs Pbo/PR48
		Difference	44.1%	40.0%
		95% CI	(24.7%, 63.6%)	(20.3%, 59.7%)
		P-value	P<0.001	P<0.001

Notes	Statistical analyses were pre-specified according to statistical analysis plan. Prior relapser: Subject had an undetectable HCV RNA level (by branched-chain deoxyribonucleic acid [bDNA], reverse transcription-polymerase chain reaction [RT-PCR], or transcription-mediated amplification [TMA]-based assay) at the end (6 weeks or less after the last dose of medication) of a prior course of at least 42 weeks of Peg-IFN/RBV therapy but did not achieve SVR Prior non-responders- Subject never had an undetectable HCV RNA level (by bDNA, RT-PCR, or TMA-based assay) during or at the end of a prior course of at least 12 weeks of Peg- IFN/RBV therapy (null-responder and partial responder). Null responders: subjects with <2-log drop in HCV RNA at Week 12 of prior therapy (null-responders) Partial responders: subjects with ≥2-log drop in HCV RNA at Week 12 of prior therapy but who never achieved undetectable HCV RNA levels while on treatment.
Analysis description	**Secondary analysis::** SVR24planned rates were similar between the T12/PR48 and T12(DS)/PR48 groups for prior relapsers and prior non-responders. The difference in SVR24planned rates (T12/PR48 versus T12(DS)/PR48) with 95% CI as estimated in the logistic regression model was -4.3% (-12.6%, 3.9%) for prior relapsers and -0.4% (-13.6%, 12.9%) for prior non-responders

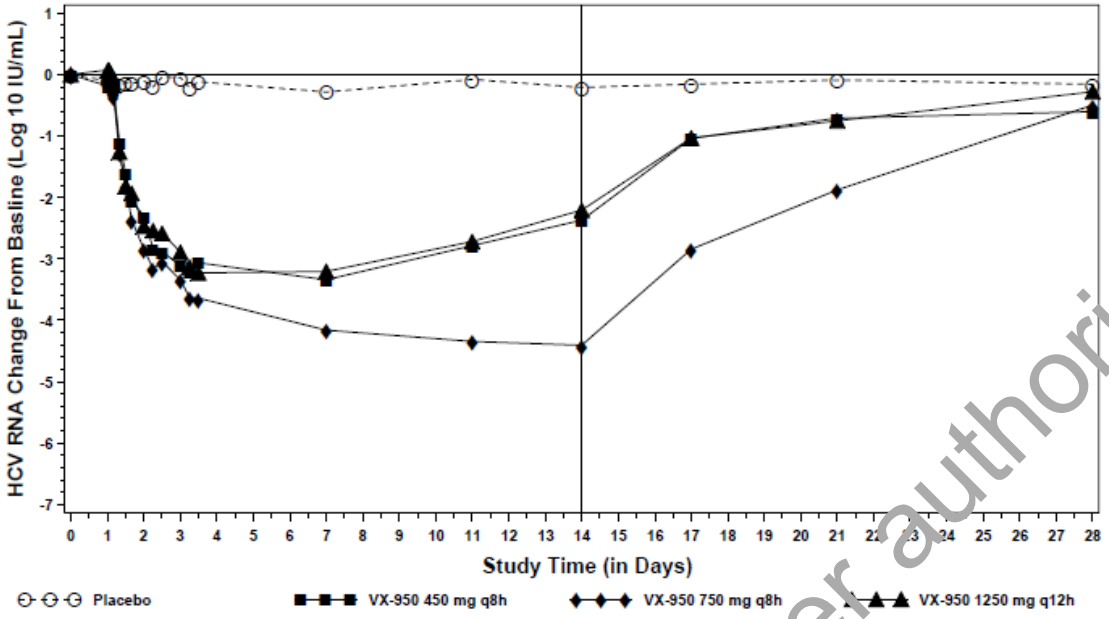
2.5.1. Dose response studies

The phase 1-2a programme

Study -101: the dose ranging monotherapy study

The first clinical study of the program was a dose-ranging monotherapy study in which three dosing regimens of telaprevir were compared: 450 mg q8h, 750 mg q8h and 1250 mg q12h. The 750 mg x 3 dose exhibited superior efficacy over 14 days. PK data showed that this dose was associated with the highest Ctroughs. Thus, the dose 750 mg x 3 was chosen for the further study. Of some interest, there was little difference in the efficacy of the three different doses during the first phase decay (day 1-3). This could indicate that all the doses reach Emax against wild-type virus, and that the primary difference between doses lies in their effect on pre-existing low-level resistant variants.

Figure 1. Median Change from Baseline in HCV RNA Levels by Dose Group Through the 2-Week Follow-up, Part B, FA Set



Note: In this analysis, HCV RNA values below the LOD were assigned a value of 5 IU/mL, and values below the LLOQ but above the LOD were assigned a value of 20 IU/mL.
Source: Figure 14.2.13.1b

Study -103 : Telaprevir 750 mg x 3 as monotherapy or in combination with peginterferon alfa-2a

This study established that telaprevir and peginterferon act in an additive/synergistic manner. In all subjects who received telaprevir (either with Peg-IFN or alone), HCV RNA levels showed a rapid decline between the first and fourth days of dosing with telaprevir. A second, sustained phase of viral decline occurred in 4 of 8 subjects in the telaprevir group and in all 8 subjects in the telaprevir + Peg-IFN group. In the telaprevir + Peg-IFN group at Day 15, HCV RNA levels were below the LLOQ in 6 subjects, and 4 subjects had undetectable HCV RNA levels. In the telaprevir group at Day 15, HCV RNA levels were undetectable in 1 subject.

Study -102 Telaprevir in combination with peginterferon alfa-2a and ribavirin over 4 weeks

This study demonstrated that all 12 subjects in an uncontrolled study treated with telaprevir 750 mg x 3 + peginterferon alfa-2a and ribavirin had undetectable HCV-RNA at week 4. It thus formed the empirical support for the triple drug combination studied in phase 2b. The other regimens studies in phase 2b included telaprevir and peginterferon without ribavirin, and telaprevir at two different dose regimens in combination with pegintereferon alfa-2b and ribavirin.

The phase 2b program in treatment naïve subjects

Study -104: A phase 2b study of telaprevir 750 mg x 3 in combination with peginterferon alfa 2a and ribavirin, aiming at SVR

This was a multicenter 48-week, randomized, placebo-controlled, double-blind study of treatment-naïve male and female adult subjects with genotype 1 HCV infection.

The treatment groups are shown in the following table 6:

Table 6. Treatment Groups

Treatment Group	Total Treatment Duration	Treatments: Telaprevir (750 mg q8h)	Treatments: Peg-IFN-alfa-2a (180 µg/week) and RBV (1000 or 1200 mg/day, depending on body weight)	Number of Subjects
T12/PR12	12 weeks	Weeks 1 through 12	Weeks 1 through 12	20
T12/PR24	24 weeks	Weeks 1 through 12	Weeks 1 through 24	80
T12/PR48	48 weeks	Weeks 1 through 12	Weeks 1 through 48	80
Pbo12/PR48	48 weeks	--	Weeks 1 through 48	80

T = telaprevir, PR = Peg-IFN-alfa-2a and RBV

SVR rates were as follows:

Table 7. Number and Proportion of Subjects With Undetectable HCV RNA at Antiviral Follow-up Weeks 12 and 24, FA Set

Time point	Telaprevir Groups: T12/PR12 N=17 n (%)	T12/PR24 N=79 n (%)	T12/PR48 N=79 n (%)	Total T/PR N=175 n (%)	Pbo12/PR48 N=75 n (%)
AVFU Week 12	6 (35.3)	42 (53.2)	46 (58.2)	94 (53.7)	27 (36.0)
P-value[a]	not done[b]	0.0418	0.0051	N/A	N/A
AVFU Week 24 (SVR)	6 (35.3)	48 (60.8)	53 (67.1)	107 (61.1)	31 (41.3)
P-value[a]	not done[b]	0.0204	0.0014	N/A	N/A

Source: *Table 14.2.1d*
N/A = not applicable
[a] versus Pbo12/PR48
[b] not done, due to small sample size

Important finding of this study include:

- SVR rates were 61-67% for the telaprevir containing arms, significantly superior to the efficacy in the standard of care arm (41.3%), which was similar to what is expected.
- The RVR (undetectable HCV-RNA at week 4 of treatment) rate in the telaprevir-containing arms was almost 80%, which has subsequently been found characteristic of a potent NS3/4A inhibitor.
- Relapse rates were very low in patients with RVR that remained undetectable throughout treatment. The relapse rate with only 12 weeks of total therapy, however, seemed higher than with 24 or 48 weeks of therapy.
- There was a trend to a higher clinical efficacy against HCV genotype 1b compared to 1a.
- Rash and anemia are important side effects of telaprevir.

Study -104: EU Telaprevir 750 mg x 3 in combination with peginterferon alfa-2a, with or without ribavirin, for a total of 12 or 24 weeks of therapy

Treatment-naïve subjects with genotype 1 chronic hepatitis C infection were included in either of the following treatment group.

Table 8. Treatment Groups

Treatment Group	Total Treatment Duration	Treatments			Number Subjects Planned
		Telaprevir (750 mg q8h)	Peg-IFN-alfa-2a (180 µg/week)	RBV (1000 or 1200 mg/day)a	
T12/PR12	12 weeks	Wks 1 – 12	Wks 1 – 12	Wks 1 – 12	80
T12/PR24	24 weeks	Wks 1 – 12	Wks 1 – 24	Wks 1 – 24	80
T12/P12	12 weeks	Wks 1 – 12	Wks 1 – 12	--	80
Pbo12/PR48	48 weeks	--	Wks 1 – 48	Wks 1 – 48	80

T: telaprevir; P: Peg-IFN-alfa-2a; PR: Peg-IFN-alfa-2a and RBV; Pbo: placebo.
a RBV dose depended on body weight.

SVR rates were as follows:

Table 9. Number and Percentage of Subjects With Undetectable HCV RNA at Week 12 and Week 24 of Antiviral Follow-up, FA Set

Time Point	Telaprevir Groups			
	T12/PR12 N = 82 n (%)	T12/PR24 N = 81 n (%)	T12/P12 N = 78 n (%)	Pbo12/PR48 N = 82 n (%)
AVFU Week 12	49 (59.8)	56 (69.1)	29 (37.2)	39 (47.6)
P-value[a]	0.1324	0.0041	0.1099	N/A
AVFU Week 24 (SVR)	49 (59.8)	56 (69.1)	28 (35.9)	38 (46.3)
P-value[a]	0.0959	0.0026	0.1089	N/A

Source: Table 14.2.1d
NA: not applicable; SVR: sustained viral response.
a *P*-value (treatment group versus Pbo12/PR48 group) were calculated by logistic regression anal (2-sided) of undetectable with treatment, race, weight, and baseline HCV RNA as factors.

The main findings of this study include:

- Twelve weeks of triple therapy followed by twelve more weeks of peginterferon and ribavirin, was significantly superior to a standard 48 week regimen of peginterferon + ribavirin (SVR rates 69% versus 46%)
- The response rate for 12 weeks of triple therapy without a further tail with peginterferon + ribavirin was 60% (p non-significant versus placebo). The relapse rate even in the subgroup of early responders to therapy was similar to the standard of care, 48 week arm (approximately 30%).
- RVR rates were 70-80% with telaprevir based triple therapy.
- Ribavirin needs to be retained in the regimen not only to prevent relapse but also to prevent viral breakthrough and augment virological efficacy. Relapse rates in the absence of ribavirin were almost 50%.
- Rash and anemia are important side effects of telaprevir.

Of note, neither the -104 or the -104EU studies contained any arm with a longer duration of telaprevir dosing than 12 weeks. This was studied in the -106 trial (see below), with no apparent evidence for a virological advantage of extending telaprevir therapy beyond 12 weeks.

Study -C208: Telaprevir administered every 12 or every 8 hours in combination with either Peg-IFN-alfa-2a (Pegasys) and ribavirin (Copegus) or Peg-IFN-alfa-2b (PegIntron) and

ribavirin (Rebetol)

Treatment-naïve subjects with chronic HCV genotype 1 infection were randomized to receive 1 of 2 different dose regimens of telaprevir in combination with standard therapy (Peg-IFN-alfa-2a [Pegasys] and RBV [Copegus] or Peg-IFN-alfa-2b [PegIntron] and RBV [Rebetol] at the standard doses).

Table 10. Treatment Overview

Treatment	Telaprevir	Peg-IFN	RBV
Treatment A: T12(q8h)/P(2a)R	750 mg q8h, oral for 12 weeks	Pegasys 180 µg/week, subcutaneous injection up to 48 weeks[a]	Copegus 1,000-1,200 mg/day[b] (twice daily regimen), oral up to 48 weeks[a]
Treatment B: T12(q8h)/P(2b)R	750 mg q8h, oral for 12 weeks	PegIntron 1.5 µg/kg/week[c], subcutaneous injection up to 48 weeks[a]	Rebetol 800-1,200 mg/day[d] (twice daily regimen), oral up to 48 weeks[a]
Treatment C: T12(q12h)/P(2a)R	1125 mg q12h, oral for 12 weeks	Pegasys 180 µg/week, subcutaneous injection up to 48 weeks[a]	Copegus 1,000-1,200 mg/day[b] (twice daily regimen), oral up to 48 weeks[a]
Treatment D: T12(q12h)/P(2b)R	1125 mg q12h, oral for 12 weeks	PegIntron 1.5 µg/kg/week[c], subcutaneous injection up to 48 weeks[a]	Rebetol 800-1,200 mg/day[d] (twice daily regimen), oral up to 48 weeks[a]

[a] Following the stopping rules and treatment duration rules in Table 1.
[b] Copegus dosing was weight-based: < 75 kg = 1,000 mg, ≥ 75 kg = 1,200 mg.
[c] PegIntron was administered with a single-dose delivery system (Redipen®), containing either 50 µg/0.5 mL, 80 µg/0.5 mL, 100 µg/0.5 mL, 120 µg/0.5 mL, or 150 µg/0.5 mL of PegIntron for a single use.
[d] Rebetol dosing was weight-based: < 65 kg = 800 mg, ≥ 65 and ≤ 85 kg = 1,000 mg, > 85 kg = 1,200 mg.

All subjects received 12 weeks of telaprevir in combination with the standard therapy (i.e., Peg-IFN and RBV). At Week 12, telaprevir dosing ended and subjects continued on standard therapy only. The duration of treatment was 24 weeks for patients with undetectable HCV-RNA at weeks 4 through 20. If the week 4 criterion was not met but undetectability was reached before week 20, total treatment duration was 48 weeks.

The main purpose of the present trial was to evaluate the short and long-term effects of different dose regimens (750 mg q8h and 1125 mg q12h) of telaprevir when co-administered with standard therapy. Another purpose was to explore the efficacy of the association of telaprevir and each of the 2 licensed Peg-IFNs (i.e., Peg-IFN-alfa-2a and Peg-IFN-alfa-2b) with RBV. This was a pilot trial, however, and it was underpowered to draw formal non-inferiority conclusions concerning either the q12h telaprevir regimen or co-treatment with peginterferon alfa-2b rather than -2a.

The main findings of this study include:

- The point estimate for SVR was approximately 80% in each of the treatment arms, regardless of whether telaprevir was dosed twice of thrice daily, and which of the peginteferons were used.
- A response guided algorithm of 24 or 48 weeks of total therapy depending on early response therapy was compatible with high response rates.
- The proportion of patients assigned to shorter therapy based on a strong early response was higher in the peginterferon alfa-2a than the –alfa-2b study (74% versus 62%). Also, data in this small study are compatible with a higher rate of viral breakthrough with peginterferon alfa-2b, compared to -2a.

The phase 2b program in treatment experienced subjects

Study -106. Telaprevir 750 mg x 3 for 12 or 24 weeks, together with peginterferon, with or without ribavirin, for a total of 24 or 48 weeks, in prior relapsers and non-responders to peginterferon/ribavirin therapy

This study was randomized, stratified, partially placebo-controlled, partially double-blind. Patients had genotype 1 HCV infection, and had been treated with Peg-IFN (either peginterferon alfa-2a or peginterferon alfa-2b) and RBV, but did not achieve SVR. The treatment population included subjects with prior nonresponse (never had undetectable HCV RNA during prior treatment), prior relapse (had undetectable HCV RNA during prior treatment, but did not have SVR) or prior viral breakthrough (had undetectable HCV RNA during prior treatment, but then had detectable HCV RNA before the end of treatment). The applicant lacked sufficient information about prior treatment to classify non-responders as "partial" or "null" responders (>2log 10 decline at week 12 but never undetectable, or <2log10 decline at week 12). Exclusion criteria included patients with decompensated liver disease or HIV/HBV co-infection. Subjects were randomized to 1 of 4 treatment groups:

Table 11. Treatment Groups

Group	Planned Sample Size	Day 1 – Week 12	Weeks 12 – 24	Weeks 24 – 48
Pbo24/PR48	110	placebo, Peg-IFN-alfa-2/ RBV	placebo, Peg-IFN-alfa-2a/RBV	Peg-IFN-alfa-2a/RBV
T24/PR48	110	telaprevir, Peg-IFN-alfa-2a/RBV	telaprevir, Peg-IFN-alfa-2a/RBV	Peg-IFN-alfa-2a/RBV
T24/P24	110	telaprevir, Peg-IFN-alfa-2	telaprevir, Peg-IFN-alfa-2a	Not applicable
T12/PR24	110	telaprevir, Peg-IFN-alfa-2a/RBV	placebo, Peg-IFN-alfa-2a /RBV	Not applicable

Peg-IFN-alfa-2a: peginterferon alfa-2a (Pegasys®); RBV: ribavirin (Copegus®).

Importantly, this is the only study in which a longer duration than 12 weeks of telaprevir treatment was investigated. Also, whereas the ribavirin-sparing arm in the 104EU study was only 12 weeks total, considered too short for maximal efficacy in most settings, it was 24 weeks in the present study.

Table 12. Subjects with SVR by Prior Treatment Response, FA Set

	Telaprevir Groups							
	T12/PR24		T24/PR48		T24/P24		Pbo24/PR48	
Prior Treatment Response	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Total	115	59 (51.3)	113	60 (53.1)	111	27 (24.3)	114	16 (14.0)
P-value		<0.001		<0.001		0.024		N/A
Nonresponse	66	26 (39.4)	64	24 (37.5)	62	7 (11.3)	68	6 (8.8)
P-value		<0.001		<0.001		0.297		N/A
Relapse	42	29 (69.0)	41	31 (75.6)	38	16 (42.1)	41	8 (19.5)
P-value		<0.001		<0.001		0.029		N/A
Breakthrough	7	4 (57.1)	8	5 (62.5)	11	4 (36.4)	5	2 (40.0)
P-value		0.596		0.879		0.830		N/A

Source: Table 14.2.1a and Table 14.2.5
N/A: not applicable.
Note: Logistic regression analysis of effect of treatment (telaprevir regimen versus control) on SVR was conducted adjusting for race, prior viral response, baseline HCV RNA, genotype, and age.

The main findings of this study were:

- Telaprevir triple therapy regimens yielded clinically and statistically significant increases in response rates for both prior non-responders and relapsers. The performance of the control arm in each subgroup was roughly as expected.
- Efficacy was higher in subtype 1b than 1a, with >60% versus 46-48% SVR rates.
- A regimen of 24 weeks of telaprevir and peginterferon without ribavirin had insufficient virological efficacy and very high relapse rates.
- Viral breakthrough rates between treatment week 12 and 24 were similar regardless of whether telaprevir was stopped according to protocol at week 12 or 24, thus not indicating any significant advantage of extending telaprevir therapy beyond 12 weeks. 24 weeks of telaprevir therapy was associated with a higher AE burden and more discontinuations than was 12 weeks. This, together with modelling data, informed the decision not to study longer duration of telaprevir than 12 weeks in the phase III trials.
- The predictive value of an eRVR for SVR was higher in patients with prior relapse than in patients with prior non-response. The predictivity of eRVR for SVR in relapsers was roughly similar (25/28 vs 21/23) regardless of whether the total duration of therapy was 24 or 48 weeks. As expected, the likelihood of SVR in case of no eRVR was higher in the 48 weeks total duration arm.
- Patients without eRVR had lower response rates in the 24 week arm than in the 48 week arm. Relapse rates were higher for prior non-responders in the 24 weeks than in the 48 weeks triple therapy arm, both in patients reaching an eRVR and in those who did not.

Study-107: A rollover protocol of telaprevir in Combination with peginterferon Alfa-2a and ribavirin in subjects enrolled in the control groups of studies-106, -104 and -104EU who did not reach SVR

All subjects received telaprevir in combination with Peg-IFN/RBV for 12 weeks. This was followed by treatment with Peg-IFN/RBV for an additional 12 (T12/PR24) or 36 weeks (T12/PR48). The main findings in this study were:

- SVR rates in prior null responders (mostly with a 48 weeks total treatment duration) was 37%, with a considerably higher point estimate in patients treated for 48 weeks rather than 24 weeks
- SVR rates among partial responders was 55% and in prior relapsers 97%
- 21/25 prior relapsers treated for 24 weeks achieved SVR. All 24 prior relapsers with eRVR that were treated for 24 weeks experienced SVR (no relapse).

2.5.2. Main studies

The phase III program

Study -108: A Phase 3 Study of 2 Dose Regimens of Telaprevir in Combination With Peginterferon Alfa-2a (Pegasys) and Ribavirin (Copegus) in Treatment-Naïve Subjects with Genotype 1 Chronic Hepatitis C

This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study. The study compared 8 or 12 weeks of planned telaprevir therapy, followed by a peginterferon ribavirin tail for a total of 24 or 48 weeks, depending on whether eRVR was reached. This was the first study aiming at SVR in which a shorter duration of telaprevir than 12 weeks was tested. The comparator arm received pegIFN alfa-2a and ribavirin as in previous placebo-controlled studies.

Methods

Study Participants

Main Inclusion Criteria: male and female subjects between 18 to 70 years of age (inclusive) with genotype 1 chronic HCV infection who had not been previously treated for HCV were eligible to participate in the study.

Main Exclusion Criteria: patients with decompensated liver disease and HIV or HBV co-infection were excluded from the study.

Treatment

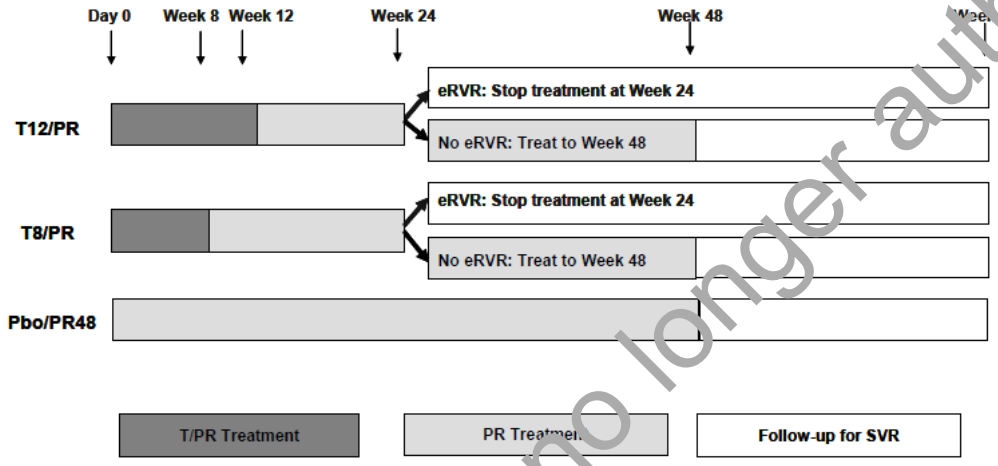
Telaprevir was administered orally in the fed state at a dose of 750 mg every 8 hours (q8h). Peg-IFN-alfa-2a was administered by subcutaneous injection once per week at a dose of 180 µg. RBV was administered orally twice daily at a dose of 1000 mg/day for subjects weighing <75 kg and 1200 mg/day for subjects weighing ≥75 kg.

Table 13. Treatment Groups

Treatment Group	Treatment		
	Telaprevir Dosing Period	Telaprevir-matching Placebo Dosing Period	Peg-IFN-alfa-2a and RBV Dosing Period
T8/PR	Day 1 through Week 8	Weeks 9 through 12	Day 1 through Week 24–with eRVR Day 1 through Week 48–without eRVR
T12/PR	Day 1 through Week 12	---	Day 1 through Week 24–with eRVR Day 1 through Week 48–without eRVR
Pbo/PR48	---	Weeks 1 through 12	Day 1 through Week 48

eRVR: extended rapid viral response (undetectable HCV RNA at Weeks 4 and 12); Pbo: placebo; PR: peginterferon alfa-2a (Pegasys®) and ribavirin (Copegus®); T: telaprevir.

Figure 1 Schematic of Study Design



eRVR: extended rapid viral response (undetectable HCV RNA at Weeks 4 and 12); Pbo: placebo; PR: peginterferon alfa-2a (Pegasys®) and ribavirin (Copegus®); T: telaprevir.

Stopping rules included that for telaprevir treated patients with HCV-RNA >1000 copies/mL at week 4, telaprevir was stopped. If HCV-RNA was >1000 copies at week 12, the patient's response was deemed virological failure. Stopping rules for the control arm were according to label for peginterferon alfa-2a and ribavirin (Copegus).

Objectives and endpoints

Primary objective:

To demonstrate the efficacy of telaprevir in combination with peginterferon alfa-2a (Peg-IFN-alfa-2a) and ribavirin (RBV) in treatment-naïve subjects with genotype 1 chronic hepatitis C.

The primary endpoint was $SVR_{planned}$ – that is, SVR 24 weeks after the planned end of therapy (after 24 or 48 weeks).

Secondary objective:

To evaluate the safety of telaprevir in combination with Peg-IFN-alfa-2a and RBV in treatment-naïve subjects with genotype 1 chronic hepatitis C (based on adverse events, physical examination findings, and clinical laboratory, vital sign, ECG assessments and Total Fatigue Score from the FSS).

All plasma HCV RNA levels were assessed using the Roche TaqMan HCV RNA assay (Version 2.0, lower limit of quantification [LLOQ] of 25 IU/mL).

Sample size

Assuming a 50% response rate in the control group, a 64% response rate in a telaprevir group, a 2-sided continuity corrected Chi-squared test, with an overall significance level of 5% (adjusted for multiple comparisons), a sample size of 350 subjects in each treatment group provides a power of 92% to demonstrate a statistically significant treatment difference.

Randomisation

The study was randomised. Subject were stratified to optimize balance among the treatment groups with regard to genotype 1 subtype and baseline viral load (HCV RNA <800000 IU/mL or ≥800000 IU/mL).

Blinding (masking)

This was a double-blind study in which the sponsor, investigator, study personnel, and study participants were to be blinded with respect to telaprevir treatment.

Results

Study subject disposition

Table 14. Treatment and Study Completion Status and Reasons for Discontinuation, Full Analysis Set

Status	T8/PR N = 364 n (%)	T12/PR N = 363 n (%)	Pbo/PR48 N = 361 n (%)
Completed treatment	**260 (71.4)**	**268 (73.8)**	**202 (56.0)**
Discontinued treatment	**104 (28.6)**	**95 (26.2)**	**159 (44.0)**
Reasons for discontinuation of treatment:			
Adverse event	37 (10.2)	36 (9.9)	26 (7.2)
Death	0	0	1 (0.3)
Lost to follow-up	3 (0.8)	4 (1.1)	4 (1.1)
Withdrawal of consent	1 (0.3)	0	2 (0.6)
Virologic failure	40 (11.0)	38 (10.5)	118 (32.7)
Other[a]	23 (6.3)	17 (4.7)	8 (2.2)
Completed study	**311 (85.4)**	**328 (90.4)**	**325 (90.0)**
Discontinued study	**53 (14.6)**	**35 (9.6)**	**36 (10.0)**
Reasons for discontinuation of study:			
Adverse Event	6 (1.6)	5 (1.4)	4 (1.1)
Death	1 (0.3)	2 (0.6)	1 (0.3)
Lost to follow-up	16 (4.4)	12 (3.3)	14 (3.9)
Withdrawal of consent	23 (6.3)	11 (3.0)	16 (4.4)
Other[a]	7 (1.9)	5 (1.4)	1 (0.3)

[a] The "Other" category includes subjects who discontinued due to noncompliance with study drug, other noncompliance, refused further treatment, and other reasons.

Source: Table 14.1.1a and Table 14.1.1b.

On treatment discontinuation rates due to adverse events were higher in the telaprevir arms compared to the control, whereas discontinuation due to virologic failure (stopping rules) was substantially more common in the placebo arm. Loss to follow up or withdrawal of consent during the entire study was between 6.3% and 10.7% in the different arms, with the highest number in the T8/PR arm. Though the mean duration of follow up after end of therapy was longer in the telaprevir arms, the loss to follow up was roughly similar between arms.

Table 15. Treatment Adherence, Full Analysis set

Treatment Adherence Rate	T8/PR N = 364 n (%)	T12/PR N = 363 n (%)	Pbo/PR48 N = 361 n (%)
Telaprevir/placebo[a]	**N = 362 n (%)**	**N = 362 n (%)**	**N = 360 n (%)**
≥95%	348 (96.1)	344 (95.0)	346 (96.1)
≥80% and <95%	10 (2.8)	18 (5.0)	14 (3.9)
≥60% and <80%	3 (0.8)	0	0
<60%	1 (0.3)	0	0
Peg-IFN-alfa-2a[b]	**N = 363 n (%)**	**N = 363 n (%)**	**N = 360 n (%)**
≥95%	298 (82.1)	300 (82.6)	303 (84.2)
≥80% and <95%	46 (12.7)	41 (11.3)	36 (10.0)
≥60% and <80%	14 (3.9)	19 (5.2)	20 (5.6)
<60%	5 (1.4)	3 (0.8)	1 (0.3)
RBV[c]	**N = 363 n (%)**	**N = 363 n (%)**	**N = 359 n (%)**
≥95%	217 (59.8)	222 (61.2)	277 (77.2)
≥80% and <95%	76 (20.9)	68 (18.7)	47 (13.1)
≥60% and <80%	55 (15.2)	53 (14.6)	27 (7.5)
<60%	15 (4.1)	20 (5.5)	8 (2.2)

Note: Treatment adherence is based on pill count, subject diaries, and documented conversations between clinical site staff and subject.
[a] For telaprevir/placebo, 4 subjects are not included due to missing dosing data.
[b] For Peg-IFN-alfa-2a, 2 subjects are not included due to missing dosing data.
[c] For RBV, 3 subjects are not included due to missing dosing data.
Source: Table 14.3.7.3a.

Estimated treatment adherence to telaprevir was very good and similar between arms. The lower ribavirin adherence in the telaprevir treatment groups would be due to the additive effects on anemia seen when telaprevir and ribavirin is combined (see section on clinical safety).

Baseline data

Demographic and baseline characteristics

This study was conducted at 123 sites in Argentina, Austria, Australia, Canada, France, Germany, Israel, Italy, Poland, Spain, United Kingdom, and the United States (including Puerto Rico).

Table 16. Subject Demography, Full Analysis Set

Variable	T8/PR N = 364 n (%)	T12/PR N = 363 n (%)	Pbo/PR48 N = 361 n (%)
Sex, n (%)			
Male	211 (58.0)	214 (59.0)	211 (58.4)
Female	153 (42.0)	149 (41.0)	150 (41.6)
Race, n (%)			
Caucasian	315 (86.5)	325 (89.5)	318 (88.1)
Black	40 (11.0)	26 (7.2)	28 (7.8)
Asian	5 (1.4)	5 (1.4)	10 (2.8)
Other[a]	4 (1.1)	7 (1.9)	5 (1.4)
Ethnicity, n (%)			
Hispanic or Latino	44 (12.1)	35 (9.6)	38 (10.5)
Not Hispanic or Latino	320 (87.9)	328 (90.4)	323 (89.5)
Region, n (%)			
North America	227 (62.4)	214 (59.0)	214 (59.3)
Europe	100 (27.5)	104 (28.7)	106 (29.4)
Other[b]	37 (10.2)	45 (12.4)	41 (11.4)
Age (years)			
Mean (SD)	47.0 (10.9)	46.5 (10.8)	46.8 (10.0)
Median	49.0	49.0	49.0
Min; max	19; 68	19; 69	18; 69
Age (years), n (%)			
≤45	139 (38.2)	142 (39.1)	143 (39.6)
>45 and ≤65	222 (61.0)	214 (59.0)	216 (59.8)
>65	3 (0.8)	7 (1.9)	2 (0.6)
BMI[c] (kg/m^2)			
Mean (SD)	27.1 (5.2)	26.3 (5.0)	27.2 (5.1)
Median	26.2	25.7	26.
Min; max	17; 46	18; 47	7; 48
BMI[c] (kg/m^2), n (%)			
<25	145 (40.1)	155 (47.9)	130 (36.0)
≥25 and <30	131 (36.2)	12 (35.)	144 (39.9)
≥30	86 (23.8)	7 (21.)	87 (24.1)

BMI: body mass index; SD: standard deviation.
[a] The "Other" subcategory for race includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Other.
[b] The "Other" subcategory for region includes Argentina, Australia, and Israel.
[c] For BMI, 362 subjects in the T8/PR group and 361 subjects in the T12/PR group were assessed.
Source: Table 14.1.2a.

Almost 60% of the population was male, and almost 90% Caucasian. Notably, blacks, known to have a lower average interferon response are not well represented in the study. About 60% of patients were treated in North America and 30% in the EU. The age distribution is representative of patients treated in the clinic, and very few patients were over 65. Almost a quarter of patients had BMI >30.

Table 17. Baseline Disease Characteristics, full Analysis Set

Variable	T8/PR N = 364	T12/PR N = 363	Pbo/PR48 N = 361
Result of most recent liver biopsy[a], n (%)			
Cirrhosis	26 (7.1)	21 (5.8)	21 (5.8)
No cirrhosis	338 (92.9)	342 (94.2)	340 (94.2)
No or minimal fibrosis	128 (35.2)	134 (36.9)	147 (40.7)
Portal fibrosis	151 (41.5)	156 (43.0)	141 (39.1)
Bridging fibrosis	59 (16.2)	52 (14.3)	52 (14.4)
HCV infection genotype (5'NC-I assay), n (%)			
1a	210 (57.7)	213 (58.7)	208 (57.6)
1b	151 (41.5)	149 (41.0)	151 (41.8)
1, unknown	3 (0.8)	1 (0.3)	2 (0.6)
HCV infection genotype (NS3 assay), n (%)			
1a	214 (58.8)	217 (59.8)	210 (58.2)
1b	148 (40.7)	142 (39.1)	149 (41.3)
1, unknown	2 (0.5)	4 (1.1)	2 (0.6)
Baseline HCV RNA (log_{10} IU/mL)			
Mean (SD)	6.3 (0.7)	6.3 (0.7)	6.3 (0.7)
Median	6.4	6.4	6.4
Min; max	4; 8	2; 7	3; 8
Baseline HCV RNA (IU/mL), n (%)			
<800000	85 (23.4)	82 (22.6)	82 (22.7)
≥800000	279 (76.6)	281 (77.4)	279 (77.3)
Baseline HCV RNA (IU/mL), n (%)			
<871000	92 (25.3)	88 (24.2)	92 (25.5)
≥871000 to 2776224.5	91 (25.0)	91 (25.1)	89 (24.7)
≥2776224.5 to 6732682	90 (24.7)	98 (27.0)	84 (23.3)
≥6732682	91 (25.0)	86 (23.7)	96 (26.6)

5'NC-I assay: 5'NC InnoLipa assay; NS3 assay: Vertex NS3 assay.
[a] Subjects had a documented liver biopsy within 1 year before the screening or were required to have a liver biopsy during the screening period for this study.
Source: Table 14.1.2a and Table 14.1.4a.

The subject baseline disease characteristics for the PP Set are provided in Table 14.1.3 and are similar to the baseline disease characteristic of the FA Set.

While the actual number of cirrhotics included is low, the percentage is roughly similar to that in the IDEAL study. As expected given that the study was largely conducted in North America, the proportion of patients with subtype 1a is higher than 1b. Mean VL is roughly similar to the IDEAL study. Baseline disease characteristics are well balanced between groups, though there is a trend to more advanced fibrosis in the T8PR arm.

Numbers analysed

All efficacy analyses were conducted using the FA Set, which consisted of the 1088 subjects who received at least 1 dose of study drug. In addition, a limited analysis of efficacy was conducted using the PP Set which consisted of 1033 subjects without any major protocol violations.

Outcomes and estimations

Primary efficacy outcome (SVR)

There were three modes of assessing SVR rates described in the protocol. The primary endpoint was $SVR_{planned}$ – that is, SVR 24 weeks after the planned end of therapy (after 24 or 48 weeks)

Table 18. $SVR24_{planned}$ Rates, Full Analysis Set

Variable	T8/PR N = 364	T12/PR N = 363	Pbo/PR48 N = 361
$SVR24_{planned}$[a]: n (%)	250 (68.7)	271 (74.7)	158 (43.8)
Odds ratio between each of the T/PR groups and Pbo/PR48	2.92	3.95	N/A
95% confidence intervals for the odds ratio	(2.14, 3.99)	(2.87, 5.45)	N/A
P value for odds ratio	<0.0001	<0.0001	N/A
Difference between each of the T/PR and Pbo/PR48 groups and 95% confidence intervals for the difference	24.9% (17.9%, 31.9%)	30.9% (24.1%, 37.7%)	N/A

N/A: not applicable; SVR: sustained viral response.
Note: Logistic regression analysis (2-sided) with $SVR24_{planned}$ as the dependent variable was used to determine the *P* value and and 95% confidence intervals with treatment, genotype, and baseline HCV RNA plasma level as factors. *P* value and 95% confidence intervals for the odds ratios are between T8/PR group (or T12/PR group) and Pbo/PR48 group.
Source: Table 14.2.1a

Both telaprevir arms were significantly superior to placebo on the primary endpoint. The response in the T12/PR arm was numerically superior to that in the T8/PR arm. The placebo arm performed at the level of efficacy that would be expected.

The difference in $SVR24_{planned}$ for T8/PR group versus T12/PR group was -6.0% (95% CI [-12.5%, 0.6%]).

SVR rates as a function of eRVR

Table 19. RVR and eRVR Rates, Full Analysis Set

Variable	T8/PR N = 364 n (%)	T12/PR N = 363 n (%)	Pbo/PR48 N = 361 n (%)
RVR	242 (66.5)	246 (67.8)	34 (9.4)
eRVR	207 (56.9)	212 (58.4)	29 (8.0)

eRVR: extended rapid viral response; RVR: rapid viral response.
Source: Table 14.2.6 and Table 14.2.7.

Table 20. $SVR24_{planned}$ Rates by eRVR Status, Full Analysis Set

	T8/PR N = 364		T12/PR N = 363		Pbo/PR48 N = 361	
Status	N	n (%)	N	n (%)	N	n (%)
Total	**364**	**250 (68.7)**	**363**	**271 (74.7)**	**361**	**158 (43.8)**
eRVR status[a]						
eRVR	207	171 (82.6)	212	189 (89.2)	29	28 (96.6)
non-eRVR	157	79 (50.3)	151	82 (54.3)	332	130 (39.2)

eRVR: extended rapid viral response; SVR: sustained viral response.
[a] For subjects in the T8/PR and T12/PR groups, subjects who had eRVR had a planned treatment duration of 24 weeks and subjects who did not have eRVR had a planned treatment duration of 48 weeks. For subjects in Pbo/PR48 group, efficacy endpoints by eRVR status are presented, but the eRVR status was not used to make any decisions on the treatment duration. All subjects in the Pbo/PR48 group had a planned treatment duration of 48 weeks.
Source: Table 14.2.2b.

Fifty seven and 58% of patients in the T8/PR and T12PR groups reached eRVR and were thus eligible for 24 weeks of therapy. Point estimates for SVR rates were higher in the T12PR group compared to the T8PR group regardless of whether eRVR (and shorter total duration of therapy) was reached or not.

Relapse rates

Table 21. Relapse$_{planned}$ Rates by eRVR Status and RVR Status

	T8/PR N = 295		T12/PR N = 314		Pbo/PR48 N = 229	
Status	N	n (%)	N	n (%)	N	n (%)
Total	**295**	**28 (9.5)**	**314**	**27 (8.6)**	**229**	**64 (27.9)**
eRVR status						
eRVR	194	18 (9.3)	207	14 (6.8)	28	0
non-eRVR	101	10 (9.9)	107	13 (12.1)	201	64 (31.8)
RVR status						
RVR	223	23 (10.3)	234	18 (7.7)	33	0
non-RVR	72	5 (6.9)	80	9 (11.3)	196	64 (32.7)

eRVR: extended rapid viral response; RVR: rapid viral response.
Note: Denominator is number of subjects with undetectable HCV RNA at end of treatment visit. For subjects in the T8/PR and T12/PR groups, subjects who had eRVR had a planned treatment duration of 24 weeks and subjects who did not have eRVR had a planned treatment duration of 48 weeks. For subjects in Pbo/PR48 group, efficacy endpoints by eRVR status are presented, but the eRVR status was not used to make any decisions on the treatment duration. All subjects in the Pbo/PR48 group had a planned treatment duration of 48 weeks.
Source: Table 14.2.14a and Table 14.2.14b.

Relapse rates in patients with eRVR were below 10% despite 24 weeks of therapy. The relapse rate in the pegIFN alfa-2a + ribavirin arm was 28%, roughly similar to that seen in the IDEAL study.

SVR rates by subgroups

Table 22. SVR24$_{planned}$ Rates by Baseline Disease Characteristics, Full Analysis Set

	T8/PR N = 364		T12/PR N =363		Pbo/PR48 N = 361	
Baseline Disease Characteristics	N	n (%)	N	n (%)	N	n (%)
Total	**364**	**250 (68.7)**	**363**	**271 (74.7)**	**361**	**158 (43.8)**
Baseline HCV RNA (IU/mL)						
<800000	85	67 (78.8)	82	64 (78.0)	82	57 (69.5)
≥800000	279	183 (65.6)	281	207 (73.7)	279	101 (36.2)
Baseline HCV RNA (IU/mL)						
<871000	92	72 (78.3)	88	70 (79.5)	92	63 (68.5)
≥871000 to 2776224.5	91	56 (61.5)	91	61 (67.0)	89	32 (36.0)
≥2776224.5 to 6732682	90	60 (66.7)	98	80 (81.6)	84	25 (29.8)
≥6732682	91	62 (68.1)	86	60 (69.8)	96	38 (39.6)
Liver Disease Status						
Cirrhosis	26	11 (42.3)	21	13 (61.9)	21	7 (33.3)
No cirrhosis	338	239 (70.7)	342	258 (75.4)	340	151 (44.4)
No or minimal fibrosis	128	101 (78.9)	134	109 (81.3)	147	67 (45.6)
Portal fibrosis	151	104 (68.9)	156	117 (75.0)	141	67 (47.5)
Bridging fibrosis	59	34 (57.6)	52	32 (61.5)	52	17 (32.7)

SVR: sustained viral response.
Source: Table 14.2.3.

Table 23. $SVR24_{planned}$ Rates by Demographic Characteristics, Full Analysis Set

	T8/PR N = 364		T12/PR N = 363		Pbo/PR48 N = 361	
Variable	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**
Total	**364**	**250 (68.7)**	**363**	**271 (74.7)**	**361**	**158 (43.8)**
Sex						
Female	153	103 (67.3)	149	112 (75.2)	150	64 (42.7)
Male	211	147 (69.7)	214	159 (74.3)	211	94 (44.5)
Age, years						
≤45	139	102 (73.4)	142	118 (83.1)	143	74 (51.7)
>45 and ≤65	222	145 (65.3)	214	150 (70.1)	216	82 (38.0)
>65	3	3 (100)	7	3 (42.9)	2	2 (100)
BMI[a], kg/m²						
<25	145	104 (71.7)	155	129 (83.2)	130	57 (43.8)
≥25 and <30	131	92 (70.2)	129	87 (67.4)	144	65 (45.1)
≥30	86	53 (61.6)	77	55 (71.4)	87	36 (41.4)
Race						
Caucasian	315	220 (69.8)	325	244 (75.1)	318	147 (46.2)
Black	40	23 (57.5)	26	16 (61.5)	28	7 (25.0)
Asian	5	4 (80.0)	5	5 (100)	10	3 (30.0)
Other	4	3 (75.0)	7	6 (85.7)	5	1 (20.0)
Ethnicity						
Hispanic or Latino	44	29 (65.9)	35	26 (74.3)	38	15 (39.5)
Not Hispanic or Latino	320	221 (69.1)	328	245 (74.7)	323	143 (44.3)
Region						
North America	227	151 (66.5)	214	156 (72.9)	214	89 (41.6)
Europe	100	74 (74.0)	104	80 (76.9)	106	49 (46.2)
Other[b]	37	25 (67.6)	45	35 (77.8)	41	20 (48.8)
Medical History						
Diabetes	23	11 (47.8)	21	15 (71.4)	21	6 (28.6)
No diabetes	341	239 (70.1)	342	256 (74.9)	340	152 (44.7)

BMI: body mass index; SVR: sustained viral response.
[a] For BMI, 362 subjects in the T8/PR group and 361 subjects in the T12/PR group were assessed.
[b] The "Other" subcategory for region includes Argentina, Australia, and Israel.
Source: Table 14.2.3.

As with standard of care, SVR rates in patients treated with telaprevir were lower in patients with bridging fibrosis and cirrhosis. Also, in patients with baseline viral load < 800,000 copies, SVR rates were higher in all treatment arms. The advantage of adding telaprevir was consistent over sex, age, BMI, race, region, baseline viral load, liver disease status and the presence or absence of diabetes.

In summary, the main findings of the pivotal -108 study in treatment naive patients were:

- Both the 12- weeks and the 8 weeks telaprevir arm, with a subsequent peginterferon/ribavirin tail for a total of 24 or 48 weeks duration depending on eRVR, were superior to 48 weeks of peginterferon/ribavirin with placebo.
- A higher on-treatment virological failure rate after telaprevir treatment completion was found in the 8 week telaprevir arm. As the viral genotype of these excess failures were wild-type or low-level resistant variants which might have been cleared by further telaprevir treatment, these data indicate a virological edge of twelve rather than eight weeks of telaprevir therapy. Since the excess number of serious adverse events with 12 rather than 8 weeks of telaprevir therapy were marginal, these data support the dosing of telaprevir for 12 weeks.
- Almost 60% of patients in the twelve week telaprevir arm achieved an eRVR and were thus assigned 24 weeks of therapy. The relapse rate in such patients was 7% in the 12-week telaprevir arm.
- SVR rates were higher in patients with subtype 1b compared to 1a (79% versus 71% in the twelve week telaprevir arm.

- The advantage of telaprevir over placebo was evident regardless of viral subtype, degree of fibrosis, baseline viral load, sex, age, gender or race.

-111 A Randomized Study of Stopping Treatment at 24 Weeks or Continuing Treatment to 48 Weeks in Treatment-Naïve Subjects with Genotype 1 Chronic Hepatitis C who Achieve an Extended Rapid Viral Response While Receiving Telaprevir, Peginterferon-alfa-2a (Pegasys), and Ribavirin (Copegus)

The study was designed to evaluate the SVR rates in subjects who achieved an eRVR (undetectable HCV RNA levels at Week 4 and Week 12 on treatment) with telaprevir in combination with Peg-IFN-alfa-2a and RBV.

Methods

Participants

Main Inclusion criteria: Male and female subjects between 18 to 70 years of age (inclusive) with genotype 1 chronic HCV infection who had not been previously treated for HCV were eligible for the study.

Main exclusion criteria: Subjects with decompensated liver disease and HIV or HBV co-infection were excluded from the study.

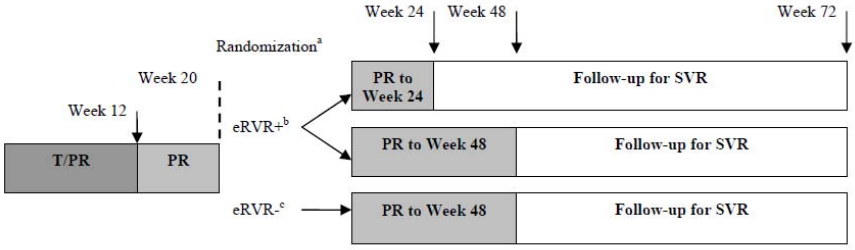
Treatment

Telaprevir was administered orally in the fed state at a dose of 750 mg every 8 hours (q8h). Peg-IFN-alfa-2a was administered by subcutaneous injection once per week at a dose of 180 µg. RBV was administered orally twice daily at a dose of 1000 mg/day for subjects weighing <75 kg and 1200 mg/day for subjects weighing ≥75 kg.

The treatment regimens were 24 or 48 weeks in duration, with telaprevir administered in combination with Peg-IFN-alfa-2a and RBV for the first 12 weeks (i.e., T12/PR24 arm or T12/PR48 arms, respectively).

The table 24 below provides a summary of the treatment regimens in this study.

Table 24. Summary of Treatment



Abbreviations: eRVR: extended rapid viral response; PR: Peg-IFN-alfa-2a and RBV; SVR: sustained viral response; T: telaprevir
Note: Subjects who received at least 1 dose of study drug, but prematurely discontinued treatment before Week 20 were not randomized or assigned to a treatment regimen. These subjects were included in a group designated 'Other'.
[a] Randomization occurred after the Week 20 visit, but before the Week 24 visit. Randomization was blocked and stratified to optimize balance among the treatment groups with regard to genotype (1a, 1b, or unknown) and race (Black or non-Black; and self-identified).
[b] Subjects who achieved eRVR and completed the Week 20 visit were randomized in a 1:1 ratio to stop all study treatment at Week 24 (T12/PR24/eRVR+ group) or to continue treatment with Peg-IFN-alfa-2a and RBV to Week 48 (T12/PR48/eRVR+ group).
[c] Subjects who did not achieve eRVR and completed the Week 20 visit were assigned treatment with Peg-IFN-alfa-2a and RBV for 48 weeks (T12/PR48/eRVR- treatment group).
Source: clinical study protocol (Appendix 16.1.1)

Subjects who achieved an eRVR and completed the Week 20 visit were randomized in a 1:1 ratio to stop all study treatment at Week 24 or to continue treatment with Peg-IFN-alfa-2a and RBV to Week 48 (T12/PR48/eRVR+ group).

Subjects who did not achieve an eRVR were assigned a total treatment with Peg-IFN-alfa-2a and RBV for 48 weeks (T12/PR48/eRVR- group). Subjects who prematurely discontinued treatment before Week 20 were not randomized or assigned to a treatment regimen. These subjects were included in the group designated 'Other'.

Objectives and endpoints

Primary objective

To estimate the difference in SVR rates between T12/PR24 and T12/PR48 treatment regimens in subjects who achieve eRVR.

The primary efficacy variable was the $SVR24_{planned}$ rate, defined as undetectable HCV RNA levels at the end of treatment (EOT) visit and at 24 weeks after the last planned dose of study treatment without any confirmed detectable HCV RNA levels in between those visits.

Secondary objective

To evaluate the safety of telaprevir in combination with Peg-IFN-alfa-2a and RBV in treatment-naïve subjects with genotype 1 chronic hepatitis C (based on adverse events, physical examination findings, and clinical laboratory, vital sign, ECG assessments and Total Fatigue Score from the FSS).

All plasma HCV RNA levels were assessed using the Roche TaqMan HCV RNA assay (Version 2.0, lower limit of quantification [LLOQ] of 25 IU/mL).

Sample size

The sample size was estimated based on a 2-sided 95% confidence interval for the treatment difference between stopping treatment at week 24 and continuing treatment to week 48, assuming an expected SVR rate of 90% in each group, based on randomization at Week 20. With SVR rates of 90% in the T12/PR24 and T12/PR48 arms and at least 157 randomized subjects in each arm, a 2-sided 95%

confidence interval on the observed treatment difference in SVR rates between stopping treatment at week 24 and continuing treatment to week 48 will have at least 80% power to exclude a 10.5% difference.

Based on data from Phase 2 clinical studies, it was assumed that the combined proportion of subjects who were likely to discontinue treatment prior to randomization and the proportion of subjects that were unlikely to achieve eRVR would be about 33% of the total number of subjects enrolled. Therefore, the target enrollment was to be 470-500 subjects.

Randomisation

The study was randomised. Subjects were stratified to optimize balance among the treatment groups with regard to genotype 1 subtype and baseline viral load (HCV RNA <800000 IU/mL or ≥800000 IU/mL).

Blinding (Masking)

This was a double-blind study in which the sponsor, investigator, study personnel, and study participants were to be blinded with respect to telaprevir treatment.

Numbers analysed

Efficacy analyses were conducted using the FA set, which consisted of the 540 subjects who received at least 1 dose of study drug. In addition, the PPA set was used to provide supportive analyses of the primary efficacy variable. The PPA set included 527 subjects who did not have any major protocol deviations

Results

Study subject disposition

Table 25. Subject Study Disposition, Full Analysis Set

	Randomized (eRVR+)		Assigned (eRVR-)		
Status	T12/PR24 N = 162 n (%)	T12/PR48 N = 160 n (%)	T12/PR48 N = 118 n (%)	Other[a] N = 100 n (%)	Total N = 540 n (%)
Discontinued study prior to last planned dose	0	6 (3.8)	8 (6.8)	29 (29.0)	43 (8.0)
Discontinued study during follow-up[b]	2 (1.2)	7 (4.4)	7 (5.9)	5 (5.0)	21 (3.9)
Discontinued study during Extended Follow-up[c]	5 (3.1)	N/A	N/A	6 (6.0)	11 (2.0)
Completed Week 72 assessment	155 (95.7)	147 (91.9)	103 (87.3)	60 (60.0)	465 (86.1)

Abbreviations: eRVR: extended rapid viral response; N/A: not applicable

[a] Subjects who received at least 1 dose of study drug, but prematurely discontinued treatment before Week 20 were not randomized or assigned to a treatment regimen.

[b] Follow-up is the time period from the last planned dose to 24 weeks after the last planned dose.

[c] Extended follow-up is the time period from 24 weeks after the last planned dose to Week 72. The extended follow-up applies to subjects in the T12/PR24/eRVR+ and Other groups.

Source: Table 14.1.1b

Table 26. Treatment and Study Completion Status and Reasons for Discontinuation

Status	Randomized (eRVR+) T12/PR24 N = 162 n (%)	Randomized (eRVR+) T12/PR48 N = 160 n (%)	Assigned (eRVR-) T12/PR48 N = 118 n (%)	Other[a] N = 100 n (%)	Total N = 540 n (%)
Completed treatment	**161 (99.4)**	**119 (74.4)**	**79 (66.9)**	**0**	**359 (66.5)**
Stopped due to virologic failure	**0**	**6 (3.8)**	**18 (15.3)**	**12 (12.0)**	**36 (6.7)**
Discontinued treatment	**1 (0.6)**	**35 (21.9)**	**21 (17.8)**	**88 (88.0)**	**145 (26.9)**
Reasons for discontinuation of treatment					
Adverse event	1 (0.6)	20 (12.5)	12 (10.2)	62 (62.0)	95 (17.6)
Death	0	0	0	0	0
Lost to follow-up	0	2 (1.3)	2 (1.7)	5 (5.0)	9 (1.7)
Non-compliance with study drug	0	0	0	1 (1.0)	1 (0.2)
Other non-compliance	0	0	0	1 (1.0)	1 (0.2)
Withdrawal of consent	0	1 (0.6)	1 (0.8)	4 (4.0)	6 (1.1)
Required prohibited medication	0	0	1 (0.8)	3 (3.0)	4 (0.7)
Refused further treatment	0	11 (6.9)	5 (4.2)	8 (8.0)	24 (4.4)
Other	0	1 (0.6)	0	4 (4.0)	5 (0.9)

Discontinuations during follow-up were roughly similar in both of the randomised groups.

The majority of the "other" category, that is, patients not reaching week 20 randomisation/assignment discontinued due to adverse events 62/540 patients dosed (11%), a figure which is comparable to the -108 study. 12/540 (2.2%) subjects discontinued prior to week 20 due to virological failure.

The total proportion of treatment discontinuations was considerably larger among patients randomised to 48, compared to 24 weeks of therapy after reaching an eRVR. Given that this was a non-inferiority study, it is acknowledged that this could theoretically have compromised the conclusions of the trial. However, given the SVR rate of 92% seen in eRVR patients randomised to 24 weeks of therapy (see below), it is considered that this likely did not affect assay sensitivity, but could rather be seen to indicate the value of a shortened treatment duration in terms of tolerability.

Baseline data

The study was conducted at 75 sites in Belgium, The Netherlands, and the United States (including Puerto Rico).

Table 27. Subject Demography, Full Analysis Set

Variable	Randomized (eRVR+) T12/PR24 N = 162 n (%)	Randomized (eRVR+) T12/PR48 N = 160 n (%)	Assigned (eRVR-) T12/PR48 N = 118 n (%)	Other N = 100 n (%)	Total N = 540 n (%)
Sex					
Male	104 (64.2)	97 (60.6)	70 (59.3)	54 (54.0)	325 (60.2)
Female	58 (35.8)	63 (39.4)	48 (40.7)	46 (46.0)	215 (39.8)
Race					
Caucasian	135 (83.3)	131 (81.9)	86 (72.9)	75 (75.0)	427 (79.1)
Black	17 (10.5)	17 (10.6)	20 (16.9)	19 (19.0)	73 (13.5)
Asian	3 (1.9)	3 (1.9)	2 (1.7)	1 (1.0)	9 (1.7)
American Indian or Alaska Native	1 (0.6)	0	1 (0.8)	3 (3.0)	5 (0.9)
Native Hawaiian or Other Pacific Islander	0	1 (0.6)	0	0	1 (0.2)
Not allowed to ask per local regulations	4 (2.5)	3 (1.9)	5 (4.2)	1 (1.0)	13 (2.4)
Other	2 (1.2)	5 (3.1)	4 (3.4)	1 (1.0)	12 (2.2)
Ethnicity					
Hispanic or Latino	18 (11.1)	11 (6.9)	8 (6.8)	17 (17.0)	54 (10.0)
Not Hispanic or Latino	140 (86.4)	146 (91.3)	105 (89.0)	82 (82.0)	473 (87.6)
Not allowed to ask per local regulations	4 (2.5)	3 (1.9)	5 (4.2)	1 (1.0)	13 (2.4)
Region					
North America	154 (95.1)	151 (94.4)	106 (89.8)	98 (98.0)	509 (94.3)
Europe	8 (4.9)	9 (5.6)	12 (10.2)	2 (2.0)	31 (5.7)
Age (years)					
Mean (SD)	48.6 (8.9)	48.3 (9.9)	49.5 (8.7)	51.6 (8.4)	49.3 (9.2)
Median	51.0	50.0	51.0	52.5	51
Min; max	22, 70	19, 67	20,63	21, 66	19,
Age (years)					
≤45	45 (27.8)	46 (28.8)	26 (22.0)	18 (18.0)	[illegible]
>45 and ≤65	113 (69.8)	111 (69.4)	92 (78.0)	81 (81.0)	397 (73.5)
>65	4 (2.5)	3 (1.9)	0	1 (1.0)	8 (1.5)
BMI (kg/m^2)					
Mean (SD)	28.7 (5.6)	27.9 (5.8)	28.1 (5.7)	27.5 (5.4)	28.1 (5.6)
Median	27.8	27.1	[illegible]	26.6	27.2
Min; max	18, 53	19, 49	9, 54	19, 44	18, 54
BMI (kg/m^2)					
<25	44 (27.2)	60 (37.5)	35 (29.7)	38 (38.0)	177 (32.8)
≥25 and <30	56 (34.6)	51 (31.9)	49 (41.5)	32 (32.0)	188 (34.8)
≥30	61 (37.7)	49 (30.6)	34 (28.8)	30 (30.0)	174 (32.2)
Missing	1 (0.6)	0	0	0	1 (0.2)

Abbreviations: eRVR: extended rapid viral response; SD: standard deviation
Note: Subjects who received at least 1 dose of study drug, but prematurely discontinued treatment before Week 20 were not randomized or assigned to a treatment regimen.
Source: Table 14.1.2

The proportion of males to females was similar to study 108. The proportion of blacks is somewhat higher, which may be explained by the fact that this was a study predominantly performed in the US (>90% of patients). The age distribution is typical, and the proportion of patients with BMI over 30 is 1/3.

Table 28. Baseline Disease Characteristics, Full Analysis Set

Variable	Randomized (eRVR+) T12/PR24 N = 162 n (%)	Randomized (eRVR+) T12/PR48 N = 160 n (%)	Assigned (eRVR-) T12/PR48 N = 118 n (%)	Other [a] N = 100 n (%)	Total N = 540 n (%)
Result of the most recent liver biopsy[b]					
Cirrhosis	18 (11.1)	12 (7.5)	12 (10.2)	19 (19.0)	61 (11.3)
No cirrhosis					
No or minimal fibrosis	46 (28.4)	48 (30.0)	27 (22.9)	26 (26.0)	147 (27.2)
Portal fibrosis	78 (48.1)	79 (49.4)	49 (41.5)	38 (38.0)	244 (45.2)
Bridging fibrosis	20 (12.3)	21 (13.1)	30 (25.4)	17 (17.0)	88 (16.3)
HCV infection genotype (LiPA 5'UTR assay)[c]					
1a	115 (71.0)	117 (73.1)	84 (71.2)	72 (72.0)	388 (71.9)
1b	46 (28.4)	43 (26.9)	33 (28.0)	27 (27.0)	149 (27.6)
1, Unknown	1 (0.6)	0	1 (0.8)	1 (1.0)	3 (0.6)
HCV infection genotype (NS3-4A assay)[c]					
1a	114 (70.4)	116 (72.5)	85 (72.0)	72 (72.0)	387 (71.7)
1b	45 (27.8)	42 (26.3)	33 (28.0)	27 (27.0)	147 (27.2)
1, Unknown	3 (1.9)	2 (1.3)	0	1 (1.0)	6 (1.1)
Baseline HCV RNA (log_{10} IU/mL)					
Mean (SD)	6.3 (0.9)	6.4 (0.7)	6.7 (0.6)	6.4 (0.7)	6.4 (0.8)
Median	6.5	6.5	6.8	6.4	6.5
Min, max	(2, 8)	(4, 8)	(4, 8)	(4, 7)	(2, 8)
Baseline HCV RNA (IU/mL)					
<800000	38 (23.5)	34 (21.3)	10 (8.5)	13 (13.0)	95 (17.6)
≥800000	124 (76.5)	126 (78.8)	108 (91.5)	87 (87.0)	445 (82.4)
Baseline HCV RNA (IU/mL)					
<1236647.25	48 (29.6)	48 (30.0)	15 (12.7)	24 (24.0)	135 (25.0)
≥1236647.25 to 3499753.5	41 (25.3)	38 (23.8)	24 (20.3)	32 (32.0)	135 (25.0)
≥3499753.5 to 9035496.75	39 (24.1)	34 (21.3)	43 (36.4)	19 (19.0)	135 (25.0)
≥9035496.75	34 (21.0)	40 (25.0)	36 (30.5)	25 (25.0)	135 (25.0)

Abbreviations: eRVR: extended rapid viral response; HCV: hepatitis C virus; LiPA: Inno-lopa line probe assay; SD: standard deviation

[a] Subjects who received at least 1 dose of study drug, but prematurely discontinued treatment before Week 2[illegible] were not randomized or assigned to a treatment regimen.

[b] Subjects had a documented liver biopsy within 1 year before the screening visit or were required to have a liver biopsy during the screening period for this study.

[c] The LiPA assay (analyzes variants in the 5' UTR region) and the NS3-4A assay (Vertex method that sequences the HCV NS3-4A protease domain) were used to determine the genotype.

Source: Table 14.1.2 and Table 14.1.4

A higher proportion and absolute number of treatment-naïve patients with cirrhosis were treated with telaprevir in this study compared to the -108. Subtype 1a is more dominant than in the -108, reflecting the mainly US population. Baseline viral load is roughly similar to the -108.

Primary outcomes (SVR)

Table 29. $SVR24_{planned}$ Rates, Full Analysis Set

Variable	Randomized (eRVR+) T12/PR24 N = 162 n (%)	Randomized (eRVR+) T12/PR48 N = 160 n (%)	Assigned (eRVR-) T12/PR48 N = 118 n (%)	Other N = 100 n (%)
$SVR24_{planned}$: n (%)	149 (92.0)	140 (87.5)	76 (64.4)	23 (23.0)
Difference between T12/PR24/eRVR+ and T12/PR48/eRVR+ groups and 95% CI for the difference	4.5% (-2.1%, 11.1%)		N/A	N/A
Odds ratio between T12/PR24/eRVR+ and T12/PR48/eRVR+ groups and 95% CI intervals for the odds ratio	1.62 (0.77, 3.38)		N/A	N/A

Abbreviations: CI: confidence interval; eRVR: extended rapid viral response; N/A: not applicable; SVR: sustained viral response

Note: Subjects who received at least 1 dose of study drug, but prematurely discontinued treatment before Week 20 were not randomized or assigned to a treatment regimen.

Source: Table 14.2.1a

SVR(planned) and SVR at week 72 was defined as in the -108 study (see above). The non-inferiority of 24 weeks duration for treatment naïve patients with eRVR was demonstrated (preset NI margin -10.5%), with a higher point estimate for response in the shorter duration arm. The absolute response

rates in eRVR positive patients are similar to study 108. The non-inferiority conclusion was supported by the SVR72 weeks dataset, as well as by the per protocol dataset.

Relapse rates

Table 30. $Relapse_{planned}$ Rates by Treatment Group

	Randomized (eRVR+)				Assigned (eRVR-)					
	T12/PR24 N = 159		T12/PR48 N = 154		T12/PR48 N = 97		Other N=59		Total N=469	
Relapse Rates	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
$Relapse_{planned}$	159	9 (5.7)	154	4 (2.6)	97	11 (11.3)	59	13 (22.0)	469	37 (7.9)
$Relapse_{actual}$	159	9 (5.7)	154	3 (1.9)	97	10 (10.3)	59	14 (23.7)	469	36 (7.7)

Abbreviations: eRVR: extended rapid viral response
Note: Denominator is number of subjects with undetectable HCV RNA at end of treatment visit. Note: Subjects in the Other group who received at least 1 dose of study drug, but prematurely discontinued treatment before Week 20 were not randomized or assigned to a treatment regimen.
Source: Table 14.2.15c and Table 14.2.16c

Relapse rates in patients with eRVR were very low in both arms (5.7% and 2.6% representing 9 and 4 subjects respectively).

SVR rates in subgroups

Table 31. $SVR24_{planned}$ Rates by Demographics, Full Analysis Set

	Randomized (eRVR+)				Assigned (eRVR-)					
	T12/PR24 N = 162		T12/PR48 N = 160		T12/PR48 N = 118		Other N = 10		Total N = 540	
Variable	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Sex										
Male	104	94 (90.4)	97	86 (88.7)	70	45 (64.3)	54	11 (20.4)	325	236 (72.6)
Female	58	55 (94.8)	63	54 (85.7)	48	31 (64.6)	46	12 (26.1)	215	152 (70.7)
Age Category										
≤ 45	45	44 (97.8)	46	42 (91.3)	26	18 (69.2)	18	4 (22.2)	135	108 (80.0)
> 45 and ≤ 65	113	102 (90.3)	111	95 (85.6)	92	58 (63.0)	81	19 (23.5)	397	274 (69.0)
> 65	4	3 (75.0)	3	3 (100)	0	0	1	0	8	6 (75.0)
BMI, kg/m²										
< 25	44	42 (95.5)	60	51 (85.0)	35	22 (62.9)	38	10 (26.3)	177	125 (70.6)
≥ 25 and < 30	56	51 (91.1)	51	47 (92.2)	49	32 (65.3)	32	6 (18.8)	188	135 (71.8)
≥ 30	61	55 (90.2)	49	43 (87.8)	34	22 (64.7)	30	7 (23.3)	174	127 (73.0)
Race										
Caucasian	135	126 (93.3)	131	114 (87.0)	86	56 (65.1)	75	19 (25.3)	427	315 (73.8)
Black	17	15 (88.2)	17	15 (88.2)	20	13 (65.0)	19	1 (5.3)	73	44 (60.3)
Asian	3	3 (100)	3	3 (100)	2	1 (50.0)	1	1 (100)	9	8 (88.9)
Other	7	5 (71.4)	9	8 (88.09)	10	6 (60.0)	5	2 (40.0)	31	21 (67.7)
Ethnicity										
Hispanic or Latino	18	17 (94.4)	11	9 (81.8)	8	6 (75.0)	17	4 (23.5)	54	36 (66.7)
Not Hispanic or Latino	140	129 (92.1)	146	128 (87.7)	105	67 (63.8)	82	19 (23.2)	473	343 (72.5)
Not allowed to ask per local regulations	4	3 (75.0)	3	3 (100)	5	3 (60.0)	1	0	13	9 (69.2)
Medical History										
Diabetes	8	6 (75.0)	5	4 (80.0)	8	4 (50.0)	14	2 (14.3)	35	16 (45.7)
No diabetes	154	143 (92.9)	155	136 (87.7)	110	72 (65.5)	86	21 (24.4)	505	372 (73.7)
Region										
North America	154	142 (92.2)	151	133 (88.1)	106	67 (63.2)	98	23 (23.5)	509	365 (71.7)
Europe	8	7 (87.5)	9	7 (77.8)	12	9 (75.0)	2	0	31	23 (74.2)

Abbreviation: eRVR: extended rapid viral response
Note: Subjects in the Other group who received at least 1 dose of study drug, but prematurely discontinued treatment before Week 20 were not randomized or assigned to a treatment regimen.
Source: Table 14.2.3b

Across demographic categories, results were consistent. This includes the small black group were patients with eRVR had similar SVR rates regardless of 24 or 48 weeks of treatment duration. Of note, however, the total sample size with black race and eRVR was a mere 17+17 patients.

Table 32. Study 111: $SVR24_{planned}$ Rates by Baseline Disease Characteristics, Full Analysis Set

	Randomized (eRVR+)				Assigned (eRVR-)					
	T12/PR24 N = 162		T12/PR48 N = 160		T12/PR48 N = 118		Other N = 100		Total N = 540	
Variable	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Baseline HCV RNA (IU/mL)										
<800000	38	38 (100)	34	27 (79.4)	10	8 (80.0)	13	8 (61.5)	95	81 (85.3)
≥800000	124	111 (89.5)	126	113 (89.7)	108	68 (63.0)	87	15 (17.2)	445	307 (69.0)
Baseline HCV RNA (IU/mL)										
<1236647.25	48	47 (97.9)	48	40 (83.3)	15	8 (53.3)	24	11 (45.8)	135	106 (78.5)
≥1236647.25 to 3499753.5	41	38 (92.7)	38	35 (92.1)	24	13 (54.2)	32	5 (15.6)	135	91 (67.4)
≥3499753.5 to 9035496.75	39	33 (84.6)	34	30 (88.2)	43	29 (67.4)	19	3 (15.8)	135	95 (70.4)
≥9035496.75	34	31 (91.2)	40	35 (87.5)	36	26 (72.2)	25	4 (16.0)	135	96 (71.1)
Liver Disease Status										
Cirrhosis	18	12 (66.7)	12	11(91.7)	12	4 (33.3)	19	3 (15.8)	61	30 (49.2)
No Cirrhosis	144	137 (95.1)	148	129 (87.2)	106	72 (67.9)	81	20 (24.7)	479	358 (74.7)
No or minimal fibrosis	46	44 (95.7)	48	40 (83.3)	27	18 (66.7)	26	7 (26.9)	147	109 (74.1)
Portal fibrosis	78	74 (94.9)	79	71 (89.9)	49	35 (71.4)	38	5 (13.2)	244	185 (75.8)
Bridging fibrosis	20	19 (95.0)	21	18 (85.7)	30	19 (63.3)	17	8 (47.1)	88	64 (72.7)

Abbreviation: eRVR: extended rapid viral response
Note: Subjects in the Other group who received at least 1 dose of study drug, but prematurely discontinued treatment before Week 20 were not randomized or assigned to a treatment regimen.
Source: Table 14.2.3b

While results were consistent regardless of baseline HCV-RNA, patients with cirrhosis and eRVR that were randomised to 48 rather than 24 weeks of total therapy had a 91.7% versus a 66.7% SVR rate. On this basis, the applicant suggested that labelling for treatment naïve patients with cirrhotics should be 48 weeks regardless of eRVR status. While the basis for this conservative approach is recognised, it is noted that it is based on subgroup analysis of a sample of 18+12 individuals, which really precludes any certain inference. The CHMP also notes that no similar trend is seen in patients categorised as bridging fibrosis, which would have supported the differential effect in cirrhotics being a real finding. All in all, it remains unknown whether 24 weeks of therapy is sufficient in treatment-naïve patients with cirrhosis and eRVR. Thus, the recommendation of 48 weeks of therapy represents a conservative interpretation of study outcome in this subgroup with the most urgent need for successful therapy.

In summary the main findings of this study were:

- Among treatment-naïve patients that reached eRVR, SVR rates were 92% in patients randomised to a total of 24 weeks of therapy, following 12 weeks of telaprevir, compared to 87.5% in patients randomised to 48 weeks of therapy (difference 4.5%, 95% CI -2. – 11%). Non-inferiority was set at -10.5%. Therefore the non-inferiority of the response guided algorithm (24 or 48 weeks depending on whether eRVR is reached) was demonstrated in this population.
- The primary outcome was consistent through the subgroups of age, gender, race, viral subtype and baseline viral load.
- Among patients with cirrhosis who achieved an eRVR, however, SVR rates were 12/18 (66.7%) with 24 weeks and 11/12 (91.7%) with 48 weeks of therapy. The difference is -25% and the 95% confidence interval, according to the CHMP's statistics, i -52% - +2%. There was no similar trend among patients with bridging fibrosis.
- As expected, there was a higher burden of AEs, SAEs, and related treatment discontinuations in the longer duration treatment group (T12/PR48/eRVR+) compared to the shorter duration treatment group (T12/PR24/eRVR+).

- This study supports the use of response guided therapy in treatment naive patients. The study is inconclusive as to whether this also applies in the case that there is cirrhosis.

C216 A randomized, double-blind, placebo-controlled, Phase III trial of 2 regimens of telaprevir (with and without delayed start) combined with pegylated interferon alfa-2a (Pegasys) and ribavirin (Copegus) in subjects with chronic genotype 1 hepatitis C infection who failed prior pegylated interferon plus ribavirin treatment.

The study was designed to compare the efficacy, safety, and tolerability of 2 regimens of telaprevir (with and without delayed start (DS) of telaprevir) combined with Peg-IFN-alfa-2a and RBV versus standard treatment (Peg-IFN-alfa-2a and RBV).

Methods

Participants

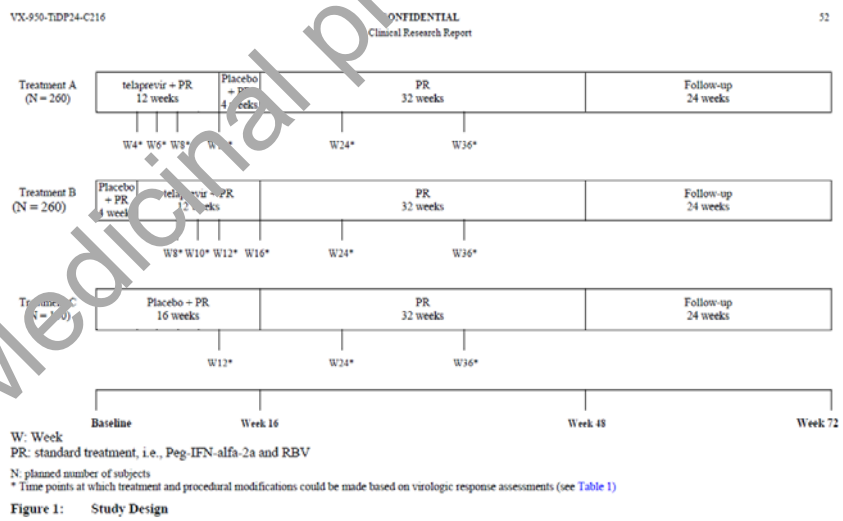
Main Inclusion criteria: Male and female subjects between 18 to 70 years of age (inclusive) who had (1) an undetectable hepatitis C virus (HCV) ribonucleic acid (RNA) level at the end of a prior course of Peg-IFN/RBV therapy but did not achieve sustained virologic response (SVR) (prior relapsers), or (2) never had an undetectable HCV RNA level during or at the end of a prior course of Peg-IFN/RBV therapy (prior non-responders) were eligible for the study.

Main Exclusion criteria: Subjects with prior viral breakthrough, evidence of decompensated liver disease, a history of organ transplant, or with HBV or HIV co-infection were excluded from the study

Treatment

Telaprevir was administered orally in the fed state at a dose of 750 mg every 8 hours (q8h). Peg-IFN-alfa-2a was administered by subcutaneous injection once per week at a dose of 180 µg. RBV was administered orally twice daily at a dose of 1000 mg/day for subjects weighing <75 kg and 1200 mg/day for subjects weighing ≥75 kg.

Figure 2. Study Design



W: Week
PR: standard treatment, i.e., Peg-IFN-alfa-2a and RBV
N: planned number of subjects
* Time points at which treatment and procedural modifications could be made based on virologic response assessments (see Table 1)

Figure 1: Study Design

Objectives and endpoints

The primary objective was to demonstrate the superior efficacy of telaprevir in combination with Peg-IFN alfa-2a and RBV compared to standard treatment in subjects with chronic HCV genotype 1 infection who failed prior treatment with Peg-IFN plus RBV.

The main efficacy variable was SVR, defined as having undetectable HCV RNA 24 weeks after the last planned dose of study drug SVR24planned.

The main Secondary objectives were to evaluate the effect of delayed start of telaprevir on the efficacy and to evaluate the safety and tolerability of telaprevir in combination with Peg-IFN alfa-2a and RBV

All plasma HCV RNA levels were assessed using the Roche TaqMan HCV RNA assay (Version 2.0, lower limit of quantification [LLOQ] of 25 IU/mL).

Sample size

Relapsers

Assuming a 55% response rate in the groups receiving Treatment A or B, a 29% response rate in the group receiving Treatment C, a 2-sided continuity corrected Chi-squared test, with an overall significance level of 5% (adjusted for multiple comparisons of A and B versus C), and a 2:2:1 randomization, a sample size of 140 subjects each in the groups receiving Treatment A or Treatment B and 70 subjects in the group receiving Treatment C provided a power of approximately 90% to demonstrate a statistically significant difference.

Non-responders

Assuming a 30% response rate in the groups receiving Treatment A or B, a 8% response rate in the group receiving Treatment C, a 2-sided continuity corrected Chi-squared test, with an overall significance level of 5% (adjusted for multiple comparisons of A and B versus C), and a 2:2:1 randomization, a sample size of 120 subjects each in the groups receiving Treatment A or Treatment B and 60 subjects in the group receiving Treatment C provided a power of approximately 90% to demonstrate a statistically significant difference. If deemed appropriate in pooling of the two telaprevir arms in the population of null responders, a total of 120 telaprevir-treated subjects would be compared with 30 control subjects which resulted in at least 80% power to demonstrate a statistically significant difference by assuming an SVR rate of 4% and 29% (25% difference) in control and combined telaprevir arms, respectively.

Overall, 350 subjects who relapsed during prior treatment with Peg-IFN plus RBV and 300 subjects who were non-responding to prior treatment with Peg-IFN plus RBV needed to be recruited, leading to a total of 650 subjects.

Randomisation

The study was randomised. Subject were stratified based on screening HCV RNA value (<800000 IU/mL or ≥800000 IU/mL) and on type of prior response (prior relapser or prior non-responder). Furthermore, for the stratum of prior non-responders, an additional stratification was for prior null-responders or prior partial responders, defined as follows: (1) subjects with <2-log drop in HCV RNA at Week 12 of prior therapy (null-responders) or (2) subjects with ≥2-log drop in HCV RNA at Week 12 of prior therapy but who never achieved undetectable HCV RNA levels while on treatment (partial responders). Enrolment was limited such that neither of these strata would represent more than 55% of the non-responder subpopulation.

Blinding (masking)

The study was partially double blinded.

Results

Study Subject disposition

Table 33. Study Termination – Overall Population, FA Set

	Overall population			
Study Termination type, n (%)	T12/PR48 N = 266	T12(DS)/PR48 N = 264	Pbo/PR48 N = 132	All subjects N = 662
Completed	245 (92.1)	248 (93.9)	110 (83.3)	603 (91.1)
Discontinued	21 (7.9)	16 (6.1)	22 (16.7)	59 (8.9)
Reason:				
Adverse event	1 (0.4)	2 (0.8)	2 (1.5)	5 (0.8)
Subject ineligible to continue the study	6 (2.3)	3 (1.1)	2 (1.5)	11 (1.7)
Subject lost to follow-up	6 (2.3)	4 (1.5)	4 (3.0)	14 (2.1)
Subject withdrew consent	8 (3.0)	7 (2.7)	13 (9.8)[a]	28 (4.2)
Other[b]	0	0	1 (0.8)	1 (0.2)

N: number of subjects with data; n: number of subjects with that observation

[a] Including subjects in the placebo group who rolled over to the VX-950-TIDP24-C219 study. In order to maintain sponsor blinding, subjects meeting criteria for roll-over were unblinded by the independent HCV RNA monitor and discontinuation reason in the C216 study was noted as consent withdrawn.

[b] No further information available in the clinical database

Source: Display GEN.2, Display GEN.7

"Discontinuation" in the table 33 above refers to study discontinuation, not treatment discontinuation. Loss to follow up and withdrawal of consent is relatively low in the telaprevir groups (approx 5%), but notably higher in the placebo group (over 12%). Many patients in the placebo arm had little chance of cure, being prior non-responders.

Table 34. Discontinuation of all Study Drug – Overall Population, FA Set

	Overall population			
Treatment termination type, n (%)	T12/PR48 N = 266	T12(DS)/PR48 N = 264	Pbo/PR48 N = 132	All subjects N = 662
Completed all 3 study drugs	166 (62.4)	185 (70.1)	50 (37.9)	401 (60.6)
Discontinued 1 or 2 study drugs	49 (18.4)	41 (15.5)	38 (28.8)	128 (19.3)
Discontinued all 3 study drugs	51 (19.2)	38 (14.4)	44 (33.3)	133 (20.1)

N: number of subjects with data; n: number of subjects with that observation

Source: Display GEN.2, Display GEN.6

Table 35. Discontinuation of Telaprevir/Placebo - Overall Population, FA Set

	Overall population			
Treatment termination type, n (%)	T12/PR48 N = 266	T12(DS)/PR48 N = 264	Pbo/PR48 N = 132	All subjects N = 662
Completed	191 (71.8)	212 (80.3)	88 (66.7)	491 (74.2)
Discontinued	75 (28.2)	52 (19.7)	44 (33.3)	171 (25.8)
Reason:				
Adverse event related	39 (14.7)	29 (11.0)	4 (3.0)	72 (10.9)
Subject met a virologic stopping rule	26 (9.8)	16 (6.1)	35 (26.5)	77 (11.6)
Subject non-compliant	1 (0.4)	2 (0.8)	2 (1.5)	5 (0.8)
Other	9 (3.4)	5 (1.9)	3 (2.3)	17 (2.6)

N: number of subjects with data; n: number of subjects with that observation

11-15% of patients in the telaprevir groups discontinued telaprevir due to adverse effects

Demographics and baseline characteristics

The study was conducted at 105 sites in 17 countries: Argentina, Australia, Austria, Belgium, Brazil, Canada, Switzerland, Germany, Spain, France, United Kingdom, Israel, Italy, The Netherlands, Poland, Sweden, and the United States.

Table 36. Demographic Data – Overall Population, FA Set

	Overall population			
Parameter	T12/PR48 N = 266	T12(DS)/PR48 N = 264	Pbo/PR48 N = 132	All subjects N = 662
Sex, n (%)				
Female	83 (31.2)	75 (28.4)	44 (33.3)	202 (30.5)
Male	183 (68.8)	189 (71.6)	88 (66.7)	460 (69.5)
Race, n (%)				
Black	11 (4.1)	8 (3.0)	11 (8.3)	30 (4.5)
Caucasian/White	246 (92.5)	252 (95.5)	117 (88.6)	615 (92.9)
Oriental/Asian	6 (2.3)	2 (0.8)	3 (2.3)	11 (1.7)
Other	3 (1.1)	2 (0.8)	1 (0.8)	6 (0.9)
Ethnicity				
Hispanic or Latino	25 (9.4)	27 (10.2)	20 (15.2)	72 (10.9)
Not hispanic or Latino	241 (90.6)	237 (89.8)	112 (84.8)	590 (89.1)
Age (years)				
age ≤45	64 (24.1)	55 (20.8)	40 (30.3)	159 (24.0)
45<age ≤65	197 (74.1)	201 (76.1)	85 (64.4)	483 (73.0)
age >65	5 (1.9)	8 (3.0)	7 (5.3)	20 (3.0)
Weight (kg)				
Mean (SD)	82.0 (16.81)	81.5 (15.84)	82.0 (16.66)	81.8 (16.38)
BMI (kg/m²)				
<25	85 (32.0)	89 (33.8)	42 (31.8)	216 (32.7)
25≤BMI <30	108 (40.6)	112 (42.6)	53 (40.2)	273 (41.[illegible])
≥30	73 (27.4)	62 (23.6)	37 (28.0)	172 (26.0)

N: number of subjects with data; n: number of subjects with that observation; SD: standard deviation
Source: Display GEN.24

Table 37. Baseline Disease Characteristics and Liver Disease History – Overall Population, FA Set

	Overall population			
Parameter	T12/PR48 N = 266	T12(DS)/PR48 N = 264	[illegible]/PR48 N = 132	All subjects N = 662
Log_{10} HCV RNA (log_{10} IU/mL)				
Mean (SD)	6.6 (0.548)	6.6 (0.5[illegible])	6.6 (0.574)	6.6 (0.559)
Baseline HCV RNA (IU/mL), n (%)				
<800000	28 (10.5)	3[illegible] (11.4)	18 (13.6)	76 (11.5)
≥800000	238 (89.5)	234 ([illegible]6)	114 (86.4)	586 (88.5)
Assessment of liver fibrosis (biopsy), n (%)				
No cirrhosis	194 (72.9)	197 (74.6)	102 (77.3)	493 (74.5)
Cirrhosis	72 (27.1)	67 (25.4)	30 (22.7)	169 (25.5)
Assessment of liver fibrosis (biopsy), n (%)				
No or minimal fibrosis	[illegible]1 (19.[illegible])	68 (25.8)	35 (26.5)	154 (23.3)
Portal fibrosis	8[illegible] (31.2)	71 (26.9)	38 (28.8)	192 (29.0)
Bridging fibrosis	60 (22.6)	58 (22.0)	29 (22.0)	147 (22.2)
Cirrhosis	[illegible]2 (27.1)	67 (25.4)	30 (22.7)	169 (25.5)
AFP at baseline, n (%)				
<50 ng/mL	259 (98.1)	256 (97.0)	129 (97.7)	644 (97.6)
≥50 ng/mL	5 (1.9)	8 (3.0)	3 (2.3)	16 (2.4)
Homa-IR, n (%)				
<2	93 (36.6)	89 (35.2)	35 (28.2)	217 (34.4)
≥2	161 (63.4)	164 (64.8)	89 (71.8)	414 (65.6)
HCV genotype ([illegible]NCT), n ([illegible])				
1	27 (10.2)	28 (10.6)	13 (9.8)	68 (10.3)
1a	118 (44.4)	120 (45.6)	59 (44.7)	297 (44.9)
1b	121 (45.5)	115 (43.7)	59 (44.7)	295 (44.6)
1c	0	0	1 (0.8)	1 (0.2)
HCV [illegible]enotype (NS3), n (%)				
N	262	262	128	652
[illegible]	136 (51.9)	149 (56.9)	67 (52.3)	352 (54.0)
[illegible]b	126 (48.1)	113 (43.1)	61 (47.7)	300 (46.0)
[illegible] since HCV diagnosis (years)				
N	264	263	129	656
Mean (SD)	10.1 (7.26)	9.2 (5.89)	9.3 (6.81)	9.6 (6.65)
Prior Peg-IFN type, n (%)				
N	265	264	131	660
Pegasys®	165 (62.3)	177 (67.0)	72 (55.0)	414 (62.7)
PegIntron®	100 (37.7)	87 (33.0)	59 (45.0)	246 (37.3)
Prior response, n (%)				
Null responder	72 (27.1)	75 (28.4)	37 (28.0)	184 (27.8)
Partial responder	49 (18.4)	48 (18.2)	27 (20.5)	124 (18.7)
Relapser	145 (54.5)	141 (53.4)	68 (51.5)	354 (53.5)

N: number of subjects with data; n: number of subjects with that observation
Source: Display GEN.25

Gender distribution shows about 70% males. About 90% of patients were Caucasian with low representation of blacks. Mean viral load was somewhat higher than in the naïve studies. Notably, almost a quarter of the patients had cirrhosis and another quarter bridging fibrosis. Viral subtypes were relatively evenly divided. Approximately half the patients were prior relapsers and half non-responders, with a balanced distribution between treatment arms.

89% of patients had baseline HCV RNA levels > 800,000 IU/ml; 22% had bridging fibrosis; 26% had cirrhosis; 54% had HCV genotype 1a; and 46% had HCV genotype 1b.

Numbers analysed

The efficacy analysis was carried out on the FA set which consisted of 662 subjects.

Primary endpoint (SVR)

Table 38. $SVR24_{planned}$ Rates and Statistical Comparison (Logistic Regression) for $SVR24_{planned}$ – Overall Population, FA Set

	Overall population		
Variable	T12/PR48 N = 266	T12(DS)/PR48 N = 264	Pbo/PR48 N = 132
$SVR24_{planned}$, n (%)	171 (64.3)	175 (66.3)	22 (16.7)
P value (in comparison to Pbo/PR48)[a]	<0.001	<0.001	N/A
Difference between each of T/PR and Pbo/PR48 groups[a]	46.8%	49.8%	
95% CI[a] for the difference	(36.8%, 56.7%)	(39.9%, 59.7%)	N/A
Difference between T12/PR48 and T12(DS)/PR48 and 95% CI[a] for the difference	-3.0% (-13.0%,7.0%)		N/A

N/A: not applicable
[a] as estimated in a logistic regression model including the following factors: treatment, type of prior response and their interaction, and baseline viral RNA as a covariate
N: number of subjects with data; n: number of subjects with SVR
Source: Display EFF.13, Display EFF.18

As the treatment duration was similar in all treatment groups, the planned assessment was at study week 72 (24 weeks after the end of therapy) for all patients. For the overall population, with subgroups that had very heterogeneous response rates (see below), superiority was demonstrated over placebo for each of the telaprevir arms. The point estimate for the difference between arms favoured the delayed start arm by 3% with confidence limits -13 – +7% in the logistic regression model.

SVR rates by prior response category

Table 39. $SVR24_{planned}$ Rates and Statistical Comparison (Logistic Regression) for $SVR24_{planned}$ –Prior Relapser Population, FA Set

	Relapser population		
Variable	T12/PR48 N = 145	T12(DS)/PR48 N = 141	Pbo/PR48 N = 68
$SVR24_{planned}$ (%)	121 (83.4)	124 (87.9)	16 (23.5)
P value (in comparison to Pbo/PR48)[a]	<0.001	<0.001	N/A
Difference between each of T/PR and Pbo/PR48 groups[a]	60.5%	64.9%	
95% CI[a] for the difference	(48.8%, 72.2%)	(53.5%, 76.2%)	N/A
Difference between T12/PR48 and T12(DS)/PR48 and 95% CI[a] for the difference	-4.3% (-12.6%, 3.9%)		N/A

N/A: not applicable
[a] as estimated in a logistic regression model including the following factors: treatment, type of prior response and their interaction, and baseline viral RNA as a covariate
N: number of subjects with data; n: number of subjects with SVR
Source: Display EFF.13, Display EFF.18

The superiority of both telaprevir treatment arms over placebo among relapsers was overwhelming. The point estimate favoured the delayed start arm over the immediate start, with a confidence interval of -12.6 – 3.9%.

Table 40. $SVR24_{planned}$ Rates and Statistical Comparison (Logistic Regression) for $SVR24_{planned}$ –Prior Partial Responder Population, FA Set

	Partial responder population		
Variable	**T12/PR48 N = 49**	**T12(DS)/PR48 N = 48**	**Pbo/PR48 N = 27**
$SVR24_{planned}$, n (%)	29 (59.2)	26 (54.2)	4 (14.8)
P value (in comparison to Pbo/PR48)[a]	<0.001	<0.001	N/A
Difference between each of T/PR and Pbo/PR48 groups[a] 95% CI[a] for the difference	44.1% (24.7%, 63.6%)	40.0% (20.3%, 59.7%)	N/A
Difference between T12/PR48 and T12(DS)/PR48 and 95% CI[a] for the difference	4.1% (-15.6%, 23.9%)		N/A

N/A: not applicable
[a] as estimated in a logistic regression model including the following factors: treatment, type of prior response and their interaction, and baseline viral RNA as a covariate
N: number of subjects with data; n: number of subjects with SVR
Source: Display EFF.13, Display EFF.18

Table 41. $SVR24_{planned}$ Rates and Statistical Comparison (Logistic Regression) for $SVR24_{planned}$ –Prior Null-Responder Population, FA Set

	Null-responder population		
Variable	**T12/PR48 N = 72**	**T12(DS)/PR48 N = 75**	**Pbo/PR48 N = 37**
$SVR24_{planned}$, n (%)	21 (29.2)	25 (33.3)	2 (5.4%)
P value (in comparison to Pbo/PR48)[a]	<0.001	<0.001	N/A
Difference between each of T/PR and Pbo/PR48 groups[a] 95% CI[a] for the difference	24.7% (11.6%, 37.7%)	29.0% (15.8%, 42.2%)	N/A
Difference between T12/PR48 and T12(DS)/PR48 and 95% CI[a] for the difference	-4.3% (-19.6%, 11.0%)		N/A

N/A: not applicable
[a] as estimated in a logistic regression model including the following factors: treatment, type of prior response and their interaction, and baseline viral RNA as a covariate
N: number of subjects with data; n: number of subjects with SVR
Source: Display EFF.13, Display EFF.18

Also among prior non-responders (in the tables above divided into prior null- and partial responders), was the superiority of adding telaprevir to standard of care fully evident, though actual response rates were lower (around 30% for null responders and nearly 60% for partial responders). The control arm performed more or less as expected. As for the relation between the two telaprevir arms, point estimates among null- and –partial responders favoured the one and the other arm by a difference of about 4%, with wide confidence limits.

SVR rates in subgroups

Table 42. SVR24$_{planned}$ Rates by Baseline Disease Characteristics –Prior Relapser Population, FA Set

Subgroup	Relapser population							
	T12/PR48		T12(DS)/PR48		Pooled T/PR48		Pbo/PR48	
Status	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Total	145	121 (83.4)	141	124 (87.9)	286	245 (85.7)	68	16 (23.5)
Genotype (NS3 method)								
1a	65	52 (80.0)	77	67 (87.0)	142	119 (83.8)	34	10 (29.4)
1b	77	67 (87.0)	63	56 (88.9)	140	123 (87.9)	31	6 (19.4)
Baseline HCV RNA								
<800000 IU/mL	21	20 (95.2)	26	23 (88.5)	47	43 (91.5)	12	3 (25.0)
≥800000 IU/mL	124	101 (81.5)	115	101 (87.8)	239	202 (84.5)	56	13 (23.2)
Baseline liver disease status								
No or minimal fibrosis	34	29 (85.3)	48	42 (87.5)	82	71 (86.6)	20	7 (35.0)
Portal fibrosis	47	38 (80.9)	38	35 (92.1)	85	73 (85.9)	18	5 (27.8)
Bridging fibrosis	36	31 (86.1)	26	22 (84.6)	62	53 (85.5)	15	2 (13.3)
Cirrhosis	28	23 (82.1)	29	25 (86.2)	57	48 (84.2)	15	2 (13.3)
Prior Peg-IFN type								
Pegasys®	93	79 (84.9)	94	80 (85.1)	187	159 (85.0)	42	8 (19.0)
PegIntron®	51	41 (80.4)	47	44 (93.6)	98	85 (86.7)	26	8 (30.8)
Baseline HOMA-IR								
<2	56	48 (85.7)	53	48 (90.6)	109	96 (88.1)	20	8 (40.0)
≥2	83	67 (80.7)	80	69 (86.3)	163	136 (83.4)	42	7 (16.7)

N: number of subjects with data; n: number of subjects with SVR
Source: Display EFF.13, Display EFF.38

Telaprevir was clearly superior to placebo in all categories above. Prior relapsers had very high SVR rates regardless of viral subtype. Also, 84% of prior relapsers with cirrhosis reached SVR.

Table 43. SVR24$_{planned}$ Rates by Baseline Disease Characteristics –Prior Partial Responder Population, FA Set

Subgroup	Partial responder population							
	T12/PR48		T12(DS)/PR48		Pooled T/PR48		Pbo/PR48	
Status	N	n (%)	N	n (%)	N	n (%)	N	n (%)
	49	29 (59.2)	48	26 (54.2)	97	55 (56.7)	27	4 (14.8)
Genotype (NS3 method)								
1a	26	13 (50.0)	29	13 (44.8)	55	26 (47.3)	16	3 (18.8)
1b	22	16 (72.7)	18	12 (66.7)	40	27 (67.5)	10	1 (10.0)
Baseline HCV RNA								
<800000 IU/mL	4	2 (50.0)	1	0	5	2 (40.0)	2	0
≥800000 IU/mL	45	27 (60.0)	47	26 (55.3)	92	53 (57.6)	25	4 (16.0)
Baseline liver disease status								
No or minimal fibrosis	7	5 (71.4)	11	6 (54.5)	18	11 (61.1)	10	0
Portal fibrosis	17	13 (76.5)	12	10 (83.3)	29	23 (79.3)	7	3 (42.9)
Bridging fibrosis	7	5 (71.4)	11	5 (45.5)	18	10 (55.6)	5	0
Cirrhosis	18	6 (33.3)	14	5 (35.7)	32	11 (34.4)	5	1 (20.0)
Prior Peg-IFN type								
Pegasys®	24	14 (58.3)	28	17 (60.7)	52	31 (59.6)	15	1 (6.7)
PegIntron®	25	15 (60.0)	20	9 (45.0)	45	24 (53.3)	11	3 (27.3)
Baseline HOMA-IR								
<2	18	10 (55.6)	13	7 (53.8)	31	17 (54.8)	7	1 (14.3)
≥2	28	18 (64.3)	33	18 (54.5)	61	36 (59.0)	19	2 (10.5)

N: number of subjects with data; n: number of subjects with SVR
Source: Display EFF.13, Display EFF.38

The superiority of telaprevir over placebo was apparent in all categories. The likelihood of SVR was 20% higher in partial responders with subtype 1b compared to 1a. In prior partial responders with cirrhosis, the SVR rates are considerably lower than in patients with less advanced liver injury.

Table 44. SVR24$_{planned}$ Rates by Baseline Disease Characteristics –Prior Null-Responder Population, FA Set

Subgroup	Null-responder population							
	T12/PR48		T12(DS)/PR48		Pooled T/PR48		Pbo/PR48	
Status	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Total	72	21 (29.2)	75	25 (33.3)	147	46 (31.3)	37	2 (5.4)
Genotype (NS3 method)								
1a	45	11 (24.4)	43	13 (30.2)	88	24 (27.3)	17	1 (5.9)
1b	27	10 (37.0)	32	12 (37.5)	59	22 (37.3)	20	1 (5.0)
Baseline HCV RNA								
<800000 IU/mL	3	2 (66.7)	3	2 (66.7)	6	4 (66.7)	4	2 (50.0)
≥800000 IU/mL	69	19 (27.5)	72	23 (31.9)	141	42 (29.8)	33	0
Baseline liver disease status								
No or minimal fibrosis	10	1 (10.0)	9	6 (66.7)	19	7 (36.8)	5	0
Portal fibrosis	19	8 (42.1)	21	9 (42.9)	40	17 (42.5)	13	1 (7.7)
Bridging fibrosis	17	7 (41.2)	21	8 (38.1)	38	15 (39.5)	9	0
Cirrhosis	26	5 (19.2)	24	2 (8.3)	50	7 (14.0)	10	1 (10.0)
Prior Peg-IFN type								
Pegasys®	48	14 (29.2)	55	15 (27.3)	103	29 (28.2)	15	2 (13.3)
PegIntron®	24	7 (29.2)	20	10 (50.0)	44	17 (38.6)	22	0
Baseline HOMA-IR								
<2	19	7 (36.8)	23	10 (43.5)	42	17 (40.5)	8	1 (12.5)
≥2	50	13 (26.0)	51	15 (29.4)	101	28 (27.7)	28	1 (3.6)

N: number of subjects with data; n: number of subjects with SVR
Source: Display EFF.13, Display EFF.38

Again superiority over placebo was apparent in all categories. In null responders, the difference in response depending on subtype is more pronounced than among relapsers, as would be expected. The number of patients with low baseline HCV-RNA is too small to make any inferences. The SVR point estimate for null responders with cirrhosis is 14% in the pooled telaprevir arms.

Table 45. SVR24$_{planned}$ Rates by Baseline Disease Characteristics –Prior Relapser Population, FA Set

Subgroup	Relapser population							
	T12/PR48		T12(DS)/PR48		Pooled T/PR48		Pbo/PR48	
Status	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Total	145	121 (83.4)	141	124 (87.9)	286	245 (85.7)	68	16 (23.5)
Sex								
Female	47	40 (85.1)	42	36 (85.7)	89	76 (85.4)	22	7 (31.8)
Male	98	81 (82.7)	99	88 (88.9)	197	169 (85.8)	46	9 (19.6)
Ethnicity								
Hispanic or Latino	17	17 (100)	16	15 (93.8)	33	32 (97.0)	12	2 (16.7)
Not Hispanic or Latino	128	104 (81.3)	125	109 (87.2)	253	213 (84.2)	56	14 (25.0)
Race								
Black	7	6 (85.7)	4	4 (100)	11	10 (90.9)	3	2 (66.7)
Caucasian/White	132	109 (82.6)	136	119 (87.5)	268	228 (85.1)	61	14 (23.0)
Oriental/Asian	3	3 (100)	1	1 (100)	4	4 (100)	3	0
Other	3	3 (100)	0	-	3	3 (100)	1	0
Age (years)								
≤45	32	27 (84.4)	31	27 (87.1)	63	54 (85.7)	18	4 (22.2)
45 <age ≤65	111	92 (82.9)	107	96 (89.7)	218	188 (86.2)	44	12 (27.3)
>65	2	2 (100)	3	1 (33.3)	5	3 (60.0)	6	0
Baseline BMI (kg/m^2)								
<25	45	37 (82.2)	50	43 (86.0)	95	80 (84.2)	19	4 (21.1)
25 ≤BMI <30	62	52 (83.9)	59	53 (89.8)	121	105 (86.8)	29	7 (24.1)
≥30	38	32 (84.2)	32	28 (87.5)	70	60 (85.7)	20	5 (25.0)
Body Weight Quartiles (kg)								
≤71	42	36 (85.7)	36	29 (80.6)	78	65 (83.3)	15	4 (26.7)
71 <body weight ≤81	38	32 (84.2)	34	30 (88.2)	72	62 (86.1)	20	4 (20.0)
81 <body weight ≤92	30	26 (86.7)	37	34 (91.9)	67	60 (89.6)	17	5 (29.4)
>92	35	27 (77.1)	34	31 (91.2)	69	58 (84.1)	16	3 (18.8)

N: number of subjects with data; n: number of subjects with SVR
Source: Display EFF.13, Display EFF.38, Display ADD.7

The advantage of telaprevir over placebo was consistent over subgroups (some of which are very small).

Table 46. $SVR24_{planned}$ Rates by Demographic Characteristics –Prior Partial Responder Population, FA Set

Subgroup	Partial responder population							
	T12/PR48		T12(DS)/PR48		Pooled T/PR48		Pbo/PR48	
Status	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Total	49	29 (59.2)	48	26 (54.2)	97	55 (56.7)	27	4 (14.8)
Sex								
Female	20	10 (50.0)	11	4 (36.4)	31	14 (45.2)	12	1 (8.3)
Male	29	19 (65.5)	37	22 (59.5)	66	41 (62.1)	15	3 (20.0)
Ethnicity								
Hispanic or Latino	4	1 (25.0)	7	4 (57.1)	11	5 (45.5)	5	0
Not Hispanic or Latino	45	28 (62.2)	41	22 (53.7)	86	50 (58.1)	22	4 (18.2)
Race								
Black	2	1 (50.0)	2	0	4	1 (25.0)	6	2 (33.3)
Caucasian/white	46	28 (60.9)	46	26 (56.5)	92	54 (58.7)	21	2 (9.5)
Oriental/Asian	1	0	0	-	1	0	0	-
Age (years)								
≤45	11	9 (81.8)	11	6 (54.5)	22	15 (68.2)	9	1 (11.1)
45 <age ≤65	36	19 (52.8)	34	19 (55.9)	70	38 (54.3)	17	3 (17.6)
>65	2	1 (50.0)	3	1 (33.3)	5	2 (40.0)	1	0
Baseline BMI (kg/m^2)								
<25	18	10 (55.6)	12	8 (66.7)	30	18 (60.0)	9	2 (22.2)
25 ≤BMI <30	21	15 (71.4)	24	11 (45.8)	45	26 (57.8)	11	0
≥30	10	4 (40.0)	11	6 (54.5)	21	10 (47.6)	7	2 (28.6)
Body Weight Quartiles (kg)								
≤71	17	9 (52.9)	12	7 (58.3)	29	16 (55.2)	6	1 (16.7)
71 <body weight ≤81	8	5 (62.5)	10	3 (30.0)	18	8 (44.4)	6	1 (16.7)
81 <body weight ≤92	11	10 (90.9)	14	10 (71.4)	25	20 (80.0)	8	0
>92	13	5 (38.5)	12	6 (50.0)	25	11 (44.0)	7	2 (28.6)

N: number of subjects with data; n: number of subjects with SVR
Source: Display EFF.13, Display EFF.38, Display ADD.7

There was a consistent superiority of telaprevir over placebo across subgroups, excepting the black population of partial responders, the size of which is simply too small. In prior partial responders, as opposed to relapsers, there appears to be an impact of BMI, with higher values associated with decreasing response.

Table 47. $SVR24_{planned}$ Rates by Demographic Characteristics –Prior Null-Responder Population, FA Set

Subgroup	Null responder population							
	T12/PR48		T12(DS)/PR48		Pooled T/PR48		Pbo/PR48	
Status	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Total	72	21 (29.2)	75	25 (33.3)	147	46 (31.3)	37	2 (5.4)
Sex								
Female	16	2 (12.5)	22	8 (36.4)	38	10 (26.9)	10	1 (10.0)
Male	56	19 (33.9)	53	17 (32.1)	109	36 (33.0)	27	1 (3.7)
Ethnicity								
Hispanic or Latino	4	0	4	0	8	0	3	0
Not Hispanic or Latino	68	21 (30.9)	71	25 (35.2)	139	46 (33.1)	34	2 (5.9)
Race								
Black	2	0	2	0	4	0	2	0
Caucasian/white	68	19 (27.9)	70	24 (34.3)	138	43 (31.2)	35	2 (5.7)
Oriental/Asian	2	2 (100)	1	0	3	2 (66.7)	0	-
Other	0	-	2	1 (50.0)	2	1 (50.0)	0	-
Age (years)								
≤45	21	8 (38.1)	13	5 (38.5)	34	13 (38.2)	13	1 (7.7)
45 <age ≤65	50	13 (26.0)	60	18 (30.0)	110	31 (28.2)	24	1 (4.2)
>65	1	0	2	2 (100)	3	2 (66.7)	0	-
Baseline BMI (kg/m^2)								
<25	22	6 (27.3)	27	9 (33.3)	49	15 (30.6)	14	1 (7.1)
25 ≤BMI <30	25	10 (40.0)	29	12 (41.4)	54	22 (40.7)	13	0
≥30	25	5 (20.0)	19	4 (21.1)	44	9 (20.5)	10	1 (10.0)
Body Weight Quartiles (kg)								
≤71	18	4 (22.2)	17	7 (41.2)	35	11 (31.4)	11	1 (9.1)
71 <body weight ≤81	15	5 (33.3)	24	5 (20.8)	39	10 (25.6)	10	0
81 <body weight ≤92	17	7 (41.2)	17	8 (47.1)	34	15 (44.1)	7	0
>92	22	5 (22.7)	17	5 (29.4)	39	10 (25.6)	9	1 (11.1)

N: number of subjects with data; n: number of subjects with SVR
Source: Display EFF.13, Display EFF.38, Display ADD.7

Telaprevir treatment appears superior to placebo in all categories that are not too small for direct conclusions. The BMI effect is likely here too.

On treatment virological failure

Viral breakthrough was defined as having a confirmed increase >1 log10 in HCV RNA level from the lowest level reached during a considered treatment phase or a confirmed value of HCV RNA >100 IU/mL in subjects whose HCV RNA level had previously been <25 IU/mL during the considered treatment phase.

Table 48. Cumulative Viral Breakthrough Rate at EOT by Genotype (NS3 Method) – Prior Relapser Population, FA Set

Subgroup	Relapser population					
	T12/PR48		T12(DS)/PR48		Pbo/PR48	
Status	N	n (%)	N	n (%)	N	n (%)
Total	145	2 (1.4)	141	2 (1.4)	68	4 (5.9)
Genotype						
1a	65	2 (3.1)	77	0	34	0
1b	77	0	63	2 (3.2)	31	3 (9.7)

N: number of subjects with data; n: number of subjects with viral breakthrough
Source: Display EFF.36, Display EFF.40

Table 49. Cumulative Viral Breakthrough Rate at EOT by Genotype (NS3 Method) – Prior Partial Responder Population, FA Set

Subgroup	Partial responder population					
	T12/PR48		T12(DS)/PR48		Pbo/PR48	
Status	N	n (%)	N	n (%)	N	n (%)
Total	49	6 (12.2)	48	10 (20.8)	27	3 (11.1)
Genotype						
1a	26	3 (11.5)	29	8 (27.6)	16	0
1b	22	3 (13.6)	18	2 (11.1)	10	3 (30.0)

N: number of subjects with data; n: number of subjects with viral breakthrough
Source: Display EFF.36, Display EFF.40

Table 50. Cumulative Viral Breakthrough Rate at EOT by Genotype (NS3 Method) – Null-Responder Population, FA Set

Subgroup	Null-responder population					
	T12/PR48		T12(DS)/PR48		Pbo/PR48	
Status	N	n (%)	N	n (%)	N	n (%)
Total	72	37 (51.4)	75	33 (44.0)	37	4 (10.8)
Genotype						
1a	45	25 (55.6)	43	22 (51.2)	17	1 (5.9)
1b	27	12 (44.4)	32	11 (34.4)	20	3 (15.0)

N: number of subjects with data; n: number of subjects with viral breakthrough
Source: Display EFF.36, Display EFF.40

Virological breakthrough is rare in prior relapsers, who have a sufficient background interferon response. In null responders breakthrough rates are between 34-55% and more frequent in subtype 1a. In genotype 1a 30/136 (22%) of patients in the immediate start arm had experienced a virological breakthrough, and 30/149 (20%) of patients in the delayed start arm. Also, at week 16, 28/121 (23%) of prior non-responders in the immediate start and 23/123 (19%) of prior non-responders in the delayed start arm had been recorded as experiencing a virological breakthrough.

Table 51. Number of Subjects Without $SVR24_{planned}$ and Reasons for not Achieving $SVR24_{planned}$ – Prior Relapser Population, FA Set

Category	Relapser population		
	T12/PR48 N = 145 n (%)	T12(DS)/PR48 N = 141 n (%)	Pbo/PR48 N = 68 n (%)
Total without $SVR24_{planned}$ for any reason	**24 (16.6)**	**17 (12.1)**	**52 (76.5)**
On-treatment virologic failure	**2 (1.4)**	**1 (0.7)**	**18 (26.5)**
Virologic stopping rule[a]	2 (1.4)	0	18 (26.5)
Detectable HCV RNA at EOT - Viral breakthrough	0	1 (0.7)	0
Detectable HCV RNA at EOT - No viral breakthrough	**8 (5.5)**	**2 (1.4)**	**6 (8.8)**
Completed treatment[b]	1 (0.7)	0	1 (1.5)
Prematurely discontinued treatment	7 (4.8)	2 (1.4)	5 (7.4)
Relapse[c]	**10 (6.9)**	**9 (6.4)**	**28 (41.2)**
Completed treatment[b]	3 (2.1)	5 (3.5)	26 (38.2)
Prematurely discontinued treatment	7 (4.8)	4 (2.8)	2 (2.9)
Undetectable HCV RNA at EOT and discontinued study before SVR	**4 (2.8)**	**5 (3.5)**	**0**
Completed treatment[b]	0	1 (0.7)	0
Prematurely discontinued treatment	4 (2.8)	4 (2.8)	0

[a] Discontinuation due to virologic stopping rules as recorded on the study termination page of the CRF
[b] Completion was defined as having completed all 3 study drugs.
[c] Note that in this table relapse rate is calculated relative to the total number of subjects in the FA set rather than relative to the number of subjects with undetectable HCV RNA levels at EOT as done elsewhere in this report.
Note that there may be more than one reason why subjects did not have $SVR24_{planned}$ and subjects are only counted for the first occurrence.
N: number of subjects with data; n: number of subjects with the observation; EOT: end of treatment
Source: Display EFF.16

In the relapse population on treatment-virological failure was rare, as is relapse. There were no differences between the delayed and immediate start arms.

Table 52. Number of Subjects Without $SVR24_{planned}$ and Reasons for not Achieving $SVR24_{planned}$ – Prior Non-Responder Population, FA Set

	Non-responder population		
Category	T12/PR48 N = 121 n (%)	T12(DS)/PR48 N = 123 n (%)	Pbo/PR48 N = 64 n (%)
Total without $SVR24_{planned}$ for any reason	**71 (58.7)**	**72 (58.5)**	**58 (90.6)**
On-treatment virologic failure	**50 (41.3)**	**44 (35.8)**	**50 (78.1)**
Virologic stopping rule[a]	41 (33.9)	35 (28.5)	49 (76.6)
Detectable HCV RNA at EOT - Viral breakthrough	9 (7.4)	9 (7.3)	1 (1.6)
Detectable HCV RNA at EOT- No viral breakthrough	**3 (2.5)**	**7 (5.7)**	**6 (9.4)**
Completed treatment[b]	1 (0.8)	2 (1.6)	0
Prematurely discontinued treatment	2 (1.7)	5 (4.1)	6 (9.4)
Relapse[c]	**16 (13.2)**	**18 (14.6)**	**2 (3.1)**
Completed treatment[b]	11 (9.1)	13 (10.6)	2 (3.1)
Prematurely discontinued treatment	5 (4.1)	5 (4.1)	0
Undetectable HCV RNA at EOT and discontinued study before SVR	**2 (1.7)**	**3 (2.4)**	**0**
Completed treatment[b]	1 (0.8)	1 (0.8)	0
Prematurely discontinued treatment	1 (0.8)	2 (1.6)	0

[a] Discontinuation due to virologic stopping rules as recorded on the study termination page of the CRF
[b] Completion was defined as having completed all 3 study drugs.
[c] Note that in this table relapse rate is calculated relative to the total number of subjects in the FA set rather than relative to the number of subjects with undetectable HCV RNA levels at EOT as done elsewhere in this report.
Note that there may be more than one reason why subjects did not have $SVR24_{planned}$ and subjects are only counted for the first occurrence.
N: number of subjects with data; n: number of subjects with the observation; EOT: end of treatment
Source: Display EFF.16

Comparing the virological outcomes of the immediate and delayed start, there were 6 more patients with on-treatment virological failure in the immediate start arm. All of these met a virologic stopping rule. Of note, these prescribed that patients with >100 IU/mL at week 4, 6 or 8 *after starting telaprevir*, in either treatment arm, should discontinue telaprevir (see above). These stopping rules inherently create a bias in favour of the delayed start arm, as its patients would have four extra weeks of lead in treatment at each futility point, compared to patients in the immediate start arm.

Relapse rates

Table 53. Relapse Week 72 Rate – Prior Relapser Population, FA Set

	Relapser population		
Category n (%)	T12/PR48 N = 145	T12(DS)/PR48 N = 141	Pbo/PR48 N = 68
Undetectable at EOT	135	138	46
No relapse	122 (90.4)	124 (89.9)	16 (34.8)
Relapse	10 (7.4)	9 (6.5)	30 (65.2)
No HCV RNA measurements during FU	3 (2.2)	5 (3.6)	0

N: number of subjects with data; n: number of subjects with observation
Source: Display EFF.29

Table 54. Relapse Week 72 Rate – Prior Partial Responder Population, FA Set

Category n (%)	Partial responder population T12/PR48 N = 49	T12(DS)/PR48 N = 48	Pbo/PR48 N = 27
Undetectable at EOT	39	36	4
No relapse	30 (76.9)	27 (75.0)	4 (100)
Relapse	8 (20.5)	9 (25.0)	0
No HCV RNA measurements during FU	1 (2.6)	0	0

N: number of subjects with data; n: number of subjects with observation
Source: Display EFF.29

Table 55. Relapse Week 72 Rate – Prior Null-responder Population, FA Set

Category n (%)	Null-responder population T12/PR48 N = 72	T12(DS)/PR48 N = 75	Pbo/PR48 N = 37
Undetectable at EOT	30	36	5
No relapse	22 (73.3)	25 (69.4)	2 (40.0)
Relapse	8 (26.7)	9 (25.0)	3 (60.0)
No HCV RNA measurements during FU	0	2 (5.6)	0

N: number of subjects with data; n: number of subjects with observation
Source: Display EFF.29

Relapse rates in prior relapsers were on the same levels as seen in treatment naïve population, whereas relapse rates in prior non-responders were in the range of 20-25%.

In summary, the main findings of this study include:

- The superiority of both immediate and delayed start telaprevir based regimens over placebo was demonstrated, with point estimates for SVR in the full treatment population of 64% (telaprevir immediate start), 66% (telaprevir, delayed start) and 17% (peginterferon+ribavirin+placebo).
- Statistically significant superiority was demonstrated for each telaprevir regimen over placebo in the three subcategories of prior response patterns, relapsers, partial responders (at least 2 log 10 decline at week 12 of prior therapy with peginterferon+ribavirin) and null responders less than 2 log 10 decline at week 12 of prior therapy.
- In prior relapsers, SVR rates in the telaprevir (immediate and delayed start) arms and in the control arm were 83%, 88% and 23.5% respectively.
- In prior partial responders, SVR rates in the telaprevir arms (immediate and delayed start) and in the control arm were 60%, 54% and 15% respectively.
- In prior null responders, SVR rates in the telaprevir (immediate and delayed start) arms and in the control arm were 30%, 33% and 5% respectively.
- The likelihood of on-treatment virological failure depends on prior virological response, indicating the importance of peginterferon activity also when a DAA is added. The rate of patients classified as on-treatment virological failure was approximately 1% in prior relapsers and about 40% among pooled prior non-responders.

- The benefit of telaprevir appear consistent over subgroups where n is large enough for direct conclusions, such as age, gender, viral subtype, baseline viral load, degree of fibrosis in the overall population. It is noted, though, that some relevant subgroups, such as prior null responders with cirrhosis, are very small. Also, the full black population in this study had n=30.

- Though formal "non-inferiority" according to pre-specified criteria was not met for immediate start versus delayed start, the study did not produce any clear indication of an advantage of the delayed start. Also, the stopping criteria created a bias in favour of the delayed start arm.

- Both on treatment virological response and prior virological response appear to be determinants of the probability of SVR.

- Though there is a likely advantage of telaprevir over placebo in all relevant subgroups, absolute SVR rates remain low in some population categories, despite the addition of telaprevir. These include, e.g. prior null responders with subtype 1a (27%) and prior null responders with cirrhosis (14%).

IL28B genotype and telaprevir response

In a seminal study by Ge et al[1] Nature Genetics 2009 describing the relation of IL28B genotype and outcome in the treatment of HCV genotype 1, a total of 1137 treatment-naïve subjects treated with Peg-IFN/RBV in the IDEAL trial were studied, of which 392 had the IL28B CC genotype, 559 the IL28B CT genotype, and 186 the IL28B TT genotype. Corresponding SVR rates were ~80% for the CC genotype, ~39% for the CT genotype, and ~25% for the TT genotype. The differences in response observed between subjects of Caucasian and African descent can also be in part explained by a difference in IL28B CC genotype frequency between these two races (39% of Caucasians, and 16% of African American).

There are data available on IL28B genotype from the pivotal studies -108 in treatment naive patients and the -216 in treatment experienced patients as presented hereafter.

IL28B as a predictor of response in treatment naive patients

In a retrospective study with de-identified data, IL28B genotype was determined for patients in the pivotal -108 trial in treatment naive patients. This sample included only patients from the US study sites. SVR rates in the pharmacogenomics subsample were comparable with outcomes in the whole study population, as shown below (table 56)

Table 56. $SVR_{planned}$ Rates for IL28 Dataset: Study 108, by Treatment Group

Treatment Group	SVR in IL28 Dataset % (n/N)	SVR Rate for All Subjects in Treatment Group	SVR Rate Among Caucasian Subjects
T8/PR	65% (100/153)	69%	70%
T12/PR	78% (109/140)	75%	75%
Pbo	38% (61/161)	44%	46%

[1] Ge D, et al. Interleukin variation in IL28B predicts hepatitis C treatment induced viral clearance. Nature. 2009: 461:399-401.

The table below show SVR outcome by IL28B genotype in the pharmacogenomics substudy:

Table 57. $SVR_{planned}$ Rates for IL28 Dataset: Study 108, by Treatment Group and Genotype

Treatment Group	CC % (n/N)	CT % (n/N)	TT % (n/N)
T8/PR	84 (38/45)	57 (43/76)	59 (19/32)
T12/PR	90 (45/50)	71 (48/68)	73 (16/22)
Pbo/PR48	64 (35/55)	25 (20/80)	23 (6/26)

SVR rates in the telaprevir arms were higher regardless of IL28B genotype in treatment naive patients. Also from a theoretical point of view, an incremental effect on SVR for each genotype is likely. Furthermore, the proportion of CC patients eligible for shortened treatment duration is likely to be considerable. As a general comment, with the addition of more antiviral potency, SVR rates will increase. When SVR rates are reaching the maximum, given treatment discontinuations due to side effects, adding further antiviral potency will still allow for a decrease in treatment duration.

IL28B as a predictor of response in treatment experienced patients

Of the 662 subjects enrolled in the pivotal study in treatment experienced patients (-216), 527 (79.6%) consented to genetic data collection and analysis. Overall, 17.6% of subjects in this study had the IL28B CC genotype, 61.5% had the IL28B CT genotype, and 20.9% had the IL28B TT genotype. By prior response, the frequency of the IL28B CC, CT, and TT genotypes was as follows:

- 26.8%, 56.3%, and 16.9%, respectively, for the prior relapser population,
- 13.1%, 67.7%, and 19.2%, respectively, for the prior partial responder population,
- 6.0%, 65.9%, and 28.1%, respectively, for the prior null-responder population.

As would be expected, among patients with prior treatment failure, CC genotype is more common with a history of prior relapse than with a history of prior non-response. In the context of interpreting the impact of IL28B genotype in patients with prior treatment failure, it should be noted that any person with CC genotype failing therapy with peginterferon+ribavirin is displaying a phenotype that is not characteristic of the genotype. Also all the impact of IL28 genotype on retreatment outcomes is considerably less investigated than in naïve patients.

Table 58. Study C216 SVR Rates by IL28B Genotype Overall and by Prior Response, FA Set

Population/ IL28B genotype	T12/PR48 N = 212		T12(DS)/PR48 N = 210		Pooled T12/PR48 N = 422		Pbo/PR48 N = 105	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Total								
CC	41	31 (75.6)	35	29 (82.9)	76	60 (78.9)	17	5 (29.4)
CT	134	84 (62.7)	132	76 (57.6)	266	160 (60.2)	58	9 (15.5)
TT	37	21 (56.8)	43	28 (65.1)	80	49 (61.3)	30	4 (13.3)
Prior Relapse								
CC	33	28 (84.8)	25	23 (92.0)	58	51 (87.9)	12	4 (33.3)
CT	59	50 (84.7)	58	50 (86.2)	117	100 (85.5)	30	6 (20.0)
TT	15	13 (86.7)	19	16 (86.7)	34	29 (85.3)	10	3 (30.0)
Prior Nonresponse								
CC	8	3 (37.5)	10	6 (60.0)	18	9 (50.0)	5	1 (20.0)
CT	75	34 (45.3)	74	26 (35.1)	149	60 (40.3)	28	3 (10.7)
TT	22	8 (36.4)	24	12 (50.0)	46	20 (43.5)	20	1 (5.0)
Prior Partial Response								
CC	3	2 (66.7)	5	3 (60.0)	8	5 (62.5)	5	1 (20.0)
CT	30	20 (66.7)	27	13 (48.1)	57	33 (57.9)	10	2 (20.0)
TT	6	4 (66.7)	8	6 (75.0)	14	10 (71.4)	5	0
Prior Null Response								
CC	5	0	5	0	10	0	0	0
CT	45	14 (31.1)	47	13 (27.7)	92	27 (29.3)	18	1 (5.6)
TT	16	4 (25.0)	16	6 (37.5)	32	10 (31.3)	15	1 (6.7)

Source: Module 5.3.5.1/VX-950-TiDP24-C216/IL28B Polymorphisms Report/Table 9, Table 10, Table 11, Table 12, and Table 13

Regardless of IL28B genotype and prior treatment response, the addition of telaprevir to peginterferon+ribavirin was more efficacious, in a treatment experienced population. As CC genotype was most common among relapsers and least common among null responders, it is not surprising that they had the highest response rate in the overall population.

In conclusion, overall, regardless of IL28B genotype, the addition of telaprevir to peginterferon+ribavirin resulted in higher SVR rates, in treatment naive- as well as experienced patients. In the light of the full body of evidence on telaprevir efficacy, the data support the positive risk benefit over all IL28B genotypes.

Analysis performed across trials

A cross study comparison was carried out to substantiate the treatment of prior relapsers with response guided therapy, since RGT has not been formally studied in this patient group. While no prior relapsers in the phase III programme were treated with 24 weeks total therapy after experiencing an eRVR, a total of 67 prior relapsers were randomised to treatment arms with 24 weeks of therapy in the phase II programme. Table 59, below, demonstrates the demographics of these patients, in comparison to the patients treated in the -216 study (prior relapsers), and those treated in the -111 study, investigating the merits of response guided therapy in treatment naive patients.

Table 59. Demographic and Baseline Disease Characteristics in Prior Relapse Populations (Total) and Treatment-Naïve Populations (eRVR+), FA Set

	Prior Relapse			Treatment-Naïve (eRVR+)	
	Study 106	Study 107	Study C216	Study 108	Study 111
Variable	T12/PR24 N = 42	T12/PR24 N = 25	T12/PR48 N = 145	T12/PR N = 212	T12/PR24 N = 162
Male, n (%)	29 (69.0)	15 (60.0)	98 (67.6)	130 (61.3)	104 (64.2)
Caucasian, n (%)	39 (92.9)	22 (88.0)	132 (91.0)	193 (91.0)	135 (83.3)
Black, n (%)	2 (4.8)	2 (8.0)	7 (4.8)	9 (4.2)	17 (10.5)
Hispanic, n (%)	2 (4.8)	2 (8.0)	17 (11.7)	18 (8.5)	18 (11.1)
Age, mean (SD) years	51.2 (7.9)	49.3 (7.8)	51.1 (8.5)	45.8 (10.6)	48.6 (8.9)
BMI, mean (SD) kg/m^2	28.3 (5.2)	25.9 (4.94)	27.6 (4.86)	26.3 (4.7)	28.7 (5.6)
BMI ≥25 kg/m^2, n (%)	NA	12 (48.0)	100 (68.9)	124 (58.5)	117 (72.2)
Genotype 1a, n (%)	26 (61.9)	15 (60.0)	65 (45.8)	126 (59.4)	114 (70.4)
HCV RNA ≥800000 IU/mL, n (%)	37 (88.1)	16 (64.0)	124 (85.5)	158 (74.5)	124 (76.5)
Cirrhosis, n (%)	10 (23.8)	1 (4.0)	28 (19.3)	9 (4.2)	18 (11.1)

Source: Module 5.3.5.1/VX06-950-106/Table 14.1.2c and Table 14.1.3c, VX-950-TIDP24-C216/Display GEN.24 and Display GEN.25, VX07-950-108/Table 14.1.2b and Table 14.1.4b, VX08-950-111/Table 14.1.2 and Table 14.1.4, Module 5.3.5.2/VX-950-107/Table 14.1.2a and Table 14.1.2e

The following considerations need to be taken into account when evaluating the likelihood that prior relapsers with an eRVR could be treated for 24 rather than 48 weeks total, without decreasing the likelihood of SVR:

- In Study 111, the SVR rate in treatment-naïve subjects with undetectable HCV RNA at Weeks 4 and 12 was 92.0% in the T12/PR24 group and 87.5% in the T24/PR48 group.
- In Study 106, the SVR rate was 69.0% in subjects with prior relapse in the *T12/PR24* group. *Among subjects with prior relapse in this treatment group who had undetectable HCV RNA at Weeks 4 and 12, the SVR rate was 89.3%.*
- In Study 107, the SVR rate was 96.0% in subjects with prior relapse in the *T12/PR24* group. *Among subjects with prior relapse in this treatment group who had undetectable HCV RNA at Weeks 4 and 12, the SVR rate was 100%.*
- In Study 108, the SVR rate was 74.7% in treatment-naïve subjects in the T12/PR group.Among subjects in this treatment group that had undetectable HCV RNA at Weeks 4 and 12, and were assigned to a Peg-IFN/RBV treatment duration of 24 weeks, the SVR rate was 89.2%.
- In Study C216, the SVR rate was 83.4% in subjects with prior relapse in the T12/PR48 group. Among subjects with prior relapse in this treatment group who had undetectable HCV RNA at Weeks 4 and 12, the SVR rate was 95.8%.
- Relapse rates were low and similar to those seen in treatment naïves, in subjects with prior relapse that received T12/PR24 regimens in the -106 and -107 studies, and had undetectable HCV RNA at Weeks 4 and 12 (table 60).

Table 60. SVR and Relapse in Subjects With Undetectable HCV RNA at Weeks 4 and 12 (eRVR), FA Set

Parameter	Subject Population/ Study	T12/PR24[a] n/N (%)	T12/PR48 n/N (%)
SVR	Treatment-naive		
	Study 108	189/212 (89.2)	NA
	Study 111	149/162 (92.0)	140/160 (87.5)
	Prior Relapse		
	Study 106	25/28 (89.3)	NA
	Study 107	24/24 (100)	NA
	Study C216	NA	91/95 (95.8)
Relapse[b]	Treatment-naive		
	Study 108	14/212 (6.6)	NA
	Study 111	9/162 (5.6)	4/160 (2.5)
	Prior Relapse		
	Study 106	2/28 (7.1)	NA
	Study 107	0/24 (0)	NA
	Study C216	NA	3/95 (3.2)

NA: not applicable
Denominator is subjects with undetectable HCV RNA at Weeks 4 and 12.
[a] In Study 108, the treatment group was T12/PR, and subjects with eRVR were assigned to receive 24 weeks of treatment.
[b] In this analysis, N = FA Set; in other descriptions of relapse rates, N = undetectable HCV RNA at end of treatment)
Source: Module 2.7.2/Summary of Clinical Pharmacology/Table 43

The demographic data in the required cross-study comparison do not preclude the conjecture that prior relapsers with eRVR might be treated for 24 weeks without loss of SVR. Also, available data do indicate that a shortened treatment duration in relapsers with eRVR is likely to yield similar high SVR rates as does 48 weeks of therapy. These data are further supported by a pharmacometric analysis conducted by the FDA and submitted to CHMP by the applicant, indicating that would-be relapsers, if treated with pegIFN and ribavirin only, had a considerable representation among patients achieving eRVR and receiving 24 weeks of therapy within the -108 and -111 studies with very high SVR rates. All in all, available data are considered sufficiently compelling for the CHMP to support the labelling of the RGT algorithm also for prior relapsers.

Clinical virology

The main findings in the clinical virology studies of telaprevir include:

- Due to the low fidelity of the HCV RNA polymerase, there is a great intra-patient diversity of viral quasispecies, including the pre-existence of drug-resistant variants, which exist at low levels due to decreased fitness. These are selected for by telaprevir therapy.
- There is cross resistance within the NS3/4A inhibitor class, but not to the drugs tested from other classes (e.g., NS5B inhibitors) or to interferon/ribavirin.
- Viral variants selected for by telaprevir were categorised by the applicant as low level (<25-fold) and high level (>25 fold) resistant variants.
- Low level resistant variants at baseline were detectable by population sequencing in approximately 3.5% of treated (DAA-naive) patients. Telaprevir appears to have reduced but clinically relevant activity in such patients, with mutants showing up to a 7.4-fold change in IC50. Preliminary data indicate that some such resistant variants may reduce, though in most cases not abrogate, the efficacy of telaprevir. The concern is most relevant for prior null responders, where 0/5 patients with resistant mutant variants at baseline reached SVR.
- Resistant variants demonstrate reduced fitness.

- In patients with genotype 1a, on-treatment virological failure during the telaprevir treatment phase was associated with the selection of high level resistant variants - predominantly double mutants with amino acid substitutions V36M+R155K.

- In patients with genotype 1b, on-treatment virological failure during the telaprevir treatment phase was associated with the selection of high level resistant variants with A156T/V substitutions.

- On treatment virological failure during the peginterferon/ribavirin tail in genotype 1a is, in about half the cases, associated with the dominance of high level resistant V36M+R155K double mutants, and in the other cases, mostly by the dominance of low level resistant single V36M or R155 mutants. In genotype 1b it is associated with either wild-type virus, or the low level resistant T54A/S and V 36 A/M single mutant variants.

- Relapse was associated with higher level resistant variants or with lower level single mutant resistant variants at position 36 or 155 in subtype 1a, and with the lower level resistant variants at position 36 or 54 in genotype 1b. Also, a considerable portion of patients appeared to relapse with wild-type. It is notable, however, that relapse is usually assessed quite some time after the discontinuation of therapy, and the true relapsing viral population may in some cases have reverted to a more fit genotype at the time of sampling.

The evolution of resistant variants after treatment discontinuation

In an interim analysis of the ongoing long term follow up -112 study, median in 89% (50/56) of subjects with resistance mutations, these were no longer detected by population sequencing, after a median follow-up of 25 months. In a subsequent clonal sequence substudy 20/20 of these samples were similar in composition to that seen at baseline, indicating a full reversibility of the selected viral population. Also, data from the follow up of the phase III trials indicated reversion to wild-type by population sequencing, with median times to reversion for the relevant single and double mutants of 15-56 weeks.

In summary, available data are indicative of a full reversion to the pretreatment population after discontinuation of therapy, at least in some patients and possibly in most patients. A conclusive assessment of the consequences of selected resistance during failed telaprevir therapy, however, would require adequately designed studies of retreatment.

Virologic stopping rules

The following stopping rules are recommended by the applicant to avoid unnecessary exposure to drugs in patients who are not likely to achieve SVR and to curtail potential evolution of telaprevir-resistant HCV variants that could occur with continued telaprevir treatment:

- Patients with >1000 IU/mL HCV RNA at Week 4 of telaprevir, Peg-IFN-alfa and RBV treatment should discontinue all drugs.

- Patients with >1000 IU/mL HCV RNA at Week 12 of telaprevir, Peg-IFN-alfa and RBV treatment should discontinue all drugs.

- In prior null-responders, consideration should be given to conduct an additional HCV RNA test between Weeks 4 and 12. If the HCV RNA is >1000 IU/mL, telaprevir, Peg-IFN-alfa and RBV treatment should be discontinued.

- In patients receiving a total of 48 weeks of treatment, Peg-IFN-alfa and RBV should be discontinued if HCV RNA is detectable at Week 24 or Week 36.

The stopping rules utilized during drug development varied between clinical trials. It should be noted that the very use of stopping rules within trials preclude a fully informed post hoc identification of optimal stopping rules, as patients in trials not meeting predefined criteria will have discontinued by default. Consequently, full information on the operative characteristics of the stopping rules is lacking. The abovementioned rules represent a simplification of the various rules used in the phase III program. This particular set of rules was not used in any of the trials, but has been agreed on with the FDA and proposed by the applicant to the CHMP.

As a background, none of the 25 subjects with HCV RNA >1000 IU/mL at Week 4 who discontinued telaprevir in the T12/PR groups of Studies 108, 111, and C216, achieved an SVR with continued Peg-IFN/RBV treatment. Therefore discontinuation of the whole regimen is recommended in this situation. In studies 108 and 111, 4/16 (25%) subjects with HCV RNA levels between 100 and 1000 IU/mL at Week 4 were able to achieve an SVR with continued telaprevir treatment. Thus the higher level of HCV-RNA is chosen for stopping.

As approximately 10% of prior null responders had virological breakthrough detected at week 6 or 8, the suggestion for more intense monitoring in this group is warranted.

In subjects with HCV RNA between 100 and 1000 IU/ml at Week 12, 2/8 (25%) achieved an SVR. On the contrary, none of the 11 subjects with HCV RNA >1000 IU/mL at Week 12 who were still on telaprevir/Peg-IFN/RBV treatment in the T12/PR groups of Studies 108, 111 and C216 achieved an SVR with continued Peg-IFN/RBV treatment. Therefore the recommendation is to stop the whole regimen if HCV-RNA at week 12 is >1000 IU/mL.

Supportive studies

The long term durability of SVR with telaprevir based therapy

The durability of SVR was investigated during Phase 2 and Phase 3 clinical studies of treatment naïve and treatment-failure subjects who received a telaprevir-based regimen. The durability of SVR was also evaluated in an interim analysis of a 3-year follow-up study (112) in subjects who had been treated with telaprevir in Phase 2 studies. The subjects in whom durability of SVR was evaluated included subjects who completed treatment as well as subjects who discontinued treatment, and subjects from all telaprevir treatment regimens in the studies, including regimens without RBV and regimens with Peg-IFN/RBV durations of 12, 24, or 48 weeks.

Study 112; cohort A

Cohort A of the long-term follow up study 112 consists of subjects who received at least 1 dose of telaprevir-based treatment and achieved an SVR in the previous telaprevir study. Approximately 150 subjects who achieve an SVR following telaprevir-based treatment in the previous clinical studies are expected to enroll in Cohort A.

The interim analysis available at the primary assessment included data for 123 subjects in Cohort A. the median duration of follow-up between the SVR time point in the previous study and the last time point available in Study 112 (as of the IA) was 22.13 months (range: 5.1 to 35.2 months).No subjects had late relapse during the observational period in Study 112, which is ongoing. These data demonstrate that late relapse in subjects treated with a telaprevir-based regimen is rare (<1%).

Overall of the 852 subjects who received a telaprevir-based regimen, had SVR, and had at least 1 post-SVR follow-up assessment, 8 subjects had late relapse during the follow-up period in their original

study, all within 6 months after SVR. All other subjects with SVR, who have been followed for up to 3 years after the end of treatment, continued to have undetectable HCV RNA. Thus, available data support the long term durability of SVR.

Clinical studies in special populations

Studies are ongoing in patients with non-genotype 1 virus and in HIV-HCV co-infected patients. No SVR outcomes were available during the assessment.

Discussion on clinical efficacy

Design and conduct of the clinical studies

The telaprevir clinical development program aiming at an indication for all treatment naïve- and experienced patients with HCV genotype 1 infection and compensated liver disease, that do not have HIV or HBV co-infection, comprises a total of 3 short term studies, 5 phase II studies targeting SVR, and three pivotal trials. The program has been quite extensive, investigating numerous possibilities in terms of combinations and durations of the treatment component. Still, the complexity of the clinical issues are well illustrated by the fact that several questions still remain concerning the optimal duration of therapy in subsets of patients. The studies reported appear to have been well conducted. The standard-of-care arms have performed as expected, and the loss to follow up has been reasonably low. Furthermore, there are interim data from a long term follow up study of the durability of SVR, as well as the evolution of resistant variants selected in patients treated with telaprevir but failing to reach SVR. Available long term follow up data indicate the durability of SVR obtained with telaprevir. Also, data indicate that the resistant viral population selected when failing a telaprevir-based regimen in most cases is likely to revert to wild-type with time. Retreatment studies, however, are not available

The efficacy of telaprevir in treatment naive patients

In the pivotal -108 study in treatment naïve patients, the SVR rate in the 12 week telaprevir arm was 74.7%, a 30.9% increase compared to the placebo+peginterferon alfa-2a+ribavirin arm, which was highly statistically significant. Apart from the SVR advantage, 58% of patients reached an eRVR, making them eligible for 24 rather than 48 weeks of total therapy. The -111 study in treatment naive patients demonstrated that this strategy of shortened therapy for early responders is non-inferior to a full 48 weeks total duration of therapy, with a point estimate for response guided therapy which was higher than for standard-duration therapy. This greatly increased efficacy and shortened treatment duration represents a very substantial improvement in therapy for HCV genotype 1.

The advantage of telaprevir was apparent across demographic and baseline disease categories, including men and women, high and low BMI, patients of black race, patients with high viral load, degree of liver injury.

Regarding IL28B genotype, the addition of telaprevir to peginterferon+ribavirin resulted in higher SVR rates regardless of genotype and treatment experience. In the light of the full body of evidence on telaprevir efficacy, this retrospective analysis supports the positive risk benefit over all IL28B genotypes.

In the -111 study, the response guided algorithm of study -106, for patients with eRVR, was compared with a 48 weeks total duration. Equivalent efficacy was apparent over all the aforementioned categories with the exception of patients with cirrhosis, for whom the point estimate favoured a longer treatment duration also in patients with eRVR.

Comments on the labelling for treatment naive patients

The label sought for treatment naïve patients is telaprevir 750 mg thrice daily in combination with a peginterferon and ribavirin, including twelve weeks of triple therapy, followed by 12 or 36 additional weeks of peginterferon and ribavirin, depending on whether an eRVR is reached or not. The exception to this rule pertains to patients with cirrhosis, for whom 48 weeks duration is prescribed regardless of early viral response.

The suggested duration of 12 weeks telaprevir therapy is adequately motivated. Findings from the -108 study imply that a shorter duration of telaprevir, though yielding high SVR rates, may not be optimal in a significant proportion of patients. Inversely, 24 weeks of telaprevir therapy was tested in the phase II -106 study in treatment experienced patients. As the rate of on-treatment virological failure did not differ between the arms with 12 and 24 weeks of telaprevir therapy, the applicant concluded that 12 weeks of therapy would suffice. Also, the side effects profile was supportive of a shorter duration. The CHMP concurs with the argument of the applicant, though it is recognised (a) that resistance data indicate that a longer telaprevir treatment duration might have been virologically motivated in prior non-responders and (b) that relapse rates for 12 versus 24 weeks of telaprevir therapy in the -106 study could not be directly compared, as the duration of P/R therapy differed between arms.

The recommended shortening of the total treatment duration to 24 weeks in case of eRVR is supported by the -111 study. The exception is the subgroup of patients with cirrhosis. In the -111 study 12/18 (66.7%) patients with cirrhosis and RVR that were assigned to 24 weeks of therapy experienced SVR, versus 11/12 (91.7%) who were assigned to 48 weeks. This difference is not statistically significant at a 95% confidence level. Also, the finding in this subgroup is not supported by any similar trend in patients with bridging fibrosis. Thus, while the difference may be a chance finding, there is prudence in the consideration of the applicant not to make an inference which, if wrong, might cause a loss of SVR in this population with more advanced liver injury.

Regarding the need for a total duration of therapy longer than 24 weeks in patients not reaching eRVR, the outcomes of the phase 2 -106 study in treatment-experienced, in which the likelihood of SVR in patients that did not reach eRVR was greater if randomised to the 48 week rather than the 24 week triple therapy arm, are notable – and this regardless of prior relapse or non-response. Data from this study, along with that from the pivotal -216 study in treatment experienced patients, also show that the predictive value of eRVR for SVR is a function of prior response, with the highest predictive value in relapsers and the lowest in null responders. Furthermore, relapse rates in the -106 study support the notion of a longer total duration of therapy in the absence of an eRVR.

The efficacy of telaprevir in treatment-experienced patients

The placebo controlled phase III -216 study was conducted in treatment-experienced patients, including prior relapsers, partial responders and null responders. All patients in the experimental arms received 12 weeks of telaprevir therapy, with or without a delayed start (1 month lead in). The planned treatment duration for all patients was 48 weeks. SVR rates in all three prior response subcategories were statistically significantly superior to placebo, with a total difference in SVR rates of + 47% with the addition of telaprevir to peginterferon alfa-2a and ribavirin. The advantage of adding telaprevir was also apparent regardless of viral subtype, baseline viral load or degree of liver injury. There is no subgroup contradicting the general conclusion, though the proportion of blacks in each of the prior response subgroups is too small to allow a direct inference. Also in treatment-experienced patients with cirrhosis, the advantage of adding telaprevir was clear, with an impressive 84% response

rate among cirrhotics with prior relapse. In cirrhotics with prior null response, however, response rates were 7/50 (14%) compared to 1/10 (10%) for placebo. While this outcome in a very small sample is compatible with a likely real increased effect with telaprevir addition, it indicates that some patients will still have a low, in some cases very low, absolute probability of cure despite the addition of telaprevir.

The labelling for treatment experienced patients

For treatment experienced patients, the indication sought is immediate start telaprevir 750 mg thrice daily, in combination with peginterferon and ribavirin, with twelve weeks of triple therapy followed by 36 weeks of peginterferon alfa-2a and ribavirin therapy, regardless of early viral response. The exception to this is in prior relapsers without cirrhosis, where 12 weeks of subsequent peginterferon alfa-2a+ribavirin therapy would suffice in case an eRVR is reached.

Regarding the comparison of a delayed start regimen (4 weeks lead in) and the immediate start, the formal design chosen by the applicant was one of non-inferiority, with delayed start treated as the "reference" and a non-inferiority margin of 10%. The CHMP has not found any elaboration of the particular rationale for this margin. As it were, in the full population, the point estimate for SVR favours a delayed start by 66.3% vs 64.3%. In a prespecified logistic regression model, the difference was modified to 3%, with a 95% CI of -13 – +7, thus failing non-inferiority criteria. The statistical power of the study, however, in relation to the non-inferiority target, is unclear to the CHMP. The applicant argues that no virological benefit of a delayed start has been demonstrated, noting that there is no clear pattern of relative advantage between subgroups and that the rates of on-treatment virological failure as well as relapse are similar regardless of immediate or delayed start. No differences were noted in the on-treatment virologic failure or relapse rate, or type of emerging viral variants between the T12/PR48 and T12(DS)/PR48 arms. Therefore the applicant concludes that triple therapy can be started immediately.

The CHMP concurs with the applicant's analysis. There is no demonstrated virological benefit with a delayed start. However, it is recognised that the total efficacy and safety of a delayed start is similar to an immediate start, and also that clinicians might be interested in the information obtained in the lead in period. The decision to treat prior null responders with telaprevir based triple therapy will need to be made by clinicians on a case to case basis, until the consequences of selection for drug resistant variants have been sufficiently investigated. In some cases deferring treatment until the availability of more potent drug combinations (e.g., quad therapy) may be the preferred choice. Despite no indication of a virological advantage, the use of a lead in to determine whether to go on with a full course of therapy may by some be considered of value in null responders. Therefore information should be available in the SmPC on the likelihood of response depending on prior response category and lead in response.

The treatment of prior relapsers with response guided therapy, as requested for labelling, has not been formally studied. The demographic data in the required cross-study comparison do not preclude the conjecture that this would be adequate. Furthermore, available data indicate that a shortened treatment duration in relapsers with eRVR is likely to yield similar high SVR rates as does 48 weeks of therapy. These data are further supported by a pharmacometric analysis conducted by the FDA, that was submitted to CHMP by the applicant,, indicating that would-be relapsers if treated with pegIFN and ribavirin only had a considerable representation among patients achieving eRVR and receiving 24 weeks of therapy within the -108 and -111 studies, with resultant very high total SVR rates. Data are considered sufficiently compelling for the CHMP to support the applicant's labelling claim.

Other labelling considerations

Reporting of efficacy outcomes in the SmPC

During the time of the CHMP assessment of the application dossier, the US FDA performed its own analysis of the study outcome data using a snapshot analysis with a visit window that enabled the imputation of SVR12 for SVR24, and that equated a detectable HCV-RNA below the limit of quantitation of the assay (25 IU/ml) with undetectable during the follow up, for the definition of SVR. The applicant submitted this analysis to the CHMP. Given the temporal pattern of relapse, and the likelihood of a detectable but unquantifiable HCV-RNA at week 12 or later being false positive, this mode of analysis is considered justified. This leads to slightly different point estimates for outcomes, but does not affect any formal conclusions. In order to avoid the confusion of having different datasets in the product information in the EU and US, the applicant has requested that data according to the FDA analysis be reported in the SmPC section 5.1. This is considered acceptable.

The two peginterferons

The applicant is requesting a labelling for use in combination with either peginterferon, despite the fact that the only relevant study in which peginterferon alfa-2b has been used is the underpowered –C208 study. Whilst recognizing the practical advantage of a non-specific label regarding peginterferon use, there are the following efficacy concerns:

Firstly, while it is recognized that SVR rates are roughly similar for peginterferon alfa-2a and -2b, as demonstrated by the very large IDEAL study, this trial demonstrated important viral kinetics differences between the two peginterferons, as evidenced, e.g., by a more than 10% higher end-of-treatment response rate with peginterferon alfa-2a. Also, both the pharmacokinetics and early viral response kinetics differ between the peginterferons.

Due to a relatively short half-life, the serum concentration of peginterferon2b is very low at the end of the dosing interval, and particularly so at the end of the first dosing intervals, when a co-administered DAA would act in virtual monotherapy. It is notable that those developing DAAs in combination with peginterferon alfa-2b have opted for the use of a lead in period, whereas those using peginterferon alfa-2a have generally not.

Presently it is unknown whether these differences between the peginterferons impact the efficacy of combination therapy with a DAA. For instance, it is not known whether there is a differential need for a lead-in period. Furthermore, with response guided therapy, the proportion of patients eligible for a shortened treatment duration may differ depending on which peginterferon is used.

In the -208 study in treatment naïve subjects SVR rates were similar and above 80% regardless of which peginterferon was used. These are the highest SVR rates in the whole phase II/III program, implying a relatively easy-to-treat population. However, with the response guided algorithm determining treatment duration, 74% of patients treated in combination with pegIFN alfa-2a were assigned to 24 weeks rather than 48 weeks of therapy, versus 62% of patients treated with pegIFN-alfa-2b. Furthermore, though the numbers are very small, the rate of on-treatment viral breakthrough was 2.5-fold higher in patients treated with pegIFN-alfa-2b. In summary, the -208 study does not provide direct support for the equivalence of the two peginterferons in the setting of co-treatment with telaprevir. Furthermore, there are no comparative data at all in treatment experienced patients, where differences in peginterferon response may be more critical to treatment outcome. For instance, the conclusion that a lead-in period is of no virological value might not be generalizable to the other peginterferon. Overall, the CHMP takes the view that the risk-benefit of telaprevir is positive in combination with either peginterferon, but that the uncertainties surrounding the relative efficacy and

the proper regimens to use with peginterferon alfa-2b in combination with telaprevir must be adequately reflected in the SmPC.

Important patient groups not sufficiently studied

All the applicant's labelling claims relate to patients with HCV genotype 1 virus and compensated liver disease. Treatment in patients with decompensated liver disease has not been studied, as peginterferon and ribavirin are contraindicated in this population, and also the optimal telaprevir dose has not been established. A pharmacokinetic study in patients with decompensated liver disease indicated substantially *lower* exposure to telaprevir in such patients. The mechanism for this finding is unknown. HIV/HCV coinfected patients are an important subgroup of HCV patients that have more rapid disease progression and lower response to peginterferon/ribavirin therapy. Improved therapies for this group are urgently needed. A pilot study is underway in this population and several relevant drug-drug interaction studies have been performed. Also, pilot studies have been performed in patients with other genotypes than 1. Telaprevir has not yet been studied in pediatric populations.

Furthermore, there are some subgroups, as stated above, including not only patients with cirrhosis, but also black patients, known to respond less well to interferon based therapy, of which numbers have been low in the pivotal trials of telaprevir.

Conclusions on clinical efficacy

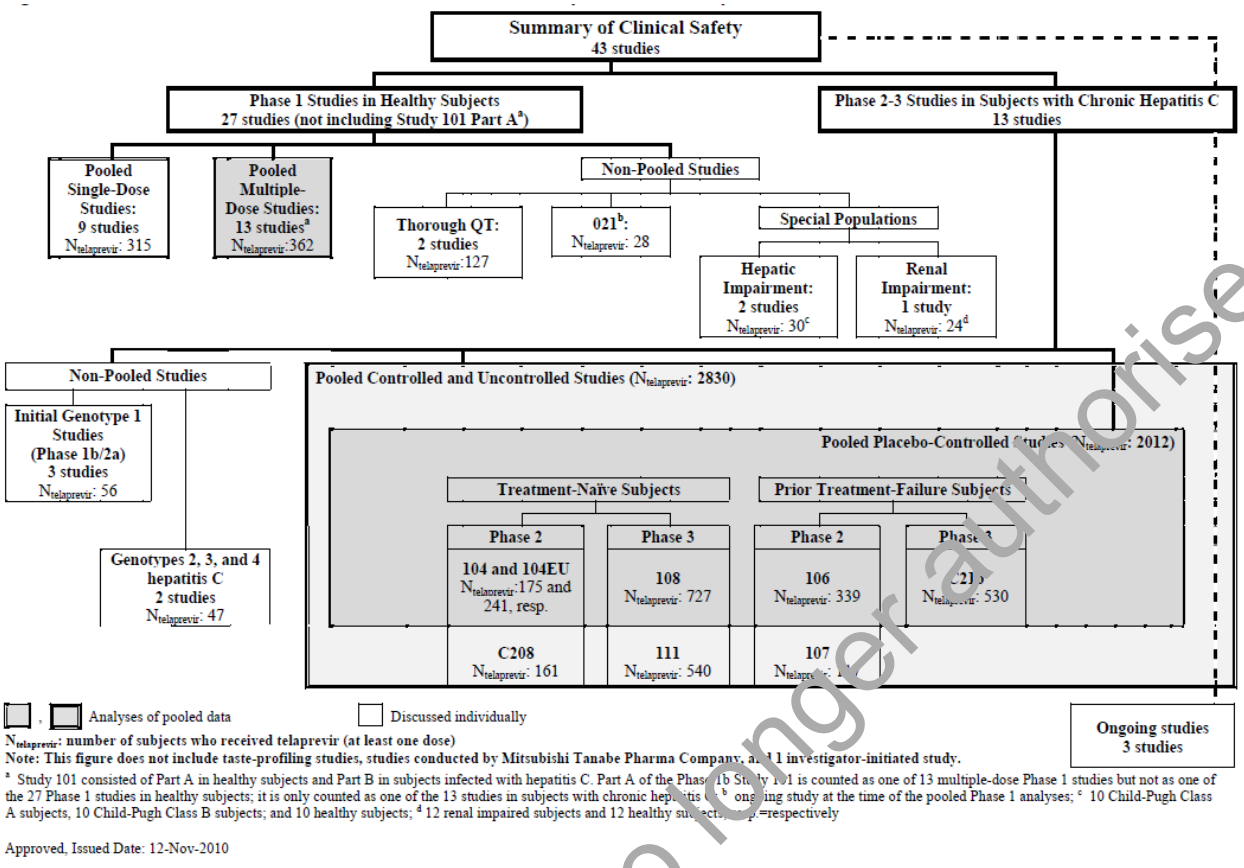
In conclusion, substantially increased SVR rates have been demonstrated when treating HCV genotype 1 infection in patients with compensated liver disease, with telaprevir in combination with peginterferon alfa-2a and ribavirin. Available data indicate that SVR obtained is durable. In most cases of treatment failure, drug resistant variants have been selected. Follow-up data indicate a gradual reversion back to wild-type after treatment discontinuation in most patients. The consequences of the selection of resistance for future treatment attempts remain unknown. The addition of telaprevir to regimens with peginterferon alfa-2a and ribavirin represents a major advance in the treatment of the dominant HCV genotype, including many patients in whom present standard therapy is unlikely to be efficacious.

Clinical safety

Patient exposure

The applicant has presented a number of pooled safety datasets (see figure below). In this assessment report, the main focus is on the pooled placebo-controlled phase II/III studies, which includes the 104, 104EU, the -105 and the three pivotal phase III trials.

Figure 3. Overview of Studies Included in the Summary of Clinical Safety



Ntelaprevir: number of subjects who received telaprevir (at least one dose)
Note: This figure does not include taste-profiling studies, studies conducted by Mitsubishi Tanabe Pharma Company, and 1 investigator-initiated study.

[a] Study 101 consisted of Part A in healthy subjects and Part B in subjects infected with hepatitis C. Part A of the Phase 1b Study 101 is counted as one of 13 multiple-dose Phase 1 studies but not as one of the 27 Phase 1 studies in healthy subjects; it is only counted as one of the 13 studies in subjects with chronic hepatitis C. [b] ongoing study at the time of the pooled Phase 1 analyses; [c] 10 Child-Pugh Class A subjects, 10 Child-Pugh Class B subjects; and 10 healthy subjects; [d] 12 renal impaired subjects and 12 healthy subjects, respectively

Approved, Issued Date: 12-Nov-2010

In the pooled placebo-controlled Phase 2-3 studies, 2012 subjects received at least one dose of telaprevir, including:

- 1346 subjects who received a regimen of 750 mg telaprevir q8h for 12 weeks in combination with Peg-IFN and RBV (T12/PR group) and
- 1823 subjects who received a regimen of telaprevir for 8, 12, or 24 weeks in combination with Peg-IFN and RBV (Any T/PR group).

Placebo in combination with Peg-IFN and RBV was received by 764 subjects (pooled control group, Pbo/PR group). The total exposure to telaprevir/placebo in the pooled placebo-controlled Phase 2-3 studies was 326.32 patient years in the T12/PR group and 190.38 patient years in the Pbo/PR group. Thus, the size of the safety database is sufficient according to ICH guidance.

The pooled safety database comprises 225 treated patients with cirrhosis. The number of patients with significant renal impairment is minimal.

Adverse events

Telaprevir/Placebo Treatment Phase

The incidence of SAEs, AEs of at least Grade 3, and AEs leading to permanent treatment discontinuation was higher in the T12/PR group than in the Pbo/PR group. A summary table of incidence of AEs during the telaprevir/placebo treatment phase is given in table 61.

Table 61. Placebo-Controlled Phase 2-3 Studies: Summary of Adverse Events – *Telaprevir/Placebo Treatment Phase*

Telaprevir/Placebo Treatment Phase

Number (%) of subjects with:	T12/PR (750 mg q8h) N = 1346	Any T/PR N = 1823	Pbo/PR N = 764
AEs	1323 (98.3)	1797 (98.6)	740 (96.9)
Deaths	0[a]	0[a]	2 (0.3)[a,o]
SAEs	93 (6.9)	121 (6.6)	22 (2.9)
AEs of at least Grade 3	321 (23.8)	417 (22.9)	94 (12.3)
AEs leading to permanent discontinuation of			
T/Pbo	191 (14.2)	273 (15.0)	31 (4.1)
all study drugs at 1 time	109 (8.1)	157 (8.6)	28 (3.7)
AEs at least possibly related to			
T/Pbo	1275 (94.7)	1746 (95.8)	707 (92.5)

[a] Refers to the number (%) of subjects who died as a result of an AE with onset during the telaprevir/placebo treatment phase.
[b] Includes 1 subject with a life-threatening AE that was not resolved at last study visit. The subject subsequently died due to this AE.
N: number of subjects with data

Virtually all patients reported AEs, also in the control arm, as expected with peginterferon and ribavirin. There were no deaths while on telaprevir treatment. The frequency of serious adverse effects and adverse effects of at least grade 3 was clearly higher with telaprevir than with placebo, as was adverse effects leading to discontinuation of telaprevir/placebo or the whole regimen.

The side effect profile in the placebo group was characteristic of peginterferon+ribavirin, and similar effects were seen when telaprevir was added. Side effects that are more frequent when telaprevir is added include rash, pruritus, anemia, nausea, diarrhoea, vomiting, dysgeusia and haemorrhoids. It is notable that hemorroids is just one of a number of terms used to describe anorectal adverse events associated with telaprevir therapy.

Serious adverse events and deaths

In the pooled placebo-controlled Phase 2-3 studies, 5 of the 2012 subjects in the telaprevir groups and 4 of the 764 subjects in the placebo group died. Of these 9 deaths, none occurred during treatment with telaprevir/placebo. One of the 5 deaths that occurred in the telaprevir groups was considered possibly related to telaprevir by the investigator. This death was caused by lung neoplasm malignant that Subject 21[illegible]8[illegible]3 from Study C216 developed 96 days after discontinuing telaprevir. The subject died 138 days after the last dose of telaprevir.

During the telaprevir/placebo treatment phase, individual SAE preferred terms were reported in less than 1.5% of the subjects in the T12/PR group, except for serious anemia (1.6%) and rash (0.7%). Serious anemia occurred less frequently in the Pbo/PR group than in the T12/PR group and serious rash was not observed in the Pbo/PR group.

Table 62. Placebo-Controlled Phase 2-3 Studies: Incidence of Adverse Events of At Least Grade 3 That Occurred in More Than 0.5% of Subjects in any Treatment Group by System Organ Class and Preferred Term – *Telaprevir/Placebo Treatment Phase*

System Organ Class Preferred Term, n (%)	T12/PR (750 mg q8h) N = 1346	Any T/PR N = 1823	Pbo/PR N = 764
Any AE of at least Grade 3	321 (23.8)	417 (22.9)	94 (12.3)
Blood and lymphatic system disorders			
Anaemia	64 (4.8)	92 (5.0)	6 (0.8)
Neutropenia	49 (3.6)	62 (3.4)	31 (4.1)
Leukopenia	29 (2.2)	32 (1.8)	10 (1.3)
Thrombocytopenia	16 (1.2)	18 (1.0)	1 (0.1)
Lymphopenia	8 (0.6)	8 (0.4)	1 (0.1)
Skin and subcutaneous tissue disorders			
Rash	29 (2.2)	41 (2.2)	1 (0.1)
Pruritus	17 (1.3)	21 (1.2)	1 (0.1)
Rash generalised	7 (0.5)	9 (0.5)	0
Rash maculo-papular	7 (0.5)	7 (0.4)	0
General disorders and administration site conditions			
Fatigue	16 (1.2)	25 (1.4)	3 (0.4)
Asthenia	11 (0.8)	11 (0.6)	3 (0.4)
Influenza like illness	6 (0.4)	7 (0.4)	4 (0.5)
Investigations			
Neutrophil count decreased	11 (0.8)	12 (0.7)	3 (0.4)
White blood cell count decreased	8 (0.6)	8 (0.4)	1 (0.1)
Blood uric acid increased	7 (0.5)	7 (0.4)	0
Gastrointestinal disorders			
Nausea	13 (1.0)	18 (1.0)	1 (0.1)
Nervous system disorders			
Headache	10 (0.7)	12 (0.7)	7 (0.9)
Psychiatric disorders			
Insomnia	7 (0.5)	8 (0.4)	2 (0.3)

N: number of subjects with data; n: number of subjects with observations
Note: If a subject has multiple events within a SOC or preferred term, the subject is counted once.
Source: Module 5.3.5.3/VX-950-SCS-Display SAF.B69

Rash and Serious Cutaneous Adverse reactions

The most important toxicity associated with telaprevir is rash. Telaprevir-based regimen rash are generally pruritic and have an eczematous appearance. Over 50% of patients treated with telaprevir developed rash, compared to 33% in the placebo group. The median time to any rash event was about a month. The median time to a grade 3 event was 7 weeks. Rash as a serious adverse event occurred exclusively in the telaprevir group. All in all, rash led to the permanent discontinuation of telaprevir in 6-7% of treated patients. A number of severe cutaneous adverse reactions occurred during the telaprevir development program, including three at least possible cases of Stevens Johnson syndrome and three at least possible cases of the DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms). There were no deaths due to skin reactions.

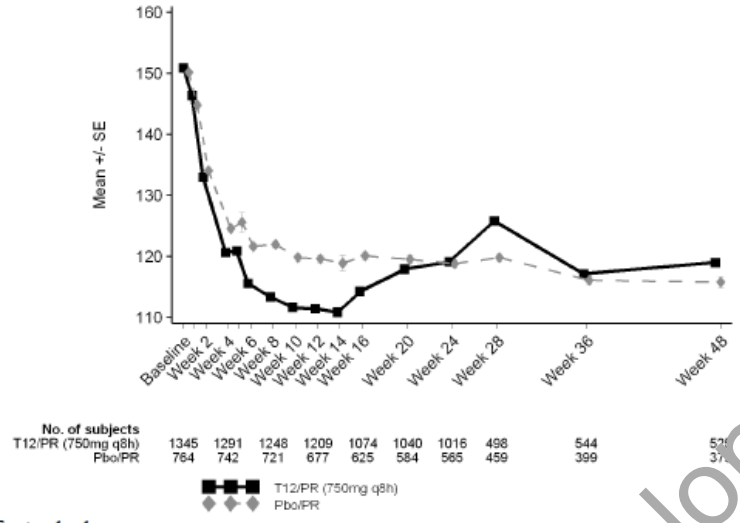
Anemia

Telaprevir adds approximately 10 g/L to the anemia induced by peginterferon and ribavirin, rapidly reversible upon discontinuation. RBV dose reductions due to anemia occurred in 21.6% of the subjects in the T12/PR group and in 9.4% of the subjects in the Pbo/PR group during the telaprevir/placebo treatment phase. Blood transfusions were received by 2.5% of the subjects in the T12/PR group and

0.7% of the subjects in the Pbo/PR group during the telaprevir/placebo treatment phase, and ESAs were used by 1.0% and 0.8% of the subjects, respectively.

Decreased hemoglobin is an exposure dependent side effect of telaprevir, and the effect rapidly reverses after telaprevir discontinuation.

Figure 4. Placebo-Controlled Phase 2-3 Studies: Mean (SE) Values of Hemoglobin (g/L) Over Time – Overall Treatment Phase



SE: standard error
Source: Module 5.3.5.3/VX-950-SCS/Display SAF.B141

Retinopathy

In the placebo-controlled Phase 2 and 3 studies, retinopathy was reported in 11 (0.8%) subjects of the T12/PR group and in 1 (0.1%) subject in the Pbo/PR group during the telaprevir/placebo treatment phase. It remains unclear whether this difference in reported rates of retinopathy is a chance finding or not.

Laboratory findings

Lymphopenia and thrombocytopenia

Grade 4 lymphopenia occurred in 4.5% of telaprevir treated patients, compared to 0.9% with placebo. There was a higher frequency of oral candidiasis in patients treated with telaprevir. There does not appear to have been any difference between groups for other infection-related adverse effect entities, including opportunistic infections that have been associated with impaired cell-mediated immunity. There was an additive effect of telaprevir on the decrease in platelets seen during peginterferon therapy. As expected the risk of thrombocytopenia was higher with increasing degrees of hepatic fibrosis.

Serum creatinine, potassium and uric acid

Telaprevir use was associated with an on-treatment increase in serum creatinine of 5-10 umol/L, which was readily reversible on discontinuation. It is unclear whether this is an effect on the glomerular filtration rate or on creatinine disposition. The identification of older age and hypertension as risk factors for this side effect may indicate the former. This effect appears reversible on discontinuation of telaprevir.

Telaprevir also causes a mild on-treatment decrease in potassium. Hypokalemia of Grade 2 or higher during the telaprevir/placebo treatment phase was observed in 1.6% of subjects in the T12/PR group and 0.3% of subjects in Pbo/PR group. The tendency to lower potassium needs to be viewed, however, in relation to the mild QT-prolonging effects of telaprevir (see below), as hypokalemia is a factor increasing the risk for arrhythmia in the presence of QT prolongation.

During the telaprevir/placebo treatment phase, hyperuricemia of Grade 2 or higher was observed in 23.6% of subjects in the T12/PR group and in 3.2% of subjects in the Pbo/PR group. Gout was reported as an AE in 3 (0.2%) subjects in the T12/PR group and no subjects in the Pbo/PR group during the telaprevir/placebo treatment phase. One of the (inactive) metabolites of telaprevir is pyrazinoic acid, which is also an active metabolite of the antimycobacterial agent pyrazinamide. This is a known inhibitor of uric acid secretion.

Endocrine side effects

Thyroid-stimulating hormone levels above normal limits during the telaprevir/placebo treatment phase were observed in 8.1% of subjects in the T12/PR group and in 5.8% of subjects in the Pbo/PR group. Further analysis shows that the frequency of TSH increases in the overall treatment was similar for the telaprevir and placebo containing arms.

Hypothyroidism is well described in association with Peg-IFN/RBV treatment. Hypothyroidism was reported as an AE during the telaprevir/placebo treatment phase in 1.1% of subjects in the T12/PR group and 0.1% of subjects in the Pbo/PR group. The AE 'blood TSH increased' was reported in 0.4% and 0.3% of subjects in these groups, respectively. The reported frequency of hypothyroidism in the placebo group (0.1%) was surprisingly low. As a comparison, in the IDEAL study, the reported rate of hypothyroidism with pegIFN+ribavirin over 48 weeks was 5%, which is similar to the rate of TSH above normal limits in the placebo group. Thus differential reporting practices may be the reason for this discrepancy.

The increased incidence of hypothyroidism observed in the T12/PR group compared to the Pbo/PR group during the telaprevir/placebo treatment phase related, in the majority of cases, to a history of hypothyroidism and requirements for adjustment of TRT, and to a lesser extent new onset hypothyroidism.

QT-prolongation

For a telaprevir 1875 mg qd regimen, which yields a similar telaprevir exposure as does 750 q8h in combination with peginterferon alfa-2a (which for unknown reasons increases telaprevir exposure by 30-40%), the upper limit of the 90% CIs for the time-matched placebo-corrected change from reference in QTcF crossed the 10-ms threshold at 3 h, 5 h, and 24 h (maximum mean time-matched placebo-corrected change from reference in QTcF interval: 8.0 ms 90% CI: 5.10;10.90). There are no data on the effect on the QT interval of supratherapeutic exposures to telaprevir. Of note, syncope was reported somewhat more often in patients treated with telaprevir, but there were no deaths and no clear recorded relation of the event to ECG abnormality.There appears to have no events in the clinical trials reported indicative of torsade des pointes.

It is noted that very few patients in the telaprevir development program were co-treated with methadone, a known QT-prolongator extensively used in the target population. It is recognized that a DDI study with telaprevir and methadone has been performed, in which ECG was monitored and no alarming findings reported. Still, due to the risk of a pharmacodynamics interaction, ECG should be monitored during co-treatment with telaprevir and methadone.

Safety in special populations

Safety in subjects with advanced fibrosis and cirrhosis

Subjects with hepatic cirrhosis were enrolled in 3 of the 5 pooled placebo-controlled Phase 2-3 studies (Studies 106, 108, and C216). This pooled dataset contained more subjects with cirrhosis at baseline in the T12/PR group than in the Pbo/PR group (179 [13.3%] subjects versus 64 [8.4%] subjects), which is due to the pre-specified randomization scheme for Study C216.

In the T12/PR group, both SAEs and AEs of at least Grade 3 were reported more frequently in subjects with cirrhosis than in subjects in the other fibrosis categories as shown in table 63 below. No new important safety signal was derived from this subgroup analysis.

Table 63. Placebo-Controlled Phase 2-3 Studies: Summary of Adverse Events by Fibrosis Category – Telaprevir/Placebo Treatment Phase

	T12/PR (750 mg q8h)				Pbo/PR			
Number (%) of subjects with:	No or minimal fibrosis N = 406	Portal fibrosis N = 518	Bridging fibrosis N = 243	Cirrhosis N = 179	No or minimal fibrosis N = 262	Portal fibrosis N = 299	Bridging fibrosis N = 139	Cirrhosis N = 64
SAEs	31 (7.6)	29 (5.6)	14 (5.8)	19 (10.6)	6 (2.3)	9 (3.0)	4 (2.9)	3 (4.7)
AEs of at least Grade 3	94 (23.2)	103 (19.9)	61 (25.1)	63 (35.2)	3[illegible] (12.6)	34 (11.4)	20 (14.4)	7 (10.9)
AEs leading to permanent discontinuation of T/Pbo	55 (13.5)	65 (12.5)	44 (18.1)	27 (15.1)	12 (4.6)	14 (4.7)	4 (2.9)	1 (1.6)

N: number of subjects with data

Safety in HCV-HIV co-infected subjects

The safety profile of telaprevir in HCV/HIV co-infected patients is currently being studied in a Phase 2a study (Study 110); This is a multicenter, two-part, randomized, double-blind, placebo-controlled, parallel-group study in subjects with chronic HCV-1/HIV-1 co-infection who were treatment-naïve for HCV and not receiving highly-active antiretroviral therapy (HAART) (Part A) or receiving HAART (Part B).

Data will be submitted from this study when available.

Safety in patients with hepatic impairment or with renal impairment

Hepatic impairment:

Two multiple-dose Phase I studies (006 and 012) were conducted to assess the pharmacokinetics, safety, and tolerability of telaprevir in subjects with either mild hepatic impairment (Child-Pugh Class A) or moderate hepatic impairment (Child-Pugh Class B). The safety data from these studies were generally consistent with those of other Phase 1 studies in healthy subjects who did not have such comorbidities. There were no AEs of unusual frequency or severity in subjects with mild hepatic impairment compared to in healthy subjects.

Renal impairment:

One Phase I study (C132) assessed the pharmacokinetics, safety, and tolerability of a single dose of telaprevir in subjects with severe renal impairment (calculated CrCl < 30 mL/min). The safety data from this study were consistent with those of Phase 1 studies in healthy subjects who did not have

such comorbidities; there were no or otherwise clinically relevant findings that have not already been described.

Pregnancy and lactation

In the Phase 2-3 telaprevir study program:

- 3 pregnancies were reported after maternal exposure to telaprevir in combination with Peg-IFN and RBV. These pregnancies were all reported during follow-up (163 to 243 days after the last dose of telaprevir). Of these subjects, 1 had a normal outcome, 1 subject opted for elective abortion, and 1 subject refused to provide follow-up information.
- 3 pregnancies were reported after paternal exposure to telaprevir in combination with Peg-IFN and RBV. Two of these pregnancies of partner were reported after the last intake of telaprevir (15 and 17 days) but during Peg-IFN/RBV. One partner pregnancy was reported during follow-up (193 days after the last dose of telaprevir). Two subject's partners opted for an elective abortion. The outcome was unknown due to the subject being lost to follow-up for the third subject.

It is not known whether telaprevir is excreted in human milk. No data on lactation and effects to a newborn child are available from the clinical studies.

Because of its teratogenic potential, the use of ribavirin is contraindicated in pregnancy, and adequate contraception required during therapy.

Safety related to drug-drug interactions and other interactions

Because telaprevir is a substrate and inhibitor of CYP3A, a substrate of P-gp, telaprevir can affect the PK of co-administered drugs that are CYP3A substrates and/or transported by P-gp. Telaprevir PK may also be affected by inhibitors and inducers of CYP3A and/or P-gp.

The high potential for drug interactions with telaprevir warrant some clear recommendations to prescribers in the SmPC/PIL. Notably, as a safety precaution, because of the potential for pharmacokinetic and/or pharmacodynamic interactions that may increase the risk of QT interval prolongation, telaprevir must not be administered concurrently with any Class Ia or III anti-arrhythmics, except for intravenous lidocaine. . Telaprevir must also not be administered with other drugs that may induce QT prolongation or Torsades de Pointes, and which are metabolized by CYP3A, unless an assessment of the benefit/risk justifies its use. The SmPC adequately reflects the available information.

Discontinuation due to AES

The proportion of patients discontinuing all study drugs due to adverse effects were around 11% in the telaprevir groups and around 7% in the placebo group. The proportion of patients discontinuing telaprevir/placebo was around 15% in the telaprevir treatment arms and 4% in the placebo arms. Approximately 5% of treated patients discontinued telaprevir due to rash/pruritus related issues and 2.5-3% due to anemia.

2.5.3. Discussion on clinical safety

The pooled placebo-controlled phase II/III studies with telaprevir, forming the core of the safety database, include 1823 subjects that received a telaprevir regimen of 8, 12 or 24 weeks. Approximately 10% of telaprevir treated patients discontinued their entire treatment regimen due to

adverse effects, compared to 7% in the placebo group. Approximately 15% discontinued telaprevir due to AE, while 4% discontinued placebo. Median time on telaprevir was 12.1 weeks. Thirty-six percent of the patients were female, 11% were non-white, 1.5% were >65 years of age, 13.3% had cirrhosis. Virtually no patients had CrCL <50 ml/min. There were no deaths during telaprevir treatment. The incidence of serious adverse events on telaprevir treatment was 6.6%, compared to 2.9% in the placebo group.

Rash including SCAR is the most important side effect of telaprevir, and the most important adverse effect cause of discontinuation. In the phase III studies, the applicant implemented a "rash management plan", which is the basis of the recommendation for rash management in the product information. The cutaneous safety of telaprevir will need to be followed post-marketing. Risk minimisation measures have been put in place as reflected in the RMP that include a Physician Education programme.

The other clinically major side effect is an additive effect on anemia which, if needed, is usually managed by ribavirin dose reduction. Also, there is an additive effect on peginterferon platetet decrease and lymphopenia, but not on neutrophil counts. The applicant will further describe the lymphopenia in terms of cellular subsets affected in ongoing trials, including those in patients with HIV/HCV co-infection. The risk of immune related disorders should be followed post-marketing.

When treating with telaprevir there was a transient and reversible rise in serum creatinine. It is unclear whether the increase in creatinine represents a decreased glomerular filtration or an otherwise altered creatinine disposition, though the identification of older age and hypertension as risk factors may indicate the former Studies on the effect of telaprevir on creatinine transport will be conducted.

Also, telaprevir treatment is associated with a modest decrease in s-potassium. The mechanism is not clear. Since telaprevir has a QT-prolongating potential, it is reassuring that more than grade 2 hypokalemia was rare, and that there were no clinical events clearly linked to ECG abnormalities. This isse is addressed in the product information.

Increased TSH levels were more common when treating with telaprevir than with placebo. Also, "hypothyroidism" was reported at a considerably higher frequency in telaprevir-treated patients – and at a comparably low rate in patients treated with peginterferon and ribavirin. As the frequency of TSH increases overall with telaprevir or placebo in the regimen is similar, it may be that TSH increases occur earlier with telaprevir therapy. Furthermore, most cases pertain to patients with a history of thyroid disease and/or thyroid replacement therapy. Thus it may be that telaprevir affects the disposition of T3 and T4. This is reflected in the product information.

Variants of retinal AE preferred terms occurred substantially more frequently during treatment with placebo. This may be a chance finding, but retinal adverse events need to be monitored post-marketing.

Conclusions on clinical safety

The addition of telaprevir leads to an increase in adverse events and treatment discontinuations, primarily due to rash or an additive effect to the anemia of ribavirin and peginterferon. A number of cases of severe skin reactions occurred during the development program. On the whole, the applicant has addressed the risks in an acceptable way in the proposed SmPC and the risk management plan, and there are no major safety concerns that have not been addressed by the applicant.

2.6. Pharmacovigilance

Detailed description of the 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

The applicant submitted a risk management plan, which included a risk minimisation plan

Table 64. Overall Summary of the Risk Management Plan

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Important identified risks:		
Rash and Severe Cutaneous Adverse Reactions	Routine pharmacovigilance as outlined in Section 2.1 The Applicant will participate in the ongoing European RegiSCAR study to monitor and characterise SCARs in patients receiving INCIVO, as described in Section 2.3. Bi-annual reports received from RegiSCAR of telaprevir-associated SCAR events will be included within PSURs The Applicant will utilise a standard questionnaire to obtain follow-up information for any individual reports of a suspected SCAR. A GWAS is planned to identify potential genetic risk factors associated with severe rash and SCAR in subjects receiving telaprevir combination therapy, as described in Section 2.3. Continued evaluation and characterisation of mild and moderate rash through a rash substudy of Study C211, as described in Section 2.3 and 2.4. Evaluation of rash in two HCV/HIV co-infection studies (110 and the planned Phase 3 study) as described in Section 2.3 and 2.4.	Section 4.4 of the proposed SmPC lists severe rash and includes recommendations for monitoring and management of cutaneous reactions. Rash, Pruritus, Eczema, Swelling face, DRESS, Urticaria, Exfoliative rash, and SJS are listed as ADRs in Section 4.8 of the proposed SmPC. The Rash Educational Programme for prescribers, will mitigate the risk for rash and SCARs The educational materials, including an INCIVO Safety Review Booklet, including a dermatological reactions summary, and an algorithm-tri-fold in a pocket format, will be submitted to the national competent authorities.
Anaemia	Routine pharmacovigilance as outlined in Section 2.1.	Section 4.4 of the proposed SmPC lists anaemia and recommends baseline haemoglobin prior to starting treatment and includes advice on monitoring of haemoglobin levels during INCIVO treatment, and guidance in case discontinuation of INCIVO or RBV is required. Anaemia is listed as ADR in Section 4.8 of the proposed SmPC
Lymphopenia	Routine pharmacovigilance as outlined in Section 2.1 Analyses of changes in lymphocyte subsets in Study C211, and analyses of changes in	Section 4.4 of the proposed SmPC recommends advice on monitoring of haematological tests prior to and during INCIVO treatment.

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
	total lymphocyte and lymphocyte subsets, and of AEs relating to possible opportunistic infections in Study 110 and the planned Phase 3 study in HCV/HIV co-infection, as described in Section 2.3 and 2.4.	Lymphopenia is listed as ADR in Section 4.8 of the proposed SmPC
Thrombocytopenia	Routine pharmacovigilance as outlined in Section 2.1	Section 4.4 of the proposed SmPC recommends baseline platelet counts prior to starting treatment, and includes advice on monitoring of haematological tests during INCIVO treatment. Thrombocytopenia is listed as ADR in Section 4.8 of the proposed SmPC
Blood creatinine increased	Routine pharmacovigilance as outlined in Section 2.1 Continued evaluation in ongoing and planned clinical studies (110, C211, C219, HPC3006 and the planned Phase 3 study in HCV/HIV co-infection), as described in Section 2.3 and 2.4.. In vitro evaluation of the effect of telaprevir on the OCT2 creatinine transporter protein as described in Section 2.3.	Section 4.4 of the proposed SmPC recommends baseline creatine clearance prior to starting treatment, and includes advice for monitoring of chemistry tests during INCIVO treatment. Blood creatinine increased is listed as ADR in Section 4.8 of the proposed SmPC
Hypothyroidism	Routine pharmacovigilance as outlined in Section 2.1	Section 4.4 of the proposed SmPC recommends adequately controlled thyroid function at baseline and advises that TSH levels should be evaluated prior to starting treatment and for monitoring of chemistry tests during INCIVO treatment. The proposed SmPC also advises that treatment should be as clinically appropriate, and that adjustment of TRT may be required in patients with pre-existing hypothyroidism. Hypothyroidism is listed as ADR in Section 4.8 of the proposed SmPC
Hyperuricaemia	Routine pharmacovigilance as outlined in Section 2.1	Section 4.4 of the proposed SmPC includes advice that UA should be evaluated prior to starting treatment, and for monitoring of chemistry tests to be conducted during INCIVO treatment. Hyperuricaemia and gout are listed as ADRs in Section 4.8 of the proposed SmPC.
Retinopathy	Routine pharmacovigilance as outlined in Section 2.1	Retinopathy is listed as ADR in Section 4.8 of the proposed SmPC.
Anorectal disorders	Routine pharmacovigilance as outlined in Section 2.1	Section 4.8 of the proposed SmPC lists haemorrhoids, proctalgia, anal pruritus, anal fissures and proctitis as ADRs and further describes anorectal disorders in clinical trials.
Important potential risks:		
Electrocardiogram QT prolonged	Routine pharmacovigilance as outlined in Section 2.1 Continued evaluation of the effect of telaprevir on QT intervals in 3 ongoing studies (Studies 110, C211, and C219) as described in Section 2.3 and 2.4.	Section 4.4 of the proposed SmPC includes; a contraindication of drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or lifethreatening events and Class I or III antiarrhythmics (except intravenous lidocaine), guidance on the concomitant use of medicinal products that are known to induce QT prolongation and which are CYP3A substrates, description of subject populations and past or current conditions in which INCIVO should be avoided or should be used with caution, and advice on monitoring of electrolyte disturbance prior to and during treatment with

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
		INCIVO
Development of drug resistance	Routine pharmacovigilance as outlined in Section 2.1 Continued evaluation through a virological follow-up study (Study 112) as described in Section 2.3 and 2.4. Options to assess the adherence to recommended stopping rules through a drug utilisation study are being evaluated, as described in Section 2.3	Section 4.2 of the proposed SmPC states that INCIVO should be used with Peg-IFN-alfa and RBV, and that the dose of INCIVO should not be reduced, to prevent treatment failure. In addition the proposed SmPC notes that taking INCIVO without food or without regard to the dosing interval may result in decreased plasma concentrations of telaprevir which could reduce it's therapeutic effect. It is indicated that HCV RNA levels should be monitored and virologic stopping rules are specified.
Important missing information		
Use in children (<18 years)	Routine pharmacovigilance as outlined in Section 2.1 Safety monitoring of studies included in the PIP, including a Phase 2 study in chronic hepatitis C infected children, as described in section 2.3 and 2.4.	Section 4.2 and 4.4 of the proposed SmPC states that INCIVO is not recommended in children and adolescents younger than 18 years of age because safety and efficacy have not been established in this population.
Use in HCV/HIV co-infection	Routine pharmacovigilance as outlined in Section 2.1 Continued evaluation through Study 110, the planned Phase 3 study in HCV/HIV coinfection, the planned EAP study HPC3005, the ongoing drug-drug interaction studies (with raltegravir [HEP1001], and with etravirine and rilpivirine [TMC125-IFD1001]) and from the results made available to the Applicant from the IIS TELAPREVIH sponsored by ANRS as described in Section 2.3 and 2.4. Options to assess the use of telaprevir in patients with HCV/HIV co-infection through a drug utilisation study are being evaluated, as described in Section 2.3	Section 4.4 of the proposed SmPC which states that there is limited clinical data assessing INCIVO in combination with Peg-IFN and RBV in HCV treatment-naïve patients who were either not on HIV antiretroviral therapy or were being treated with efavirenz or atazanavir/rtv in combination with TDF and emtricitabine or lamivudine.
Use in elderly (>65 years)	Routine pharmacovigilance as outlined in Section 2.1	Section 4.2 of the proposed SmPC which states that there is limited data available of the use in patients older than 65 years.
Use in moderate hepatic impairment (CPB)	Routine pharmacovigilance as outlined in Section 2.1 Evaluation of the pharmacokinetics, safety and tolerability of telaprevir in nonchronic hepatitis C-infected subjects with moderate hepatic impairment in the planned study to further investigate the mechanism behind the lower exposure to telaprevir in subjects with hepatic impairment, as described in section 2.3 and 2.4.	Section 4.2 and 4.4 of the proposed SmPC states that dose modification of INCIVO is not required when administered to hepatitis C patients with mild hepatic impairment (Child-Pugh A, score 5-6). INCIVO is not recommended in patients with moderate to severe hepatic impairment (Child-Pugh B or C, score ≥ 7) or decompensated liver disease.
Use in liver transplantation	Routine pharmacovigilance as outlined in Section 2.1 Evaluation of telaprevir treatment in liver transplant subjects with genotype 1 chronic hepatitis C in the planned study HPC3006 as described in Section 2.3 and 2.4 Options to assess the use of telaprevir in liver transplant recipients through a drug utilisation study are being evaluated, as described in Section 2.3.	Section 4.4 of the proposed SmPC states that no clinical data are available regarding the treatment of pre-, peri-, or post-liver or other transplant patients with INCIVO in combination with Peg-IFN-alfa and RBV.
Use in moderate and severe renal impairment	Routine pharmacovigilance as outlined in Section 2.1	Section 4.2 and 4.4 of the proposed SmPC states that the safety and efficacy have not been established in patients with moderate or severe renal impairment (CrCl < 50 ml/min) or

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
		in patients on hemodialysis.
Use in HCV/HBV co-infection	Routine pharmacovigilance as outlined in Section 2.1 Options to assess the use of telaprevir in patients with HCV/HBV co-infection through a drug utilisation study are being evaluated, as described in Section 2.3.	Section 4.4 of the proposed SmPC states that no data exist on the use of INCIVO in patients with HCV/HBV co-infection.
Use in other HCV genotypes	Routine pharmacovigilance as outlined in Section 2.1	Section 4.4 of the proposed SmPC states there are not sufficient clinical data to support the treatment of patients with HCV genotypes other than genotype 1. Therefore, the use of INCIVO in patients with non-genotype-1 HCV is not recommended.
Use in pregnancy and lactation	Routine pharmacovigilance as outlined in Section 2.1, including targeted follow-up of spontaneous reports of exposure to telaprevir during pregnancy, including pregnancy outcome. Reporting of pregnancy after exposure to telaprevir combination therapy in female patients, or in partners of male patients, to the Ribavirin Pregnancy Registry.	Section 4.4 and 4.6 of the proposed SmPC includes guidance on the need to avoid pregnancy and lactation during treatment with INCIVO and advice regarding the requirements for contraception during treatment with INCIVO.
Repeated use of telaprevir	Routine pharmacovigilance as outlined in Section 2.1	Section 4.2 and 4.4 of the proposed SmPC state that there are no clinical data on re-treating patients who have failed HCV NS3-4A protease inhibitor-based therapy.
Drug-drug interactions	Routine pharmacovigilance as outlined in Section 2.1 Continued evaluation through planned in vitro studies of (i) the involvement of CYP2C8 and other enzymes such as aldo-keto reductases in the metabolism of telaprevir ; (ii) the potential induction effects of telaprevir and the metabolite VRT-127394 on CYP1A2, CYP2C9, CYP2C19, CYP2B6 and CYP3A4 including the measurement of RNA levels. If induction cannot explain the observed in-vivo results, the mechanism for decreased exposure will be further investigated; (iii) the potential effect of telaprevir on UGT1A3, 1A9 and 2B7; (iv) the potential effect of telaprevir and the metabolite VRT-127394 on a broad range of transporters such as organic anion-transporting polypeptide OATP1B1 and efflux transport proteins including MRPs, and the potential effect of telaprevir on OATs. In addition continued evaluation through the ongoing clinical interaction study of buprenorphine/naloxone as described in Section 2.3 and 2.4.	Section 4.3 of the proposed SmPC lists drugs for which co-administration with INCIVO are contraindicated. Section 4.5 of the proposed SmPC lists drugs for which coadministration with INCIVO are contraindicated, or should be used with caution, or should be avoided, or requires specific monitoring, and provides a tabular summary of established and other potentially significant drug interactions.

The CHMP considered that the applicant should take the following points into consideration at the next update of the RMP and no later that the submission of the first PSUR: the Applicant should include final outcome measures (e.g. ADR occurrence, risk avoidance) in the proposal of assessment of the effectiveness of the rash educational programme.

The following additional risk minimisation activities were required:

INCIVO Rash Educational Programme:

A Rash Educational Programme will be carried out by the applicant to mitigate the risk for rashes and SCARs including DRESS and SJS in patients treated with INCIVO by ensuring prescriber awareness and providing guidance on appropriate management of INCIVO associated cutaneous reactions.

User consultation

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

3. Benefit-Risk Balance

Benefits

The primary endpoint in the pivotal trials is sustained viral response (SVR), defined as undetectable virus 24 weeks after the end of therapy. This is virtually equivalent of cure of hepatitis C, as evidenced by data indicating that less than 1% of patients will relapse after this time-point. Achieving SVR effectively stops the progression of the liver injury caused by hepatitis C virus. SVR is a universally accepted endpoint in trials aiming at the cure of HCV infection.

Beneficial effects

In the pivotal -108 study in treatment naive patients, the SVR rate in the 12 week telaprevir arm was 74.7%, a 30.9% increase compared to the placebo+peginterferon alfa-2a+ribavirin arm. Shortened treatment duration compared to the present standard of care was possible for nearly 60% of treatment naive patients. The advantage of telaprevir was apparent across demographic and baseline disease categories.

In the pivotal -216 study in treatment experienced patients SVR rates in all three prior response subcategories were statistically significantly superior to placebo, with a total difference in SVR rates of + 47% with the addition of telaprevir to peginterferon alfa-2a and ribavirin. The advantage of adding telaprevir was also apparent regardless of viral subtype, baseline viral load or degree of liver injury. Also, in treatment naive and –experienced patients increased efficacy was evident across IL28B genotypes.

Available long term follow up data indicate the durability of SVR obtained with telaprevir. The addition of telaprevir to regimens with peginterferon alfa-2a and ribavirin represents a major advance in the treatment of the genotype 1, the quantitatively dominant HCV genotype.

Uncertainty in the knowledge about the beneficial effects

The optimal duration of therapy in treatment naive patients with cirrhosis is unclear. Also, the suggested treatment algorithm for relapsers is to some extent based on inference, though, taking the totality of data into account the evidence is considered sufficient for its approval. Moreover, it is recognised that treatment durations might be further individualised, entailing the possibility of, e g., still shorter duration in very early responders. The efficacy of telaprevir in several important subgroups of patients, such as HIV co-infected patients and paediatric patients have not been studied. The possibility of using telaprevir in novel treatment regimens (e.g., regimens without peginterferon) in patients with decompensated liver disease is unclear, as there is considerable uncertainty about the appropriate dose to use. Clarifying the reasons for the low exposure to telaprevir found in non-HCV infected patients with moderate liver impairment (Child Pugh B) is of importance to clarify the potential for use of telaprevir in this population. Finally, the impact on SVR of baseline resistant variants in telaprevir-naive patients, which can be detected by population sequencing, has not yet been fully clarified due to low frequency of such predominant baseline variants.

Risks

The main risks identified during the telaprevir development program include severe rash and serious cutaneous adverse reactions, and the selection of drug resistant variants in patients failing to reach SVR. Other risks include a moderate propensity to QT prolongation (supratherapeutic telaprevir

exposure data are lacking). This may be a concern mainly when telaprevir is co-prescribed with other QT-prolongators, the most important in the target population being methadone.

Unfavourable effects

The major known risk associated with telaprevir therapy is severe rash, including serious cutaneous reactions. Approximately 5% of patients experience a grade 3 rash during treatment, and there were three at least possible cases of Stevens Johnson syndrome during the telaprevir development program. The frequency of severe cutaneous events (DRESS, Stephens Johnson Syndrome) is less than 0.5%.

Increased on treatment rates of anemia, lymphopenia and retinopathy were also seen. Also, in most cases treatment failure is associated with the selection of a telaprevir resistant viral population, likely cross resistant to other drugs in the class (though not to antivirals of other classes). Follow-up data indicate a gradual reversion back to the baseline population after treatment discontinuation in most patients. The consequences of the selection of resistance for future treatment attempts, however, remain unclear.

The applicant has instituted adequate virological stopping rules to prevent unnecessary exposure to failing telaprevir regimens. Also, the applicant has agreed to present data in the SmPC on the relation between lead-in response in the DS arm of the pivotal -216 study in the respective categories of prior non-responders, and the likelihood of SVR. Such data may in some cases be helpful for the clinician to make an informed decision on whether to treat with telaprevir or to wait for future treatment options, in patients that may have a relatively low likelihood of SVR even with the addition of telaprevir to peginterferon alfa-2a and ribavirin.

With some minor additions by the CHMP, the applicant has instituted appropriate warnings in the SmPC concerning the proclivity to QT-prolongation, including the risk of enhanced effects due to drug interactions.

Uncertainty in the knowledge about the unfavourable effects

While telaprevir related cutaneous adverse events and their management have been carefully characterised in the development program, there remains some uncertainty on how this will impact telaprevir treatment in a "real life" setting outside clinical trials. There was an excess reporting of retinopathy events during telaprevir treatment. It is unclear whether there is causality or if this is a chance finding. Importantly, as stated above, the consequences of selected resistant variants in patients failing therapy, as regards the efficacy of future therapies including NS3/4A inhibitors, are still not fully elucidated. As ribavirin is a teratogen, adequate anti-conceptive measures are necessary during therapy. Telaprevir causes a moderate decrease in ethinylestradiol and minor decrease in norethindrone exposure. It is unknown whether the magnitude of the decrease is sufficient to impair the efficacy of combination oral contraceptives and therefore appropriate warnings and recommendations have been included in the SmPC. Finally, it is unknown whether there are any human-specific metabolites not present in non-clinical toxicity studies.

Importance of favourable and unfavourable effects

Approximately 70% of HCV infections in the Western world are genotype 1. After about 20 years of infection, around 20–30% of patients with HCV will have progressed to cirrhosis, 5–10% will have end stage liver disease and 4–8% will have died of liver-related causes. In patients with cirrhosis, the 5-year risk of hepatic decompensation is approximately 15-20% and the risk of hepatocellular carcinoma 10%. HCV is the most common cause of liver transplantation in Europe. In this light, the public health gain with telaprevir therapy is likely considerable, and this benefit also applies to many of the individuals that will be cured by telaprevir. While the occurrence of severe cutaneous reactions is

recognised and is an important concern in the management of patients treated with telaprevir, these were reversible and there were no fatal cases in the development program. As previously stated, the putative negative effects of selection of resistant variants is not full characterised, but may be more limited than thought prior to the emerging results of the telaprevir long-term follow up study.

Benefit-risk balance

Reaching SVR effectively ends the progression of HCV-related hepatic injury. In this light, the greatly increased SVR rates seen with telaprevir therapy must be weighed against a higher risk of side effects the main one being rash, including serious cutaneous reactions, and the risk of incurring drug resistance, which theoretically could compromise future treatment attempts, in case of failure. Rash events are in most cases mild to moderate, and also the severe cases generally remit after discontinuation of telaprevir. It is recognised that a handful of severe cutaneous adverse reactions were seen during the program, though no deaths. This remains an important risk associated with telaprevir therapy. However, a number of measures are foreseen to mitigate the risk as reflected in the Risk management plan; these include close monitoring of dermatological safety profile of telaprevir and a physician educational programme aimed at advising physicians on the management of rash and severe cutaneous reactions. In addition appropriate warnings are instituted in the SmPC. Overall the risk of severe rash/serious cutaneous reactions does not outweigh the benefit of greatly increased SVR rates. Regarding the risk associated with selection of resistance, this only pertains to patients that fail telaprevir-based therapy. Such patients would not have reached SVR with the present standard of care. Available data indicate that in most cases there is a reversion to wild-type after discontinuation. Even if there in fact would be consequences for retreatment due to resistant variants selected during telaprevir therapy, this does not outweigh the benefit of the increased SVR rates with telaprevir.

4. Recommendations

Outcome

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

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the marketing authorisation

- ***Pharmacovigilance system***

The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1. of the Marketing Authorisation is in place and functioning before and whilst the medicinal product is on the market.

- ***Risk Management Plan (RMP)***

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

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

The Marketing Authorisation Holder shall agree to the format and content of the healthcare professional educational pack with the National Competent Authority prior to launch in the Member State.

The Marketing Authorisation Holder shall ensure that all physicians who are expected to prescribe or use INCIVO are provided with a healthcare professional educational pack containing the following:

- The Summary of Product Characteristics
- The Patient Information Leaflet
- The Physician Leaflet

The Physician Leaflet should contain the following key elements:

- Rash and Severe Cutaneous Adverse Reactions safety data from Phases 2 and 3
- Incidence of rash and severe cutaneous reactions
- Grading and management of rash and severe cutaneous reactions, particularly with respect to criteria for the continuation or discontinuation of telaprevir and the other treatment components.
- Pictures of rash according to different grades

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

The Member States should ensure that all conditions or restrictions with regard to the safe and effective use of the medicinal product described below are implemented:

The Member States shall agree the final healthcare educational pack with the Marketing Authorization Holder (MAH) prior to launch of the product in their territory.

The Member States shall ensure that the MAH provides all physicians who are expected to prescribe or use INCIVO a healthcare professional educational pack containing the following:

- The Summary of Product Characteristics
- The Patient Information Leaflet
- The Physician Leaflet

The Physician Leaflet should contain the following key elements:

- Rash and Severe Cutaneous Adverse Reactions safety data from Phases 2 and 3
- Incidence of rash and severe cutaneous reactions
- Grading and management of rash and severe cutaneous reactions, particularly with respect to criteria for the continuation or discontinuation of telaprevir and the other treatment components.
- Pictures of rash according to different grades

New active substance status

Based on the CHMP review of data on the quality, non-clinical and clinical properties of the active substance, the CHMP considers that telaprevir is to be qualified as a new active substance.