20 March 2014
EMA/CHMP/285947/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

OLYSIO

International non-proprietary name: SIMEPREVIR

Procedure No. EMEA/H/C/002777/0000

Note

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

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List of abbreviations

AASLD	American Association for the Study of Liver Diseases
ADR	adverse drug reaction
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCRP1	breast cancer resistance protein 1
b.i.d.	bis in die; twice daily
BMI	body mass index
BSEP	bile salt export pump
CDER	Center for Drug Evaluation and Research
cEVR	complete early virologic response
CHMP	Committee for Medicinal Products for Human Use
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum plasma concentration
CRF	Case Report Form
CSR	Clinical Study Report
CYP	cytochrome P450
DAA	direct-acting antiviral agent
DBP	diastolic blood pressure
DDI	drug-drug interaction
EASL	European Association for the Study of the Liver
ECI	event of clinical interest
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOT	end of treatment
eRVR	extended rapid virologic response
ESI	event of special interest
FC	fold change
FDA	Food and Drug Administration
GAM	generalized additive modeling
GI	gastrointestinal
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV(-1)	human immunodeficiency virus (type 1)
ICH	International Conference on Harmonisation
IFN	interferon
INN	International Nonproprietary Name
i.v	intravenous
J-NDA	Japan-New Drug Application
Ki	kinetic inhibition constant
MAA	Marketing Authorization Application
MDRD	Modification of Diet in Renal Disease
MRP2	multidrug resistance-associated protein 2

NDA	New Drug Application
NNRTI	non-nucleoside reverse transcriptase inhibitor
NOAEL	no observed adverse effect level
N(t)RTI	nucleoside (nucleotide) reverse transcriptase inhibitor
NTCP	Na+ taurocholate cotransporting polypeptide
OAT	organic anion transporter
OATP	organic anion transporting polypeptides
PBO	placebo
PegIFN(α)	pegylated interferon (alfa)
PegIFN/RBV	combination of PegIFN and RBV
P-gp	P-glycoprotein
PI	protease inhibitor
PIP	Paediatric Investigation Plan
PMDA	Pharmaceuticals and Medical Devices Agency (in Japan)
PR	PegIFN and RBV
PT	preferred term
q.d.	quaque die; once daily
QTc	QT interval corrected for heart rate
RBV	ribavirin
RGT	response-guided treatment
SBP	systolic blood pressure
RVR	rapid virologic response
SVR	sustained virologic response
t_{max}	time to reach Cmax
UGT1A1	uridine diphosphate glucuronosyltransferase polypeptide 1A1

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Janssen-Cilag International N.V. submitted on 24 April 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for OLYSIO, 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 July 2012.

The applicant applied for the following indication:

"*Olysio is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 or genotype 4 infection, in combination with peginterferon alfa and ribavirin, in adults with compensated liver disease (including cirrhosis) with or without human immunodeficiency virus-1 (HIV-1) co-infection who are treatment-naïve or who have failed previous interferon therapy (pegylated or non-pegylated) with or without ribavirin (see section 5.1)*."

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that Simeprevir was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0276/2012 on the agreement of a paediatric investigation plan (PIP).

New active Substance status

The applicant requested the active substance simeprevir contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advices from the CHMP on 19 March 2009, 18 November 2010, and 20 October 2011. The Scientific Advices pertained to insert quality, non-clinical and clinical aspects of the dossier.

Licensing status

A new application was filed in the following countries: Switzerland, South Africa, Australia, New Zealand, Peru, Mexico and Brazil. The product is licensed in USA, Canada, Russia and Japan.

1.2. Manufacturers

Manufacturer responsible for batch release

Janssen-Cilag S.p.A.
Via C. Janssen
Borgo San Michele
Latina
04100
Italy

1.3. Steps taken for the assessment of the product

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

Rapporteur: Arantxa Sancho-Lopez Co-Rapporteur: Daniela Melchiorri

- The application was received by the EMA on 24 April 2013.
- The procedure started on 22 May 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 2 August 2013 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 9 August 2013 (Annex 2).
- During the meeting on 19 September 2013, 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 September 2013 (Annex 4).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 November 2013.
- The integrated inspection report of the GCP inspections carried out at two clinical investigator sites in New Zealand and one clinical investigator site in Canada, between 18 September and 29 October 2013 was issued on 29 November 2013. .
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 30 December 2013 (Annex 5).
- During the CHMP meeting on 23 January 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant (Annex 6).
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 17 February 2014.
- During the meeting on 20 March 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to OLYSIO.

2. Scientific discussion

2.1. Introduction

HCV infection is a serious human liver health problem. Persistent HCV infection can lead to chronic hepatitis C, which is a significant risk of serious hepatic diseases such as hepatic steatosis, hepatic fibrosis, cirrhosis and hepatocellular carcinoma.

Combination of pegylated interferon (PEG-IFN) plus ribavirin (RBV) was considered the standard of care for HCV genotype 1 (GT1) infection until 2011, when the first DAAs (boceprevir and telaprevir) were approved. For the other HCV genotypes, the PEG-IFN plus ribavirin treatment regimen remains the standard of care.

Telaprevir and boceprevir were granted an indication in GT1-infected patients, in combination with peginterferon alfa and ribavirin. At the time of the approval of these medicines in Europe, there were no large studies on-going with different combinations e.g. interferon-free regimens. Moreover, it had indeed only very recently been demonstrated for products in development that SVR could be reached without an interferon. Thus, the only drugs for which combination therapy could be relevant for these DAAs, were PEG+RBV, both of which were needed for reasonable efficacy.

Presently, an entirely different landscape is emerging in the treatment of chronic hepatitis C. DAAs of four distinct classes (NS3/4A protease inhibitors, NS5A inhibitors, non-nucleoside and nucleos(t)ide inhibitors of the NS5B polymerase) are now in advanced stages of development. Sofosbuvir, an inhibitor of the HCV NS5B RNA-dependent RNA polymerase, has recently been approved in the EU. Developmental drugs of all of these classes have been studied in various combinations (including with and without PEG-IFN and ribavirin), with agents of each class having shown efficacy contributions when combined with the others.

In this respect, the evolving treatment landscape for CHC now bears similarity to that in HIV, where the beneficial antiviral effect of combining agents that lack evidence of cross resistance is well established. Also, it is anticipated that regimen selection for patients with experience of failure on regimens containing DAA will be individualised based on an understanding of resistance and cross-resistance, like in the HIV field. In summary, the evolving field of hepatitis C therapeutics is similar to that of antiretroviral therapy in the following aspects:

- Combination therapy is anticipated in all cases
- Agents with different mechanisms of action or lack of cross-resistance consistently show additive antiviral effects
- Failure of antiviral therapy is in many cases associated with selection of drug-resistant viral variants which may impact future therapeutic option. Furthermore, in hepatitis C, there are naturally occurring viral polymorphisms that impact the activity of some agents.
- Consequently, individual viral drug susceptibility will need to be taken into account when selecting an appropriate combination regimen

Antiretrovirals used against HIV are generally approved for use “in combination with other agents”, with the particular information needed for rational regimen selection provided in relevant sections

of the SmPC. The emerging treatment landscape indicates that the same approach would be appropriate for hepatitis C medicines in the light of the numerous combinations of medicinal products in this field.

Thus, the CHMP considers that there is sufficient evidence to indicate the HCV medicines for use “in combination with other medicinal products”. The particular information for each compound, which is needed for rational regimen selection, should be provided in the relevant sections of the SmPC (i.e. mainly 4.2, 4.5, 5.1) as appropriate.

2.2. Quality aspects

2.2.1. Introduction

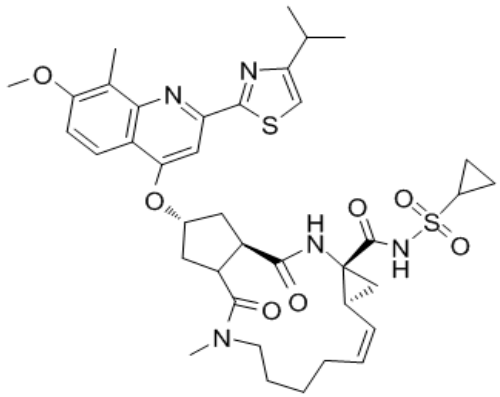
Olysio is presented as hard capsules containing 150 mg of simeprevir, in the form of sodium salt, as the active substance.

Other ingredients are: sodium lauryl sulphate, magnesium stearate, colloidal anhydrous silica, croscarmellose sodium and lactose monohydrate (components of the capsule content), gelatine and titanium dioxide (components of the capsule shells), shellac and iron oxide black (components of the black printing ink).

The capsules are packed in polyvinylchloride/polyethylene/polyvinylidenechloride aluminium (PVC/PE/PVDC/Alu) push-through blisters.

2.2.2. Active Substance

Simeprevir (INN) is chemically designated as 2R,3aR,10Z,11aS,12aR,14aR)-N-(cyclopropylsulfonyl)-2-[[2-(4-isopropyl-1,3-thiazol-2-yl)-7-methoxy-8-methyl-4-quinolinyl]oxy]-5-methyl-4,14-dioxo 2,3,3a,4,5,6,7,8,9,11a,12,13,14,14a, tetradecahydrocyclopenta[c]cyclopropa[g][1,6]diazacyclotetradecinen-12a(1H)-carboxamide, and has the following structure:



Simeprevir is a white to almost white crystalline powder. The active substance is optically active. It is a single enantiomer containing 5 asymmetric carbon atoms (chiral centres) with fixed

configurations: *R, R, S, R, R* at the C2, C3a, C11a, C12a, C14a chiral centres respectively and one stereogenic centre: (Z)-double bond. The substance is non-hygroscopic. It is practically insoluble in aqueous media over a wide pH range and solubility in organic solvents varies.

In Biopharmaceutics Classification System (BCS) simeprevir is classified as a Class IV compound (expressing low solubility and low permeability).

Simeprevir exhibits polymorphism, Polymorph I is the most thermodynamically stable form. Other crystal forms and transient solvates observed during the polymorph screening study have all been found to be less thermodynamically stable than Polymorph I. Sufficient evidence was provided to demonstrate that Polymorph I is obtained by the employed manufacturing process of the active substance.

Manufacture

The synthesis of simeprevir consists of eight steps. All steps include a chemical transformation but only 2 intermediates and simeprevir active substance obtained in step 5, 6 and 8, respectively, are isolated. The manufacturing process has been suitably described in flow charts and a narrative description. The length of the synthesis was justified in terms of control of purity profile of starting materials.

A science-based criticality analysis approach based on the ICH Guidelines Q7 and Q8 to determine the critical steps and controls for the active substance manufacturing process was employed. Based on an extensive development knowledge, the active substance manufacturing process was systematically evaluated to determine which process steps, process parameters and material attributes have an impact on the critical quality attributes (CQAs) of the active substance. For all critical process parameters (CPPs) proven acceptable ranges (PARs) have been established, however no design space (DS) was claimed for the manufacturing process. PARs implemented for the CPPs of the synthesis were confirmed by performing boundary experiments at the proposed limits of the PARs and compared to the experiments done with CPPs set at target values. The purity results at all synthesis steps and the final active substance were comparable and within the applicable specifications, confirming that the synthesis performed within the PARs will result in the substance meeting its purity specifications. Therefore, the PARs of the CPPs were considered justified.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Confirmation of the chemical structure of simeprevir was provided by elemental analysis (confirmation of the determined elementary composition), spectroscopic methods as UV-VIS, IR, ^{1}H-NMR, ^{13}C-NMR as well as by mass spectral (MS) analysis.

Potential and actual impurities were well discussed with regards to their origin and characterised. No potential genotoxic impurities were identified.

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

The active substance specification includes tests for appearance, identification (IR and HPLC), assay (HPLC), chromatographic purity (HPLC), residual solvents (GC), water content (KF), residue on ignition, sulphated ash and heavy metals.

Particle size and polymorphism were not considered critical quality attributes of the active substance as simeprevir is dissolved during the manufacturing process of the finished product. Therefore no test on particle size determination and polymorphism was included in the specification.

Furthermore the active substance specification does not include any test for enantiomeric purity as the enantiomeric purity is assured by controlling the enantiomeric purity of the starting materials with appropriate specifications. The formation of additional enantiomers is not possible during the downstream synthesis as it requires simultaneous epimerization of all 5 chiral centers, which is statistically and chemically impossible. This rationale was further supported by the available batch analysis data demonstrating the absence of enantiomer impurities in all simeprevir batches manufactured to date. Therefore, in line with ICH Q6A, the established specifications for enantiomeric purity of the starting materials are adequate to assure the enantiomeric purity of the final active substance and no test for enantiomeric purity was included in the active substance specifications.

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

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

Batch analysis results for simeprevir have been presented. All batches were manufactured by the proposed commercial manufacturer according to the proposed process. Batches were used in clinical studies, stability studies and process validation. In total 11 batches of simeprevir have been manufactured and tested during the development phase. In addition, batch results were presented for batches manufactured using different synthesis methods used in earlier steps of the development. It can be concluded that the batch analysis results indicate that the manufacturing process is reproducible and under control.

Stability

Stability studies were performed according to ICH requirements. Stability studies on simeprevir were conducted on 3 primary stability batches and 1 site stability batch that were manufactured according to the proposed manufacturing process and packed in the proposed container closure system. 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 test used for stability testing are the same as those used for release testing. Two additional tests (enantiomeric purity and microbiological purity) are only performed in the stability studies. The HPLC method for enantiomeric purity has been appropriately validated and demonstrated to be stability indicating. Microbiological purity is tested according to Ph. Eur.

Forced degradation studies were also performed to further characterise the active substance. The study design included testing of the effects of thermal, oxidative, acidic, neutral and alkaline

conditions on the active substance in solution, as well as photolysis on the solid substance. Furthermore, this study was also initiated to confirm the stability indicating properties of the HPLC purity method.

In general, no substantial stability related changes were observed during storage of the active substance under long term and accelerated conditions. However, under ICH light conditions, the appearance failed, and a decrease of the assay and an increase of the unspecified impurities were observed. The results demonstrated that simeprevir is stable at long term and accelerated storage conditions, when protected from light.

The post-approval stability protocol is acceptable and a sufficient number of batches from the supply chains will be added to the program.

Based on the available stability data, simeprevir showed to be a stable when packaged in the proposed container closure system and protected from light.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The aim of the pharmaceutical development was to obtain an immediate release solid, oral dosage form that would deliver the required dose (maximum 150 mg) of the active substance. The challenge in developing such a formulation for simeprevir was resulting from the limited solubility of the substance (crystalline free form) in aqueous media. Several variants of the active substance (various salt and physical forms) have been investigated with respect to solubility and stability. After an extensive salt screening effort four formulation intermediate concepts were selected and used to make tablets or capsules for testing in clinical studies. For the initial phase 1 clinical trials, simeprevir was formulated as an oral solution. A similar ^{14}C-radiolabeled oral solution was also prepared and used for PK studies. However due to the need of obtaining an oral solid dosage form, various oral capsule and tablet formulations have been developed and tested in clinical trials versus solution or between each other in five relative bioavailability trials. The capsule formulation based on the spray-dried amorphous sodium salt was selected for use in the phase 2a clinical trials. This formulation was also used in the phase 2b clinical trials, together with 2 dose proportional capsule presentations. A development of 150-mg dosage strength was required for the phase 3 clinical trials with a capsule size small enough to allow easy swallowing and bioavailability matching previous capsule formulation. On the basis of the results, the capsule formulation containing amorphous sodium salt produced by a solvent based spray drying process was selected for commercialization. During the course of development, the composition of the spray solution (choice and amount of solvents) has been modified to improve the manufacturability by ensuring rapid and complete dissolution of simeprevir during spray solution preparation. The formulations used for the clinical phase 3 trials, for the primary stability studies, and for commercialization have essentially the same composition.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The robustness of the proposed commercial formulation towards processing solvents, sodium hydroxide, and excipient composition was verified by a number of experiments and design of experiment (DoE) studies. Based on these studies, appropriate control strategy has been implemented to mitigate the risks identified initially and to ensure that the characteristics specified in the Quality Target Product Profile (QTPP) will be met consistently.

A dissolution method has been developed for quality control (QC) during release and stability testing of the finished product, and to demonstrate similarity between dissolution profiles of clinical batches and batches produced at the commercial manufacturing facility. The developed dissolution method has shown to provide the expected discriminative capabilities towards the presence of crystalline material in the spray-dried powder and compression of the powder blend during encapsulation.

The manufacturing process development has been well documented. The development of manufacturing process was performed through a science-based criticality analysis based on ICH Guideline Q8 and Q9. This included the identification of the critical quality attributes (CQAs), determination of critical process parameters (CPPs) and the design of an effective control strategy. Process steps and parameters, including assessment of in-process controls (IPCs) that affect the CQAs of the finished product were identified. The 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.

Adventitious agents

Among excipients used in the medicinal product gelatine (component of the capsule shell) and lactose (component of the capsule fill) are of animal origin.

Ph. Eur. TSE Certificates of Suitability were provided for gelatine.

It has been certified by the supplier that lactose is produced in compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products" (EMEA/410/01). Lactose is produced from milk obtained from healthy cattle under the same conditions as milk intended for human consumption.

Magnesium stearate is of vegetal origin and relevant certificates from manufacturers of this excipient have been provided.

Manufacture of the product

A standard process is employed for the manufacture of Olysio hard capsules. Overall, the description of the manufacturing process was adequate. Critical steps have been identified and properly evaluated at the commercial scale. The in-process controls are adequate for this type of process. The reproducibility of the process has been suitably demonstrated during the development.

Formal validation will be performed post-approval on the first three consecutive commercial batches, prior to launching the product. An acceptable validation plan has been provided. Since the

process is a standard manufacturing process and in addition it has been extensively evaluated and the critical process parameters for the process have been identified and characterised at full scale it was considered sufficient to provide a validation plan and perform the validation post-approval.

Product specification

The finished product is controlled by testing attributes relevant for this dosage form. The finished product specification includes tests for appearance, identity of the active (UV and HPLC), assay (HPLC), chromatographic purity (HPLC), uniformity of dosage units, dissolution, water content (KF) and microbiological purity. The shelf life specification contains the same tests except uniformity of dosage units and microbiological purity tests.

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.

Batch results are provided for 4 production scale batches. 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

Stability studies have been initiated according to ICH guidelines on 3 batches (primary stability batches) and on 1 additional batch of the finished product manufactured at the commercial facility. Data were provided from six months of accelerated conditions (40°C/75% RH), 18 months of intermediate conditions (30°C/75% RH) and 18 months of long term conditions (25°C/60 % RH). Samples were tested for appearance, assay, chromatographic purity, dissolution, water content, amorphicity and microbiological purity. The analytical procedures used are stability indicating. No significant changes or trends in any of the parameters monitored have been seen and all data are within proposed specifications.

In addition stability data from photostability studies were provided. Product in its primary packaging and unprotected capsules were exposed to light in accordance with the ICH conditions. The study demonstrated that the product is light sensitive. Due to light sensitivity, the product should be stored in the original packaging in order to protect from light, as reflected in SmPC.

The results generated during the stability studies support the proposed shelf-life and storage conditions as defined in the SmPC.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The information provided about the active substance, simeprevir, was of acceptable quality. 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.

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 hard gelatine capsules containing 150 mg of simeprevir. 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 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 (simeprevir) and the finished product (hard capsules 150 mg) have been appropriately characterised and generally satisfactory documentation has been provided thus ensuring that the quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. The overall results of the conducted studies indicate that simeprevir as well as the capsules can be reproducibly manufactured. Therefore the product should have a satisfactory and uniform clinical performance.

2.3. Non-clinical aspects

2.3.1. Introduction

Pharmacology studies were carried out to investigate and assess the mechanism of action of TMC435 in order to support the use of the drug in the requested conditions against HCV genotype infection. Likewise safety pharmacology a core battery of studies was carried out. The pharmacokinetic studies part of the forwarded dossier included pharmacokinetic and toxicokinetic data in different species (mice, rats, rabbits, dogs, and Cynomolgus and Rhesus monkeys), with distribution, metabolism and excretion studies of TMC435. Additional non clinical safety was obtained from classic toxicity studies assessing the potential toxicity in single and repeated doses of the product. Additional studies were conducted in order to qualify toxicologically the safety profile of five impurities. The drug product contains no novel excipients. The excipients used in the drug product are standard pharmaceutical components.

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

2.3.2. Pharmacology

Primary pharmacodynamic studies

TMC435 (simeprevir) is a macrocyclic inhibitor of the HCV NS3/4A protease, developed for the treatment of chronic HCV infection. TMC435 is expected to bind by hydrogen bonds to the HCV NS3 protease spanning the S3-S1' subsites. The large P2 group of TMC435 binds with an induced-fit mechanism leading to occupation of an extended S2 subsite, partially shielding the catalytic region of the enzyme.

The inhibitory activity of TMC435 against HCV NS3/4A proteases shows a K_i of 0.5 against genotype 1a (H77) and 1.4 nM against genotype 1b (Con1b). When inhibitory activity was assessed against proteases from a panel of HCV genotype 1a, 1b, 2b, 3a, 4a, 5a, and 6a isolates, fold change in EC_{50} values of TMC435 were ≤5 for the HCV genotype 1, 2, 4 and 6 genotypes while 3 and 5 isolates were less susceptible. The variation in IC_{50} ranged from 8.3 to 148 for genotype 3a and 71 fold for a single 5 genotype protease.

The inhibitory activity of TMC435 against HCV genotype 1a, 1b, 2a, and 3a NS5B polymerases in a primer-dependent transcription assay revealed IC_{50}s of 8.0 µM, 7.1 µM, 13 µM, and 6.0 µM respectively with a selectivity index (SI), defined as the ratio of the median IC_{50} value against HCV NS5B polymerase over the median IC_{50} against HCV NS3 wild type (Con1), ranged from 1162 for the HCV genotype 3a, to 2577 for the genotype 2a protease. The SI value ranged from 154 to 1115 for these 6 proteases and was >3846 for other tested proteases in FRET-based and para-nitroaniline (pNA)-based assays. In a panel of cellular human protein or lipid kinases, TMC435 inhibitory activity revealed that the activity was not reduced by ≥90% in any of the studied kinases. TMC435 did not display significant specific activity against the HCV NS5B polymerase, cellular proteases, and human kinases tested with SI generally >1000, suggesting that the product is a selective inhibitor of the HCV NS3/4A protease.

In genotype 1b Huh7-Luc cells with luciferase read-out TMC435 displayed high inhibition of HCV replication with an EC_{50} of 9.4 and EC_{90} of 19 nM. Bearing in mind that clinical data indicates that the lowest plasma concentration at the proposed dose of 150mg q.d. was 1579 ng/mL, resulting in a C_{min}/EC_{50} of 224 and C_{min}/EC_{90} 111 ratio, it suggests that in principle *in vitro* data could support efficacy in the clinical practice. The EC_{50} values ranged from 3.7 to 25 nM for 3 genotype 1b and were 23 and 28 nM for 2 genotype 1a replicon-containing cells. The EC_{50} values ranged from 23 and 28 nM for 2 genotype 1a replicon-containing cells, using qRT-PCR read-out.

The addition of human serum or its components results in a moderate negative shift in TMC435 anti-HCV activity.

In vitro data suggests that TMC435 is a specific inhibitor compound of HCV replication. TMC435 displayed CC_{50}>10 µM in all cells tested resulting in an SI>1100 and showed no specific antiviral activity against a panel of 11 different viruses including related flaviviruses such as yellow fever virus (YFV) and West Nile virus (WNV) as well as against ssRNA viruses of other virus families (i.e. respiratory syncytial virus (RSV), Coxsackie virus, and Sindbis virus [SinV]) and DNA virus herpes simplex virus (HSV), hepatitis B virus (HBV), bovine viral diarrhea virus (BVDV), influenza A virus, vesicular stomatitis virus(VSV), or HIV-1.

TMC435 was able to restore the Rig-I and TLR3-dependent signalling involved in activation of IRF-3 and IFN-α/β synthesis by inhibiting the NS3/4A-induced cleavage or degradation of the adaptor proteins MAVS and TRIF, respectively, but only at high concentrations well over EC_{50}.

In *in vitro* selection of HCV-resistant replicons, the resistance profile of simeprevir was studied by selection experiments using HCV genotype 1a, 1b replicon-containing human hepatoma (Huh) cells and HCV genotype 2a infected cells. Most TMC435-selected replicon-containing cell colonies (96%) harboured 1 or more mutations at NS3 protease positions 43, 80, 155, 156, and/or 168. D168 was the most frequently observed (78%).

Single or combinations of mutations at NS3 positions 43, 80, 122, 155, 156, and 168 result in the most pronounced reductions in TMC435 activity with D168V having the largest effect although some cross resistance mutations within the class macrocylic (TMC435) and mutations associated with resistance to boceprevir (BOC) and/or telaprevir (TVR) were reported as protease inhibitors (PIs) bind at the active site of NS3 therefore some overlap in resistance profiles is observed.

The TMC435-associated mutations described at NS3 position 43, 80, 155, 156 were mapped onto 2.4-Å-resolution crystal structure of the TMC435-NS3/4A protease complex. The predominant mutations arising in response to TMC435 exposure *in vitro* studies were grouped around the inhibitor binding site.

Combinations of TMC435 with HCV NS5B NIs, NS5B NNIs, NS5A inhibitors, IFN-α, or RBV resulted in additive to synergistic anti-HCV replicon activity in Huh7-Luc cells for all combinations tested while no evident antagonistic effects were observed. Reduction in replicon cell colony formation with TMC435 was dose dependent and though resistance was not totally suppressed, combinations with anti-HCV agents with a different mode of action (HCV NS5B NIs, NS5B NNIs, NS5A inhibitors, IFN-α, or RBV) resulted in additive to synergistic anti- HCV activity, suppressing or completely preventing the formation of resistant replicon cell colonies. A higher reduction was seen together with other DAAs and the triple combination with NS5B NI and an NS5B NNI was the highest reduction in replicon RNA and complete replicon clearance at all concentrations tested (100 nM, 25 µM and 1 µM respectively). Combination of TMC435 with HIV PIs does not affect anti- HCV activity.

Secondary pharmacodynamic studies

No significant effects were observed in the central nervous system (CNS) or gastrointestinal systems, or on allergy or inflammation. Delayed gastric emptying and pancreas findings in rats and mice were associated with toxicity findings of the product. A moderate interaction was observed with cholecystokinin (CCK) receptor CCKA/CCK1. CCK is a hormone responsible for stimulating the digestion of fat and protein. It is synthesized by I-cells in the duodenum and secreted into the blood, activating the release of digestive enzymes and bile from the pancreas and gall bladder.

Safety pharmacology programme

Even though in the study that assessed effects of TMC435 on the membrane K^+ current (IKr) in HERG-transfected HEK293 cells the compound induced no relevant effects on the K^+ current at up to 0.3 µM (0.22 µg/mL), no definitive conclusions can be made from the study as it was observed cell leakage upon depolarization. It was also seen probable accumulation reported as low recovery of the drug (13%) at 3 µM. The TMC435 has been reported to block the cardiac Na^+ channel at a concentration of 0.22 µg/mL. In the isolated guinea pig atrium assay decrease in the rate and force

of contraction and ERF was reported at 7.5 µg/mL indicating a plausible Na-block involvement. Also in this study accumulation of the product in the heart was reported. In isolated Langendorff-perfused rabbit hearts APD_{60} was shortened at 2.25 and intraventricular conduction time tended to increase at 7.5 µg/mL and also concomitant Na block. Ventricular fibrillation in 4 out of 6 hearts, early after depolarizations in 1 out of 6 hearts, and torsades de pointes in 1 out of 6 hearts. In pharmacokinetic studies a two to almost three fold concentration of the product was reported in the heart. Some compounds known to block Na channels and some K channels may lead to accumulation of the drug in the heart and result in disturbance in intraventricular conduction and prolonged action potentials, consistent with arrhythmia and prolonged QT. No QT effects of the product have been reported in clinical trials nor in *in vivo* studies in dogs.

TMC435 was also assessed *in vivo* in anesthetized and conscious dogs. It should be noted that ventricular ectopic arrhythmias, were induced in both groups although seem somehow higher in dosed groups. TMC435 did not induce other relevant changes in pulmonary, cardio-hemodynamic and cardio- electrophysiological parameters up to exposures of 67.2 and 90.8 µg/ml in anesthetized and in conscious male dogs, respectively.

When CNS effects of TMC435 were studied in rat, findings reported were not marked and included reduced alert, narrowing of the palpebral fissure. Myoclonic movements of the jaws were not reproduced in toxicity studies. Gastrointestinal assessment of TMC435 revealed delay gastric emptying in rats.

2.3.3. Pharmacokinetics

TMC435 pharmacokinetics was studied in vitro and also in vivo in Albino Swiss mice, Sprague-Dawley (SD) rats, Syrian Hamsters, NZW Rabbits, Beagle dogs and Cynomolgus and/or Rhesus monkeys using various formulations and via of administration, trying to achieve relevant exposures to the drug.

In vitro evaluation of TMC435 absorption was assessed in vitro in Caco-2 cell monolayers. Data confirms that low apparent permeability to the product and that it is subject to efflux through P-glycoprotein.

The mean highest plasma concentration of TMC435 was achieved in the range of one to five hours. The exposure increased with dose although it was not homogeneous among species. It was found in rodents that exposure increased less than dose-proportional while in dogs the increase was found to be more than dose-proportional manner in dogs and not that marked in Rhesus monkey. Exposures were lower in rats and higher in mice, dogs and monkeys. Exposure measured as AUC in repeated administration via gavage of non-pregnant mice decreased significantly from five to fold and also in and pregnant animals (2-4-fold). This decrease was not reported in other species where exposures were higher after repeated than after single dosing.

When high doses were administered *in vivo*, the absorption of the drug tended to slow down evidenced as a prolonged absorption flattening the plasma concentration-time profiles from Tmax onwards, evidenced as a larger $t_{1/2}$ and AUC.

In the data provided no significant gender differences after oral gavage administration were observed although TMC435 exposure was lower in males than that of females (2- to 4-fold) after

diet administration. Due to the continuous access to the test product in the diet no Cmax could be calculated. After dietary administration, exposure in female rats was greater than in male rats.

The absolute bioavailability of TMC435 following oral administration was very variable among species and with added variability in fasted vs. fed animals, ranging from a lowest value reported in rabbits of 2.5% against a maximum seen in rhesus monkey (88% fasted), followed by dogs (71.6 % fed, 57.8% fasted), rat (44% fed), hamster (40% fed) or and (fasted) in Cynomolgus monkey 18.8% fed 25.4% fasted (20 mg/kg) and the lowest in fed rabbit 2.5%. When TMC435 was given IV at high dose levels in rats and dogs, the plasma clearance and steady state distribution volume slightly decreased with increasing dose levels of TMC435.

Plasma clearance in rabbit was very high accounting to 7.2 L/h/kg following IV administration. Oral and subcutaneous administration resulted in exposures often below LLOQ. As a result the rabbit was not used as an animal model in reproduction toxicity studies. Plasma clearance in rats was 2.3 L/h/kg in rats and hamsters, while clearance was calculated at 0.2-0.4 L/h/kg in dog and monkey. The steady state distribution volume was estimated at 41 L/kg in rabbits (Vdz), 5.9 L/kg in hamsters (Vdz), 5.3 L/kg in rats, 0.8 L/kg in dogs and 0.5 (Cynomolgus) or 1.1 L/kg (Rhesus) in monkeys.

The half-life was variable among species accounting to 4.0 h in rats, 3.7 h in rabbits and dogs and 5 to 6 h in Rhesus and Cynomolgus monkeys.

The distribution of TMC435 was studied in mice, rats, hamster, dog and monkey.

In rats and pigmented mice, following single oral administration of 14C-TMC435, radioactivity was mostly seen in the liver and the gastrointestinal system and in rats also associated to the bile and pancreatic ducts. Concentrations in liver were higher than in plasma (liver-to-plasma ratios 11 -149), and in heart T/P ratio was 2 fold following repeated dose administration in mice. In rats, liver to plasma ratios were comparable across groups.

The concentrations in melanin-containing tissues (skin or eyes), were similar to or below those in blood. After repeated dosing, the tissue distribution was similar to single dose distribution studies.

The plasma protein binding of TMC435 was high (>99.8%) in all species including man. The blood to plasma concentration ratio of 14C-TMC435 was between 0.42 and 0.56 in the dog and between 0.66 and 0.69 in man suggesting limited distribution into the RBCs.

When 14C-TMC435 was administered to pregnant rats, placental transfer was negligible. Total radioactivity in foetal liver and foetus were below the LLOQ, indicating limited distribution of TMC435-related radioactivity to the procreative tissues.

The in vitro metabolism of 14C-TMC435 was investigated in hepatocytes and liver microsomes of mouse, rat, rabbit, monkey and human. The metabolic activity reported in vitro from animals and man was low. Phase II conjugation pathways of Phase I metabolites were formed in hepatocytes. Parent TMC435 was found in much greater levels than any metabolite in vitro. More than 20 metabolites were identified. The metabolic Phase I route of highest importance were O-demethylation of unchanged drug (particularly in animals), oxidation of unchanged drug and oxidized metabolites (particularly in monkey and man) and glucuronidation was the major Phase II of oxidized metabolites (less in human). Only one human metabolite identified in vitro not seen in rat or dog was M22 (oxidized unchanged drug) but this metabolite was identified in rat (faeces). In

vivo data reveals that the main moiety present in plasma of rat, dog and man was parent TMC435. The major metabolites reported in vivo in plasma from animals and human were M18 and M21.

O-desmethyl-TMC435 M21 was the only common circulating metabolite found in rat dog and human plasma (M21: 8% of the mean TMC435 plasma and only small traces in dogs), while M18 was common to plasma of rats and dogs but with respect to the parent compound they appeared with low concentrations (M18: between 28.9% and 12.5% in rats, with only small traces in dogs). Only traces of metabolites M18, M21 and M8 formed by O-demethylation and oxidation at the aromatic moiety were reported in dog plasma.

M21 represents less than 10% of unchanged drug and also total radioactivity therefore systemic exposure to M21 was not assessed in the safety evaluation studies. M21 did not appear to accumulate in man.

In bile from rats, moderately high levels of parent compound were reported (0.11 to 17.2%). TMC435 metabolites in this matrix were formed mainly by hydroxylation and O-demethylation and also by glucuronidation.

Unchanged TMC435 was the most important moiety present in faeces of rat (84.2-95.3%), dog (52.1%) and man (12.2 and 42.4 %). The most important metabolic route TMC435 in rat and dog was O-demethylation of the parent drug to M18 (12.8%- 6.4% male-female rats; 18.8% dogs). In rats other metabolites were formed by oxidation of M18 and oxidation of unchanged drug. In dogs, further oxidation of M18 to M14 and M8, and of the unchanged drug to M21, M16 and M11 were also reported as minor routes. The human metabolism profile suggests that TMC435 is mainly metabolized by two main routes, (1) oxidation of unchanged drug, either at the macrocyclic moiety (M27, M21 and M22), or at the aromatic moiety (M26 and M16), or both (M23, M24, M25 and M11) and (2) the O-demethylation of unchanged drug to M18, followed by oxidation on the macrocyclic moiety to M14 and by oxidation on the aromatic moiety to M5, appears to be the secondary metabolic pathway in man.

M21 and M22 were the most important metabolites in human faeces. Other relevant metabolites (1% of the dose) were M11, M16, M27 and M18. All metabolites detected in human faeces were detected in vitro and/or in vivo in rat and/or dog faeces.

The main CYP enzymes involved in TMC435 metabolism were CYP3A enzymes although in vitro data suggests the involvement of CYP2C8 and CYP2C19.

The data suggests that the animal models used in order to evaluate the safety of TMC435 were suitable for this purpose.

The most important moiety excreted was parent TMC435 in faeces as urine excretion was minimal in all studied species and also in man. The amount of total radioactivity recovered in faeces accounted to more than 98% in rats and 96% in dogs. Most of the total dose was excreted within 48 hours. Unchanged drug accounted to 84.2% in male rats, 95.3% in female rats and 52.1% in dogs. Biliary excretion may be considered an important route of excretion next to metabolism accounting to 0.11 to 17.2% of the total unchanged drug in rats. Urine excretion accounted to only very low concentrations in all species including human (0.02-0.038%).

Excretion values in man were similar to those reported in animals with unchanged TMC435 being the most important excreted compound (12.2-42.4%), and most of the administered dose was recovered in faeces (mean 91.1%) while excretion in urine accounted to only 0.038% in man.

No measurements were made on milk, nonetheless it was observed that in rat suckling pups TMC435 was identified in plasma and liver samples suggesting the observed exposure may probably due to absorption of the drug from milk.

TMC435 possible interactions with the metabolism of compounds (budesonide, diazepam, digoxin, glybenclamide, metoprolol, paroxetine and simvastatin) that may be co-administered in a clinical scenario revealed no significant concerns for coadministration with TMC435. TMC435 potential to induce and inhibit human CYP450 activities was assessed in vitro in hepatocytes and human liver microsomes respectively. Results show that TMC435 does not induce CYP1A2 or CYP3A4 metabolism and that the drug is a modest inhibitor of CYP2A6, CYP2C8 and CYP2D6 and a minor inhibitor of CYP2C19 and CYP3A. TMC435 was not found to be not an inhibitor of uridine diphosphate glucuronosyl transferase (UGT) 1A1 (bilirubin glucuronidation) and low in vitro interaction potential for TMC435 on the activity of cathepsin A was seen in vitro.

In *ex vivo* hepatic microsomes in mice, rats and in dogs dosed with TMC435, no relevant induction of microsomal CYP4A in mice, and CYP2B and CYP3A forms in rats was reported. TMC435 did not seem to affect or induce peroxisome proliferation (in rats) or UGT activity, CYP1A or CYP2E. TMC435 was an inhibitor of CYP2B in mice and additionally in CYP1A, CYP3A, CYP2E, CYP4A and thyroxine UGT with microsomal protein and total CYP content were decreased.

TMC435 was substrate uptake transporters of the solute-carrier gene superfamily (OATP1B3, and OATP2B1), and of the efflux ATP-Binding cassette (ABC) transporter superfamily (P-gp/MDR1, MRP2 and BCRP1). In dogs, ritonavir co-administration increased the TMC435 exposure by 2- to 3-fold, mainly because of ritonavir-mediated inhibition of CYP3A.

In vitro studies showed that CYP3A enzymes (CYP3A4 and CYP3A5) are principally involved in the metabolism of TMC435 and the formation of the metabolites M18, M23 and M25. Involvement of CYP2C8 and CYP2C19 cannot be excluded.

Hence, it could be concluded that TMC435 is not an inducer of CYP1A2 or CYP3A4 in vitro and is therefore considered unlikely to demonstrate induction-based drug-drug-interactions when co-administered with corresponding substrates.

Inhibition of CYP2D6, CYP2C8, CYP2A6, CYP2C19 and CYP3A4 by TMC435350 was observed with IC50-values ranging between 32.2 µg/ml and 116 µg/ml (7 and 26 fold higher the human total Cmax).

Available data indicated that it is unlikely that TMC435 or ribavirin can give a relevant in vivo interaction on glucuronidation of bilirubin.

A low interaction potential for TMC435 on the activity of cathepsin A was seen in vitro.

In *ex vivo* experiments, TMC435 had no or very limited effect on hepatic microsomal parameters in rodent and non-rodent except for the higher dose tested in dogs (45 mg/kg, corresponding to a Cmax and AUC of 41 µg/ml and 475 µg.h/mL) which elicited significant inhibitory effects on various microsomal CYP dependent enzyme activities and also lower microsomal protein CYP450 concentrations were measured.

In a series of adequate and well performed studies (non GLP) it was shown that:

- Several membrane transporters were involved in the absorption and disposition of TMC435, including various uptake transporters of the SLC superfamily and efflux pumps (P-gp/MDR1, MRP2, BCRP). TMC435 itself was also an inhibitor of several uptake (OATP1B1, NTCP) and efflux (P-gp, MRP2, BSEP) transporters.
- Combination of TMC435 with ritonavir did not or only partially inhibit the transport of TMC435.
- Ribavirin, which is part of the standard-of-care of HCV treatment, did not inhibit OATP1B1, NTCP or BSEP transport.

2.3.4. Toxicology

Single dose toxicity

Single oral TMC435 administration was evaluated in mice, rats, dogs and monkey. As a result of the product administration, no findings of relevant toxicity were reported up to doses of 500 mg/kg in mice, 1000 mg/kg in rats, 160 mg/kg in dogs and 150 mg/kg in monkey. Animals displayed limited adverse effects such as decreased general activity in mice and soft or low amount of faeces in mice and rats. Deaths reported at doses >1000 mg/kg were attributed to dosing accidents in both rodent species. In dogs a decrease in cholesterol and triglycerides was reported. Additionally in dogs and monkeys increases in plasma bilirubin and/or AST were also seen.

Repeat dose toxicity

GLP, as well as non GLP compliant repeated dose toxicity studies in mice, were carried out with TMC435 given via gavage (up to 3 months), and diet (13 week); in rats also via gavage (up to 6 months), and diet (up to 13 weeks); dogs only by gavage (up to 39 weeks) and monkeys by gavage (up to 28 days).

Mice received TMC435 by gavage and also included in the diet. No significant differences were reported in findings observed in gavage or diet studies with the exception of a marked decrease in deaths in diet dosed animals related to administration of the product. Differences in exposure were not very marked independently of the administration (gavage vs. diet) in long term studies in rodents, and in such long studies exposures were often within the range of that expected or not much higher than that found in the clinical scenario at the recommended dose. In the 13-weeks diet study in mice, tissue distribution was investigated, showing that the concentrations in the duodenum, liver and pancreas were higher than those found in plasma.

The main and most evident target organs in tested species were liver, pancreas and the gastrointestinal system.

In mice main findings consisted of increases in liver enzymes including ALT, ASL, ALP (0.9 fold the clinical exposure), decrease in cholesterol and liver centrilobular hypertrophy (1.7 fold the clinical exposure). An increase in levels of bilirubin up to 4 fold was also observed with decreases in haematocrit and haemoglobin. Bilirubin increases were often within the range of transaminase increase or at subsequent exposures. Adverse findings in the gastrointestinal system of mice included swelling and vacuolization of apical enterocytes in jejunum and/or duodenum. A frequent

finding in the stomach of mice was epithelial hyperplasia. No significant differences were reported in findings observed in gavage or diet studies with the exception of a marked decrease in deaths in diet dosed animals related to administration of the product. Pancreas was another target organ in this species. Adverse findings consisted of diffuse vacuolization of the exocrine pancreas with more prominent apoptotic acinar cells and decreased zymogen/basophilia; pancreas findings were often seen at exposures close to the clinical one (AUC 57.5 µg.h/mL).

Rat repeated dose toxicity studies revealed adverse findings similar to those reported in mice. Exposures achieved in rats were only marginally over the expected exposure in human. ALP, AST and ALT activities were significantly increased in this species (1.1 fold the clinical exposure) while cholesterol and triglycerides were decreased within similar exposures. Gastrointestinal adverse findings included cecum distension and as in mice, vacuolization of apical enterocytes in the jejunum. ATTP decrease was another finding reported in rats with decreases in haematocrit. In addition, in pancreas prominent apoptotic acinar cells were seen with organ weight increase. Gavage dosing resulted in several deaths probably due to the viscous formulation coupled with of delayed gastric emptying resulting in regurgitation/aspiration of formulation into the upper airways with subsequent inflammatory/necrotizing changes. Ischemic heart lesions (oedema, multifocal presence of acute degenerating/necrotizing fibres and mixed inflammatory infiltrate in mainly left ventricular subendocardial region, associated with pericarditis at the apex) were also seen in one animal.

In rodents only pancreas adverse findings were reported without increases in plasma CCK. No recovery was assessed. Toxicity is probably linked with the long term exposure of the product in the intestine and effects of the protease inhibitor (PI) TMC435. Other PIs result in suppression of intestine pancreatic proteases, resulting in an elevation of mucosal CCK that could be related to the toxicity reported. Delayed stomach emptying may be associated with high CCK levels, and the described pancreas related findings were related to an increased secretory activity of the exocrine pancreas. Apical enterocytes vacuoles may be linked to the absorption delay and an increase in fat digestion. *In vitro* data indicates no effect or only moderate inhibition of the CCK receptor.

In monkeys 8-fold increases in total bilirubin and AST were seen in a dead animal receiving 200mg/kg, animal that displayed severe lesions in the lung probably due to aspiration of the product. Other animals also displayed high bilirubin (up to 7-fold) and AST levels (up to 4-fold). As in rodents and dogs, TMC435 administration displayed also effects in faeces revealed in this species as clear stool. In monkeys dosed at 20 mg/kg/day for 2 weeks increases in AST (up to 4-fold) and hypersalivation were noted. Additional effects were reported in animals that accidentally inspired the dosed formulation.

Genotoxicity

TMC435 genotoxicity assessment revealed a low risk for mutagenic and clastogenic potential when evaluated *in vitro* and *in vivo*. Simeprevir was non-genotoxic in a test battery comprising the following assays: Ames test, L5178Y TK+/- mouse lymphoma cells and *in vivo* mouse micronuclei test (at a plasma C_{max} around 30 µg/mL).

Carcinogenicity

The lack of carcinogenicity studies was justified by the Applicant in line with ICH S1A and based on the proposed treatment duration of 12 weeks for TMC435. Of note, it was one of the issues raised

in the Scientific advice from the CHMP. The Applicant confirmed that in any case the duration of the treatment would be up to 12 weeks of duration.

Reproduction Toxicity

TMC435 administration to rats did not reveal any adverse effects related with reproductive performance and fertility at the tested doses. It should be noted that the exposures are lower than the expected to be found in a clinical scenario following at the clinical dose after 12 weeks treatment at 150 mg per day.

Mice and rats were chosen instead of rabbits for the evaluation embryo-foetal development. In pharmacokinetic studies it was observed that NZW rabbits exposure was not sufficient for the evaluation and even though IV administration was tested as well, clearance of TMC435 very high (7.21 L/h/kg) resulting as well in low exposure to TMC435. As sufficient exposure was not achieved by any of the routes tested (oral; IV) the albino Swiss mice were chosen instead as sufficient exposure was obtained in this animal model. Exposures achieved in rats were higher but not comparable to those obtained in clinical trials. In a mice study at 1000 mg/kg/day 2 animals died with poor clinical condition, weight and food consumption. These deaths were probably treatment related. Total embryo resorption was reported in these animals and also at this dose level a higher incidence of late embryo-foetal death was seen. Exencephaly was also reported at this dose with supernumerary ribs with incomplete ossification of cranial centres, thoracic vertebrae and metacarpals/metatarsals as well as a higher incidence of foetuses/litters with 8^{th} costal cartilage connected to sternum and left umbilical artery.

In the pre-postnatal development study in rats two females were sacrificed due to poor condition and respiratory difficulties at 1000 mg/kg/day. Respiration effects were seen from ≥500 mg/kg/day and effects on body weight and food consumption were seen at all dose tested (F0). F0 exposures were at the same level of exposure when administered at the highest dose than the expected human exposure therefore the relevance of the findings is limited. Pre- and post-natal developmental evaluations suggest that simeprevir has no effects on natural delivery in rats up to 500 mg/kg but it may have adverse effects on the growth of offsprings as evidenced by lower absolute body weight at the end of lactation; however, no effects on development, litter size at birth, offspring survival, functional development and reproductive performance of the F1 offspring in any of the treated groups were observed. In these experimental conditions, the NOAEL was 500 mg/kg for the F0 females and for the pre- and post-natal development of the F1 offspring.

The offspring (F1) revealed lower body weights probably related to exposure to TMC435 through the milk. Delay in the vaginal opening was also reported and was attributed to the reported lower body weight.

Local Tolerance

Simeprevir was slightly irritant for the eye and did not induce delayed contact hypersensitivity in the murine Local Lymph Node Assay. TMC-435 elicits phototoxic effects on BALB/c 3T3 fibroblasts in the absence and presence of protein supplements when tested *in vitro*.

Other toxicity studies

The toxicology data available of the product does not suggest that TMC435 has any significant antigenic, immunotoxic or dependence potential.

2.3.5. Ecotoxicity / environmental risk assessment

In the PBT screening TMC435 was determined to have log10Pow values of ≥5.5 over the entire pH range of environmental relevance (4 to 9) . Therefore, TMC435 is a potential PBT substance and further assessment was performed.

Persistance was determined by means of the Adsorption – Desorption Using a Batch Equilibration Method (OECD106) and the Aerobic and Anaerobic Transformation in Aquatic Sediment Systems (OECD 308) studies. The substance shows high affinity for sediments and soils (K_{oc} = 17900 – 80000 on soils; K_{oc} = 42900 – 63200 on sewage sludge) where degradation is very slow ($DT_{50, sediment}$ = 45.9 – 175 days, $DT_{50, soil}$ = 62.3 – 129 days). An assessment of acute and long-term effect on the terrestrial compartment was then carried out.

The reference NOEC for the terrestrial compartment was aclulateted according to OECD Guideline No. 216 to be is 3.15 mg/kg as recorded in the Soil Micro organisms (Nitrogen Transformation Test).

The bioconcentration in fish (BCF) value for the determination of bioaccumulative properties has not been calculated. The study could not be conducted under flow-through conditions nor under semi-static conditions due to poor solubility. The Applicant was asked to perform a new bioaccumulation study with dietary exposure (OECD 305-III study), which is specifically designed for substances where the aqueous exposure methodology is not practicable. However The Applicant claims that carrying out this study would only provide a confirmation on what has been already established that TMC435 is a bioaccumulative product (TMC435 log Kow =5.5). TMC435 is considered to be bioaccumulative

The Fish, Early Life Stage Toxicity Test (OECD 210) revealed that post-hatch survival of *Pimephales promelas* was affected adversely at concentrations of at least ≥3.21 µg/L. (NOEC 1.08 µg/mL).

Based on the above assessment, TMC435350 is considered as a PBT-substance which may pose a risk to the environment.

Table 1. Summary of main study results

Substance (INN / Invented Name): 0923604-59-5			
CAS-number (if available): SIMEPREVIR / Olysio			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log P_{ow} = 6.0 (pH 4) log P_{ow} = 5.5 (pH 7) log P_{ow} = 5.9 (pH 9)	Potential PBT (Y)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	log P_{ow}5.5 (pH 7)	B
	BCF	Not calculated	
Persistence	DT50 or ready	See OECD 106 and 308	P

	biodegradability				
Toxicity	NOEC	1.08 µg/L			T
PBT-statement :	The compound is considered as PBT				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.0006	µg/L			> 0.01 threshold N
Other concerns (e.g. chemical class)					N
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} =17900-80000 in soil K_{oc} = 42000-63200 in sludge			> threshold TMC-435350 has a high potential for binding to soils and sewage sludge. Phase II Tier B terrestrial compartment studies are necessary
Ready Biodegradability Test	OECD 301F	ThOD = 66% (3d)			Not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ =2.6-3.4 $DT_{50, sediment}$ = 45.9-175 $DT_{50, whole\ system}$ =33.5-124 %shifting to sediment=53			> threshold
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	71.3	µg/L	Species *Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	55.9	µg/L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	1.08	µg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC50/90	>390	mg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	N/A	L/kg	This study was not completed due to technical reasons
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$	 101 129 62.3 66.7	days	for all 4 soils Elmton Drayton Bromsgro Fladbury
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect	25	mg/kg	Sandy loam
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC	1000	mg/kg	Species: cabbage, mung bean, sugar beet, tomato, ryegrass and

					wheat Tested in dry soil
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	1000	mg/kg	*Eisenia fetida*
Collembola, Reproduction Test	OECD 232	NOEC	308.6	mg/kg	*Folsomia candida*
Sediment dwelling organism	OECD 218	NOEC	1202	mg/kg	*Chironomus riparius*

2.3.6. Discussion on non-clinical aspects

Simeprevir is a specific inhibitor of the HCV NS3/4A serine protease, which is essential for viral replication.

In non-clinical in vitro and in vivo data TMC-354 results to be an inhibitor of the uptake transporters OATP1B1, NTCP and of the efflux transporters P-gp/MDR1, MRP2 and BSEP. These results as well as those on CYP 450 are consistent with the clinical drug drug interaction (DDI) finding.

The pancreas and GI alterations findings in rodents were not considered relevant for man in view of the much higher local exposure in rodents together with gavage dosing of a viscous formulation with a longer transit time in preclinical species, even if frequent GI effects are reported in humans with TMC435 (nausea and diarrhoea at a frequency of 22.2% and 11.0%, respectively, during the first 12 weeks phase, and constipation of severity grades 2 to 4 but not at a frequency comparable to that of the first two AEs). Correlation between non clinical and clinical GI findings is not worth due to species-specific related effects, and the non-clinical toxicity findings are hence not to be considered relevant from a clinical point of view.

Overall, in spite of the relatively low exposures obtained, target organs (liver, GI and pancreas) were identified. The question of low exposures was put to the Applicant. They clarified that they could not obtain an increased exposure despite numerous efforts. The Applicant did not use the i.v. dose in order to maximise the exposure in line with the Scientific Advice from the CHMP as a parental route of administration was not feasible due to the potential problems related to the high dose administration. In summary, despite the Applicant efforts, no suitable safety margins were achieved. This issue is reflected in the SmPC.

Increases in transaminases were observed and histopathological changes in the liver were described in animal models, altogether suggestive of presumptive hepatic damage. It was then clarified that only dogs have shown hepatic findings revealed as small foci of hepatocellular necrosis following two weeks, 1 month and 6 months of repeated administration of the product, with considerable safety margins of clinical exposure, while during longer periods of administration up to 39 weeks dosing no hepatic effects were reported (4-fold the clinical exposure). Findings in this animal model were completely restored following a one month reversal period. Such events have not been reported in Phase IIb/III studies.

Safety ratios animal-human were low being inferior or slightly above one in the rat (Cmax 0.9-1.6; AUC0-24h 0.5-0.9) and somehow higher in dogs (Cmax 2.4-3.9; AUC0-24h 0.8-1.2).

In the 13-weeks diet study in mice, tissue distribution was investigated, showing that the concentrations in the duodenum, liver and pancreas were higher than those found in plasma (highest to lowest tissue exposure: duodenum, liver and pancreas).

Simeprevir was non-genotoxic in a test battery comprising the following assays: Ames test, L5178Y TK+/- mouse lymphoma cells and in vivo mouse micronuclei test (at a plasma Cmax around 30 µg/mL), therefore the Applicant was asked discuss if the bone marrow cells in the micronucleus study was exposed to TMC435. The amount of TMC435 found in bone was comparable to that found in blood for both mice and rats, (15 µg/mL, as showed in the in vivo mouse micronucleous test). This exposure exceeded about 3 times the clinical Cmax (4 µg/mL).

The lack of carcinogenicity studies was justified by the Applicant in line with ICH S1A and based on the proposed treatment duration of 12 weeks for TMC435. This point was discussed in Scientific advice from the CHMP. The Applicant confirmed that in any case the duration of the treatment would be up to 12 weeks of duration. A wording related retreatment has been included in the SmPC.

Reproductive and developmental toxicity studies did not demonstrate any effect on fertility in rats and no adverse effects on embryo-fetal development in mice or rats. In the pre- and postnatal developmental study, there were no adverse effects on mating performance, fertility, pre-coital interval and litter data for F1 animals derived from treated groups. There was also no evidence of a selective adverse effect on development of offspring from dams treated with TMC435.

In pregnant rats, simeprevir concentrations in placenta, fetal liver and foetus were lower compared to those observed in blood. When administered to lactating rats, simeprevir was detected in plasma of suckling rats likely due to excretion of simeprevir via milk.

Although data did not indicate significant findings fertility in the studies carried out in rats, embryo-foetal or development related at any of the tested doses, the exposure achieved was not as the exposure reported in humans. Consequently the relevance of data in rat is limited. The SmPC reflects this information.

In an oral developmental toxicity study in mice, short supernumerary ribs or full supernumerary with other adverse effects on ossification were reported. This finding was observed at doses over 500mg/kg/day (4-fold safety marging with expected clinical exposure). This is reflected in the SmPC. Additionally, the need of evaluating this issue in juvenile studies may need to be reconsidered and discussed in the future in possible extension of the indication to the paediatric population.

Simeprevir was slightly irritant for the eye and did not induce delayed contact hypersensitivity in the murine Local Lymph Node Assay.

TMC-435 elicits phototoxic effects on BALB/c 3T3 fibroblasts in the absence and presence of protein supplements when tested in vitro and this information has been reported in the SmPC.

2.3.7. Conclusion on the non-clinical aspects

Simeprevir is a specific inhibitor of the HCV NS3/4A serine protease, which is essential for viral replication.

There were no adverse effects of simeprevir on vital functions (cardiac, respiratory and central nervous system) in animal studies.

Simeprevir was not genotoxic in a series of in vitro and in vivo tests. Carcinogenicity studies with simeprevir have not been conducted. The Applicant's justification was considered acceptable to the CHMP. In any case, the duration of the treatment with simeprevir would be up to 12 weeks of duration. A wording related retreatment has been included in the SmPC.

Simeprevir is classified as a PBT (persistent, bioaccumulative and toxic) substance and may pose a risk to the environment. This is reflected in sections 5.3 and 6.6 of the SmPC.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- **Tabular** overview of clinical studies

Table 2. Clinical Studies Providing Efficacy Data for TMC435 in Combination With PegIFN/RBV in Chronic HCV Infection

Study ID	Country(ies): No. of Sites	Study Description/Design	Total No. of Subjects in Study (TMC435+Control)	TMC435 Regimen(s) and Treatment Duration(s)	Active Drug(s), Formulation(s) and Route of Administration
Phase I					
C101	NLD: 1	Randomized, double-blind, placebo-controlled study in healthy subjects to evaluate the safety, tolerability, and pharmacokinetics of increasing oral doses of TMC435 after single and multiple dosing, followed by an open-label multiple dosing session in HCV genotype 1 infected subjects (non-placebo-controlled).	HCV- infected: Enrolled: 6 Treated: 6	HCV-infected: TMC435 200 mg q.d. administered for 5 days as monotherapy	TMC435 100 mg/mL oral solution (F002)
Phase IIa					
C201	BEL, FRA, DEU, POL, NLD, GBR: 25	Randomized, double-blind, placebo-controlled study in HCV genotype 1 infected subjects to evaluate the efficacy, safety, tolerability, and pharmacokinetics of repeated doses of TMC435, with or without PegIFNα-2a and RBV.	Randomized: 120 Treated: 116	TMC435 25, 75, 150 or 200 mg q.d. administered as monotherapy for 7 days or in combination with PegIFN/RBV for up to 28 days	TMC435 25 mg and 100 mg oral capsules (F008 and F007) PegIFNα-2a 180 µg s.c. (Pegasys®) RBV 200 mg oral tablets (Copegus®)[a]
C202	BEL, DEU, THA: 12	Open-label study in HCV genotype 2, 3, 4, 5, or 6 infected subjects to evaluate the antiviral activity, safety, tolerability, and pharmacokinetics of TMC435 administered as monotherapy for 7 days.	Enrolled: 37 Treated: 37	TMC435 200 mg q.d. administered for 7 days as monotherapy	TMC435 100 mg oral capsules (F007)
Phase IIb					
C205	AUS, NZL, CAN, AUT, BEL, DEU, ESP, FRA, POL, RUS, USA, NOR, DNK: 79	Randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of TMC435 as part of a treatment regimen including PegIFNα-2a and RBV in treatment-naïve HCV genotype 1 infected subjects.	Randomized: 388 Treated: 386	TMC435 75 or 150 mg q.d. administered as TMC435 12 Wks PR 24/48, TMC435 24 Wks PR 24/48[b]	TMC435 75 mg oral capsules (F021) PegIFNα-2a 180 µg s.c. (Pegasys®) RBV 200 mg oral tablets (Copegus®)[a]
C206	RUS, FRA, DEU, POL, ISR, BEL, GBR, AUT, PRT, NOR, USA, CAN, AUS, NZL: 89	Randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of TMC435 as part of a treatment regimen including PegIFNα-2a and RBV in HCV genotype 1 infected subjects who failed to respond to or relapsed after at least 1 course of PegIFNα-2a/b and RBV.	Randomized: 463 Treated: 462	TMC435 100 or 150 mg q.d. administered as TMC435 12 Wks PR 24/48, TMC435 24 Wks PR 24/48, TMC435 48 Wks PR 48	TMC435 75 mg and 100 mg oral capsules (F021 and F020) PegIFNα-2a 180 µg s.c. (Pegasys®) RBV 200 mg oral tablets (Copegus®)[a]
Phase III					
C208	AUS, CAN, DEU, ESP, GBR, ITA, MEX, NZL, PRI, ROM, RUS, UKR, USA: 71	Randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of TMC435 vs placebo as part of a treatment regimen including PegIFNα-2a and RBV in treatment-naïve, HCV genotype 1 infected subjects.	Randomized: 395 Treated: 394	TMC435 150 mg q.d. administered as TMC435 12 Wks PR 24/48[b]	TMC435 150 mg oral capsules (G007) PegIFNα-2a 180 µg s.c. (Pegasys®) RBV 200 mg oral tablets (Copegus®)[a]

Study ID	Country(ies): No. of Sites	Study Description/Design	Total No. of Subjects in Study (TMC435+Control)	TMC435 Regimen(s) and Treatment Duration(s)	Active Drug(s), Formulation(s) and Route of Administration
C212	FRA, DEU, PRT, GBR, ESP, CAN, USA: 39	Open-label study to evaluate the efficacy, safety, and tolerability of TMC435 as part of a treatment regimen including PegIFNα-2a and RBV in HCV genotype 1 infected subjects who are co-infected with HIV-1.	Enrolled: 107 Treated: 106	TMC435 150 mg q.d. administered as TMC435 12 Wks PR 24/48[b]	TMC435 150 mg oral capsules (G007) PegIFNα-2a 180 µg s.c. (Pegasys®) RBV 200 mg oral tablets (Copegus®)[a]
C213	ARG, AUS, AUT, BEL, BRA, BGR, CAN, FRA, DEU, GBR, ISR, ITA, MEX, NLD, NZL, POL, PRT, ROU, RUS, ESP, TUR, UKR, USA: 33	Open-label study to evaluate the efficacy, safety, and tolerability of TMC435 as part of a treatment regimen including PegIFNα-2a and RBV in HCV genotype 1 infected subjects who failed PegIFN/RBV therapy in the control group of a Phase II/III TMC435 study, or participated in selected Phase I studies evaluating short-term (up to 14 days) DAA therapy for HCV infection.	Enrolled: 54 Treated: 50 Planned: 270	TMC435 150 mg q.d. administered as TMC435 12 Wks PR 24/48[b]	TMC435 150 mg oral capsules (G007) PegIFNα-2a 180 µg s.c. (Pegasys®) RBV 200 mg oral tablets (Copegus®)[a]

Study ID	Country(ies): No. of Sites	Study Description/Design	Total No. of Subjects in Study (TMC435+Control)	TMC435 Regimen(s) and Treatment Duration(s)	Active Drug(s), Formulation(s) and Route of Administration
C216	ARG, AUT, BEL, BGR, BRA, ESP, FRA, DEU, NLD, POL, PRT, SVK, TUR, USA: 76	Randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of TMC435 vs placebo as part of a treatment regimen including PegIFNα-2a and RBV or PegIFNα-2b and RBV in treatment-naïve, HCV genotype 1 infected subjects.	Randomized: 393 Treated: 391	TMC435 150 mg q.d. administered as TMC435 12 Wks PR 24/48[b]	TMC435 150 mg oral capsules (G007) PegIFNα-2a 180 µg s.c. (Pegasys®) or PegIFNα-2b prefilled pens per weight band, s.c. (PegIntron®) RBV 200 mg oral tablets (Copegus®) or oral capsules (Rebetol®)[a]
HPC3002	BEL, CAN, DEU, FRA, POL, RUS, USA: 48	Prospective, 3-year follow-up study in subjects previously treated in a Phase IIb or Phase III study with a TMC435-containing regimen for the treatment of HCV infection.	Enrolled: 195[c] Planned: 250[d]	No treatment	Not applicable, no study treatment is being provided
HPC3007	AUS, AUT, BEL, CAN FRA, DEU, ESP, GBR, ITA, NZL, POL, PRI, RUS, USA: 81	Randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of TMC435 vs placebo as part of a treatment regimen including PegIFNα-2a and RBV in HCV genotype 1 infected subjects who relapsed after previous IFN-based therapy.	Randomized: 394 Treated: 393	TMC435 150 mg q.d. administered as TMC435 12 Wks PR 24/48[b]	TMC435 150 mg oral capsules (G007) PegIFNα-2a 180 µg s.c. (Pegasys®) RBV 200 mg oral tablets (Copegus®)[a]
HPC3011	BEL, FRA: 8	Open-label study to evaluate the efficacy, safety, and tolerability of TMC435 as part of a treatment regimen including PegIFNα-2a and RBV in treatment-naïve or treatment-experienced HCV genotype 4 infected subjects.	Enrolled: 136 Treated: 107	TMC435 150 mg q.d. administered as TMC435 12 Wks PR 24/48[b]	TMC435 150 mg oral capsules (G019) PegIFNα-2a 180 µg s.c. (Pegasys®) RBV 200 mg oral tablets (Copegus®)[a]

DAA: direct-acting antiviral; HCV: hepatitis C virus; HIV-1: human immunodeficiency virus type 1; IFN: interferon; PegIFN: pegylated interferon; q.d.: once daily; RBV: ribavirin; s.c.: subcutaneously

2.4.2. Pharmacokinetics

During the clinical development of TMC435, a bioanalytical assay was developed and validated for the analysis of TMC435 in plasma pharmacokinetic samples. The performance of this assay was carried out in line with international bioanalytical guidelines. The CHMP concluded that the Applicant has sufficiently justified the acceptability of the method.

Absorption

TMC435 is practically insoluble in aqueous media over a wide pH range, and switch from practically insoluble to soluble depending on the organic solvent. Because of the low solubility and low in vivo permeability, TMC435 is a Biopharmaceutics Classification System class 4 compound.

Dose proportionality studies concluded that simeprevir exposure increase more than dose-proportionality, both in healthy and HCV patients. An absorption lag-time for the higher dose groups is observed after multiple dosing.

Food effect on the oral bioavailability of TMC435 was investigated in 3 biopharmaceutic studies (C116, C121, and HPC1002), and also in the context of a Phase I dose-escalation study (C101). The results demonstrated that simeprevir exposure decreases under fasted conditions (AUC decrease up to 41%).

Distribution

Simeprevir is highly bounded (>99.9%) to plasma proteins, mainly to albumin. A mass-balance study (C103) showed that most of the 14C-TMC435-related radioactivity from a single 200-mg dose of 14C-TMC435 administered as oral solution was excreted in faeces, with individual values ranging from 59-100% of the total given dose. The total recovery of radioactivity in urine was very low (0.009% to 0.138%). Of all radioactivity recovered in plasma, by far the major TMC435-related circulating substance in plasma was UD. The major metabolites in human faeces extract samples were M21 and M22. Metabolites detected in faeces demonstrate that TMC435 is eliminated via 2 main metabolic pathways oxidation and O-demethylation.

Elimination

After administration of a single iv infusion of 100 µg [^{3}H]-TMC435 (100 µCi), radioactivity was mainly excreted in faeces (approximately 85% of the total radioactive dose), both after administration in combination with a single oral 50-mg and 150-mg dose of TMC435.

The fraction of total administered radioactivity excreted in urine was low for both treatments (approximately 2% of the total radioactive dose was recovered in urine in both treatments).

Mean value of the total recovery of the administered radioactive dose (sum of faeces and urine) was approximately 87%, and similar in both treatments.

Simeprevir is suggested to be eliminated mainly by CYP3A4 metabolism, but involvement of CYP2C8/CYP2C19 as well as uptake into the hepatocytes by active transport (via OATP1B1) has also been indicated.

Dose proportionality and time dependencies

Dose proportionality was studied in healthy subjects who received single oral doses (i.e. 50-600 mg) or multiple doses (100-400 mg q.d or 200 mg b.i.d). TMC435 is orally available. C_{max} was attained approximately at 4-6 hours, independently of the dose. After single or multiple dose the AUC of simeprevir increase more than dose proportionally at doses above 100 mg q.d. After a single dose, the mean terminal elimination half-life of TMC435 was approximately 10-13 hours; it is increased with the dose. According to the simulation based on the PBPK model, the non-linear PK of simeprevir in function of dose is probably mainly driven by saturation of gut CYP3A4 metabolism, saturation of hepatic uptake and hepatic first-pass metabolism. However, at the therapeutically relevant doses of 100 mg q.d. or 150 mg q.d. simeprevir the first pass extraction in the gut is simulated to be low.

In HCV patients dose proportionality was studied after administration of doses between 25-200 mg q.d in combination with PegIFN and RBV. The same t_{max} as in healthy subjects was observed, the increase in exposure was more than dose-proportional in both treatment naïve and treatment experienced at doses above 75 mg q.d. The mean terminal half-life was 41.3 hours after multiple dosing at 200 mg q.d.

Special populations

Renal Impairment

Based on the findings from the mass balance study (Study C103) the renal elimination (0.009% to 0.138% of the administered dose) does not play an important role in the excretion of simeprevir. Therefore, the influence of mild or moderate renal impairment should not be investigated, and only the impact of severe renal impairment on simeprevir exposure was studied in Study C126. Following administration of simeprevir at 150 mg q.d. in patients with severe renal impairment, the mean C_{min}, C_{max}, and AUC_{24h} values for TMC435 were increased 1.71-, 1.34-, and 1.62-fold, respectively, relative to matched patients with normal renal function. Therefore, it was observed an increased exposure to simeprevir in non-HCV patients with severe renal impairment.

Hepatic Impairment

In study C113, following administration of TMC435 at 150 mg q.d. in patients with moderate hepatic impairment, the mean C_{max} and AUC_{24h} values for TMC435 were 1.71- and 2.44-fold higher, respectively, relative to matched patients with normal hepatic function. In patients with severe hepatic impairment, the mean C_{max} and AUC_{24h} values for TMC435 were 3.13- and 5.22-fold higher, respectively, relative to (non-matched) patients with normal hepatic function. The median t_{max} was 6 hours for all treatment groups.

When compared with historical data from patients with chronic HCV genotype 1 infection and compensated liver disease, the mean C_{max} and AUC_{24h} values for TMC435 in patients with moderate hepatic impairment were decreased by 7% and increased 1.30-fold, respectively, following administration of TMC435 at 150 mg q.d. In patients with severe hepatic impairment, these values were increased 1.69- and 2.78-fold, respectively, when compared with historical data. The median t_{max} was 6 hours for all treatment groups.

Percentage unbound TMC435 was very low in all patients (≤ 0.064%) and was comparable for patients with normal hepatic function and patients with moderate hepatic impairment. Because of methodological difference in the plasma protein binding experiment, absolute values of unbound fraction cannot be compared between severely hepatic impaired patients in both groups of treatment.

In the final pharmacokinetics model, 99.9% of the patients had a Child-Pugh liver score of 5-6, which corresponds to a Child-Pugh class A, 0.1% had a score of 7-9 (class B) and 0% had a liver score >10 (class C). This underrepresentation of patients with moderate to severe liver dysfunction (class B and C) leaded to the decision of not testing Child-Pugh score in the model.

Simulations in HCV-infected patients with mild hepatic impairment suggest that Caucasians with mild hepatic failure and HCV exhibit more than 2-fold higher exposures (C_{max} and AUC_{∞}) following 150 mg once-daily compared to healthy Caucasian patients. The difference in exposure based on the simulations was in agreement with the differences observed in clinical studies (approximately 2- to 3-fold higher exposure in HCV infected patients).

Other factors

Subgroup analyses in different studies revealed no difference in the pharmacokinetics of TMC435 by sex and race. According to the results in the population pharmacokinetics model, gender, race and weight have no clinically relevant effect on the pharmacokinetics of TMC435 in HCV-infected patients.

The effect of age was evaluated in a population pharmacokinetics model. Based on these simulations, age has apparently no clinically relevant effect on the pharmacokinetics of simeprevir in HCV-infected patients. However, patients included in the model showed an age range of 18-73 years, with a median of 49 years and 5%-95% percentiles of 25 and 63 years respectively. This makes elderly population (i.e. >65) underrepresented. No PK studies were performed in paediatric population.

Pharmacokinetic interaction studies

Simeprevir as the victim, transporter level:

In vitro studies indicate that simeprevir is a substrate for:

a) ABC transporters P-gp, MRP2 and BRCP1;

b) OATPs, and particularly OATP1B1 and 1B3. Studies with human hepatocytes have shown that the uptake of simeprevir has an active component and OATP inhibitors (Cyclosporin A, Rifampicin) inhibit the uptake by human hepatocytes *in vitro*;

c) NTCP.

In vivo data and simulations show that interaction at the transporter level does influence the exposure to simeprevir. The effect of P-gp inhibitors appear to be modest at therapeutically doses. For example, ritonavir, which completely blocks intestinal P-gp, only increased simeprevir Cmax by 38%. This is probably due to the low first pass extraction in the intestine at therapeutic doses. The effect of OATP inhibitors has not been investigated with a dedicated study, but it has been evaluated by performing simulation based on the DDI study with cyclosporine and rifampin. Based

on these simulations, and on comparison with pooled data of phase 1 studies, the effect of OATP inhibitors appear to be greater than that of P-gp inhibitors. After a single dose of rifampin, simulations estimated an increase in AUC and C_{max} of approx. 2-folds. However, the effect may be greater after multiple administrations.

Simeprevir as the victim, enzyme level:

Simeprevir is metabolised in the liver mainly by CYP3A enzymes. However, involvement of CYP2C8 and CYP2C19 cannot be excluded. In *in vitro* study NC116 the effect of CYP inhibitors on the formation of metabolites 18, 23 and 25 were investigated, as these 3 metabolites are predominant *in vitro*. However, *in vivo* (humans) the main circulating metabolite was M21, and the main metabolites in faeces were M21 and M22. Thus, the CYP isoforms responsible for the formation of the main *in vivo* metabolites are not known. Nor it is known the role of the various isoforms on the overall metabolic rate (that is, on the rate of disappearance of the parent drug). However, available *in vitro* data show that CYP2C8 and CYP2C19 may account for more than 25% of some metabolic reactions or pathways (formation of M18, M23 and M25).

The large effect seen on the PK of simeprevir (exposure increase 7.47 fold) after coadministration with erythromycin (a moderate CYP3A4 inhibitor) was in the same range as that of the strong CYP3A4 inhibitor ritonavir (7.18 fold).

Simeprevir as the perpetrator, transporter level:

In vitro, simeprevir inhibits: 1) P-gp; 2) NTCP and OATPs and, consequently, the biliary excretion of Taurocholate (NTCP) and 17β-estradiol-glucuronide (OATP1B1); 3) ABCC2 (MRP2) and ABCB11 (BSEP). There was no a clear rationale for the choice of transporters investigated. It appears that the studies on the inhibitory potential of simeprevir on transporters were mainly driven by the clinical finding of hyperbilirubinemia without increases in AST or ALT in healthy subjects.

Overall, results of DDI studies with statins indicate that simeprevir inhibits OATP1B1/ OATP1B3 *in vivo*, in agreement with *in vitro* data, and this may have clinical relevance. *In vivo*, inhibition of renal P-gp appears to have little clinical relevance with drug substrates other than digoxin. Inhibition of intestinal P-gp may be responsible for the increase in exposure of erythromycin and ritonavir by simeprevir.

HMG CoA-reductase inhibitors use OATP1B1 transporter. Co-administration of atorvastatin or simvastatin with simeprevir has been studied and increased exposure of both drugs has been detected, suggesting an inhibition of this transporter. Regarding simeprevir as a substrate of OATP1B1 transporter, no major changes in plasma exposure of simeprevir were observed when co-administered with a single dose of cyclosporine; however, the median t_{max} of simeprevir was decreased compared to the median t_{max} after administration of simeprevir alone, confirming that simeprevir is a substrate of drug transporters which are inhibited by co-administration of cyclosporine.

Inhibition of OATP1B1 and/or MRP2 may be responsible for the observed hyperbilirubinemia, which also be due, at least partially, to inhibition of UGT1A1. Simeprevir also inhibits, at clinically relevant concentrations, the hepatic uptake of taurocholate (mediated by NTCP transporter) and taurocholate biliary efflux capacity (BSEP transporter). Simeprevir has therefore the potential for

decreasing biliary secretion of taurocholate and other bile salts, therefore increasing their serum levels.

Simeprevir as enzyme inhibitor:

In vitro data indicate that simeprevir is a weak inhibitor of CYP2D6, CYP2C8, CYP2A6, CYP2C19 and CYP3A4. The inhibitory potential towards CYP2B6 has not been tested. In addition, results of study NC117 should be interpreted with caution because some control inhibitors used as positive controls did not reach 50% inhibition. DDI studies with CYP substrates indicate a lack of relevant inhibition in the liver. The increase in exposure after oral but not after i.v. midazolam indicates that simeprevir slightly inhibits intestinal CYP3A4-mediated metabolism.

Potential for interaction with endogenous compounds:

In vitro data show that at concentrations reached with therapeutic doses, simeprevir inhibits hepatic uptake and biliary efflux of 17-β-estradiol glucoronide, which is mainly a substrate for the OATP1B1 uptake transporter and the MRP2 canalicular efflux transporter, and is used as representative probe for bilirubin and bilirubin glucuronides. Inhibition of OATP1B1 and/or MRP2 may therefore be responsible for the observed hyperbilirubinemia. Hyperbilirubinemia might also be due to inhibition of UGT1A1. The apparent inhibition constant of the UGT1A1 mediated bilirubin glucuronidation was determined to be 119±14 µM. Therefore inhibition may occur at levels predicted in the liver (about 400 µg/ml due to a 20 to 40 fold liver to plasma ratio in tissue distribution). Simeprevir also inhibits, at clinically relevant concentrations, the hepatic uptake of taurocholate (mediated by NTCP transporter) and taurocholate biliary efflux capacity (BSEP transporter). Simeprevir has therefore the potential for decreasing biliary secretion of taurocholate and increasing its serum levels.

Simeprevir was classified as a substrate of rat BCRP *in vitro*. Simeprevir was classified as a substrate of rat Brcp1 in vitro. Studies were performed in mouse Bcrp1 instead of human BCRP as at the time of the experiment no stable human BCRP cell line was available. Mouse Bcrp1 and human BCRP are 86% homologous, show very similar substrate specificities, and hydrophobicity plots of both proteins are almost identical, which indicates that observations with mouse Bcrp1 most probably also hold true for human BCRP. Also, a study with Cyclosporin A indicated that the role of BCRP is limited in the overall exposure of simeprevir.

2.4.3. Pharmacodynamics

Mechanism of action

Simeprevir is a specific inhibitor of the HCV NS3/4A serine protease, which is essential for viral replication.

Primary and Secondary pharmacology

The antiviral activity of TMC435 has been assessed in the Phase IIa proof-of-principle studies C201 and C202, the Phase IIb studies C205 and C206, and the Phase III studies C208, C212, C216, HPC3007, and HPC3011.

In the multivariate modelling to assess the relationship between plasma concentration and effect, results suggests that simeprevir exposure is not a clinically relevant predictor of SVR12, as it is only a significant covariate when only early response parameters and exposure are considered together. When baseline factors, early response parameters and simeprevir exposure are considered altogether, AUC_{24h} is not significant. Early-response variables (eRVR and meeting RGT criteria) were the most important discriminative factors for reaching SVR12.

Clinical virology

TMC435 is a macrocyclic inhibitor of the HCV NS3/4A protease. The *in vitro* median 50% and 90% effective concentration (EC50 and EC90) of TMC435 was 9.4 and 19 nM, respectively, in genotype 1b replicon-containing Huh7-Luc cells with luciferase read-out.

Antiviral Activity against different genotypes

TMC435 is active against HCV genotype 1, 4 ,5 and 6, has shown antiviral activity in 3/6 HCV genotype 2 infected patients (all baseline isolates carried the S122R, median reduction in TMC435 activity of 25 fold) and no activity against HCV genotype 3 (all HCV genotype 3 baseline isolates carried the D168Q polymorphism, median reduction in TMC435 activity of 1014 fold).

In vitro Drug Resistance

In vitro and *in vivo* studies revealed a pattern of amino acids substitutions conferring resistance to TMC435 antiviral activity. The mutations most frequently observed in the NS3 protease in all cell lines cultured with TMC435 were found to be located at position 168. Amino acid substitutions in D168 were found in a high percentage of clones assayed (85/109 sequences - 78%), with the majority harbouring a D168V (44/109 sequences - 40%) or a D168A mutation (32/109 sequences - 29%). D168A mutation was the most frequent mutation in genotype 1a replicon cells, while the D168V mutation was the most abundant in genotype 1b replicon cells. Other NS3 protease amino acid substitutions were observed in these set of experiments including a substitution of F43 to S (in 4/109 sequences), of Q80 to R, K, or H (in 9, 4, and 1 out of 109 sequences, respectively), of R155 to K (in 7/109 sequences), as well as an amino acid substitution of A156 to V, T, or G (in 6, 2, and 2 out of 109 sequences, respectively). R155K amino acid substitution was found only in genotype 1a replicon-containing cells; genotype 1b replicon containing cells did not show this mutation either after selection.

Different resistance avenues are observed depending on the genotype context. In particular D168V was selected only in genotype 1b replicons *in vitro* whereas mutations at positions 80 and 155 were almost exclusive of genotype 1a. Frequencies obtained in the selection of these mutations are actually higher as these numbers should then be referred to the relative number of sequences of each replicon subtype.

TMC435 antiviral activity was also assessed against NS3 protease sequences from clinical isolates derived from TMC435 treated patients enrolled in the clinical studies (C101, C201, C202, C205, and C206) through replicon backbone assay. Simultaneously, TMC435 anti-HCV activity was evaluated in Site Direct Mutants (SDMs) carrying NS3 specific nucleotide substitutions in a transient replicon assay. Sensitivity of clinical isolates to the drug was then compared with that of the corresponding SDMs. Q80K mutations resulted in a reduction of TMC435 activity more than 10-fold with respect to Wild Type (WT), in a chimeric replicon assay, whereas R155K polymorphism

resulted in a median reduction of TMC435 activity of 95- to 100-fold, The Applicant established a biological cut-off values that differentiates isolates or SDMs susceptible to TMC435 from those with reduced TMC435 activity (2.0 and 50.0 FC in EC_{50}). Clinical isolates or SDMs with an FC value of ≤2.0, 2-50, ≥50 were considered respectively fully susceptible, low resistant, and high resistant to TMC435. According to this cut-off, four major mutations (Q80K, D168E D168V and R155K) give resistance to TMC435. These results fit well with clinical studies observation. An effect of simeprevir over placebo on short term virological response against Q80K containing variants is evident, based on the data provided, the Q80K mutation might be considered as "low level resistance" mutation only *in vitro*. The *in vivo* presence of this mutation is associated to a higher failure rate (higher viral breakthrough and relapse rates) resulting in lower SVR12 rates compared to SMV/PR-treated HCV genotype 1a infected patients without Q80K mutation at baseline.

Baseline Polymorphisms

Data from patients treated with 150 mg q.d. TMC435/PR in the Phase IIb studies C205 and C206, and in the Phase III studies C208, C216, and HPC3007, were pooled and analysed (N=1125 patients with sequence data). In addition, the prevalence of baseline polymorphisms present in all patients enrolled in these 5 studies (N=2007 patients with sequence data) was analysed. The effect of baseline polymorphisms on outcome with a treatment of TMC435/PR (12 weeks of 150 mg q.d) in combination with a response-guided overall treatment duration of 24 or 48 weeks of PegIFN/RBV in HCV genotype 1 infected treatment-naïve patients was assessed in the efficacy pooling of study C208 and C216 (N=515 TMC435 treated patients with sequence data).

The highest prevalence was observed for polymorphisms at NS3 positions 174 (24.4%), 170 (19.2%), 80 (16.5%), 132 (16.5%), and 122 (12.8%). Q80K baseline polymorphism was present in 274 of 2007 (13.7%) patients with sequencing data available: 269 of 911 patients (29.5%) with HCV genotype 1a, and 5 of 1096 patients (0.5%) with HCV genotype 1b.

The effect of baseline polymorphisms on treatment outcome was investigated in the efficacy pooling of studies C208 and C216 studies (phase III studies). Mean changes in HCV RNA from baseline were more rapid and pronounced in TMC435/PR treated HCV genotype 1 infected patient with and without a baseline Q80K polymorphism than in patients in the PBO/PR arm. However, in HCV genotype 1a infected patients without Q80K polymorphism at baseline showed a trend for a greater reduction in HCV RNA levels.

In HCV genotype 1a infected patients treated with TMC435, SVR12 was reached in 58.3% of the patients with a Q80K polymorphism at baseline, and 83.6% of patients without Q80K at baseline, whereas in PBO/PR arms SVR12 was reached in with 47.3% of patients with and without Q80K. On treatment failure and relapse rates were generally higher in TMC435/PR treated patients with a Q80K polymorphism compared with patients without Q80K baseline. Except in C206 and C216 clinical trials, lower virologic response rates and higher viral relapse and on-treatment failure rates were observed in TMC435/PR-treated HCV genotype 1a infected patients with a Q80K polymorphism compared with patients without Q80K at baseline

Emergence of Mutations

Clinical studies also revealed that a set of emerging mutations that conferred resistance to TMC 435 antiviral activity was found in patients who experienced a viral breakthrough or a viral relapse after treatment. Overall, treatment failure occurred in 245 of 1136 patients who received 150 mg

q.d. TMC435 in studies C205, C206, C208, C216, and HPC3007. Of the 197 patients with treatment failure and NS3 sequence information available, 116 patients had HCV genotype 1a and 81 had HCV genotype 1b infection. Most patients (180 of 197 [91.4%] overall, i.e., 110 of 116 [94.8%] genotype 1a and 70 of 81 [86.4%] genotype 1b infected patients) had emerging mutations at NS3 positions 80, 122, 155, and/or 168. Emerging mutations were similar between patients with on-treatment failure and viral relapse.

In phase III studies, the emergence of resistant variants and virological breakthrough was more common in patients infected with HCV subtype 1a than 1b, suggesting a higher genetic barrier in HCV subtype 1b. This different barrier to resistance was observed between GT1 subtypes 1a and 1b in the case of R155K. This mutation is barely detected in HCV genotype 1b infected patients because two nucleotide changes are required to generate and amino-acid change in subtype 1b while only one is needed for subtype 1a. Thus subtyping may play an important role in helping to select future treatment regimens and predict the development of resistance.

Cross resistance between TMC435 and linear PIs was observed, mutations conferring cross resistance to these drugs have been defined (positions 36, 155, 156 are particularly relevant and are adopted in the guidelines of the IAS-USA panel of experts). No cross resistance was observed *in vitro* between TMC435 and NS5A inhibitors and NS5B polymerase inhibitors (nucleos(t)ide and non-nucleoside).

Evolution of resistant variants after treatment discontinuation

In the pooled analysis of the Phase IIb studies C205 and C206 and the Phase III studies C208, C216 and HPC3007, (median follow-up time of the EOS visit from the time of failure of 28.4 weeks (range 0.0-69.9 weeks)), for 50.0% of patients (90/180) who failed 150 mg TMC435/PR treatment with emerging mutations at time of failure, emerging mutations were not observed at end of study, but wild type or the same amino acid sequence as the baseline sequence was observed at this time point. For 13.3% (24/180) patients a new mutation profile compared with the one at time of failure was observed at end of study. In 36.7 % (66/180) patients, emerging mutations were still detected at the end of study.

Analysis of NS3 at positions 43, 80, 122, 155, 156 and 168 at EOS by mutations at time of failure and baseline Q80K polymorphism showed that in patients without Q80K the most common emerging mutation at failure was 168V mutation (returning to baseline or changing to new mutations at EOS in 66.7% and 6.3% of patients, respectively) whereas in patients with Q80K the most common emerging mutation at failure was R155K mutation (returning to baseline or changing to new mutations at EOS in 63.4 % and 0% of patients, respectively).

Persistence over time of emerging mutations has been analysed. The median time to loss of emerging mutations was shorter in patients with HCV genotype 1b compared with HCV genotype 1a. The mutations D168V were those having the shorter median time to return to baseline to WT, compared to mutations like R155K. Moreover, the Q80K polymorphism at baseline made the R155K mutations in HCV genotype 1a infected patients, undetectable faster with respect to those mutations not carrying such polymorphism.

2.4.4. Discussion on clinical pharmacology

Discussion on pharmacokinetics

The pharmacokinetics (PK) of simeprevir was extensively and, in general, adequately investigated. TMC435 is a potent and selective inhibitor of the HCV NS3/4A protease being developed for the treatment of chronic HCV infection. The pharmacokinetics of TMC435 was assessed either as a primary or secondary objective in most of Phase I, Phase II and Phase III studies.

Food effect on the oral bioavailability of TMC435 has been assessed in four clinical trials. According to the results, simeprevir exposure decreases under fasted conditions (AUC decrease up to 41%). Based on these findings, simeprevir must be taken with food. Of note, in the phase III studies which are the basis for the submission (C208, C216, and HPC3007), simeprevir was administered without regard to food intake because the results of study C116 were not available. The Applicant performed a questionnaire on food intake in patients included in phase III studies concluding that more than 80% of patients had taken simeprevir with food and approximately 15% of patients had taken simeprevir mostly with a meal. Only 2.7-5.8% of patients had sometimes taken simeprevir with a meal, and 1.2-3.0% had never taken simeprevir with a meal. In the pivotal phase III studies it has been observed a great inter-patient variability in the exposure to simeprevir without consequences in the efficacy.

The exposure in HCV patients is 2-3 fold higher and the half-life of simeprevir is clearly longer than in healthy patients. Thus, the elimination is slower in HCV patients. There is a dose-dependency in the elimination of simeprevir showing that an elimination mechanism is saturated and the dose-proportionality pattern differs between HCV patients and healthy patients.

Renal elimination of simeprevir is negligible. Therefore, it is not expected that renal impairment will have a clinically relevant effect on the exposure to simeprevir. However, severe renal failure is known to affect the absorption, transport and metabolism of several drugs through unknown mechanisms. Extrapolation of the data from non-HCV infected patients with severe renal failure to HCV-infected patients with severe renal failure remains unclear. Indeed, differences in exposure have been observed in HCV-infected patients without renal failure compared to matched healthy patients. It remains unclear how this difference in exposure translates to HCV-infected patients with severe renal failure. Hence, as exposure may be increased in HCV infected patients with severe renal impairment, caution is recommended in the SmPC when prescribing simeprevir to these patients.

No dose adjustment of simeprevir is necessary in patients with mild or moderate hepatic impairment. However, no dose recommendation can be made for patients with severe hepatic impairment (Child Pugh class C).

Dose adjustments are not required in elderly patients as the clinical impact of age in bioavailability is irrelevant; however, there is no data on patients aged above 75 years.

The potential for interaction of simeprevir is high, as also observed with other drug with similar mechanism. It has been evaluated by in vitro and in vivo studies, and by using simulation based on PBPK models. In general, the overall approach, and the design and conduct of the single studies were in line with the Guideline on the Investigation of Drug Interactions (CPMP/EWP/560/95/Rev.

1 Corr.*). Fifteen in vivo studies were conducted to examine the DDI potential of simeprevir to evaluate drug-drug interactions of simeprevir with different drugs.

In most of the in vivo studies the simeprevir dose used was 150 mg qd, except in studies with rifampin and ritonavir where the dose used was 200 mg qd and the study with darunavir/ritonavir in which the dose used was 50 mg qd.

All DDI studies were conducted in healthy subjects except in the study with methadone in which were included patients HCV negative on stable methadone maintenance therapy.

According to the Guideline on the Investigation of Drug Interactions (CPMP/EWP/560/95/Rev. 1 Corr.*), the potential for interaction with any of the transporters known to be involved in clinically relevant in vivo drug interactions should be investigated. The Applicant has reasonably justified the lack of studies investigating the potential interactions at the level of OCT1 and OATs. The inhibitory potential of simeprevir on human OCT2, BCRP and OATP1B3 will be investigated in vitro as a post authorisation measure and it has been included in the RMP.

The primary enzyme involved in the biotransformation of simeprevir is CYP3A4. Co administration of simeprevir with moderate or strong inhibitors of CYP3A4 (i.e. erythromycin) may significantly increase the plasma exposure of simeprevir, while co administration with moderate or strong inducers of CYP3A4 may significantly reduce the plasma exposure of simeprevir and lead to loss of efficacy. Therefore, co administration of simeprevir with substances that moderately or strongly inhibit or induce CYP3A4 is not recommended. This has been reflected in the SmPC.

Coadministration of macrolides or rifampin with simeprevir is not recommended because of a strong interaction. Both classes of drugs are treatment for tuberculosis and non-tuberculous micobacteria, which are frequently found in HCV/HIV co-infected patients. Tuberculosis treatment consists on a combination therapy consisting of more than one drug to which the organism is susceptible. Therefore, the possibility of interaction is increased. Therefore the CHMP recommends that Applicant should update, if applicable, the SmPC including information of newly authorised medicinal products for tuberculosis treatment.

The Applicant has conducted DDI studies with atorvastatin and simvastatin, both substrates of OATP1B1 transporter and CYP3A4. Coadministration of atorvastatin or simvastatin with simeprevir resulted in an increase of the pharmacokinetic parameters. Also, HMG-CoA reductase inhibitory activity was increased when atorvastatin or simvastatin were coadministered with simeprevir relative to administration of either statin alone. Interaction between simeprevir and rosuvastatin, which is an OATP1B1 substrate, has also been studied in another DDI study. Given the pharmacokinetics properties of the other statins, similar results could be expected.

In a DDI with ethinylestradiol (study C124), the median AUC values were in line with the observed average simeprevir exposures in other Phase 1 studies. A 3 fold exposure increase of sofosbuvir was observed. This increase was not clinically relevant. However, the Applicant is recommended to investigate the mechanism behind this interaction.

Discussion on clinical pharmacology and clinical virology

Simeprevir is a specific inhibitor of the HCV NS3/4A serine protease, which is essential for viral replication.

Polymorphism Q80K negatively affects the virological response to TMC435. Q80K amino acid substitution at baseline was found in almost 14% of patients treated with TMC435. Lower virologic response rates and higher viral relapse and on-treatment failure rates were observed in TMC435/PR-treated HCV genotype 1a infected subjects with a Q80K polymorphism compared with patients without Q80K at baseline. Also, the percentage of patients with Q80K polymorphism who had SVR12 after treatment with TMC435/PR was not significantly different from patients with the same mutation treated with PR.

The presence of Q80K polymorphism in genotype 1a HCV –independently of the in vitro IC50 and emergence of further mutations - is strongly associated with virological failure. Hence, testing for the presence of the Q80K polymorphism in patients with HCV genotype 1a is strongly recommended when considering therapy with simeprevir in combination with PR. Alternative therapy should be considered for patients infected with HCV genotype 1a with the Q80K polymorphism or in cases where testing is not accessible. Appropriate information, including a warning has been included in the SmPC.

Cross resistance between TMC435 and first generation protease inhibitors was observed according to the mutations associated with failure to treatment regimens containing TMC435.

Macrocyclic and linear PIs bind at the active site of NS3 and for that reason there is some overlap in resistant profiles.

The clinical significance of antiviral resistance variants that emerge during PI therapy remain uncertain until data on retreated patients become available. No measures are required until these data are available.

Clinical studies also revealed that a set of emerging mutations conferring resistance to TMC 435 antiviral activity was found in patients who experienced a viral breakthrough or a viral relapse after treatment. In particular, in line with data generated by *in vitro* studies, R155K emerging mutation was described to give a high resistance to TMC435 antiviral activity. Moreover, data showed that resistant viral variants evolved overtime. Selective pressure over time, generated by the wide use of TMC435 in the clinical setting, could potentially favour the selection of acquired mutations and give origin to resistant genotypes.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics of simeprevir was extensively and, in general, adequately investigated.

Simeprevir exposure decreases under fasted conditions (AUC decrease up to 41%). Based on these findings, simeprevir must be taken with food.

The primary enzyme involved in the biotransformation of simeprevir is CYP3A4. Therefore, co administration of simeprevir with substances that moderately or strongly inhibit or induce CYP3A4 is not recommended.

The presence of Q80K polymorphism in genotype 1a HCV –independently of the in vitro IC_{50} and emergence of further mutations - is strongly associated with virological failure Hence, testing for the presence of the Q80K polymorphism in patients with HCV genotype 1a is strongly recommended when considering therapy with simeprevir in combination with PR. Alternative therapy should be considered for patients infected with HCV genotype 1a with the Q80K

polymorphism or in cases where testing is not accessible. Appropriate information, including a warning has been included in the SmPC.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

- The inhibitory potential of simeprevir on human OCT2, BCRP and OATP1B3 should be investigated in vitro. Final Study report expected by 1Q2015 (MEA).

2.5. Clinical efficacy

The evaluation of the efficacy profile of TMC435 in combination with PegIFN/RBV (PR) for the treatment of chronic HCV is based on 12 core studies conducted in North and South America, Europe, and Australia/New Zealand. Main efficacy results for this application derived from 1 phase IIa study (HP2002), 2 phase III studies (C205, C206) and 3 phase III double blind, placebo-controlled studies (C208, C216, HPC3007).

2.5.1. Dose response study(ies)

There were two phase IIb dose-response studies: study C205, which enrolled treatment-naïve HCV genotype 1 infected patients; and C206, which enrolled treatment-experienced HCV genotype 1 infected patients. Both of them were double-blind, randomized, placebo-controlled studies.

Study C205 evaluated 75mg and 150mg for a duration of 12 or 24 weeks; and study C206 evaluated 100mg and 150mg for a duration of 12, 24 or 48 weeks. The following table provides a summary of the key efficacy results in study C205 (treatment naïve patients):

Table 3. Summary of Key Efficacy Results – Study C205

n/N (%) or n (%)	TMC435 75 mg 12 Wks PR 24/48 N=78	TMC435 75 mg 24 Wks PR 24/48 N=75	TMC435 150 mg 12 Wks PR 24/48 N=77	TMC435 150 mg 24 Wks PR 24/48 N=79	PBO 24 Wks PR 48 N=77
Sustained Virologic Response (Intent-to-treat population)					
SVR12	65/78 (83.3)	57/75 (76.0)	62/77 (80.5)	68/79 (86.1)	51/77 (66.2)
SVR24	64/78 (82.1)	56/75 (74.7)	62/77 (80.5)	68/79 (86.1)	50/77 (64.9)
SVRW72	63/78 (80.8)	53/75 (70.7)	60/77 (77.9)	67/79 (84.8)	50/77 (64.9)
Met protocol-defined RGT criteria and completed PegIFN/RBV treatment at Week 24					
Met protocol-defined RGT criteria	64 (82.1)	61 (81.3)	61 (79.2)	68 (86.1)	NA
SVR12	59/64 (92.2)	53/61 (86.9)	57/61 (93.4)	65/68 (95.6)	NA
SVR24	58/64 (90.6)	52/61 (85.2)	57/61 (93.4)	65/68 (95.6)	NA
SVRW72	57/64 (89.1)	50/61 (82.0)	56/61 (91.8)	64/68 (94.1)	NA
On-Treatment Virologic Response at Week 4 (Intent-to-treat population)[a]					
Week 4					
HCV RNA <25 IU/mL					
Undetectable (RVR)	59 (75.6)	51 (68.0)	58 (75.3)	59 (74.7)	4 (5.2)
Detectable	8 (10.3)	15 (20.0)	12 (15.6)	13 (16.5)	8 (10.4)
Reasons for Not Achieving Sustained Virologic Response (SVR24)					
Total without SVR24	14 (17.9)	19 (25.3)	15 (19.5)	11 (13.9)	27 (35.1)
On-treatment failure[b]	6 (7.7)	2 (2.7)	6 (7.8)	3 (3.8)	15 (19.5)
Viral relapse	8 (10.3)	14 (18.7)	6 (7.8)	6 (7.6)	11 (14.3)

N: number of subjects with data; n: number of subjects with that observation; NA: not applicable; PBO: placebo;
PR:PegIFN/RBV; RGT: response-guided treatment; RVR: rapid virologic response; SVRX: sustained virologic response X weeks after the planned end of treatment
a Treated subjects with missing information were considered treatment failures.
b Confirmed detectable HCV RNA at end of treatment

The following table summarizes the main efficacy results from study C206 (pre-treated patients):

Table 4. Key Efficacy Parameters – Pooled TMC435 Dose Groups – Study C206

n/N (%)	Pooled TMC435 100 mg dose groups	Pooled TMC435 150 mg dose groups	PBO 48 Wks PR 48
Sustained Virologic Response (SVR12 and SVR24)			
Prior null responders			
SVR12	23/50 (46.0)	26/51 (51.0)	3/16 (18.8)
SVR24	23/50 (46.0)	26/51 (51.0)	3/16 (18.8)
Prior partial responders			
SVR12	40/68 (58.8)	52/69 (75.4)	2/23 (8.7)
SVR24	39/68 (57.4)	52/69 (75.4)	2/23 (8.7)
On-Treatment Virologic Response at Week 4 (intent-to-treat population)[a]			
Prior null responders	**N = 50**	**N = 51**	**N = 16**
HCV RNA ≥25 IU/mL undetectable (RVR)	17/50 (34.0)	20/51 (39.2)	0/16 (0.0)
HCV RNA ≥25 IU/mL detectable	11/50 (22.0)	18/51 (35.3)	0/16 (0.0)
Prior partial responders	**N = 68**	**N = 69**	**N = 23**
Undetectable (RVR)	38/68 (55.9)	46/69 (66.7)	0/23 (0.0)
Detectable	12/68 (17.6)	13/69 (18.8)	0/23 (0.0)
Reasons for Not Achieving Sustained Virologic Response (SVR24)			
Prior null responders	**N = 50**	**N = 51**	**N = 16**
On treatment Virologic Failure	16/50 (32.0)	15/51 (29.4)	12/16 (75.0)
Viral Relapse	6/50 (12.0)	8/51 (15.7)	1/16 (6.3)
Prior partial responders	**N = 68**	**N = 69**	**N = 23**
On treatment Virologic Failure	12/68 (17.6)	11/69 (15.9)	18/23 (78.3)
Viral Relapse	11/68 (16.2)	2/69 (2.9)	2/23 (8.7)

N: number of subjects with data; n: number of subjects with that observation; RVR: rapid virologic response; SVRX: sustained virologic response X weeks after the planned end of treatment
a Treated subjects with missing information were considered treatment failures.

2.5.2. Main studies

Study C208

Multicenter, randomized, double-blind, 2-arm, placebo-controlled study to investigate the efficacy, safety, and tolerability of TMC435 (150 mg q.d. administered for 12 weeks), in combination with 24- or 48-week response-guided treatment with PegIFNα-2a/RBV in treatment-naïve HCV genotype 1 infected patients.

Methods

Study Participants

Inclusion criteria: Adult patients with compensated CHC (HCV genotype 1), screening plasma HCV-RNA levels ≥10,000 IU/mL and with no previous treatment for CHC were eligible for the study. Patients had to have a liver biopsy within 3 years of the screening visit (or between screening and baseline visits) with findings compatible with chronic HCV infection. Patients with METAVIR score F3 or F4 (bridging fibrosis) had to have an ultrasound done within 6 months of the screening visit (or between screening and baseline visit) without findings suspicious for hepatocellular carcinoma.

Exclusion criteria: Patients with de-compensated liver disease, patients with any liver disease of non-HCV etiology, with any HCV non-genotype 1 (co-)infection, or with human immunodeficiency virus (HIV) or hepatitis B co-infection were excluded. Prior treatments with any approved or investigational drug for the treatment of hepatitis C were not allowed.

Treatments

Patients had to take the investigational drug (TMC435/placebo) once a day, starting the morning or evening of the baseline visit on Day 1. The investigational drug had to be taken at the same time each day throughout the entire treatment period. PegIFNα-2a was administered once weekly in the morning or evening, following local practice. Ribavirin had to be administered twice daily (b.i.d.) under fed conditions.

Objectives

The primary objective was to demonstrate the superiority of TMC435 versus placebo as part of a treatment regimen including PegIFNα-2a and RBV, with respect to the proportion of patients achieving SVR12.

Key secondary objectives included to demonstrate the superiority of TMC435+ PegIFNα-2a/RBV versus placebo+ PegIFNα-2a/RBV, with respect to the proportion of patients achieving SVR24; to compare the incidence of on-treatment failure in both treatment groups; to evaluate the relapse rate after treatment in both treatment groups; to determine the proportion of patients in the TMC435 treatment group who met criteria for shortening treatment and were able to complete all treatments at Week 24; to determine the viral NS3/4A sequence in patients not achieving an SVR in the TMC435 treatment group; compare the safety and tolerability of TMC435+ PegIFNα-2a/RBV versus placebo+ PegIFNα-2a/RBV.

Outcomes/endpoints

The primary endpoint of study C208 was the proportion of patients in each treatment arm achieving SVR 12 weeks after the planned end of treatment, defined as having HCV RNA <25 IU/mL undetectable at the end of treatment and HCV RNA <25 IU/mL 12 weeks after the planned end of treatment.

The primary efficacy analysis was based on the intent-to-treat (ITT) population, which included all randomized patients who took at least 1 dose of investigational drug (TMC435/placebo).

Key secondary efficacy endpoints include the proportion of patients: with SVR24; with SVR 72; with ≥ 2 log10 reduction in HCV RNA at all-time points during treatment and follow-up; with undetectable HCV RNA (<25 IU/mL undetectable) and/or HCV RNA levels <25 IU/mL at all-time points during treatment and follow-up, with focus on Weeks 4, 12, 24, 36, 48, 60, and 72; with

viral breakthrough; with viral relapse; with on-treatment failure; with normalized ALT levels at the end of treatment and at the time points of SVR assessment; who stopped HCV therapy (due to early virologic response) versus those who continued PegIFNα-2a/RBV at Week 48 in the TMC435 group.

Other evaluations: resistance determinations; exploratory biomarker and pharmacogenomic analyses (host IL28B, CYP3A5, CYP2C19 and transporter genotyping); pharmacokinetic and safety evaluations.

Sample size

The primary efficacy parameter was SVR12, defined as the proportion of patients with undetectable HCV RNA (<25 IU/mL undetectable) at the end of treatment and HCV RNA <25 IU/mL 12 weeks after the planned end of treatment.

Randomisation and Blinding (masking)

Central randomization was implemented in this study. Patients were randomly assigned in a 2:1 ratio (TMC435:placebo) based on a computer-generated randomization schedule prepared by or under the supervision of the Sponsor. The randomization was balanced by using randomly permuted blocks and was stratified by HCV genotype 1 subtype (1a, 1b, other) and IL28B genotype (CC, CT, TT) based on a polymorphism on chromosome 19 (SNP rs12979860).

Statistical methods

The analysis population was the intent-to-treat (ITT) population, which included all randomized patients who took at least 1 dose of investigational drug (TMC435/placebo). A per protocol analysis (excluding the patients with major protocol deviations) was planned to be performed in case of >10% of patients with a major protocol deviation.

The null hypothesis that was tested to address the primary objective of this study was that there is no statistically significant difference between the active treatment arm (TMC435 plus PegIFNα-2a and RBV) and the control group (placebo plus PegIFNα-2a and RBV) for the primary efficacy endpoint (SVR12). In addition, several null hypotheses were tested to address some of the secondary objectives.

The significance level for the comparison between treatment groups for the primary efficacy endpoint was 5%.

The primary analysis method for comparing the SVR12 between the 2 treatment groups was the Cochran-Mantel-Haenszel (CMH) test, controlling for the stratification factors (genotype subtype and IL28B genotype). A Breslow-Day test for homogeneity of odds ratios based on this model was also performed. In addition, the 95% CI was constructed around the response rate in each treatment group.

Results

Participant flow

Study dates: 18/01/2011 – 29/01/2013

Baseline data

Most patients were enrolled in Europe and North America, the additional patients were enrolled in Australia and New Zealand.

Table 5. Demographic Characteristics; ITT population

	PBO 12 Wks PR 48	TMC435 150mg 12 Wks PR 24/48	Total
Analysis Set: Intent-to-treat	130	264	394
Gender			
N	130	264	394
Female	56 (43.1%)	116 (43.9%)	172 (43.7%)
Male	74 (56.9%)	148 (56.1%)	222 (56.3%)
Race			
N	130	262	392
White	122 (93.8%)	227 (86.6%)	349 (89.0%)
Black or African American	4 (3.1%)	27 (10.3%)	31 (7.9%)
American Indian or Alaska Native	0	1 (0.4%)	1 (0.3%)
Native Hawaiian or Other Pacific Islander	1 (0.8%)	1 (0.4%)	2 (0.5%)
Asian	3 (2.3%)	5 (1.9%)	8 (2.0%)
Multiple	0	1 (0.4%)	1 (0.3%)
Ethnicity			
N	130	264	394
Hispanic or Latino	14 (10.8%)	35 (13.3%)	49 (12.4%)
Not Hispanic or Latino	116 (89.2%)	229 (86.7%)	345 (87.6%)
Age (years)			
N	130	264	394
≤45	53 (40.8%)	115 (43.6%)	168 (42.6%)
>45 - ≤65	76 (58.5%)	143 (54.2%)	219 (55.6%)
>65	1 (0.8%)	6 (2.3%)	7 (1.8%)
Age (years)			
N	130	264	394
Mean (SD)	45.7 (11.04)	46.3 (10.98)	46.1 (10.99)
Median	48.0	48.0	48.0
Range	(20; 66)	(19; 68)	(19; 68)
Body weight (kg)			
N	130	264	394
Mean (SD)	82.52 (21.478)	80.13 (17.316)	80.92 (18.797)
Median	80.60	78.70	78.91
Range	(42.0; 155.0)	(47.5; 135.3)	(42.0; 155.0)
Body mass index (kg/m^2)			
N	130	264	394
<25	47 (36.2%)	96 (36.4%)	143 (36.3%)
≥25 - <30	41 (31.5%)	100 (37.9%)	141 (35.8%)
≥30	42 (32.3%)	68 (25.8%)	110 (27.9%)
Body mass index (kg/m^2)			
N	130	264	394
Mean (SD)	28.15 (6.477)	27.48 (5.703)	27.70 (5.969)
Median	26.70	26.55	26.60
Range	(17.0; 53.5)	(16.5; 45.2)	(16.5; 53.5)
IL28B Genotype[a]			
N	130	264	394
CC	37 (28.5%)	77 (29.2%)	114 (28.9%)
CT	76 (58.5%)	150 (56.8%)	226 (57.4%)
TT	17 (13.1%)	37 (14.0%)	54 (13.7%)

[a] Results obtained from the central laboratory: may not be the same

According to METAVIR score available at baseline, 43.1% patients had METAVIR score F0 or F1, 26.9% patients had METAVIR score F2, 17.7% patients had METAVIR score F3, and 12.3% patients had METAVIR score F4. Four patients did not have METAVIR score available at baseline.

In total, 56.1% of patients were infected with HCV genotype 1a and 43.9% with HCV genotype 1b. Q80K polymorphism was present at baseline in 23.3% of the overall population with sequence data. All but 1 patient with Q80K polymorphism at baseline was infected with HCV genotype 1a; the proportion of patients with HCV genotype 1a and Q80K was 41.1%. Median HCV RNA at baseline was 6.48 log10 IU/mL (range: 1.4 to 7.6 log10 IU/mL), and 79.7% of patients had high HCV RNA values at baseline defined as >800,000 IU/mL. The proportion of patients with an HCV RNA value at baseline >800,000 IU/mL was higher in the TMC435/PR group (82.6%) compared with the PBO/PR group (73.8%).

Overall, the baseline disease characteristics are balanced across both treatment groups.

Outcomes and estimation

Sustained Virologic Response

Efficacy of TMC435 in combination with PegIFN/RBV was statistically significantly superior (p<0.001) to placebo in combination with PegIFN/RBV. SVR12 was achieved in 79.5% of patients in the TMC435/PR group versus 50.0% of patients in the PBO/PR group.

In the TMC435/PR group, all patients with SVR12 and who had reached the SVR24 assessment time point at the time of data cut-off for the Week 60 primary analysis (205 of 210 patients) also achieved SVR24. None of the patients in the TMC435/PR group had viral relapse after the time point of SVR12 assessment. At the time of the analysis, 247 patients in the TMC435/PR group and 30 patients in the PBO/PR group had reached the Week 24 visit or discontinued the study earlier. The SVR24 rate was 83.0% in the TMC435/PR group compared with 60.0% in the PBO/PR group.

Table 6. Sustained Virologic Response (SVR12 and SVR24) – Stratified Cochran-Mantel-Haenszel Approach; Intent-to-Treat Population – Study C208 Primary Week 60 Analysis

	Observed	Stratum Adjusted	Comparison versus PBO	
	n/N (%)	% (95% CI)[c]	Difference in Proportions (95% CI)[b]	p-value[a]
SVR12				
PBO 12 Wks PR 48	65/130 (50.0)	50.1 (42.1; 58.1)		
TMC435 150 mg 12 Wks PR 24/48	210/264 (79.5)	79.4 (74.7; 84.0)	29.3 (20.1; 38.6)	<0.001
SVR24				
PBO 12 Wks PR 48	18/30 (60.0)	60.7 (43.2; 78.3)		
TMC435 150 mg 12 Wks PR 24/48	205/247 (83.0)	78.8 (73.0; 84.7)	18.1 (-0.4; 36.6)	0.025

Subgroup Analyses

Subgroup analyses evaluated the impact of several factors on virologic response, such as stratification factors (HCV geno/subtype and IL28B genotype), presence of Q80K baseline polymorphism, baseline HCV RNA (≤ 800,000 or >800,000 IU/mL), and baseline METAVIR score.

In both treatment groups, SVR12 rates were lower in patients with IL28B genotype TT (vs genotypes CC and CT), baseline METAVIR score F4 (vs F0-F2), and baseline HCV RNA >800,000

IU/mL (vs ≤ 800,000 IU/mL). In patients with IL28B genotype TT, the observed SVR12 rate was 64.9% in the TMC435/PR group compared with 23.5% in the PBO/PR group. In patients with METAVIR score F4 (cirrhosis), the observed SVR12 rate was 58.1% and 29.4% in the TMC435/PR and PBO/PR groups, respectively.

Based on a logistic regression model, statistically significantly higher SVR12 rates were achieved in the TMC435/PR group compared with the PBO/PR group, regardless of demographics and IL28B genotype, baseline METAVIR score, and baseline HCV RNA.

The observed SVR12 rate was lower in patients infected with HCV genotype 1a (71.4%) versus 1b (89.7%) in the TMC435 group and was comparable between HCV genotypes in the PBO/PR group (genotype 1a, 48.6%; genotype 1b, 51.8%). Further, the observed SVR12 rate was lower in TMC435/PR-treated patients infected with HCV genotype 1a with Q80K (51.7%) versus patients without Q80K (84.9%), whereas the rate was higher in the PBO/PR group for patients with HCV genotype 1a with Q80K (53.3%, Q80K; 44.2%, no Q80K). A statistically significantly higher SVR12 rate was achieved in the TMC435/PR group compared with the PBO/PR group for both HCV geno/subtypes (1a vs 1b) and in patients with HCV genotype 1a and no Q80K polymorphism at baseline. This was not observed for HCV genotype 1a infected patients with the Q80K polymorphism at baseline.

Response-Guided Treatment

Most (84.8%) patients in the TMC435/PR group met the protocol-stipulated RGT criteria for shortening duration of PegIFN/RBV treatment to 24 weeks; of these, 90.6% achieved SVR12.

On-Treatment Virologic Response

On-treatment virologic response rates at Week 4 and Week 12 were consistently higher in the TMC435/PR group compared with the PBO/PR group (Table 27). RVR (HCV RNA <25 IU/mL undetectable at Week 4) was achieved in 79.5% of patients in the TMC435/PR group compared with 11.8% of patients in the PBO/PR group. The proportion of patients with cEVR (HCV RNA <25 IU/mL undetectable at Week 12) was 92.8% and 50.8% in the TMC435/PR and PBO/PR groups, respectively.

Treatment Failure

In the ITT population, patients failing treatment (ie, not achieving SVR12 or relapsing thereafter) were classified as experiencing on-treatment failure (confirmed detectable HCV RNA at EOT) or post-treatment failure (undetectable HCV RNA at EOT followed by viral relapse or missing HCV RNA data at the SVR12 time point).

The proportion of patients with on-treatment failure was 9.1% in the TMC435/PR group versus 33.8% in the PBO/PR group. Viral relapse was documented in 8.0% of patients in the TMC435/PR group compared with 13.8% of patients in the PBO/PR group.

In the TMC435/PR group, the proportion of patients who met any treatment stopping rule was higher in patients with HCV genotype 1a (14/147, 9.5%) versus 1b (4/117, 3.4%).

In C208, viral breakthrough was not a treatment stopping rule and was analyzed retrospectively. Stopping rules requiring treatment discontinuations could have influenced the frequency of viral breakthrough in the TMC435/PR group.

Overall, 13 patients (4.9%) in the TMC435/PR group and 10 patients (7.7%) in the PBO/PR group met criteria for viral breakthrough. Most patients with viral breakthrough also met a treatment stopping rule (92.3% [12 of 13 patients], TMC435/PR; 100% [10 of 10 patients], PBO/PR). Within the TMC435/PR group, viral breakthrough occurred more frequently in patients infected with HCV genotype 1a (11 patients, 7.5%) versus 1b (2 patients, 1.7%).

Seven of the 13 viral breakthroughs in the TMC435/PR group occurred before Week 12 and 6 viral breakthroughs occurred after Week 12 of treatment. Of the 6 viral breakthroughs after Week 12 (completion of TMC435 dosing), 5 patients (all with Q80K at baseline) had HCV RNA ≥ 25 IU/mL at Week 4, and at Week 12, they had HCV RNA <25 IU/mL undetectable/detectable (2 patients) or HCV RNA ≥ 25 IU/mL (3 patients). One patient with viral breakthrough after Week 12 (no Q80K at baseline) had HCV RNA <25 IU/mL undetectable/detectable at Week 4 and HCV RNA <25 IU/mL undetectable at Week 12 and completed all treatment; the viral breakthrough occurred concomitantly with grade 3 neutropenia.

Viral relapse was also assessed considering only patients with undetectable HCV RNA at EOT and available follow-up HCV RNA data. In this analysis, viral relapse was the PBO/PR group. In the TMC435/PR group, viral relapse occurred in 11.5% and 6.3% of patients infected with HCV genotype 1a and 1b, respectively.

Almost all viral relapses occurred during the first 12 weeks after EOT, both in the TMC435/PR group (20 of 21 patients) and PBO/PR group (16 of 18 patients). The patient in the TMC435/PR group with viral relapse after Week 12 of follow-up had prematurely discontinued all study drugs due to noncompliance. The patient discontinued treatment at Week 8, and HCV RNA was undetectable 8 weeks after end of treatment. At the next available time point (16 weeks after end of treatment), viral relapse was detected. None of the patients had documented viral relapse after Week 24 of follow-up.

Based on population sequencing, treatment failure in TMC435-treated patients was usually associated with emerging mutations at one or more of the 6 NS3 positions of interest (80, 155, and/or 168) (see also Section 1.7.5). Most (35 of 38, 92.1%) patients with treatment failure and sequence information had emerging mutations at one or more of these positions (28 of 30 patients [93.3%] with HCV genotype 1a, 7 of 8 patients [87.5%] with HCV genotype 1b).

Study C216

Multicenter, randomized, double-blind, 2-arm, placebo-controlled studies to investigate the efficacy, safety, and tolerability of TMC435 (150 mg q.d. administered for 12 weeks), in combination with 24- or 48-week response-guided treatment with PegIFNα-2a/ RBV or PegIFNα-2b/RBV (in selected countries), in treatment-naïve HCV genotype 1 infected patients.

Methods

Study participants

Key inclusion criteria: Adult treatment-naïve patients, with documented chronic HCV genotype 1 infection, a screening plasma HCV RNA level of >10,000 IU/mL; liver biopsy within 3 years prior to the screening visit (or between the screening and baseline visit) with histology consistent with chronic HCV infection; patients with Metavir score F3- F4 had to have an ultrasound taken within 6

months prior to the screening visit (or between the screening and baseline visit) with no findings suspicious for hepatocellular carcinoma (HCC).

Key exclusion criteria: Patients with de-compensated liver disease ; Patients with any liver disease of non-HCV etiology or with human immunodeficiency virus (HIV) or hepatitis B co-infection were excluded; and prior treatment with any approved or investigational drug for the treatment of hepatitis C was not allowed.

Treatments

In the first 24 weeks, patients were to receive 12 weeks TMC435 150 mg or placebo once daily (q.d.) plus PegIFNα-2a/RBV or PegIFNα-2b/RBV, followed by 12 weeks of PegIFNα-2a/RBV or PegIFNα-2b/RBV alone. As part of a response-guided treatment (RGT) duration, HCV therapy had to be stopped at Week 24 in patients in the TMC435 treatment group if they achieved HCV RNA levels <25 IU/mL (detectable or undetectable) at Week 4 and <25 IU/mL undetectable at Week 12. All other patients had to continue PegIFN/RBV alone until Week 48. In the control group, all patients had to continue PegIFN/RBV alone until Week 48.

The use of PegIFNα-2b was limited to a selected number of countries where patients were randomized in a 1:1 ratio to PegIFNα-2a/RBV or PegIFNα-2b/RBV.

Objectives

The primary objective was to demonstrate the superiority of TMC435 versus placebo as part of a treatment regimen including pegylated interferon alpha-2a (PegIFNα-2a)/ribavirin (RBV) or PegIFNα-2b/RBV, with respect to the proportion of treatment-naïve hepatitis C virus (HCV) genotype 1 infected patients with SVR12.

Main secondary objectives were: to demonstrate the superiority of TMC435+ PegIFN/RBV versus placebo+ PegIFN/RBV with respect to SVR 24; to demonstrate the superiority of TMC435 versus placebo as part of a treatment regimen including PegIFNα-2a/RBV or PegIFNα-2b/RBV, with respect to the proportion of patients with SVR at Week 72; to compare the antiviral activity of TMC435 versus placebo as part of a treatment regimen including PegIFNα-2a/RBV or PegIFNα-2b/RBV at all time points, with focus on Weeks 4, 12, 24, 36, 48, 60, and 72; to compare the incidence of on-treatment failure in both treatment groups; to evaluate the incidence of viral breakthrough during the treatment period in both treatment groups; to evaluate the relapse rate following treatment in both treatment groups; to evaluate the pharmacokinetics of TMC435 and the relationship between TMC435 pharmacokinetics and efficacy and safety parameters; to compare the safety and tolerability of TMC435 versus placebo as part of a treatment regimen including PegIFNα-2a/RBV or PegIFNα-2b/RBV.

Outcomes/endpoints

The primary efficacy endpoint was the proportion of patients in each treatment group achieving SVR12.

Secondary efficacy parameters include the proportion of patients with: SVR24; SVR72 (last study-related visit); ≥ 2 log10 reduction in HCV RNA at all time points during treatment and follow-up; undetectable HCV RNA (<25 IU/mL undetectable) and/or HCV RNA levels <25 IU/mL at all time points during treatment and follow-up, with focus on Weeks 4, 12, 24, 36, 48, 60, and 72;

viral breakthrough; viral relapse; on-treatment failure; normalized ALT levels at the end of treatment and at the time points of SVR assessment; who stopped HCV therapy (due to early virologic response) versus those who continued PegIFNα-2a/RBV at Week 48 in the TMC435 group.

Sample size

The primary efficacy parameter was SVR12, defined as the proportion of patients with undetectable HCV RNA (<25 IU/mL undetectable) at the end of treatment and HCV RNA <25 IU/mL 12 weeks after the planned end of treatment.

Randomisation and blinding

Central randomization was implemented in this study. Patients were randomly assigned to 1 of 2 treatment groups in a 2:1 ratio (TMC435:placebo) based on a computer-generated randomization schedule. The randomization was balanced by using randomly permuted blocks and was stratified by HCV genotype 1 subtype (1a, 1b, other) and IL28B genotype (CC, CT, TT) based on a polymorphism on chromosome 19 (SNP rs12979860).

Statistical methods

The analysis population was the intent-to-treat (ITT) population, which included all randomized patients who took at least 1 dose of investigational drug (TMC435/placebo). In addition, analyses were performed separately for a) subjects receiving PegIFNα-2a and RBV (European Medicines Agency [EMA] countries), b) subjects receiving PegIFNα-2b and RBV (EMA countries) and c) subjects receiving PegIFNα-2a/RBV (outside EMA).

A per protocol analysis (excluding subjects with major protocol deviations) was planned to be performed on the primary endpoint if there were more than 10% of subjects in all ITT subjects with a major protocol deviation.

The null hypothesis was that there is no statistically significant difference between the active treatment arm and the control group for the primary efficacy endpoint (SVR12). The significance level for the comparison between treatment groups for the primary efficacy endpoint was 5%. Additional null hypotheses were tested to address some of the secondary objectives.

The null hypotheses were tested in a certain order as part of a closed testing procedure, i.e., the first secondary endpoint was only planned to be tested if the null hypothesis for the primary efficacy endpoint was rejected at the 5% significance level etc. This allowed the significance level for the comparison between treatment groups to be 5% in each test, given that the previous comparison was significant.

The primary analysis method for comparing the SVR12 between the 2 treatment groups was the Cochran-Mantel-Haenszel (CMH) test controlling for type of PegIFN and stratification factors genotype subtype and IL28B genotype. A Breslow-Day test for homogeneity of odds ratios based on this model was also performed. In addition, the 95% CI was constructed around the response rate in each treatment group. As sensitivity analysis with respect to the model, the SVR12 response rate in the TMC435 treatment group was compared with the SVR12 response rate in the control group using a logistic regression model including baseline log10 HCV RNA (included as continuous parameter), type of PegIFN and the stratification factors genotype 1 subtype and IL28B genotype. The 95% CI around the difference in proportions of response was constructed based on

this model. Additional sensitivity analyses with respect to missing information were done by applying different imputation rules for missing data.

Results

Participant flow

Study dates: 18/01/2011 – 05/02/2013

The study was conducted at 76 sites in 14 countries: Austria, Belgium, Bulgaria, Germany, Spain, France, Netherlands, Poland, Portugal, Slovakia, Turkey, United States, Argentina and Brazil. By region, 65% of subjects were enrolled in Europe, 20% in North America, and 15% in South America.

Baseline data

Overall, most subjects were enrolled in Europe (64.5%) followed by North America (20.2) and South America (15.3%). More than half of the subjects were male (55.5%) and the majority were white (92.1%); other races were represented to a minor extent (26 subjects (6.6%) were black, and 3 subjects (0.8%) were Asian). The median age was 47.0 years (range: 18 to 73 years). In total, 18.8% of subjects had a BMI ≥ 30 kg/m2. Regarding METAVIR score at baseline, 49.7% had METAVIR score F0 or F1, 28.0% had METAVIR score F2, 13.9% had METAVIR score F3, and 8.4% had METAVIR score F4. METAVIR score F4 was more common in the PBO/PR group (11.2%) than in the TMC435/PR group (6.9%). A total of 9 subjects did not have a METAVIR score available at baseline.

In total, 40.7% of subjects were infected with HCV genotype 1a and 58.1% with HCV genotype 1b. Q80K polymorphism was present at baseline in 10.2% of the overall population with sequence data. All but 1 subject with Q80K polymorphism at baseline were infected with HCV genotype 1a; Q80K was present in 24.2% of genotype 1a infected subjects. Median HCV RNA at baseline was 6.51 log10 IU/mL (range: 4.0 to 7.6 log10 IU/mL), and 76.0% of subjects had high HCV RNA values at baseline defined as >800,000 IU/mL. Overall, 29.9% of subjects had IL28B genotype CC, 54.5% had IL28B genotype CT, and 15.6% had IL28B genotype TT.

Outcomes and estimation

The proportion of subjects who completed their planned treatment with at least 1 study drug was 92.2% in the TMC435/PR group and 60.4% in the PBO/PR group.

<u>Sustained Virologic Response</u>

Efficacy of TMC435 in combination with PegIFN/RBV was statistically significantly superior ($p<0.001$) to placebo in combination with PegIFN/RBV. SVR12 was achieved in 81.3% of subjects in the TMC435/PR group versus 50.0% of subjects in the PBO/PR group.

In the TMC435/PR group, all but 3 subjects (206/209) with SVR12 also achieved SVR24 (Table 30). Two subjects did not achieve SVR24 because they had viral relapse after achieving SVR12; for 1 of these subjects, viral relapse had not been confirmed at the cut-off date for analysis (see Section 3.1.2.2.2.5). One subject with SVR12 had not yet reached the SVR24 assessment time point at the data cut-off date for the Week 60 primary analysis. At the time of the analysis, 253 subjects in the

TMC435/PR group and 61 subjects in the PBO/PR groups had reached the Week 24 visit or discontinued the study earlier. The SVR24 rate was 81.4% in the TMC435/PR group compared with 45.9% in the PBO/PR group.

Table 7. Sustained Virologic Response (SVR12 and SVR24) – Stratified Cochran-Mantel-Haenszel Approach; Intent-to-Treat Population – Study C216 Primary Week 60 Analysis

	Observed	Stratum Adjusted	Comparison versus PBO	
	n/N (%)	% (95% CI)[c]	Difference in Proportions (95% CI)[b]	p-value[a]
SVR12				
PBO 12 Wks PR 48	67/134 (50.0)	49.7 (42.0; 57.3)		
TMC435 150 mg 12 Wks PR 24/48	209/257 (81.3)	81.9 (77.2; 86.6)	32.2 (23.3; 41.2)	<0.001
SVR24				
PBO 12 Wks PR 48	28/61 (45.9)	46.4 (36.0; 56.8)		
TMC435 150 mg 12 Wks PR 24/48	206/253 (81.4)	79.6 (74.0; 85.2)	33.2 (21.4; 45.0)	<0.001

Subgroup Analyses

Subgroup analyses evaluated the impact of several factors on virologic response, such as type of PegIFN/RBV, stratification factors (HCV geno/subtype, IL28B genotype), presence of Q80K baseline polymorphism, baseline HCV RNA (≤ 800,000 or >800,000 IU/mL), and baseline METAVIR score.

In both treatment groups, SVR12 rates were generally higher in subjects treated with PegIFNα-2a/RBV versus PegIFNα-2b/RBV and lower in subjects with IL28B genotype TT (vs genotypes CC and CT), baseline METAVIR score F4 (vs F0-F2), and baseline HCV RNA >800,000 IU/mL (vs ≤ 800,000 IU/mL). In subjects with the IL28B genotype TT, the observed SVR12 rate was 57.5% in the TMC435/PR group versus 19.0% in the PBO/PR group. Similarly, in subjects with METAVIR score F4 (cirrhosis), the observed SVR12 rate was 64.7% and 40.0% in the TMC435/PR and PBO/PR groups, respectively. Based on a logistic regression model, statistically significantly higher SVR12 rates were achieved in the TMC435/PR group compared with the PBO/PR group, regardless of demographics and IL28B genotype, baseline HCV RNA, and baseline METAVIR score.

Within the TMC435/PR group, observed SVR12 rates were comparable between subjects infected with HCV genotype 1a (80.4%) and 1b (82.0%) and tended to be lower in subjects with HCV genotype 1a with Q80K at baseline (75.0%) versus subjects without Q80K (82.3%). In the PBO/PR group, the observed SVR12 rate was lower in subjects with HCV genotype 1a (45.6%) versus 1b (53.2%), and higher in subjects with HCV genotype 1a with Q80K (50.0%) versus subjects without Q80K (42.5%). A statistically significantly higher SVR12 rate was achieved in the TMC435/PR group compared with the PBO/PR group for both HCV geno/subtypes (1a vs 1b) and in subjects with HCV genotype 1a and no Q80K polymorphism at baseline. Although the SVR rate was numerically higher in TMC435/PR group compared with the PBO/PR group for subjects infected with HCV genotype 1a and Q80K, the treatment difference was not statistically significant.

In subjects randomized to PegIFNα-2a/RBV, the observed SVR12 rate was 88.3% in the TMC435/PR group compared with 62.2% in the PBO/PR group. In subjects randomized to PegIFNα-2b/RBV, the observed SVR12 rate was 77.5% and 41.9% in the TMC435/PR and PBO/PR groups, respectively. For non-randomized subjects who received PegIFNα-2a/RBV, these rates

were 79.0% in the TMC435/PR group and 45.7% in the PBO/PR group. Based on a logistic regression model, a statistically significantly higher SVR12 rate was achieved in the TMC435/PR group compared with the PBO/PR group, regardless of type of PegIFN/RBV.

Response-Guided Treatment

Subjects in the TMC435/PR group who met the protocol-stipulated RGT criteria had a planned PegIFN/RBV treatment duration of 24 weeks.

Most (91.4%) subjects in the TMC435/PR group met the protocol-stipulated RGT criteria for shortening duration of PegIFN/RBV treatment to 24 weeks; of these, 86.0% achieved SVR12. The majority of subjects (75.9%) met the protocol-stipulated RGT criteria and had HCV RNA <25 IU/mL undetectable at Week 4, and in these subjects, the SVR12 rate was 91.3%. Forty subjects (15.6%) met the protocol-stipulated RGT criteria and had HCV RNA <25 IU/mL detectable at Week 4, with an SVR12 rate of 60.0%.

On-Treatment Virologic Response

On-treatment virologic response rates at Week 4 and Week 12 were higher in the TMC435/PR group compared with the PBO/PR group. RVR (HCV RNA <25 IU/mL undetectable at Week 4) was achieved in 79.2% of subjects in the TMC435/PR group compared with 12.8% of subjects in the PBO/PR group. The proportion of subjects with cEVR (HCV RNA <25 IU/mL undetectable at Week 12) was 96.8% and 44.9% in the TMC435/PR and PBO/PR groups, respectively.

Treatment Failure

In the ITT population for the efficacy analysis, subjects failing treatment (ie, not achieving SVR12 or relapsing thereafter) were classified as experiencing on-treatment failure (confirmed detectable HCV RNA at EOT) or post-treatment failure (undetectable HCV RNA at EOT followed by viral relapse or missing HCV RNA data at the SVR12 time point).

The proportion of subjects with on-treatment failure was 7.0% in the TMC435/PR group versus 32.1% in the PBO/PR group. Viral relapse was documented in 11.7% of subjects in the TMC435/PR group compared with 15.7% of subjects in the PBO/PR group.

In the TMC435/PR group, the rate of on-treatment failure was lower in subjects randomized to PegIFNα-2a/RBV (2.6%) than in subjects randomized to PegIFNα-2b/RBV (8.8%). The rate of on-treatment failure was 9.0% in subjects who were not randomized to a particular type of PegIFN and received PegIFNα-2a.

In the TMC435/PR group, the proportion of subjects who met any treatment stopping rule was comparable between subjects with HCV genotype 1a (6/107, 5.6%) and 1b (6/150, 4.0%).

In this study, viral breakthrough was not a treatment stopping rule and was analyzed retrospectively. Stopping rules requiring treatment discontinuations could have influenced the frequency of viral breakthrough in the TMC435/PR group.

Overall, 12 subjects (4.7%) in the TMC435/PR group and 14 subjects (10.4%) in the PBO/PR group met criteria for viral breakthrough. Most subjects with viral breakthrough also met a treatment stopping rule (83.3% [10 of 12 subjects], TMC435/PR; 100% [14 of 14 subjects], PBO/PR). Within the TMC435/PR group, the proportion of subjects with viral breakthrough was the same for each HCV geno/subtype (4.7% each: 5/106 subjects, 1a; 7/150, 1b).

Three of the 12 viral breakthroughs in the TMC435/PR group occurred before Week 12 and 9 viral breakthroughs occurred after Week 12 of treatment. Of the 9 viral breakthroughs after Week 12 (completion of TMC435 dosing), 8 breakthroughs occurred between Weeks 12 and 24 of treatment. Of these, 4 subjects had reached HCV RNA <25 IU/mL undetectable at Week 4 and 4 reached HCV RNA <25 IU/mL undetectable Week 12. One subject never reached HCV RNA undetectable HCV RNA and broke through after treatment at Week 24. None of the subjects with viral breakthrough in C216 harboured Q80K polymorphism at baseline.

In the TMC435/PR group, the rate of viral breakthrough was lower in subjects randomized to PegIFNα-2a/RBV (1.3%) compared with subjects randomized to PegIFNα-2b/RBV (6.3%). The rate of viral breakthrough was 6.0% in subjects who were not randomized to a particular type of PegIFN and received PegIFNα-2a.

Viral relapse was also assessed considering only subjects with undetectable HCV RNA at EOT and available follow-up HCV RNA data. In this analysis, viral relapse was documented in 12.7% of subjects in the TMC435/PR group compared with 23.9% of subjects in the PBO/PR group. In the TMC435/PR group, viral relapse occurred in 9.5% and 14.9% of subjects infected with HCV genotype 1a and 1b, respectively.

Viral relapse primarily occurred during the first 12 weeks of follow-up, both in the TMC435/PR group (25 of 30 subjects) and the PBO/PR group (all 21 subjects). Of the 5 TMC435-treated subjects with viral relapse on or after Week 12 of follow-up, 1 subject completed treatment at Week 24, and viral relapse was documented at the SVR12 assessment time point; 2 subjects had viral relapse after the SVR24 assessment time point (after achieving SVR12); and 1 subject had relapse after the SVR24 assessment time point (after achieving SVR12 and SVR24). In one subject, viral relapse occurring after SVR24 assessment time point was not confirmed by subsequent assessment; thus, this subject is not considered as having confirmed relapse. The 3 TMC435/PR-treated subjects who achieved SVR12 with confirmed viral relapse thereafter met the RGT criteria (with undetectable HCV RNA at Week 4) and completed 24 weeks of PegIFNα-2a/RBV treatment. HCV RNA was <25 IU/mL detectable at Week 2 for 2 subjects and was 27 IU/mL in the third subject.

In the TMC435/PR group, the rate of viral relapse was slightly lower in subjects randomized to PegIFNα-2a/RBV (10.7%) compared with subjects randomized to PegIFNα-2b/RBV (15.1%).

The rate of viral relapse was 12.5% in subjects who were not randomized to a particular type of PegIFN and received PegIFNα-2a.

Based on population sequencing, treatment failure in TMC435-treated subjects was usually associated with emerging mutations at one or more of the 6 NS3 positions of interest (80, 122, 155, and/or 168). Most (41 of 42, 97.6%) subjects with treatment failure and available sequence information had emerging mutations at one or more of these positions (all 16 subjects [100%] with HCV genotype 1a, and 25 of 26 subjects [96.2%] with HCV genotype 1b).

Study HPC3007

HPC3007 is a multicenter, randomized, double-blind, 2-arm, placebo-controlled study to investigate the efficacy, safety and tolerability of TMC435 (150 mg q.d. for 12 weeks), in combination with 24- or 48-week response-guided treatment with PegIFNα-2a/RBV, in HCV genotype 1 infected subjects who had viral relapse after previous IFN-based therapy.

Methods

Study participants

Main inclusion criteria: Male or female, aged ≥ 18 years; liver biopsy within 3 years prior to the screening visit (or between the screening and baseline visit) with histology consistent with chronic HCV infection; HCV genotype 1 infection (confirmed at screening); plasma HCV RNA of >10,000 IU/mL at screening; and received (Peg)IFN-based therapy for at least 24 weeks with documented undetectable HCV RNA at the last measurement on treatment or an undetectable HCV RNA within 2 months after the actual end of treatment and a subsequent detectable HCV RNA level within 1 year after the last drug intake. Subjects with Metavir score F3-F4 had to have an ultrasound taken within 6 months prior to the screening visit (or between the screening and baseline visit) with no findings suspicious for hepatocellular carcinoma (HCC).

Main exclusion criteria: Subjects with de-compensated liver disease; Subjects with any liver disease of non-HCV etiology or with human immunodeficiency virus (HIV) or hepatitis B co-infection. Previous treatment with any HCV therapy other than (Peg)IFN and RBV, including any direct-acting anti-HCV agents (e.g., inhibitors of NS5B polymerase, NS3/4A protease, NS5A protein, or cyclophilin), was not allowed.

Treatments

In the first 24 weeks, subjects were to receive 12 weeks of TMC435 150 mg (n=250) or placebo (n=125) once daily (q.d.) plus PegIFNα-2a/RBV (PR), followed by 12 weeks of PR alone. As part of a response-guided treatment (RGT) duration, HCV therapy had to be stopped at Week 24 in subjects in the TMC435 treatment group if they achieved HCV RNA levels < 25 IU/mL (detectable or undetectable) at Week 4 and < 25 IU/mL undetectable at Week 12. All other subjects had to continue PR until Week 48. In the control group, all subjects continued PR until Week 48.

Objectives

The primary objective was to demonstrate the superiority of TMC435+ PegIFNα-2a/RBV versus placebo+ PegIFNα-2a/RBV with respect to the proportion of subjects with SVR12.

The main secondary objectives included to demonstrate the superiority of TMC435 versus placebo with respect to the proportion of subjects with SVR 24; to compare the relapse rates following treatment and also the safety and tolerability of each treatment group; in the TMC435 group additional secondary objectives were to determine the proportion of subjects who met criteria for shortening treatment and were able to complete all treatments at Week 24 and to determine the viral NS3/4A sequence in subjects not achieving an SVR in the TMC435 treatment group.

Outcomes/endpoints

The primary efficacy endpoint was the proportion of subjects in each treatment group achieving SVR12 (proportion of subjects with undetectable HCV RNA [<25 IU/mL undetectable] at the actual end of treatment and HCV RNA <25 IU/mL detectable or undetectable 12 weeks after the planned end of treatment).

Secondary efficacy endpoints include the proportion of subjects: with SVR24; with SVR at Week 72 (last study-related visit); with ≥ 2 log10 reduction in HCV RNA at all time points during treatment

and follow-up; with undetectable HCV RNA (<25 IU/mL undetectable) and/or HCV RNA levels <25 IU/mL at all time points during treatment and follow-up, with focus on Weeks 4, 12, 24, 36, 48, 60, and 72; with viral breakthrough; with viral relapse; with on-treatment failure; with normalized ALT levels at the end of treatment and at the time points of SVR assessment; who stopped HCV therapy (due to early virologic response) versus those who continued PR at Week 48 in the TMC435 group.

Sample size

Phase III data from telaprevir and boceprevir showed a strong correlation between SVR12 and SVR24. Similarly, a very good correlation was also observed in the Phase IIb studies with TMC435 (Studies C205 and C206). Therefore, sample size calculation that was based on the SVR24 response parameter was also regarded as applicable for SVR12.

Randomisation and blinding (masking)

Central randomization was implemented in this study. Subjects were randomly assigned to 1 of 2 treatment groups in a 2:1 ratio (TMC435:placebo) based on a computer-generated randomization schedule prepared by or under the supervision of the Sponsor before the study. The randomization was balanced by using randomly permuted blocks and was stratified by HCV genotype 1 subtype (1a, 1b, other) and IL28B genotype (CC, CT, TT).

Statistical methods

The primary analysis was performed when all randomized subjects had completed the Week 60 visit or discontinued earlier. The final analysis will be performed when all randomized subjects have completed the last study-related visit (Week 72) or discontinued earlier.

All analyses were performed on the intent-to-treat (ITT) population, which was defined as those subjects who received at least 1 dose of investigational drug (TMC435/placebo).

The primary analysis method for comparing the SVR12 rate between the 2 treatment groups was the Cochran-Mantel-Haenszel (CMH) test, controlling for the stratification factors HCV genotype 1 subtype and IL28B genotype. A Breslow-Day test for homogeneity of odds ratios based on this model was also performed. In addition, the 95% confidence interval (CI) was constructed around the response rate in each treatment group. A sensitivity analysis with respect to the model, the SVR12 rate in the TMC435 treatment group was compared with the SVR12 rate in the control group using a logistic regression model including baseline log10 HCV RNA (included as continuous parameter) and the stratification factors HCV genotype 1 subtype and IL28B genotype. The 95% CI around the difference in proportions of response was constructed based on this model. Additional sensitivity analyses were done by applying different imputation rules for missing data.

For the secondary endpoints, several null hypotheses were tested to address them.

Results

Participant flow

Study dates: 18/01/2011 – 04/02/2013

Baseline data

The majority of subjects were enrolled in Europe, followed by North America and Australia and New Zealand.

The IFN-based HCV therapy that subjects had received prior to this study was mainly PegIFNα-2a/RBV (67.7%) or PegIFNα-2b/RBV (27.0%).

Overall, more than half of the subjects were male (65.6%) and the majority were white (94.4%). Other races were represented to a lesser extent (11 black subjects [2.8%] and 9 Asian subjects [2.3%]). The median age was 52.0 years (range: 20 to 71 years). In total, 102 subjects (26.0%) had a BMI ≥ 30 kg/m2. Regarding METAVIR scores at baseline, 35.1% had METAVIR score F0 or F1, 34.3% had METAVIR score F2, 15.4% had METAVIR score F3, and 15.2% had METAVIR score F4 (11 sujects did not have a baseline METAVIR score available).

Median HCV RNA at baseline was 6.49 log10 IU/mL (range: 3.1 to 7.7 log10 IU/mL), and 83.7% of subjects had high HCV RNA values at baseline defined as >800,000 IU/mL. The proportion of subjects with HCV genotype 1a or 1b was 41.7% and 58.0%, respectively. Q80K polymorphism was present at baseline in 13.1% of the overall population with sequence data. All but 1 subject with Q80K had HCV genotype 1a; the proportion of subjects with HCV genotype 1a and baseline Q80K was 30.7%. The proportion of subjects with HCV genotype 1a and baseline Q80K was higher in subjects in North America (58.6%) compared with other regions (range: 4.0% to 18.8%).

Overall, 24.4% of subjects had IL28B genotype CC, 63.6% had IL28B genotype CT, and 12.0% had IL28B genotype TT.

Polymorphism Q80K was present at baseline in 51 of 390 (13.1%) subjects overall and in 31 of 257 (12.1%) subjects in the TMC435/PR treatment arm and in 20 of 133 (15.0%) subjects in the PBO/PR treatment arm. Of these 51 subjects with Q80K at baseline, only 1 subject was infected with HCV genotype 1b (enrolled in the TMC435/PR arm). The prevalence of Q80K at baseline in subjects infected with HCV genotype 1a/other was thus 30.7% (50 of 163 HCV genotype 1a/other infected subjects).

Baseline Q80K polymorphism was most prevalent in subjects from North America with 34 of 86 (39.5%) subjects overall and 34 of 58 (58.6%) subjects infected with HCV genotype 1a carrying a Q80K polymorphism. In Europe, 16 of 272 (5.9%) overall and 15 of 80 (18.8%) HCV genotype 1a infected subjects carried the Q80K polymorphism. In the subjects enrolled from Asia-Pacific (Australia and New Zealand only), 1 of 32 (3.1%) overall and 1 of 25 (4.0%) HCV genotype 1a infected subject had Q80K polymorphism.

Numbers analysed

Three hundred and seventy-five subjects with documented chronic HCV genotype 1 infection, who received at least 24 weeks of an (Peg)IFN-based therapy and relapsed within 1 year after the last drug intake, were planned to be included. At the time of the primary analysis, 393 subjects had been randomized and treated (ITT population), of which 184 had completed the study, 185 were still in the study, and 24 had discontinued prematurely.

Outcomes and estimation

The analysis of efficacy was performed on the ITT population, since the overall percentage of major protocol deviations was <10%, no per protocol analysis was performed.

Primary endpoint

The proportion of subjects with SVR12 was 79.2% in the TMC435/PR arm versus 36.8% in the PBO/PR arm, resulting in a significant p-value for the CMH test controlling for the stratification factors (p <0.001; adjusted difference [95% CI] between treatment arms was 43.0% [33.8%; 52.3%]).

Almost all subjects (199 of 206) in the TMC435/PR group with SVR12 also achieved SVR24. Five subjects did not achieve SVR24 because they relapsed after having achieved SVR12. Two subjects with SVR12 had not yet reached the SVR24 assessment time point at the data cut-off date for the Week 60 primary analysis. At the time of the analysis, 254 subjects in the TMC435/PR group and 64 subjects in the PBO/PR group had reached the Week 24 visit or discontinued the study earlier. The SVR24 rate was 78.3% in the TMC435/PR group compared with 31.3% in the PBO/PR group.

Table 8. Sustained Virologic Response (SVR12 and SVR24) – Stratified Cochran-Mantel-Haenszel Approach; Intent-to-Treat Population – Study HPC3007 Primary Week 60 Analysis

	Observed	Stratum Adjusted	Comparison versus PBO	
	n/N (%)	% (95% CI)[c]	Difference in Proportions (95% CI)[b]	p-value[a]
SVR12				
PBO 12 Wks PR 48	49/133 (36.8)	36.6 (28.7; 44.5)		
TMC435 150 mg 12 Wks PR 24/48	206/260 (79.2)	79.6 (74.8; 84.4)	43.0 (33.8; 52.3)	<0.001
SVR24				
PBO 12 Wks PR 48	20/64 (31.3)	31.2 (19.9; 42.5)		
TMC435 150 mg 12 Wks PR 24/48	199/254 (78.3)	78.3 (73.3; 83.3)	47.1 (34.8; 59.5)	<0.001

CI: confidence interval; SVR*X*: sustained virologic response *X* weeks after the planned end of treatment

[a] Based on the Cochran-Mantel-Haenszel test controlling for stratification factors.
[b] Difference in proportions (active – placebo) adjusted for stratification factors, with corresponding 95% CI based on the normal approximation.
[c] Proportions adjusted for stratification factors, with corresponding 95% CIs based on the normal approximation. Stratification factors were HCV geno/subtype (1a or 1b) and *IL28B* genotype (CC, CT, or TT).

The p-value for the Breslow-Day test for homogeneity of odds ratios was 0.948 for SVR12 and 0.072 for SVR24.

Source: Mod5.3.5.1/HPC3007-W60-CSR/Tab26 and /Tab34

Results from a snapshot SVR12 analysis, in which only the last available HCV RNA data from samples collected at or beyond follow-up Week 12 were considered, were consistent with those from the primary analysis.

Response-Guided Treatment

Subjects in the TMC435/PR group who met the protocol-stipulated RGT criteria (ie, HCV RNA <25 IU/mL at Week 4 and undetectable HCV RNA at Week 12) had a planned PegIFN/RBV treatment duration of 24 weeks.

Most (92.7%) subjects in the TMC435/PR group met the protocol-stipulated RGT criteria for shortening duration of PegIFN/RBV treatment to 24 weeks; of these, 83.0% of subjects achieved SVR12. The majority of subjects (75.8%) met the protocol-stipulated RGT criteria with HCV RNA <25 IU/mL undetectable at Week 4, and in these, the SVR12 rate was 87.3%. A total of 44 subjects (16.9%) who met the protocol-stipulated RGT criteria had HCV RNA <25 IU/mL detectable at Week 4, with an SVR12 rate of 63.6%.

On-Treatment Virologic Response

On-treatment virologic response rates at Week 4 and Week 12 were consistently higher in the TMC435/PR group compared with the PBO/PR group (Table 74). RVR (HCV RNA <25 IU/mL undetectable at Week 4) was achieved in 77.2% of subjects in the TMC435/PR group compared with 3.1% of subjects in the PBO/PR group. The proportion of subjects with cEVR (HCV RNA <25 IU/mL undetectable at Week 12) was 98.0% in the TMC435/PR group compared with 27.4% in the PBO/PR group.

Treatment Failure

In the primary population for the efficacy analysis, defined as all subjects who received at least 1 dose of TMC435 or TMC435-matched placebo, subjects failing treatment (ie, not achieving SVR12 or relapsing thereafter) were classified as experiencing on-treatment failure (confirmed detectable HCV RNA at EOT) or post-treatment failure (undetectable HCV RNA at EOT followed by viral relapse or missing HCV RNA data at the SVR12 time point).

The on-treatment failure rate was 3.1% in the TMC435/PR group compared with 27.1% in the PBO/PR group. Viral relapse occurred in 17.7% of subjects in the TMC435/PR group versus 33.8% of subjects in the PBO/PR group.

The proportion of subjects who met a treatment stopping rule at Weeks 12, 24, or 36 was 1.9% in the TCM435/PR group compared with 11.3% in the PBO/PR group; in the TMC435/PR group, the proportion of subjects who met a treatment stopping rule at these time points was comparable between HCV genotypes: HCV genotype 1a (2/111, 1.8%) and HCV genotype 1b (3/149, 2.0%).

The proportion of subjects who met a treatment stopping rule at Week 4 was 1.9% in the TCM435/PR group compared with 69.9% in the PBO/PR group; in the TMC435/PR group, the proportion of subjects who met a treatment stopping rule at Week 4 was 1.8% (2/111) in subjects with HCV genotype 1a and 2.0% (3/149) in subjects with HCV genotype 1b.

In this study, viral breakthrough was not a treatment stopping rule and was analyzed retrospectively. Stopping rules requiring treatment discontinuations could have influenced the frequency of viral breakthrough in the TMC435/PR group.

Six subjects (2.3%) in the TMC435/PR group and no subjects in the PBO/PR group met the criteria for viral breakthrough (Table 76). In the TMC435/PR group, the viral breakthrough rate was similar between HCV geno/subtypes (1a, 2.7%; 1b, 2.0%) and was higher in subjects with HCV genotype 1a with Q80K at baseline (6.7%) versus without Q80K (1.3%). All but 1 of the TMC435-treated subjects with viral breakthrough met any treatment stopping rule (5 of 6 subjects, 83.3%).

In the TMC435/PR group, 5 of the 6 cases of viral breakthrough occurred before Week 12. One subject experienced viral breakthrough during treatment with PegIFN/RBV alone (Week 36).

This subject (no Q80K at baseline) had HCV RNA <25 IU/mL detectable at Week 12; a confirmatory sample demonstrated HCV RNA <25 IU/mL undetectable.

Among subjects with undetectable HCV RNA at EOT and available follow-up HCV RNA data, 18.5% of subjects in the TMC435/PR group and 48.4% of subjects in the PBO/PR group experienced viral relapse. In the TMC435/PR group, viral relapse occurred in 27.6% and 11.8% of subjects infected with HCV genotype 1a and 1b, respectively, and in 44.4% and 22.4% of subjects infected with HCV genotype 1a with and without Q80K at baseline, respectively.

Viral relapse primarily occurred during the first 12 weeks after EOT, both in the TMC435/PR group (40 of 46 subjects) and PBO/PR group (42 of 45 subjects). Five of the 6 subjects in the TMC435/PR group with viral relapse achieved SVR12 but subsequently had viral relapse at the SVR24 assessment time point. The sixth subject in the TMC435/PR group experienced viral relapse after Week 24 of follow-up. This subject had missing HCV RNA data after EOT until the time point of SVR24 assessment (Week 48). At Week 48, the subject had an HCV RNA value of 3,470,000 IU/mL. The subject had met the RGT criteria, discontinued PegIFN/RBV at Week 22 due to an adverse event, and had undetectable HCV RNA at EOT (Week 20 measurement).

Based on population sequencing, treatment failure in TMC435-treated subjects was usually associated with emerging mutations at one or more of the 6 NS3 positions of interest (80, 122, 155, and/or 168) (see also Section 1.7.5). Most (47 of 52, 90.4%) subjects with treatment failure and sequence information had emerging mutations at one or more of these positions (30 of 32 subjects [93.8%] with HCV genotype 1a, 17 of 20 subjects [85.0%] with HCV genotype 1b).

Sustained Virologic Response and Viral Relapse by Virologic Response at Week 4 and Week 12

SVR12 rates and viral relapse rates were also assessed based on on-treatment HCV RNA levels at Week 4 and HCV RNA levels at Week 12 to further support the selection of the RGT criteria and treatment stopping rules proposed for the clinical use of TMC435.

The majority of subjects in the TMC435/PR group achieved RVR (HCV RNA <25 IU/mL undetectable at Week 4) (76.9%); the SVR12 rate in this group was high (86.5%) and the viral relapse rate was 12.8%. In subjects with HCV RNA <25 IU/mL detectable at Week 4 (18.1% of all TMC435-treated subjects), the SVR12 rate was lower (59.6%) and the viral relapse rate was higher (40.0%). In addition, 4.6% of subjects in the TMC435/PR group did not achieve HCV RNA <25 IU/mL at Week 4; the SVR12 rate in this group was 41.7% (5/12) and the viral relapse rate was 37.5% (3/8).

Summary of main studies

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).

Table 9. Summary of efficacy for trial TMC435-TiDP16-C208 (QUEST-1)

SUMMARY OF EFFICACY FOR TRIAL TMC435-TiDP16-C208 (QUEST-1)		
TITLE: A Phase III, randomized, double-blind, placebo-controlled study to investigate the efficacy, safety and tolerability of TMC435 vs. placebo as part of a treatment regimen including peginterferon α-2a and ribavirin in treatment-naïve, genotype 1 hepatitis C-infected subjects		
Study identifier	TMC435-TiDP16-C208 (QUEST-1) EudraCT Number: 2010-020444-36	
Design	Prospective, multicentre, randomized, double-blind, 2-arm, placebo-controlled trial	
	Duration of main phase:	72 weeks
	Duration of Run-in phase:	not applicable

	Duration of Extension phase:		not applicable	
Hypothesis	Superiority			
Treatments groups	TMC435 arm	Treatment	PegIFNα-2a 180 µg/week, Ribavirin 1000 or 1200 mg/day, depending on body weight (< 75 or ≥ 75 kg, respectively), TMC435 150 mg once daily	
		Duration	12 weeks PegIFNα-2a; Ribavirin; TMC435 + 12 weeks PegIFNα-2a; Ribavirin + 24 weeks PegIFNα-2a; Ribavirin according to response-guided therapy	
		Number randomized	264	
	Placebo arm	Treatment	PegIFNα-2a 180 µg/week, Ribavirin 1000 or 1200 mg/day, depending on body weight (< 75 or ≥ 75 kg, respectively), Placebo	
		Duration	12 weeks PegIFNα-2a; Ribavirin; Placebo + 36 weeks PegIFNα-2a; Ribavirin	
		Number randomized	130	
Endpoints and definitions	Primary endpoint	SVR12	The proportion of subjects in each treatment arm achieving SVR 12 weeks after the planned end of treatment (SVR12), defined as having HCV RNA <25 IU/mL undetectable at the end of treatment and HCV RNA <25 IU/mL 12 weeks after the planned end of treatment	
Database lock	Study ongoing; date study initiated: 18 January 2011; cut-off date for the Primary analysis: 26 October 2012			
<u>Results and analysis</u>				
Analysis population and time point description	Intent-to-treat; Week 60			
Descriptive statistics and estimate	Treatment group	TMC435 arm	Placebo arm	
	Number of	264	130	

variability	subjects		
	Stratum adjusted SVR12 (%)	79.4	50.1
	Confidence interval (%)	74.7;84.0	42.1;58.1
Effect estimate per comparison	SVR12	Comparison groups	TMC435 arm; Placebo arm
		Difference between stratum adjusted proportions (%)	29.3
		Confidence interval (%)	20.1;38.6
		P-value - Asymptotic distribution of the generalized Cochran-Mantel-Haenzel statistic controlling for stratification factors.	<0.001

Table 10. Summary of efficacy for trial TMC435-TiDP16-C216 (QUEST-2)

SUMMARY OF EFFICACY FOR TRIAL TMC435-TiDP16-C216 (QUEST-2)			
TITLE: A Phase III, randomized, double-blind, placebo-controlled study to investigate the efficacy, safety and tolerability of TMC435 vs. placebo as part of a treatment regimen including pegylated Interferon alpha-2a (Pegasys) and ribavirin (Copegus) or pegylated Interferon alpha-2b (PegIntron) and ribavirin (Rebetol) in treatment-naive, genotype 1 hepatitis-C infected subjects.			
Study identifier	TMC435-TiDP16-C216 (QUEST-2) EudraCT Number: 2010-021174-11		
Design	Prospective, multicentre, randomized, double-blind, 2-arm, placebo-controlled trial		
	Duration of main phase:		72 weeks
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis	Superiority		
Treatments groups	TMC435 arm	Treatment	PegIFNα-2a 180 µg/week and Ribavirin 1000 or 1200 mg/day, depending on body weight (<75 or ≥ 75 kg, respectively) or PegIFNα-2b and Ribavirin 800-1400 mg/day, depending on body weight (≤65 kg: total daily dose 800 mg; >65 kg - ≤80

			kg: total daily dose was 1,000 mg; >80 - ≤105 kg: total daily dose was 1200 mg; >105 kg: total daily dose was 1,400 mg); TMC435 150 mg once daily.
		Duration	12 weeks PegIFNα-2a or PegIFNα-2b; Ribavirin; TMC435 + 12 weeks PegIFNα-2a or PegIFNα-2b; Ribavirin + 24 weeks PegIFNα-2a or PegIFNα-2b; Ribavirin according to response-guided therapy.
		Number randomized	257
	Placebo arm	Treatment	PegIFNα-2a 180 µg/week and Ribavirin 1000 or 1200 mg/day, depending on body weight (<75 or ≥ 75 kg, respectively) or PegIFNα-2b and Ribavirin 800-1400 mg/day, depending on body weight (≤65 kg: total daily dose 800 mg; >65 kg - ≤80 kg: total daily dose was 1,000 mg; >80 - ≤105 kg: total daily dose was 1200 mg; >105 kg: total daily dose was 1,400 mg); Placebo.
		Duration	12 weeks PegIFNα-2a or PegIFNα-2b; Ribavirin; Placebo + 36 weeks PegIFNα-2a or PegIFNα-2b; Ribavirin
		Number randomized	134
Endpoints and definitions	Primary endpoint	SVR12	The proportion of subjects in each treatment arm achieving SVR 12 weeks after the planned end of treatment (SVR12), defined as having HCV RNA <25 IU/mL undetectable at the end of treatment and HCV RNA <25 IU/mL 12 weeks after the planned end of treatment
Database lock	Study ongoing; date study initiated: 18 January 2011; cut-off date for the Primary analysis: 22 October 2012		
Results and analysis			
Analysis population and time point	Intent-to-treat; Week 60		

description			
Descriptive statistics and estimate variability	Treatment group	TMC435 arm	Placebo arm
	Number of subjects	257	134
	Stratum adjusted SVR12 (%)	81.9	49.7
	Confidence interval (%)	77.2;86.6	42.0;57.3
Effect estimate per comparison	SVR12	Comparison groups	TMC435 arm; Placebo arm
		Difference between stratum adjusted proportions (%)	32.2
		Confidence interval (%)	23.3;41.2
		P-value - Asymptotic distribution of the generalized Cochran-Mantel-Haenzel statistic controlling for stratification factors.	<0.001
Treatments groups	TMC435/PegIFNα-2a arm	Treatment	PegIFNα-2a 180 µg/week and Ribavirin 1000 or 1200 mg/day, depending on body weight (<75 or ≥ 75 kg, respectively); TMC435 150 mg once daily.
		Duration	12 weeks PegIFNα-2a; Ribavirin; TMC435 + 12 weeks PegIFNα-2a; Ribavirin + 24 weeks PegIFNα-2a; Ribavirin according to response-guided therapy.
		Number randomized	77
	Placebo/PegIFNα-2a arm	Treatment	PegIFNα-2a 180 µg/week and Ribavirin 1000 or 1200 mg/day, depending on body weight (<75 or ≥ 75 kg, respectively); Placebo.
		Duration	12 weeks PegIFNα-2a; Ribavirin; Placebo + 36 weeks PegIFNα-2a; Ribavirin
		Number randomized	45

Endpoints and definitions	Primary endpoint	SVR12	The proportion of subjects in each treatment arm achieving SVR 12 weeks after the planned end of treatment (SVR12), defined as having HCV RNA <25 IU/mL undetectable at the end of treatment and HCV RNA <25 IU/mL 12 weeks after the planned end of treatment
Database lock	Study ongoing; date study initiated: 18 January 2011; cut-off date for the Primary analysis: 22 October 2012		
<u>Results and analysis</u>			
Analysis population and time point description	Intent-to-treat; Week 60		
Descriptive statistics and estimate variability	Treatment group	TMC435/PegIFNα-2a arm	Placebo/PegIFNα-2a arm
	Number of subjects	77	45
	SVR12 (%)	91.5	57.6
	Confidence interval (%)	86.4;96.6	42.5;72.6
Effect estimate per comparison	SVR12	Comparison groups	TMC435/PegIFNα-2a arm; Placebo/PegIFNα-2a arm
		Difference between proportions (%)	33.9
		Confidence interval (%)	21.0;46.8
Treatments groups	TMC435/PegIFNα-2b arm	Treatment	PegIFNα-2b and Ribavirin 800-1400 mg/day, depending on body weight (≤65 kg: total daily dose 800 mg; >65 kg - ≤80 kg: total daily dose was 1,000 mg; >80 - ≤105 kg: total daily dose was 1200 mg; >105 kg: total daily dose was 1,400 mg); TMC435 150 mg once daily.
		Duration	12 weeks PegIFNα-2b; Ribavirin; TMC435 + 12 weeks PegIFNα-2b; Ribavirin + 24 weeks PegIFNα-2b; Ribavirin according to response-guided therapy.

		Number randomized	80
	Placebo/PegIFNα-2b arm	Treatment	PegIFNα-2b and Ribavirin 800-1400 mg/day, depending on body weight (≤65 kg: total daily dose 800 mg; >65 kg - ≤80 kg: total daily dose was 1,000 mg; >80 - ≤105 kg: total daily dose was 1200 mg; >105 kg: total daily dose was 1,400 mg); Placebo.
		Duration	12 weeks PegIFNα-2b; Ribavirin; Placebo + 36 weeks PegIFNα-2b; Ribavirin
		Number randomized	43
Endpoints and definitions	Primary endpoint	SVR12	The proportion of subjects in each treatment arm achieving SVR 12 weeks after the planned end of treatment (SVR12), defined as having HCV RNA <25 IU/mL undetectable at the end of treatment and HCV RNA <25 IU/mL 12 weeks after the planned end of treatment
Database lock	Study ongoing; date study initiated: 18 January 2011; cut-off date for the Primary analysis: 22 October 2012		
<u>Results and analysis</u>			
Analysis population and time point description	Intent-to-treat; Week 60		
Descriptive statistics and estimate variability	Treatment group	TMC435/PegIFNα-2b arm	Placebo/PegIFNα-2b arm
	Number of subjects	80	43
	SVR12 (%)	81.0	34.9
	Confidence interval (%)	72.2;89.8	21.1;48.8
Effect estimate per comparison	SVR12	Comparison groups	TMC435/PegIFNα-2b arm; Placebo/PegIFNα-2b arm

		Difference between proportions (%)	46.1
		Confidence interval (%)	33.9;58.3

Table 11. Summary of efficacy for trial TMCHPC3007 (PROMISE)

SUMMARY OF EFFICACY FOR TRIAL TMC HPC3007 (PROMISE)				
TITLE: A Phase III, randomized, double-blind, placebo-controlled study to investigate the efficacy, safety and tolerability of TMC435 vs. placebo as part of a treatment regimen including peginterferon α-2a and ribavirin in hepatitis C, genotype 1 infected subjects who relapsed after previous interferon-based therapy				
Study identifier	TMC435HPC3007 (PROMISE); EudraCT Number: 2010-021113-23; NCT No.: NCT01281839; Clinical Registry No.: CR017371			
Design	Prospective, multicentre, randomized, double-blind, 2-arm, placebo-controlled trial			
	Duration of main phase:		72 weeks	
	Duration of Run-in phase:		not applicable	
	Duration of Extension phase:		not applicable	
Hypothesis	Superiority			
Treatments groups	TMC435 arm	Treatment	PegIFNα-2a 180 µg/week, Ribavirin 1000 or 1200 mg/day, depending on body weight (< 75 or ≥ 75 kg, respectively), TMC435 150 mg once daily	
		Duration	12 weeks PegIFNα-2a; Ribavirin; TMC435 + 12 weeks PegIFNα-2a; Ribavirin + 24 weeks PegIFNα-2a; Ribavirin according to response-guided therapy	
		Number randomized	260	
	Placebo arm	Treatment	PegIFNα-2a 180 µg/week, Ribavirin 1000 or 1200 mg/day, depending on body weight (< 75 or ≥ 75 kg, respectively), Placebo	
		Duration	12 weeks PegIFNα-2a; Ribavirin; Placebo + 36 weeks PegIFNα-2a; Ribavirin	
		Number randomized	133	
Endpoints and definitions	Primary endpoint	SVR12		The proportion of subjects in each treatment arm achieving SVR 12 weeks after the planned end of

			treatment (SVR12), defined as having HCV RNA <25 IU/mL undetectable at the end of treatment and HCV RNA <25 IU/mL 12 weeks after the planned end of treatment
Database lock	Study ongoing; date study initiated: 18 January 2011; cut-off date for the Primary analysis: 26 October 2012		
Results and analysis			
Analysis population and time point description	Intent-to-treat; Week 60		
Descriptive statistics and estimate variability	Treatment group	TMC435 arm	Placebo arm
	Number of subjects	260	133
	Stratum adjusted SVR12 (%)	79.6	36.6
	Confidence interval (%)	74.8;84.4	28.7;44.5
Effect estimate per comparison	SVR12	Comparison groups	TMC435 arm; Placebo arm
		Difference between stratum adjusted proportions (%)	43.0
		Confidence interval (%)	33.8;52.3
		P-value - Asymptotic distribution of the generalized Cochran-Mantel-Haenzel statistic controlling for stratification factors.	P<0.001

Analysis performed across trials (pooled analyses and meta-analysis)

Naïve subjects (Phase III studies C208 and C216)

The results of Phase III studies C208 and C216 were pooled in accordance with the International Conference on Harmonisation (ICH) guideline on statistical principles for clinical studies (ICHE9). Pooling of these studies was considered appropriate given the similarities in the study designs and populations. The main purpose of the pooled analysis was to evaluate the overall treatment

responses in the treatment-naïve population and in pre-specified relevant subgroups with higher precision. In the pooled C208/C216 studies, a total of 785 treatment-naïve subjects were randomized and treated (521 in the TMC435/PR group and 264 in the PBO/PR group).

At the time of data cut-off for the primary Week 60 analysis, 252 of 785 subjects (32.1%) had already completed the studies; 60 subjects (7.6%) had discontinued the study prematurely and 473 subjects (60.3%) were still in follow-up. The proportion of subjects who discontinued study participation prematurely was slightly lower in the TMC435/PR group (6.3%) compared with the PBO/PR group (10.2%). The main reasons (>2% of subjects) for early study discontinuation overall were loss to follow-up (25 subjects, 3.2%) and withdrawal of consent (20 subjects, 2.5%). Premature study discontinuations due to loss to follow-up were slightly more common in the PBO/PR group (4.5%) than in the TMC435/PR group (2.5%).

The demographics and baseline characteristics were generally well balanced between treatment groups.

Efficacy of TMC435 in combination with PegIFN/RBV was statistically significantly superior ($p<0.001$) to placebo in combination with PegIFN/RBV. SVR12 was achieved in 80.4% of subjects in the TMC435/PR group compared with 50.0% of subjects in the PBO/PR group. At the time of the analysis, 500 subjects in the TMC435/PR group and 91 subjects in the PBO/PR groups had reached the Week 24 visit or discontinued the study earlier.

In the pooled analysis that included both pivotal studies, SVR12 was achieved in 80.4% of subjects in the TMC435/PR group compared with 50.0% of subjects in the PBO/PR group. SVR24 rates showed similar rates (82.2% vs 50.5%) and were also statistically significantly to PegIFN/RBV. The addition of TMC435 to the Standard Of Care (SOC) therapy represents a clinically relevant gain with regards to SVR12.

Table 12. Sustained Virological Response (SVR12 and SVR24 – Stratified Cochran-Mantel-Haenszel Approach; ITT population – Study TMC435-C0000007, Efficacy pool)

	Observed	Stratum Adjusted	Comparison versus PBO	
	n/N (%)	% (95% CI)[c]	Difference in Proportions (95% CI)[b]	p-value[a]
SVR12				
PBO 12 Wks PR 48	132/264 (50.0)	49.9 (44.4; 55.5)		
TMC435 150 mg 12 Wks PR 24/48	419/521 (80.4)	80.4 (77.2; 83.7)	30.5 (24.1; 36.9)	<0.001
SVR24				
PBO 12 Wks PR 48	46/91 (50.5)	51.6 (41.8;61.4)		
TMC435 150 mg 12 Wks PR 24/48	411/500 (82.2)	79.5 (75.6;83.4)	27.9 (17.3;38.4)	<0.001

CI: confidence interval; SVR*X*: sustained virologic response *X* weeks after the planned end of treatment

[a] Based on the Cochran-Mantel-Haenszel test controlling for stratification factors.

[b] Difference in proportions (active – placebo) adjusted for stratification factors, with corresponding 95% CI based on the normal approximation.

[c] Proportions adjusted for stratification factors, with corresponding 95% CIs based on the normal approximation. Stratification factors were HCV geno/subtype (1a or 1b), *IL28B* genotype (CC, CT, TT), and study ID (C208, C216).

The p-value for the Breslow-Day test for homogeneity of odds ratios was 0.417 for SVR12 and 0.712 for SVR24.

[TEFSVR01A.rtf] [TMC435\Z_SCE\DBR_P23_2013_NDA\RE_2013_NDA\tefsvr01.sas] 11JAN2013, 12:31
[TEFSVR01B.rtf] [TMC435\Z_SCE\DBR_P23_2013_NDA\RE_2013_NDA\tefsvr01.sas] 11JAN2013, 12:31

Subjects in the TMC435/PR group who met the protocol-stipulated RGT criteria (ie, HCV RNA <25 IU/mL at Week 4 and undetectable HCV RNA at Week 12) had a planned PegIFN/RBV treatment duration of 24 weeks.

Table 13. Analyses of SVR12 by RGT and response at Week 4

	n/N (%)	SVR12 n/N (%)
All subjects		
Met RGT criteria	459/521 (88.1)	405/459 (88.2)
HCV RNA <25 IU/mL undetectable at Week 4 (eRVR)	389/521 (74.7)	357/389 (91.8)
HCV RNA <25 IU/mL detectable at Week 4	68/521 (13.1)	46/68 (67.6)

eRVR: extended rapid virologic response (undetectable HCV RNA at Week 4 and Week 12); RGT: response-guided treatment; SVR12: sustained virologic response 12 weeks after the planned end of treatment

Table 14. Observed SVR12 rates and results of logistic regression for selected demographics

	PBO 12 Wks PR 48		TMC435 150 mg 12 Wks PR 24/48		Difference Between Groups (TMC435 - PBO)
	n/N (%)	% (95% CI)	n/N (%)	% (95% CI)	95% CI
Gender					
Male	72/151 (47.7)	46.8 (38.4;55.2)	227/288 (78.8)	84.5 (80.2;88.9)	37.8 (29.7;45.8)
Female	60/113 (53.1)	47.8 (38.5;57.2)	192/233 (82.4)	85.1 (80.6;89.5)	37.2 (28.8;45.7)
Race					
Black	5/14 (35.7)	48.0 (31.0;65.1)	29/43 (67.4)	85.1 (76.9;93.4)	37.1 (25.9;48.3)
Caucasian	124/245 (50.6)	47.5 (39.7;55.2)	378/464 (81.5)	84.8 (81.0;88.7)	37.4 (29.4;45.3)
Other	1/1 (100)	-	4/5 (80.0)	-	-
Asian	2/4 (50.0)	-	6/7 (85.7)[a]	-	-
Age category (yrs)					
≤45 yrs	61/111 (55.0)	56.1 (46.9;65.4)	206/237 (86.9)	89.0 (85.3;92.8)	32.9 (24.7;41.1)
>45 to ≤65 yrs	70/148 (47.3)	40.6 (32.2;49.0)	203/273 (74.4)	81.3 (76.4;86.1)	40.7 (32.4;49.0)
>65 yrs	1/5 (20.0)	-	10/11 (90.9)	85.3 (68.6;100.0)	-
BMI category					
<25 kg/m^2	53/103 (51.5)	53.1 (43.6;62.5)	175/207 (84.5)	87.7 (83.5;91.9)	34.6 (26.3;42.9)
≥25 to <30 kg/m^2	49/89 (55.1)	46.8 (36.9;56.8)	160/201 (79.6)	84.7 (80.0;89.5)	37.9 (29.2;46.6)
≥30 kg/m^2	29/70 (41.4)	39.6 (29.2;50.1)	84/113 (74.3)	80.5 (73.9;87.2)	40.9 (32.4;49.4)
Region					
Europe	75/142 (52.8)	50.5 (41.3;59.6)	239/276 (86.6)	86.9 (82.8;91.0)	36.4 (28.1;44.7)
North America	36/86 (41.9)	36.5 (26.7;46.2)	115/168 (68.5)	78.9 (72.4;85.3)	42.4 (34.0;50.7)
Asia-Pacific	11/17 (64.7)	67.8 (49.1;86.5)	32/36 (88.9)	93.2 (87.6;98.8)	25.4 (11.5;39.3)
South America	10/19 (52.6)	52.2 (34.0;70.3)	33/41 (80.5)	87.6 (79.8;95.5)	35.5 (23.3;47.6)
US versus Non-US					
USA	27/64 (42.2)	39.6 (28.9;50.3)	93/134 (69.4)	80.6 (74.2;87.1)	41.0 (32.4;49.6)
Non-USA	105/200 (52.5)	49.6 (41.6;57.6)	326/387 (84.2)	86.2 (82.5;89.9)	36.6 (28.7;44.5)

In both treatment groups, the observed SVR12 rates were lower in:

- Black versus white subjects;
- Subjects older than 45 years;
- Subjects with higher BMI;
- Subjects from North America versus other regions.

Table 15. Observed SVR12 rates and results of logistic regression for selected baseline characteristics

	PBO 12 Wks PR 48		TMC435 150 mg 12 Wks PR 24/48		Difference Between Groups (TMC435 - PBO)
	n/N (%)	% (95% CI)	n/N (%)	% (95% CI)	95% CI
Baseline HCV RNA[a]					
≤800,000 IU/mL	54/70 (77.1)	76.5 (67.5;85.5)	96/104 (92.3)	95.5 (93.1;97.9)	19.0 (11.6;26.4)
>800,000 IU/mL	78/194 (40.2)	36.9 (29.1;44.7)	323/417 (77.5)	79.3 (74.8;83.8)	42.4 (34.2;50.6)
HCV Q80K geno/subtype					
1a[b]	62/131 (47.3)	43.4 (33.1;53.7)	191/254 (75.2)	79.3 (73.6;85.1)	35.9 (24.6;47.3)
with baseline Q80K[c]	23/44 (52.3)	49.8 (31.4;68.1)	49/84 (58.3)	59.6 (46.9;72.4)	9.9 (-11.9;31.7)
without baseline Q80K[c]	36/83 (43.4)	37.2 (25.0;49.5)	138/165 (83.6)	87.8 (82.7;93.0)	50.6 (37.5;63.7)
1b[b]	70/133 (52.6)	51.2 (40.9;61.4)	228/267 (85.4)	89.1 (85.3;93.0)	38.0 (27.4;48.5)
IL28B genotype[d]					
CC	63/79 (79.7)	84.0 (77.4;90.6)	144/152 (94.7)	97.0 (95.4;98.6)	13.0 (7.5;18.5)
CT	61/147 (41.5)	38.5 (31.0;46.0)	228/292 (78.1)	79.6 (75.1;84.1)	41.1 (33.0;49.2)
TT	8/38 (21.1)	17.9 (10.4;25.4)	47/77 (61.0)	57.5 (47.1;68.0)	39.7 (32.0;47.4)
IP-10[e]					
≤600 pg/mL	121/219 (55.3)	50.9 (43.0;58.7)	381/456 (83.6)	86.8 (83.3;90.3)	35.9 (27.9;43.8)
>600 pg/mL	11/45 (24.4)	27.2 (16.8;37.6)	38/64 (59.4)	70.3 (59.9;80.7)	43.1 (35.1;51.1)
METAVIR score					
F0-F2[f]	106/192 (55.2)	54.2 (46.1;62.3)	317/378 (83.9)	88.4 (85.0;91.8)	34.2 (26.3;42.1)
F3-F4[f]	26/72 (36.1)	29.6 (20.5;38.7)	89/130 (68.5)	73.0 (65.4;80.6)	43.4 (35.3;51.6)
F3[g]	15/40 (37.5)	34.0 (22.5;45.6)	60/82 (73.2)	76.9 (68.4;85.4)	42.9 (34.4;51.4)
F4[g]	11/32 (34.4)	23.4 (12.4;34.3)	29/48 (60.4)	66.3 (53.7;79.0)	43.0 (34.9;51.1)

In both treatment groups, the observed SVR12 rates were lower in subjects with:

- Baseline HCV RNA >800,000 IU/mL versus ≤800,000 IU/mL;
- HCV genotype 1a versus 1b;
- IL28B genotype TT versus CT and CC;
- Baseline METAVIR score F4 versus F0-F2 and F3.

In subjects with cirrhosis (METAVIR score F4), the SVR12 rate was 60.4% in the TMC435/PR group versus 34.4% in the PBO/PR group. In subjects with IL28B genotype TT, the SVR12 rate was 61.0% in the TMC435/PR group versus 21.1% in the PBO/PR group.

In subjects with IL28B genotype CC, known for having high response rates to PegIFN/ RBV therapy alone, the SVR12 rate was high with both treatments (94.7%, TMC435/PR; 79.7%, PBO/PR), but still statistically significantly in favour of the TMC435/PR group (stratum-adjusted difference between treatments 13.0 [95%: 7.5; 18.5]).

The SVR12 rates were also higher in the TMC435/PR group compared with the PBO/PR group in subjects with HCV genotype 1a with Q80K (58.3% vs 52.3%, respectively) and without Q80K (83.6% vs 43.4%, respectively) at baseline, although the difference between treatments was not statistically significant in subjects with Q80K. Within the TMC435/PR group, the SVR12 rate was lower in subjects with HCV genotype 1a with Q80K (58.3%) versus without Q80K (83.6%). In the

PBO/PR group, subjects with HCV genotype 1a with Q80K had a higher SVR12 rate (52.3%) compared with subjects with genotype 1a without Q80K (43.4%).

Clinical studies in special populations

Study C212 (HCV genotype 1 infection and HIV-1 co-infection)

C212 is a multicenter, open-label, uncontrolled phase III study to evaluate the safety, tolerability and efficacy of TMC435 (150 mg q.d. for 12 weeks), in combination with PegIFNα-2a/RBV, in HCV treatment-naïve and treatment-experienced subjects with HCV genotype 1 infection and HIV-1 co-infection. Subjects could be enrolled regardless of whether they were on HAART (ie, a combination of at least 3 antiretroviral agents) or not.

At enrollment, HCV treatment-experienced subjects were further classified as null responder, partial responder, or relapser, based on their response to prior PegIFN/RBV therapy. Response-guided 24- or 48-week total treatment duration for PegIFNα-2a/RBV is evaluated in treatment naïve subjects and prior relapsers without cirrhosis. In prior non-responders and subjects with cirrhosis (regardless of treatment experience), the total treatment duration with PegIFN/RBV is 48 weeks.

Study Design

The primary analysis set for efficacy was the ITT population (subjects who were enrolled and received at least one dose of study medication).

The primary efficacy endpoint was SVR12. Other key secondary endpoints included: SVR24, meeting response guided treatment (RGT) criteria for shortened treatment to 24 weeks, on- and post-treatment failure o HIV viral load and CD4+ cell count over time, confirmed HIV virologic failure rates.

Results

Baseline data

Most of the subjects were enrolled in Europe (53.7%) and North America (46.2%). Most subjects were male (84.9%) and white (82.1%). Fifteen subjects (14.2%) were black or African American, 1 subject (0.9%) was Asian, and 6 subjects (5.7%) were Hispanic or Latino. The median age was 48.0 years (range: 27 to 67 years). In total, 13 subjects (12.3%) had a BMI $\geq$ 30 kg/m2. Based on invasive and non-invasive assessments, 13 subjects (12.3%) had cirrhosis at baseline; the incidence of cirrhosis was highest among prior null responders (8 subjects, 28.6%).

METAVIR score available at baseline for 68 subjects. Of them, 24 (35.3%) had METAVIR score F0 or F1, 22 (32.4%) had METAVIR score F2, 13 (19.1%) had METAVIR score F3, and 9 (13.2%) had METAVIR score F4.

Based on prior treatment response, 53 subjects (50.0%) were classified as treatment-naïve, 15 (14.2%) as prior relapsers, 10 (9.4%) as prior partial responders, and 28 (26.4%) as prior null responders.

In total, 87 subjects (82.1%) had HCV genotype 1a, 18 subjects (17.0%) had HCV genotype 1b, and 1 subject (0.9%) had HCV genotype 1d. Q80K polymorphism was present at baseline in 28.3% (30 of 106) of the overall population with sequence data; all subjects with Q80K had HCV genotype 1a. Q80K polymorphism was mainly present in prior null responders (42.9%, 12 of 28). Median HCV RNA at baseline was 6.51 log10 IU/mL (range: 4.9 to 7.5 log10 IU/mL), and 91 subjects (85.8%) had high HCV RNA values at baseline defined as >800,000 IU/mL.

Data on IL28B genotype were available for 105 subjects. Of these, 28 (26.7%) had genotype CC, 59 (56.2%) had genotype CT, and 18 (17.1%) had genotype TT.

At baseline, 93 subjects (87.7%) were receiving HAART. The most common HIV antiretroviral therapies were nucleoside reverse transcriptase inhibitors (92 subjects) and the integrase inhibitor raltegravir (81 subjects). Subjects receiving HAART were required to have a screening HIV viral load <50 copies/mL; in these subjects, the median CD4+ cell count at baseline was 561.00 x 106 cells/mL (range: 275.0 to 1407.0 x106 cells/mL). In the subjects not on HAART, the median HIV viral load at baseline was 4.18 log10 copies/mL (range: 1.3 to 4.9 log10 copies/mL) and the median CD4+ cell count was 677.00 x 106 cells/mL (range: 489.0 to 1076.0 x 106 cells/mL).

Overall, 96 subjects (90.6%) completed TMC435 treatment and 10 subjects (9.4%) prematurely discontinued TMC435 treatment due to adverse events (3.8%, 4 of 106 subjects) and meeting a treatment stopping rule (5.7%, 6 of 106 subjects).

In total, 51 subjects (48.1%) completed all study treatment, including 38 of 53 HCV treatment-naïve subjects (71.7%) and 13 of 15 prior relapsers (86.7%). Six HCV treatment-naïve subjects and 1 prior relapser are still on treatment; 9 treatment-naïve subjects and 1 prior relapser prematurely discontinued treatment due to adverse events (5 subjects), meeting a treatment stopping rule (2 subjects), sponsor's decision (1 subject), and other (2 subjects).

Eight of 10 prior partial responders (80.0%) and 19 of 28 prior null responders (67.9%) are still on treatment; the remaining 2 partial responders and 9 null responders prematurely discontinued treatment.

Outcomes and estimation

Sustained Virologic Response

Thirteen subjects had reached the time point for SVR12 assessment (8 treatment-naïve subjects, 5 prior relapsers), and 35 subjects were evaluable for SVR4 (25 treatment-naïve subjects, 10 prior relapsers). In total, 10 of the 13 subjects (76.9%) achieved SVR12. By prior treatment response category, 6 of 8 treatment-naïve subjects (75.0%) and 4 of 5 prior relapsers (80.0%) achieved SVR12.

SVR4 was achieved in 30 of 35 subjects (85.7%) overall. By prior treatment response category, SVR4 was achieved in 21 of 25 treatment-naïve subjects (84.0%) and 9 of 10 prior relapsers (90.0%).

Response-Guided Treatment

Fifty-two subjects (88.1%) met RGT criteria required for shortening duration of PegIFN/RBV treatment. Of these, 90.4% completed treatment at Week 24. Within the group of subjects meeting RGT criteria, preliminary SVR12 and SVR4 rates were 75.0% (9 of 12) and 87.9% (29 of

33), respectively. By prior treatment response category, the preliminary SVR12 rates were 71.4% (5 of 7) in treatment-naïve subjects and 80.0% (4 of 5) in prior relapsers; the preliminary SVR4 rates were 83.8% (20 of 24) in treatment-naïve subjects and 90.0% (9 of 10) in prior relapsers. Of the 52 subjects who met the RGT criteria but did not complete treatment, 3 subjects were still receiving PegIFN and/or RBV and 2 subjects had prematurely discontinued PegIFN and RBV.

On-Treatment Virologic Response

The overall RVR (HCV RNA <25 IU/mL undetectable at Week 4) rate was 66.4%, 71.2% in treatment-naïve subjects, 93.3% in prior relapsers, 80.0% in prior partial responders, and 37.0% in prior null responders. cEVR (HCV RNA <25 IU/mL undetectable at Week 12) was achieved in 94.8% of subjects overall, 95.8% of treatment-naïve subjects, all prior relapsers and partial responders, and 87.5% in prior null responders.

Prediction of SVR12 Rates Using Validated Viral Kinetic Modeling

Validated viral kinetic modeling based on available on-treatment HCV RNA data up to Week 12 was used to predict SVR12 rates in subjects in C212. This modelling analysis yielded a predicted SVR12 rate of 71.7% in treatment-naïve subjects, 80.0% in prior relapsers and prior partial responders, and 57.1% in prior null responders

Treatment Failure

At the time of data cut-off for the interim analysis, the overall treatment failure rate was 20.8%, with the highest rate observed in prior null responders (35.7%). Note that the study is ongoing and not all subjects had reached the same time point.

On-treatment failure was reported in 16 of 22 subjects (15.1%) of the overall population. Viral relapse occurred in 5 of 106 subjects (4.7%). Eighteen of the 28 null responders (64.3%) had not experienced treatment failure at the time of the interim analysis.

In the overall population, the proportion of subjects who met a treatment stopping rule was higher in subjects with HCV genotype 1a (11.4% [1 treatment-naïve subject and 9 prior null responders]) versus 1b (5.6% [1 treatment-naïve subject]).

Overall, 10 subjects (9.5%) met criteria for viral breakthrough (it was not a stopping rurel in this study). All but 1 viral breakthrough occurred in subjects with HCV genotype 1a. Seven of the 10 subjects with viral breakthrough also met a treatment stopping rule (3 subjects at Week 4; 4 subjects at Week 24). The incidence of viral breakthrough was higher in prior null responders (21.4%, 6 of 28) than in the other subpopulations (range: 0.0% to 10.0%).

In total, 12 subjects had population sequence data at the time of treatment failure of whom 6 (50%) had Q80K polymorphism at baseline. All 12 subjects had emerging mutations, usually R155K alone or in combination with mutations at NS3 amino acid position 80 or 168. All but 1 of the 12 subjects had HCV genotype 1a.

With regards to HIV virologic failure, 2 of 93 (2.2%) subjects on HAART had HIV virologic failure based on confirmed HIV RNA ≥50 copies/mL after having HIV RNA <50 copies/mL. At subsequent time points, the subjects had a HIV viral load <50 copies/mL without any change in HAART. None of the subjects had confirmed HIV RNA ≥200 copies/mL.

Study HPC3011 (HCV genotype 4 infected subjects)

Study Design

Multicenter, Phase 3, open label single arm study to evaluate the efficacy, safety and tolerability of TMC435 in combination with PegIFNα-2a and RBV ('PR') triple therapy in adult treatment-naïve or treatment-experienced chronic HCV genotype 4 infected subjects. Subjects had to have a compensated liver disease with a screening plasma HCV RNA level of >10,000 IU/mL. Subjects with any liver disease of non-HCV etiology, with HCV genotype other than 4, with hepatitis B, or with human immunodeficiency virus (HIV) co-infection were excluded.

Treatment duration/Trial duration: screening period of 6 weeks duration at most; 12 weeks of treatment with TMC435; response-guided PR treatment duration of 24 or 48 weeks in HCV treatment-naïves and relapsers to prior HCV therapy or fixed 48 week PR treatment duration in all other subjects; post-treatment follow-up period up to 72 weeks after the start of treatment.

Primary analysis set for efficacy: Intent-to-treat population which includes all subjects who were enrolled and received at least one dose of study medication.

Primary efficacy endpoint: sustained virologic response 12 weeks after the planned end of treatment (SVR12).

Major secondary endpoints:

- Efficacy endpoints: sustained virologic response 4 and 24 weeks after the planned end of treatment (SVR4 and SVR24)
- Proportion of subjects meeting response-guided treatment criteria for shortened treatment of 24 weeks (RGT), on- and off-treatment failure, subgroup analysis by response to previous PegIFN/RBV therapy
- Safety and tolerability.

Because this trial was a single arm study, no formal hypothesis testing and no formal

sample size calculation were performed.

A total of 100 HCV genotype 4 infected subjects were expected to be enrolled in this study.

Subjects enrolled were classified according to the following definitions:

Primary Objective: To evaluate the efficacy of TMC435 in combination with PegIFNα-2a/RBV in subjects with chronic HCV genotype 4 infection with respect to the proportion of subjects achieving SVR 12 weeks after planned end of treatment (SVR12) in the overall population as well as in the different subpopulations (treatment-naïve, prior relapsers and previous non-responders [ie null and partial responders]).

Results

In this open label, multicenter study 107, genotype 4, HCV-infected subjects were enrolled, 35 were treatment-naïve, 22 prior relapser, 10 prior partial responder and 40 prior null-responder.

The majority of subjects was white (72%) with the remainder (28%) being black and 21.5% of the subjects were female. The median age was 49.6 years. The distribution of IL28B genotypes CC, CT

and TT distribution was 7.5%, 57.5%, and 34.9%, respectively, and 28.8% had METAVIR F4. Majority of subjects were infected with HCV genotype 4a (42.5%) and 4d (23.6%) with remainder (33.9%) being infected with a broad range of other HCV genotype 4 subtypes. None of the subjects had a Q80K polymorphism at baseline.

Efficacy Results; ITT (Study HPC3011)

n/N (%)	Simeprevir 150 mg 12 Wks PR 24/48 Interim Analysis Submitted in Initial Application	Simeprevir 150 mg 12 Wks PR 24/48 Current Interim Analysis
All subjects	N=107	N=107
On treatment response at:		
Week 4: <25 IU/mL undetectable/detectable	89/104 (85.6)	89/104 (85.6)
Week 12: <25 IU/mL undetectable	75/89 (84.3)	86/103 (83.5)
SVR4	18/20 (90.0)	59/66 (89.4)
SVR12	7/9 (77.8)	52/61 (85.2)
SVR24	NA	40/45 (88.9)
On-treatment failure[a]	15/107 (14.0)	25/84 (29.8)
Viral relapse[b]	2/19 (10.5%)	5/62 (8.1)
Treatment-naïve subjects	N=35	N=35
On treatment response at:		
Week 4: <25 IU/mL undetectable/detectable	31/35 (88.6)	31/35 (88.6)
Week 12: <25 IU/mL undetectable	28/30 (93.3)	32/35 (91.4)
SVR4	10/11 (90.9)	29/32 (90.6)
SVR12	3/3 (100.0)	28/32 (87.5)
SVR24	NA	20/23 (87.0)
On-treatment failure[a]	3/35 (8.6)	4/35 (11.4)
Viral relapse[b]	1/11 (9.1%)	2/31 (6.5)
Prior relapsers	N=22	N=22
On treatment response at:		

Week 4: <25 IU/mL undetectable/detectable	19/20 (95.0)	19/20 (95.0)
Week 12: <25 IU/mL undetectable	19/20 (95.0)	19/20 (95.0)
SVR4	8/9 (88.9)	20/21 (95.2)
SVR12	4/6 (66.7)	19/21 (90.5)
SVR24	NA	17/19 (89.5)
On-treatment failure[a]	2/22 (9.1)	2/22 (9.1)
Viral relapse[b]	1/8 (12.5%)	1/20 (5.0)
Prior partial responders	N=10	N=10
On treatment response at:		
Week 4: <25 IU/mL undetectable/detectable	9/10 (90.0)	9/10 (90.0)
Week 12: <25 IU/mL undetectable	8/9 (88.9)	8/10 (80.0)
SVR4	NA	4/5 (80.0)
SVR12	NA	1/3 (33.3)
SVR24	NA	1/1 (100.0)
On-treatment failure[a]	0/10	2/5 (40.0)
Viral relapse[b]	0	1/4 (25.0)
Prior null responders	N=40	N=40
On treatment response at:		
Week 4: <25 IU/mL undetectable/detectable	30/39 (76.9)	30/39 (76.9)
Week 12: <25 IU/mL undetectable	20/30 (66.7)	27/38 (71.1)
SVR4	NA	6/8 (75.0)
SVR12	NA	4/5 (80.0)
SVR24	NA	2/2 (100.0)
On-treatment failure[a]	10/40 (25.0)	17/22 (77.3)
Viral relapse[b]	0	1/7 (14.3)

NA: not available, SVR*X*: sustained virologic response *X* weeks after the planned end of treatment.
[a] Confirmed detectable HCV RNA levels at actual end of treatment. Note: The denomination in the interim analysis with a data cut-off date of 17 January 2013 is all subjects, while the denomination in the interim analysis with a data cut-off date of 16 September 2013 is based on the number of subjects who are evaluable for failure.
[b] The denominator is the number of subjects with undetectable HCV RNA (or unconfirmed detectable) at the end of treatment and with at least one follow-up HCV RNA measurement.

HPC2002

Study Design

This study is an ongoing randomized, open-label, multicenter Phase IIa study to investigate the efficacy and safety of 12 weeks or 24 weeks of TMC435 (150 mg once daily [qd]) plus sofosbuvir (400 mg qd) with or without ribavirin (RBV) (1000-1200 mg/day) in hepatitis C (HCV) genotype 1 infected prior null responders to previous peginterferon (PegIFN)/RBV therapy or HCV treatment-naïve subjects with compensated liver disease.

Two cohorts were sequentially enrolled in the study: Cohort 1 included only prior null responders to previous PegIFN/RBV therapy without advanced hepatic fibrosis (Metavir score F0, F1, or F2); Cohort 2included only subjects with advanced hepatic fibrosis (Metavir score F3 or F4) who are prior null responders to previous PegIFN/RBV therapy or are HCV treatment naïve.

A target number of 90 subjects was randomly assigned with a 2:1:2:1 ratio to the 4 arms: TMC435/PSI-7977/RBV 24 weeks (n=30), TMC435/PSI-7977 24 weeks (n=15), TMC435/PSI-7977/RBV 12 weeks (n=30), TMC435/PSI-7977 12 weeks (n=15) in each cohort. Randomization of Cohort 1 was stratified by HCV geno/subtype (1a, non-1a) and IL28B (CC, CT, TT), randomization of Cohort 2 will be stratified by subpopulation (HCV prior null responders, treatment-naïves) and HCV geno/subtype (1a, non-1a).

Treatment duration/Trial duration: screening period of maximum 6 weeks; 12- or 24-weeks of treatment followed by a post-treatment phase (follow-up) up to Week 48 (i.e., 36 weeks of follow-up in subjects who received 12 weeks of treatment and 24 weeks in subjects who received 24 weeks of treatment).

Primary analysis set for efficacy: Intent-to-treat population which includes all subjects who were randomized and received at least one dose of study medication.

Primary efficacy variable/Primary Timepoint: Sustained Virologic Response (SVR) 12 weeks after the planned end of treatment (SVR12).

Major secondary variables:

- efficacy variables: SVR4, SVR24 and SVR at Week 48, early predictors of response (rapid virologic response [RVR]), on- and off-treatment virologic failure
- safety and tolerability

Primary Objective: To investigate the efficacy as defined by SVR12 of a 12-week or 24-week dual or triple regimen including TMC435 (150 mg qd) plus PSI-7977 (400 mg qd) with or without RBV (1000-1200 mg/day) in HCV genotype 1 infected subjects who are null responders to previous PegIFN/RBV therapy or HCV treatment-naïves.

Results

In Cohort 1 (n=80), 71% of subjects were white and 29% were African-American; 61% of the subjects were male and the mean age was 54 years. Overall, 77.5% of subjects were infected with HCV genotype 1a, and 22.5% had HCV genotype non-1a (all of them HCV genotype 1b); 69.6% of subject had IL28B genotype CT, while 6.3% and 24.1% had IL28B genotype CC and TT, respectively.

Table 16. Baseline Disease Characteristics – Cohort 1; Intent-to-treat (Study TMC435HPC2002)

	TMC435 PSI-7977 RBV 24 Wks	TMC435 PSI-7977 24 Wks	TMC435 PSI-7977 RBV 12 Wks	TMC435 PSI-7977 12 Wks	Total
Analysis Set: Intent-to-treat	24	15	27	14	80
Baseline log_{10} HCV RNA level (IU/mL)					
N	24	15	27	14	80
Mean (SD)	6.73 (0.419)	6.74 (0.322)	6.66 (0.440)	6.71 (0.316)	6.70 (0.388)
Median	6.82	6.77	6.81	6.83	6.80
Range	(5.7; 7.4)	(6.3; 7.2)	(5.0; 7.2)	(6.1; 7.0)	(5.0; 7.4)
HCV RNA category (IU/mL)					
N	24	15	27	14	80
<400000	0	0	1 (3.7%)	0	1 (1.3%)
≥400000 - ≤800000	1 (4.2%)	0	0	0	1 (1.3%)
>800000	23 (95.8%)	15 (100.0%)	26 (96.3%)	14 (100.0%)	78 (97.5%)
Metavir fibrosis score					
N	24	15	27	14	80
Score F0-F1	11 (45.8%)	3 (20.0%)	11 (40.7%)	8 (57.1%)	33 (41.3%)
Score F2	13 (54.2%)	12 (80.0%)	16 (59.3%)	6 (42.9%)	47 (58.8%)
Baseline ALT WHO toxicity grade					
N	24	15	27	14	80
Grade 0	8 (33.3%)	4 (26.7%)	12 (44.4%)	6 (42.9%)	30 (37.5%)
Grade 1	10 (41.7%)	8 (53.3%)	7 (25.9%)	4 (28.6%)	29 (36.3%)
Grade 2	4 (16.7%)	2 (13.3%)	5 (18.5%)	4 (28.6%)	15 (18.8%)
Grade 3	2 (8.3%)	1 (6.7%)	3 (11.1%)	0	6 (7.5%)
Grade 4	0	0	0	0	0
HCV geno/subtype (NS5B)[a]					
N	24	15	27	14	80
1a	20 (83.3%)	11 (73.3%)	21 (77.8%)	10 (71.4%)	62 (77.5%)
1b	4 (16.7%)	4 (26.7%)	6 (22.2%)	4 (28.6%)	18 (22.5%)
Time since diagnosis (years)					
N	24	15	27	14	80
Mean (SD)	11.06 (8.428)	9.80 (5.785)	11.51 (5.834)	11.06 (6.049)	10.98 (6.648)
Median	9.25	8.60	11.20	9.35	9.65
Range	(2.2; 38.0)	(1.2; 25.3)	(2.5; 24.5)	(2.7; 26.7)	(1.2; 38.0)

[a] HCV geno/subtype is based on the NS5B assay, and if not available, on LIPA HCV II or Trugene results.

In Cohort 2 (n=87), 46% of subjects were treatment naïve, 54% were prior null responders and 47% had METAVIR score F4 (cirrhosis). Overall, 91% of subjects were white and 9% were African American; 67% of the subjects were male, and the mean age was 57 years. Overall, 78.2% of subjects were infected with HCV genotype 1a and 21.8% had HCV genotype non-1a (all of them HCV genotype 1b); 56.3% of subject had IL28B genotype CT while 20.7% and 23.0% had IL28B genotype CC and TT, respectively.

Table 17. Baseline Disease Characteristics – Cohort 2; Intent-to-treat (Study TMC435HPC2002)

	TMC435 PSI-7977 RBV 24 Wks	TMC435 PSI-7977 24 Wks	TMC435 PSI-7977 RBV 12 Wks	TMC435 PSI-7977 12 Wks	Total
Analysis Set: Intent-to-treat	30	16	27	14	87
Baseline log_{10} HCV RNA level (IU/mL)					
N	30	16	27	14	87
Mean (SD)	6.18 (0.796)	6.54 (0.438)	6.56 (0.515)	6.69 (0.483)	6.45 (0.635)
Median	6.27	6.64	6.70	6.70	6.63
Range	(3.9; 7.3)	(5.4; 7.1)	(5.2; 7.1)	(5.9; 7.4)	(3.9; 7.4)
HCV RNA category (IU/mL)					
N	30	16	27	14	87
<400000	5 (16.7%)	1 (6.3%)	1 (3.7%)	0	7 (8.0%)
≥400000 - ≤800000	4 (13.3%)	0	2 (7.4%)	1 (7.1%)	7 (8.0%)
>800000	21 (70.0%)	15 (93.8%)	24 (88.9%)	13 (92.9%)	73 (83.9%)
Metavir fibrosis score					
N	30	16	27	14	87
Score F3	17 (56.7%)	6 (37.5%)	16 (59.3%)	7 (50.0%)	46 (52.9%)
Score F4	13 (43.3%)	10 (62.5%)	11 (40.7%)	7 (50.0%)	41 (47.1%)
Baseline ALT WHO toxicity grade					
N	30	16	27	14	87
Grade 0	3 (10.0%)	1 (6.3%)	4 (14.8%)	5 (35.7%)	13 (14.9%)
Grade 1	15 (50.0%)	10 (62.5%)	13 (48.1%)	5 (35.7%)	43 (49.4%)
Grade 2	10 (33.3%)	4 (25.0%)	8 (29.6%)	3 (21.4%)	25 (28.7%)
Grade 3	2 (6.7%)	1 (6.3%)	2 (7.4%)	0	5 (5.7%)
Grade 4	0	0	0	1 (7.1%)	1 (1.1%)
HCV geno/subtype (NS5B)[a]					
N	30	16	27	14	87
1a	23 (76.7%)	12 (75.0%)	22 (81.5%)	11 (78.6%)	68 (78.2%)
1b	7 (23.3%)	4 (25.0%)	5 (18.5%)	3 (21.4%)	19 (21.8%)
Time since diagnosis (years)					
N	30	16	27	14	87
Mean (SD)	10.90 (9.383)	8.16 (6.487)	15.50 (10.748)	14.58 (6.766)	12.42 (9.316)
Median	9.05	6.85	13.00	13.05	11.00
Range	(0.7; 43.1)	(0.7; 19.1)	(0.6; 47.1)	(7.0; 29.0)	(0.6; 47.1)
Population as stratified					
N	30	16	27	14	87
Naive	13 (43.3%)	8 (50.0%)	12 (44.4%)	7 (50.0%)	40 (46.0%)
Prior Null Responders	17 (56.7%)	8 (50.0%)	15 (55.6%)	7 (50.0%)	47 (54.0%)

[a] HCV geno/subtype is based on the NS5B assay, and if not available, on LIPA HCV II or Trugene results.

The SVR12 results for all treatment arms of both cohorts of the COSMOS study were provided by the Applicant.

The overall SVR12 in subjects receiving 12 weeks of simeprevir in combination with sofosbuvir with or without RBV were high: 95% (39/41) and 93% (38/41) in Cohort 1 and Cohort 2, respectively (see table below). Similarly, the overall SVR12 rate in subjects receiving 24 weeks of simeprevir in combination with sofosbuvir with or without RBV were high: 85% (33/39) and 96% (44/46) in Cohort 1 and Cohort 2, respectively.

Table 18. SVR12 Rates (Study HPC2002); Intent to Treat Analysis Set

n/N (%)	SMV + SOF + RBV 24 Wks	SMV + SOF 24 Wks	SMV + SOF + RBV 12 Wks	SMV + SOF + 12 WKS
Cohort 1 – prior null responder patients with METAVIR F0-F2 and compensated liver disease				
SVR12	19/24 (79.2%)	14/15 (93.3%)	26/27 (96.3%)	13/14 (92.9%)
Cohort 2 – prior null responder and treatment-naïve patients with METAVIR F3-F4 and compensated liver disease				
SVR12	28/30 (93.3%)	16/16 (100.0%)	25/27 (92.6%)	13/14 (92.9%)

SMV: simeprevir; SOF: sofosbuvir; Wks: weeks

Separate outcomes of the virologic response by prior treatment and METAVIR score is provided in Table below.

Table 19. SVR12 by population; Intent to Treat Analysis Set (Study HPC2002)

	TMC435 PSI-7977 RBV 24 Wks	TMC435 PSI-7977 24 Wks	TMC435 PSI-7977 RBV 12 Wks	TMC435 PSI-7977 12 Wks	Total
Analysis set: intent-to-treat	54	31	54	28	167
All patiente (F0-F4)	47/54 (87.0 %)	30/31 (96.8 %)	51/54 (94.4 %)	26/28 (92.9 %)	154/167 (92.2 %)
All Patients (F0-F3)	35/41 (85.4 %)	20/21 (95.2 %)	41/43 (95.3 %)	20/21 (95.2 %)	116/126 (92.1 %)
All Patients (F4)	12/13 (92.3 %)	10/10 (100.0 %)	10/11 (90.9 %)	6/7 (85.7 %)	38/41 (92.7 %)
All Null Responders (F0-F4)	34/41 (82.9 %)	22/23 (95.7 %)	40/42 (95.2 %)	20/21 (95.2 %)	116/127 (91.3 %)
Null Responders (F4)	9/10 (90.0 %)	4/4 (100.0 %)	4/5 (80.0 %)	4/4 (100.0 %)	21/23 (91.3 %)
Naives (F4)	3/3 (100.0 %)	6/6 (100.0 %)	6/6 (100.0 %)	2/3 (66.7 %)	17/18 (94.4 %)

The study enrolled a high proportion of HCV genotype 1a subjects with a baseline Q80K polymorphism: 45% (58/130) of genotype 1a subjects had a baseline Q80K polymorphism overall. In Cohort 2, which enrolled treatment-naïve and null responder subjects with METAVIR F3-F4, overall SVR12 was achieved by 95% (38/40) of subjects without Q80K and by 96% (26/27) of subjects with a baseline Q80K polymorphism. In the 12-week treatment arms specifically, SVR12 was achieved by 95% (20/21) of subjects without Q80K and by 91% (10/11) of subjects with a baseline Q80K polymorphism. SVR12 rates (12-week and 24-week treatment arms) from the COSMOS study by treatment arm and Q80K status are provided in the table below.

Table 20. SVR rates in Adult Patients With Genotype 1 Infection who Were Null Responders to Prior PegInf and RBV therapy or treatment Naïve by Geno/Subtipe and Q80K Baseline Polymorphism – Intent-to-Treat Analysis set (Study HPC2002)

	Cohort 1 (Prior null responders; METAVIR F0-F2)		Cohort 2 (Treatment-naïve and prior null responders; METAVIR F3-F4)	
n/N (%)	SMV + SOF + RBV	SMV + SOF	SMV + SOF + RBV	SMV + SOF
12-week treatment arms				
Genotype 1a	20/21 (95%)	9/10 (90%)	20/22 (91%)	10/11 (91%)
Q80K	8/9 (89%)	5/6 (83%)	7/8 (88%)	3/3 (100%)
No Q80K	12/12 (100%)	4/4 (100%)	13/14 (93%)	7/7 (100%)
Genotype 1b	100% (6/6)	4/4 (100%)	5/5 (100%)	3/3 (100%)
24-week treatment arms				
Genotype 1a	15/20 (75%)	11/11 (100%)	22/23 (96%)	12/12 (100%)
Q80K	8/12 (67 %)	4/4 (100%)	11/11 (100%)	5/5 (100%)
No Q80K	7/8 (88%)	7/7 (100%)	11/12 (92%)	7/7 (100%)
Genotype 1b	4/4 (100%)	3/4 (75%)	6/7 (86%)	4/4 (100%)

SMV: simeprevir; SOF: sofosbuvir; Wks: weeks
150 mg once daily (qd) simeprevir for 12 weeks with 400 mg qd sofosbuvir with or without RBV. SVR12: sustained virologic response 12 weeks after planned end of treatment.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study C205 evaluated 75mg and 150mg for a duration of 12 or 24 weeks; and study C206 evaluated 100mg and 150mg for a duration of 12, 24 or 48 weeks. The dose of 150 mg TMC435 for 12 weeks was chosen for the phase III studies for all patients (naïve and previously treated), while the duration of SOC therapy was 24 or 48 weeks based on the response for treatment-naïve patients and prior relapsers and 48 weeks for all prior null and partial responders. In order to assess the potential benefit of a longer simeprevir treatment duration, the Applicant provided an overview of the occurrence of viral breakthrough and viral relapse occurred in study C206. These data did not indicate a clear benefit with simeprevir treatments longer than 12 weeks. This treatment duration was therefore considered adequate by the CHMP.

The 3 pivotal Phase III studies were double-blind, randomized, placebo-controlled studies, which evaluated 150mg TMC435 for 12 weeks, in combination with PegIFN/RBV (RGT duration, 24 or 48 weeks). The primary efficacy endpoint was SVR12. The originally planned primary efficacy endpoint in the Phase III studies (SVR24) was changed to SVR12, based on the strong correlation observed between SVR12 and SVR24 in the TMC435 Phase IIb studies (C205 and C206). This change was endorsed by SAWP.

The study populations were chronic HCV genotype 1 infected adult patients (naïve or pre-treated). Main exclusion criteria were co-infection with HIV or HBV. Naïve patients (studies C208, C216) should not have received prior treatment for hepatitis C; Prior relapser patients who failed to achieve sustained virological response (SVR) after a previous treatment with PEG/RBV or relapsed afterwards, were included in study HPC3007.

Prior partial and null responders were not included in the Phase III confirmatory studies. The Applicant has based the whole efficacy of TMC435 for partial and null responders mostly on results from study C206. It is notable, however, that a considerable proportion of a treatment naïve

population would have been partial or null responders, had they previously been exposed to PEG/RBV.

During the conduct of the Phase IIb studies, the importance of the host IL28B genotype in the response to IFN/RBV-based treatment was recognized and the IL28B genotype was used as a stratification factor in the Phase III studies C208, C216 and HPC3007. Given the differences in response expected between HCV genotype 1 subtypes, patients in the Phase IIb/III studies were randomized by genotype 1a and 1b. These factors were included in statistical models used to compare efficacy between treatment groups. The following table summarized the stratification for the main clinical studies:

Table 21. Randomization and Stratification Factors-Placebo-Controlled, Double-Blind Phase IIb and Phase III Studies

C205	• HCV genotype 1 subtype (1a, 1b, or other) • Race (black, white, or other)[a]
C206	• HCV genotype 1 subtype (1a, 1b, or other) • Response to prior PegIFN/RBV therapy (null response, partial response, or relapse)
C208, C216[b], HPC3007	• HCV genotype 1 subtype (1a, 1b, or other) • *IL28B* genotype (CC, CT, or TT)

a For efficacy comparisons, the factor race was omitted from the logistic regression model due to fitting issues.
b A subpopulation in study C216 in selected countries was also randomized by use of PegIFNα-2a/RBV or PegIFNα-2b/RBV.

Patients had to take the investigational drug (150mg TMC435/placebo) once a day for 12 weeks. The investigational drug had to be taken at the same time each day throughout the entire treatment period. PegIFNα-2a/2b was administered once weekly in the morning or evening, following local practice. Ribavirin had to be administered twice daily (b.i.d.) under fed conditions. Dose modifications of the SOC therapy were allowed according to the currently approved SmPC, to manage AEs.

In the Phase IIb/III studies of the core clinical development program, TMC435 was evaluated in combination with PegIFNα-2a/RBV (Pegasys and Copegus). TMC435 was used in combination with PegIFNα-2b/RBV (PegIntron and Rebetol) in a subgroup of patients in the Phase III study C216. Patients in selected countries in the C216 study were randomized in a 1:1 ratio to PegIFNα-2a/RBV or PegIFNα-2b/ RBV, leading to approximately 30% of the overall population randomized to a PegIFNα-2b-containing regimen. The obtained SVR results indicate that the efficacy of TMC435 in combination with PegIFNα-2b/RBV might be lower than in combination with PegIFNα-2a/RBV. These findings have been reflected in the SmPC.

Efficacy data and additional analyses

The baseline characteristics of the population included were in line with what can be expected in treatment naïve/pre-treated chronic HCV genotype 1 patients. An adequate number of patients from the EU were included. There were a higher proportion of male patients across all studies and most of the patients were White. Overall most patients had viral loads > 800.000 IU/ml (close to 90% in some of the studies), and most patients did not have cirrhosis or advanced fibrosis (almost 80%).

The number of patients enrolled from certain subpopulations, such as black patients and elderly patients, was limited and did not allow a full characterization of TMC435 efficacy. This has been adequately reflected in the SmPC and the RMP.

With regards to main efficacy endpoints, the differences in the SVR12 rate between the TMC435 150mg (during 12 weeks)+SOC therapy and placebo were statistically significant across all core clinical studies and a strong correlation between SVR12 and SVR24 was observed across the core studies. The addition of TMC435 to SOC therapy provided a significant gain in SVR12 and SVR24 in naïve as well as previously treated patients.

In the pooled analysis that included both pivotal studies, SVR12 was achieved in 80.4% of patients in the TMC435/PR group compared with 50.0% of patients in the PBO/PR group. SVR24 rates showed similar rates (82.2% vs 50.5%) and were also statistically significantly to PegIFN/RBV. The addition of TMC435 to the SOC therapy represents a clinically relevant gain with regards to SVR12.

Prior partial and null responders were not included in the phase III confirmatory studies. Taking into consideration that the pivotal study HP3007 only included prior relapsers, the Applicant bases the whole efficacy of TMC435 for partial and null responders mainly on results from study C206. Main efficacy results in relapsers are consistent with those of study C206 (which did not apply RGT duration). Adding TMC435 to SOC therapy represented a gain of 43% in terms of SVR12 and 47.1% in terms of SVR24 for prior relapsers.

SVR rates for patients with HCV genotype 1a and Q80K polymorphism at baseline were consistently lower across all core studies (when compared with non-Q80K polymorphism patients and non HCV G 1a patients) andcomparable to those in the placebo group in study C205.

A response-guided total PegIFN/RBV treatment duration (24 or 48 weeks) based on the on-treatment virologic response was proposed for naïve and for patients who relapsed to prior PR treatment. However, a fixed 24-week PR treatment duration was then proposed by the Applicant based on the below arguments:

- In Phase 3 studies a very high proportion of naïve patients (88.1%, pooled data of C208 and 216 trial) and prior relapsers (92.7%, HPC3007 trial) met the response-guided treatment criteria (HCV RNA <25 UI/mL, detectable or undetectable, at week 4 and undetectable at week 12) being eligible for 24 weeks of treatment, with SVR12 rates of 88.2% and 83%, respectively.
- Excluding Gt1a Q80K patients from this analysis, 91.8% of naïve patients and 94.4% of prior relapsers qualified for 24 weeks treatment, with SVR12 rates of 88.2% and 83%, respectively.
- Only 41.7% of naïve patients and 50.0% of prior relapsers without Gt1a Q80K assigned to the 48 week therapy completed treatment, resulting in approximately 2% of all simeprevir-treated patients in the Phase 3 studies receiving this length of therapy.
- Overall SVR rates (completers and non-completers) in patients assigned to 48 weeks of therapy were modest (33.3% in naïve patients and 60.0% in prior relapsers).

Of note, RGT is not applicable for partial and null responders.

The Applicant's proposal was endorsed taking into account that this more restrictive stopping rule will limit unnecessary exposure to peginterferon/RBV in the present landscape.

Other subpopulations

Study HPC3011 (HCV genotype 4 infected patients)

The data demonstrate that the efficacy in HCV genotype 4 is similar to that observed for genotype 1 and support the use of simeprevir in HCV genotype 4 infected patients. Since the study is on-going, the Applicant commits to provide the final data (see Section 2.8).

Study C212 (HCV/HIV co- infected patients)

SVR12 data from the week 60 primary analysis was available for all patients (n=106). Overall, 78 (73.6%) patients achieved SVR12. By prior HCV treatment history, SVR12 was achieved in 42 (79.2%) treatment-naïve patients, 13 (86.7%) prior relapsers, 7 (70.0%) prior partial responders and 16 (57.1%) prior null responders. The data demonstrate that the efficacy in HCV/HIV co-infected patients is similar to that observed for mono-infected patients and support the use of simeprevir in HCV/HIV co-infected patients. Such findings of similar efficacy of a DAA in co-infected and monoinfected patients has been seen other DAA drug development programs. Since the study is on-going, the Applicant commits to provide the final data (see Section 2.8).

Interferon-free regimen: Efficacy in adults with HCV genotype 1 treated with interferon-free regimens Study HPC2002 (COSMOS)

The overall SVR12 in patients receiving 12 weeks of simeprevir in combination with sofosbuvir with or without RBV were high: 95% (39/41) and 93% (38/41) in Cohort 1 and Cohort 2, respectively. Similarly, the overall SVR12 rate in patients receiving 24 weeks of simeprevir in combination with sofosbuvir with or without RBV were high: 85% (33/39) and 96% (44/46) in Cohort 1 and Cohort 2, respectively. The study enrolled a high proportion of HCV genotype 1a patients with a baseline Q80K polymorphism: 45% (58/130) of genotype 1a patients had a baseline Q80K polymorphism overall. In Cohort 2, which enrolled treatment-naïve and null responder patients with METAVIR F3-F4, overall SVR12 was achieved by 95% (38/40) of patients without Q80K and by 96% (26/27) of patients with a baseline Q80K polymorphism. In the 12-week treatment arms specifically, SVR12 was achieved by 95% (20/21) of patients without Q80K and by 91% (10/11) of patients with a baseline Q80K polymorphism. SVR12 rates (12-week and 24-week treatment arms).

Taking into consideration that patients included in cohort 2 are considered a hard-to-treat population, including patients with prior null response and/or cirrhosis, the observed results are very relevant, with >90% of patients achieving SVR12 after 12 or 24 weeks of treatment with SMV+SOF±RBV. The overall results are in line with those previously provided for cohort 1 and represent a large gain in SVR rate compared with other currently available treatment options.

Regarding the efficacy in patients with baseline Q80K polymorphism SVR rates in Cohort 1 patients with that polymorphism are slightly lower than those observed in patients without it. However, for both cohorts, a total of 6 relapses were reported in COSMOS: 4 occurred in G1a patients having Q80K mutation at baseline, 1 was reported in a G1a patient without Q80K and the remaining in a G1a patient with unknown Q80K status. In comparison with Peg-INF/RBV regimens, the impact of Q80K on efficacy seems to be smaller, but the actual magnitude of the effect of thispolymorphism in the SMV+SOF combination is not well understood at present. Until confirmatory data becomes available, testing for the presence of the Q80K polymorphism in patients with HCV genotype 1a should be considered before initiating therapy with simeprevir and sofosbuvir. This finding is adequately reflected on the SmPC.

Based on the evidence available from the COSMOS study, efficacy with 12 weeks of therapy was very high in patients with compensated cirrhosis. The SVR12 in this subgroup of patients (METAVIR score= F4) receiving 12 weeks of simeprevir in combination with sofosbuvir with or without RBV were: 90.9% (10/11) and 85.7% (6/7), respectively. The SVR12 in subjects receiving 24 weeks of simeprevir in combination with sofosbuvir with or without RBV were: 92.3% (12/13) and 100%% (10/10), respectively. Hence, it is the recommended duration. However, while patients with advanced liver fibrosis are more vulnerable to experience AEs and longer treatment duration is expected to be less well-tolerated, longer treatment duration, up to 24 weeks, may be considered on an individual basis to potentially optimize the likelihood of SVR, in particular if there may be no more opportunities in case of relapse. This is reflected in the SmPC.

Data from the COSMOS study does not indicate that the addition of RBV to the simeprevir + sofosbuvir combination contributes to higher SVR rates. However, since the available evidence is limited at this stage, it is indicated in the SmPC that ribavirin could be added to the treatment combination based on a clinical assessment of each individual patient.

Results from the COSMOS study support the use in patients infected with HCV genotype 1 with or without cirrhosis. Due to absence of phase III data, the CHMP is of the opinion to limit the target population to patients intolerant to or ineligible for IFN therapy and in urgent need of treatment. This is reflected in the SmPC.

It is well established that the contribution of exogenous or endogenous interferon response to the efficacy of treatment regimens against hepatitis C differ between genotypes, with genotype 1 considered the most “difficult to treat” or “worst case scenario” in this respect, followed in rank order by genotype 4, genotype 3 and genotype 2. Of note, the public health importance of an interferon free treatment alternative for European patients with genotype 4 infection is considerable and the medical need urgent.

Evidence from the COSMOS study is indicative that the combination of simeprevir+sofosbuvir demonstrates very high efficacy rates in patients infected with HCV genotype 1. While there are no data on the combination of simeprevir+sofosbuvir in genotype 4, sofosbuvir is indicated in patients infected with HCV genotype 4 and simeprevir has demonstrated similar efficacy against genotypes 1 and -4 when used in other combinations. The Q80K mutation does not appear to be a conserved polymorphism in genotype 4, where no prevalent baseline mutation clearly impacting the efficacy of simeprevir has been identified. Based on these data, the efficacy demonstrated by the combination of simeprevir + sofosbuvir (+/- ribavirin) in genotype 1 can be bridged to patients with genotype 4 infection. This information is reflected in the SmPC.

Since the COSMOS study is on-going, the Applicant commits to provide the final data (see Section 2.8). In addition, the Applicant plans to perform several phase III studies with the simeprevir + sofosbuvir combination to further characterize its efficacy/safety. Genotype 4 patients will be enrolled in these confirmatory studies. The Applicant will provide the final data (see Section 2.8).

2.5.4. Conclusions on the clinical efficacy

The addition of TMC435 to SOC therapy resulted in higher SVR rates when treating HCV genotype 1 infection in patients with compensated liver disease.

The presence of baseline Q80K polymorphism is clearly associated with lower SVR rates, and therefore, it translates into a lower clinical benefit for the triple therapy with simeprevir, in comparison with the benefit observed in patients without that polymorphism.

Thus, clear recommendations for baseline Q80K polymorphism screening of HCV genotype 1a patients prior to startingtherapy with simeprevir in combination with PEG/RBV, as well as indications on the clinical management of these patients in locations without access to the baseline testing have been included in the SmPC. In the presence of the Q80K mutation or when this testing is not available, alternative treatments for patients with HCV genotype 1a should be considered.

Data on HCV and HIV co-infected patients indicate a similar efficacy of simeprevir in these populations and support treatment recommendations

Data demonstrate that the efficacy in HCV genotype 4 is similar to that observed for genotype 1 and support the use of simeprevir in this population.

Regarding the use of simeprevir + sofosbuvir (+/- ribavirin), available data from the on-going study HPC2002 (COSMOS), shows very convincing efficacy results in prior non-responders without advanced degree of fibrosis (cohort 1) and also in patients with advanced fibrosis either null responders or naïve (Cohort 2). Based on the available data, dosing recommendations for patients infected with HCV genotype 1 and 4 with/without cirrhosis are included in the SmPC. Due to absence of phase III data, the CHMP restricted the target population to patients intolerant to or ineligible for IFN therapy.

The CHMP considers the following measures necessary to address issues related to efficacy:

- The Applicant should submit the final study report for HPC2002 (COSMOS) by 1Q2015 (MEA)
- The Applicant should submit the results of the phase III studies to evaluate the efficacy and safety of simeprevir in combination with medicinal products other than peginterferon alfa and ribavirin as part of an interferon-free regimen in patients infected with genotypes 1 and 4. (MEA)
- Final study report should be provided for Study C212 (HCV/HIV co- infected patients) by 3Q2014 (MEA)
- Final study report should be provided for the study HPC3011 in treatment-naïve and treatment-experienced genotype 4 infected patients by 1Q2015 (MEA)
- Final study report should be provided for the study C213 in patients with HCV genotype 1 infection who failed PegIFN/RBV treatment in the control group of a Phase II or Phase III study with TMC435, or participated in selected Phase I studies evaluating short-term DAA therapy, by 2Q2016 (MEA)
- Final study report should be provided for the study HPC3002 in patients who received a simeprevir-containing regimen (Phase IIb/III studies), to evaluate the durability of SVR and to evaluate sequence changes in the HCV NS3/4A region over time in patients who had confirmed detectable HCV RNA at the last visit of the previous study by 3Q2017 (MEA)

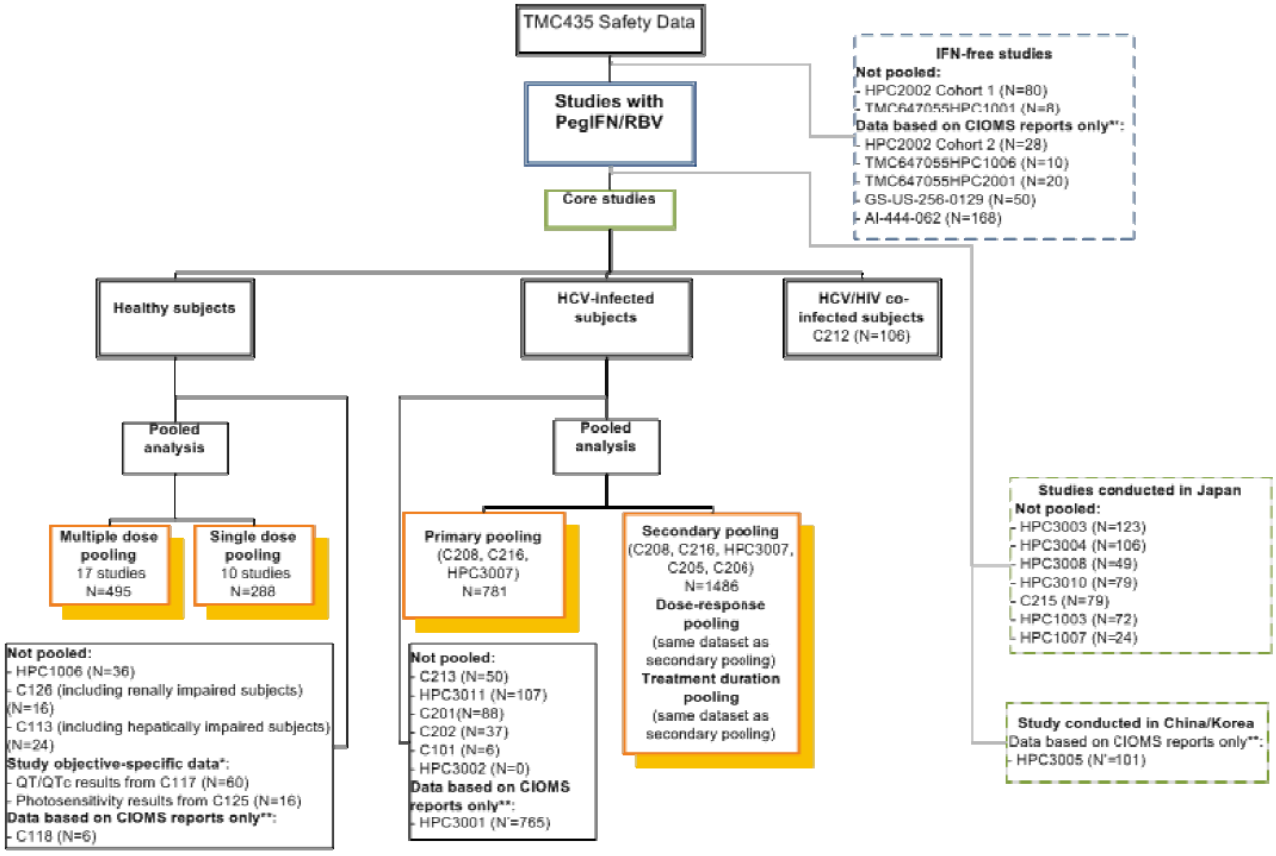
2.6. Clinical safety

The evaluation of the safety profile of TMC435 in combination with PegIFN/RBV is based on the safety data from 38 studies: 7 Phase III studies, 2 Phase IIb studies, 2 Phase IIa studies, and 27 Phase I studies, in which 1846 HCV-infected subjects and 806 healthy subjects received TMC435.

A total of 1153 HCV-infected subjects were treated with the proposed posology (TMC435 150 mg q.d. for 12 weeks).

Six pooled datasets have been performed, four including data from phase IIb/III. The overview of studies included in the analysis was summarized in the figure 3 below:

Figure 3: Overall safety evaluation plan for the TMC435 summary of clinical safety



HCV-infected subjects=HCV mono-infected subjects, unless specified otherwise; N=number of TMC435-exposed subjects; N'= number of subjects enrolled and treated up to 18 January 2013 (blinded)
*General safety results are included in the multiple dose pooling.
**safety data on deaths, other SAEs and pregnancies
Post-hoc for studies for which only data based on CIOMS reports are reported.

Patient exposure

Overall, 1153 subjects received the proposed regimen (TMC435 150 mg q.d for 12 weeks)

The exposure is consistent with the recommendations of ICH Topic E1 "Note for guidance on population exposure: the extent of population exposure to assess clinical safety" (CPMP/ICH/375/95 – June 1995). In the primary pooling, the total median duration of

TMC435/PBO treatment was 12.0 and 5.9 weeks for TMC435-treated subjects and subjects on placebo, respectively. Overall, this difference in duration was because of the implementation of the treatment stopping rule at Week 4 (applicable for both treatment groups), which required TMC435/PBO treatment to be stopped if HCV RNA > 1000 IU/mL. The total median duration of PegIFN/RBV treatment was 24.1 and 48.0 weeks for TMC435-treated subjects and subjects on placebo, respectively. This difference in duration was because 89.2% of TMC435-treated subjects were eligible for shortening of the total treatment duration to 24 weeks, according to the RGT criteria. Of note, 66.5% in subjects in placebo arms discontinued the study drug early due to the virologic stopping rule (compared to 6.7% in simeprevir arms). For the same reason, the median duration was 5.9 weeks in placebo-treated arms in comparison to 12 weeks in simeprevir-treated arms. Overall, patient's exposure in both primary and secondary poolings is considered adequate.

In general, the key demographics and baseline characteristics of subjects in the primary pooling (phase III) studies were generally well balanced across treatment groups. However, very few patients had advanced fibrosis at baseline (51 [12.9 %] in placebo and 87 [11.5%] in simeprevir arm) and only 29 patients were over 65 years old (8 in placebo arms and 21 in simeprevir arms).

Adverse events

Table 22 shows a summary of AEs in the first 12 week phase/ entire treatment phase for both TMC435/PBO groups in the primary pooling.

Table 22. AE summary table; ITT (primary pooling)

	First 12 Weeks Phase		Entire Treatment Phase	
	PBO	TMC435 150 mg	PBO	TMC435 150 mg
Analysis Set: ITT	397	781	397	781
Any AE	376 (94.7%)	744 (95.3%)	382 (96.2%)	757 (96.9%)
Worst grade 1 or 2 AE	278 (70.0%)	565 (72.3%)	246 (62.0%)	527 (67.5%)
Worst grade 1	158 (39.8%)	274 (35.1%)	104 (26.2%)	229 (29.3%)
Worst grade 2	120 (30.2%)	291 (37.3%)	142 (35.8%)	298 (38.2%)
Worst grade 3 or 4 AE	98 (24.7%)	179 (22.9%)	136 (34.3%)	230 (29.4%)
Worst grade 3	87 (21.9%)	156 (20.0%)	118 (29.7%)	197 (25.2%)
Worst grade 4	11 (2.8%)	23 (2.9%)	18 (4.5%)	33 (4.2%)
At least possibly related to TMC435/PBO	21 (5.3%)	56 (7.2%)	21 (5.3%)	59 (7.6%)
Treatment-related AE	373 (94.0%)	731 (93.6%)	379 (95.5%)	742 (95.0%)
At least possibly related to TMC435/PBO	229 (57.7%)	542 (69.4%)	230 (57.9%)	543 (69.5%)
At least possibly related to RBV	280 (70.5%)	596 (76.3%)	321 (80.9%)	633 (81.0%)
At least possibly related to PegIFN	370 (93.2%)	707 (90.5%)	376 (94.7%)	720 (92.2%)
Any AE with fatal outcome	0	0	0	3 (0.4%)
Any SAE[a]	10 (2.5%)	16 (2.0%)	28 (7.1%)	40 (5.1%)
At least possibly related to TMC435/PBO	1 (0.3%)	3 (0.4%)	1 (0.3%)	4 (0.5%)
AE leading to permanent stop[b]	18 (4.5%)	20 (2.6%)	31 (7.8%)	26 (3.3%)
TMC435/PBO[c]	5 (1.3%)	14 (1.8%)	5 (1.3%)	14 (1.8%)
TMC435/PBO only	2 (0.5%)	4 (0.5%)	2 (0.5%)	4 (0.5%)
TMC435/PBO and PegIFN	0	0	0	0
TMC435/PBO and RBV	0	0	0	0
TMC435/PBO, PegIFN and RBV	3 (0.8%)	10 (1.3%)	3 (0.8%)	10 (1.3%)
PegIFN and/or RBV	13 (3.3%)	8 (1.0%)	26 (6.5%)	14 (1.8%)
PegIFN only	0	1 (0.1%)	1 (0.3%)	1 (0.1%)
RBV only	1 (0.3%)	2 (0.3%)	4 (1.0%)	3 (0.4%)
PegIFN and RBV	13 (3.3%)	5 (0.6%)	23 (5.8%)	10 (1.3%)

[a] Including fatal AEs.
[b] Permanent stop of at least one drug.
[c] Without regard to PegIFN and RBV.

Overall, almost all patients experienced an adverse event during the studies. When simeprevir is added to Peg-IFN and RBV, there is an increased risk of developing treatment-related AEs at least possibly related to TMC435/PBO compared to the standard of care (difference = 11.7%). However, the incidence of grade 3 and 4 AE, SAE, AE leading to permanent stop and AE with fatal outcome appears rather similar among treatment arms, which is reassuring. This applies both to the initial 12-week comparison and to the entire treatment phase.

Incidence of Adverse Events by SOC and PTs

During the first 12 week phase, TMC435-treated patients had a higher number of skin and subcutaneous tissue disorders (TMC435-treated subjects 48.5% vs PBO subjects 38.0%).

Trends towards higher percentages of blood and lymphatic system disorders (TMC435-treated subjects 25.5% vs 20.4% subjects on PBO) and gastrointestinal disorders (TMC435-treated subjects 45.5 % vs 39.8% subjects on PBO), infections and infestations (TMC435-treated subjects 17.5 % vs 13.1% subjects on PBO) were noted in TMC435-treated patients when compared to PBO-treated ones.

With regard to infections and infestations occurrence, no relevant differences between simeprevir and placebo by High-Level Term were identified.

Taking into account AEs by PTs the following have been reported more frequently in TMC435-treated patients:

Table 23. Number (%) of Subjects with AEs in at Least 5% of Subjects in the TMC435 Group During the First 12 Weeks Phase; ITT (Primary Pooling)

	First 12 Weeks Phase		Entire Treatment Phase	
SOC **PT**	**PBO**	**TMC435 150 mg**	**PBO**	**TMC435 150 mg**
Analysis Set: ITT	397	781	397	781
Any AE	376 (94.7%)	744 (95.3%)	382 (96.2%)	757 (96.9%)
General disorders and administration site conditions	317 (79.8%)	603 (77.2%)	329 (82.9%)	618 (79.1%)
Fatigue	157 (39.5%)	278 (35.6%)	167 (42.1%)	288 (36.9%)
Influenza like illness	84 (21.2%)	203 (26.0%)	88 (22.2%)	206 (26.4%)
Pyrexia	104 (26.2%)	184 (23.6%)	111 (28.0%)	194 (24.8%)
Asthenia	71 (17.9%)	125 (16.0%)	84 (21.2%)	141 (18.1%)
Chills	41 (10.3%)	68 (8.7%)	41 (10.3%)	71 (9.1%)
Injection site erythema	22 (5.5%)	44 (5.6%)	23 (5.8%)	47 (6.0%)
Skin and subcutaneous tissue disorders	151 (38.0%)	379 (48.5%)	215 (54.2%)	456 (58.4%)
Pruritus	54 (13.6%)	161 (20.6%)	92 (23.2%)	203 (26.0%)
Rash	44 (11.1%)	106 (13.6%)	64 (16.1%)	139 (17.8%)
Dry skin	27 (6.8%)	60 (7.7%)	47 (11.8%)	84 (10.8%)
Alopecia	21 (5.3%)	44 (5.6%)	59 (14.9%)	99 (12.7%)
Gastrointestinal disorders	158 (39.8%)	355 (45.5%)	194 (48.9%)	398 (51.0%)
Nausea	70 (17.6%)	173 (22.2%)	82 (20.7%)	186 (23.8%)
Diarrhoea	45 (11.3%)	86 (11.0%)	53 (13.4%)	104 (13.3%)
Vomiting	20 (5.0%)	51 (6.5%)	26 (6.5%)	59 (7.6%)
Nervous system disorders	176 (44.3%)	338 (43.3%)	191 (48.1%)	369 (47.2%)
Headache	141 (35.5%)	259 (33.2%)	148 (37.3%)	275 (35.2%)
Dizziness	20 (5.0%)	48 (6.1%)	24 (6.0%)	58 (7.4%)

	First 12 Weeks Phase		Entire Treatment Phase	
SOC **PT**	**PBO**	**TMC435 150 mg**	**PBO**	**TMC435 150 mg**
Psychiatric disorders	151 (38.0%)	299 (38.3%)	183 (46.1%)	330 (42.3%)
Insomnia	67 (16.9%)	131 (16.8%)	85 (21.4%)	157 (20.1%)
Mood altered	46 (11.6%)	74 (9.5%)	56 (14.1%)	84 (10.8%)
Depression	29 (7.3%)	60 (7.7%)	45 (11.3%)	74 (9.5%)
Anxiety	17 (4.3%)	40 (5.1%)	22 (5.5%)	42 (5.4%)
Musculoskeletal and connective tissue disorders	115 (29.0%)	254 (32.5%)	152 (38.3%)	286 (36.6%)
Myalgia	53 (13.4%)	126 (16.1%)	62 (15.6%)	136 (17.4%)
Arthralgia	31 (7.8%)	80 (10.2%)	47 (11.8%)	91 (11.7%)
Back pain	17 (4.3%)	49 (6.3%)	31 (7.8%)	62 (7.9%)
Respiratory, thoracic and mediastinal disorders	85 (21.4%)	200 (25.6%)	121 (30.5%)	236 (30.2%)
Cough	36 (9.1%)	72 (9.2%)	63 (15.9%)	91 (11.7%)
Dyspnoea	22 (5.5%)	60 (7.7%)	25 (6.3%)	73 (9.3%)
Blood and lymphatic system disorders	81 (20.4%)	199 (25.5%)	126 (31.7%)	256 (32.8%)
Neutropenia	50 (12.6%)	109 (14.0%)	70 (17.6%)	140 (17.9%)
Anaemia	40 (10.1%)	93 (11.9%)	82 (20.7%)	129 (16.5%)
Metabolism and nutrition disorders	69 (17.4%)	141 (18.1%)	85 (21.4%)	162 (20.7%)
Decreased appetite	56 (14.1%)	120 (15.4%)	64 (16.1%)	128 (16.4%)
Infections and infestations	52 (13.1%)	137 (17.5%)	120 (30.2%)	217 (27.8%)
Investigations	59 (14.9%)	127 (16.3%)	83 (20.9%)	167 (21.4%)
Eye disorders	35 (8.8%)	67 (8.6%)	59 (14.9%)	90 (11.5%)
Injury, poisoning and procedural complications	9 (2.3%)	43 (5.5%)	26 (6.5%)	64 (8.2%)
AEs are coded using MedDRA version 15.0				

Treatment related AE

Overall the safety profile of triple therapy is in line with that previously observed for the PR therapy. A higher incidence of some TEAEs as compared to IFN-RBV treated arm were reported, mainly skin and subcutaneous disorders (prurito and rash); gastrointestinal disorders (nausea); decreased appetite, insomnia, blood and lymphatic system disorders; injury, poisoning and procedural complications (sunburn).

The most frequent TMC435/PBO-related AEs by PT reported were fatigue (TMC435 19.8% and PBO 19.9%), nausea (TMC435 17.5% and PBO 13.1%), and pruritus (TMC435 15.6% and PBO 8.1%), overlapping with those most commonly reported independently from causality.

Of note, the overall frequencies of AEs reported in simeprevir studies appear lower to those previously reported for the bitherapy when considering the known adverse events associated with PR therapy, e.g., flu-like symptoms, psychiatric effects, (adverse events associated with PEG2b), anaemia and rash (adverse events associated with RBV treatment), visual disturbances, hearing impairment, and cardiovascular and gastrointestinal disorders.

Table 24. Number (%) of subjects with AEs at least possibly related to TMC435/PBO in at least 5% of subjects in the TMC435 group during the entire treatment phase; ITT (primary pooling)

	First 12 Weeks Phase		Entire Treatment Phase	
	PBO	TMC435 150 mg	PBO	TMC435 150 mg
Analysis Set: ITT	397	781	397	781
Any TMC435/PBO-Related AE	229 (57.7%)	542 (69.4%)	230 (57.9%)	543 (69.5%)
Skin and subcutaneous tissue disorders	79 (19.9%)	288 (36.9%)	79 (19.9%)	291 (37.3%)
Pruritus	32 (8.1%)	122 (15.6%)	32 (8.1%)	123 (15.7%)
Rash	26 (6.5%)	91 (11.7%)	26 (6.5%)	92 (11.8%)
Dry skin	12 (3.0%)	39 (5.0%)	12 (3.0%)	40 (5.1%)
General disorders and administration site conditions	124 (31.2%)	250 (32.0%)	124 (31.2%)	250 (32.0%)
Fatigue	79 (19.9%)	155 (19.8%)	79 (19.9%)	155 (19.8%)
Asthenia	25 (6.3%)	60 (7.7%)	25 (6.3%)	60 (7.7%)
Gastrointestinal disorders	92 (23.2%)	235 (30.1%)	92 (23.2%)	236 (30.2%)
Nausea	52 (13.1%)	137 (17.5%)	52 (13.1%)	137 (17.5%)
Diarrhoea	25 (6.3%)	53 (6.8%)	25 (6.3%)	53 (6.8%)
Nervous system disorders	82 (20.7%)	158 (20.2%)	82 (20.7%)	159 (20.4%)
Headache	67 (16.9%)	113 (14.5%)	67 (16.9%)	114 (14.6%)
Psychiatric disorders	42 (10.6%)	97 (12.4%)	44 (11.1%)	97 (12.4%)
Insomnia	19 (4.8%)	40 (5.1%)	20 (5.0%)	41 (5.2%)
Metabolism and nutrition disorders	30 (7.6%)	86 (11.0%)	30 (7.6%)	86 (11.0%)
Decreased appetite	26 (6.5%)	77 (9.9%)	26 (6.5%)	77 (9.9%)
Respiratory, thoracic and mediastinal disorders	19 (4.8%)	66 (8.5%)	19 (4.8%)	66 (8.5%)
Investigations	14 (3.5%)	58 (7.4%)	14 (3.5%)	61 (7.8%)
Musculoskeletal and connective tissue disorders	33 (8.3%)	58 (7.4%)	33 (8.3%)	59 (7.6%)
Blood and lymphatic system disorders	26 (6.5%)	53 (6.8%)	26 (6.5%)	55 (7.0%)

AEs are coded using MedDRA version 15.0.

Adverse Events by Severity

During the first 12 weeks phase, most AEs were grade 1 or 2. Grade 3 AEs were reported in 20.0% of TMC435-treated subjects and in 21.9% of subjects on placebo. Grade 4 AEs were reported in 2.9% and 2.8%, respectively. By PT, all grade 3 or 4 AEs were reported in < 5.0% of subjects, with

the exception of neutropenia which was reported in 9.2% of TMC435-treated subjects and in 8.6% of subjects on placebo.

Overall the frequency and the profile of severe AEs, at least grade 3, were rather similar among treatment groups.

Although infrequent, grade 3 or 4 skin and subcutaneous tissue disorders were significantly more common in the TMC345 group than in the PBO-group (0 PBO, 8 cases at week 12 and 12 cases in the entire treatment phase in TMC435-treated patients).

A trend showing a higher frequency of hepatobiliary disorders, mainly hyperbilirubinaemia (0.3% PBO vs 1.4% TMC435) and thrombocytopenia (0.5% PBO vs 1.4% TMC435) is noted in the TMC345 subjects mainly in the first 12 weeks.

With regard to neutropenia, the number of grade 3 or 4 events considered as percentage was similar in TMC345 and PBO subjects with a slight increase over time. These data highlight the role of the background therapy (PegINF+Ribavirin).

There was no other significant difference in the number (as percentage) of grade 3 and 4 AEs between TMC345- and PBO-treated patients.

Adverse Events over Time

The temporal reading of AEs documents a trend towards a higher incidence of AEs in the second 4 weeks of treatment in the TMC345- than in the PBO-treated patients.

In depth, the difference between week 4 and week 8 was of 54.7% in TMC345 group versus 49.1% in PBO group.

Secondary pooling/treatment duration pooling

No relevant differences were observed between the secondary/treatment duration and the primary poolings with respect to AE occurrence between the TMC435 150 mg 12 weeks group and the PBO group. It is noted that the difference between incidence of SAEs, TMC435/PBO-related AEs and AEs leading to discontinuation between patients on TMC435 and those on PBO is substantially stable at different TMC435 treatment durations.

The incidence of grade 3 or 4 AEs was higher in groups with longer duration of TMC435 treatment (150 mg or any dose). Indeed, the delta of grade 3 or 4 AEs between patients on TMC435 150 mg or any dose and those on PBO was: 1.3% and 0.6%, respectively, in patients doing 12 weeks therapy with TMC435; 8.6% and 6.5%, respectively, in patients doing 24 weeks therapy with TMC435; 12.7% and 3.3%, respectively, in patients doing 48 weeks therapy with TMC435.

The incidence of AE and that of grade 3 or 4 AEs, SAEs and AEs leading to discontinuation during the 24 weeks of treatment was comparable between the simeprevir 24 weeks group and the simeprevir 12 weeks and placebo groups.

No relevant differences were observed between treatment duration and the primary pooling with respect to AE occurrence (at least 5% of patients) between the TMC435 150 mg 12 weeks group and the PBO group. It is noted that the incidence of asthenia, neutropenia and dyspnoea with respect to the PBO counterpart increases with increasing duration of TMC435 treatment.

In particular, a clear trend from 12 to 24 and finally 48 weeks of TMC435 treatment is observed for neutropenia (14.7% w12, 24% w24, 30.8% w48) and dyspnoea (7.5% w12, 8.8% w24, 15.4% w48).

When the events of special/clinical interest are considered in the secondary pooling/dosing pooling it is noted that the incidence of increased bilirubin and photosensitivity conditions increased with increasing dose of TMC435, while this is not true for rash. Overall, the safety profile of phase IIb C205 and C206 studies in particular with regard to AE occurrence by severity seems more influenced by higher doses than by treatment duration.

Subgroup Analyses (Primary pooling)

AEs were analysed by the following subgroups: age, sex, race, geographical region, BMI, renal function, METAVIR fibrosis score. The most important findings are reported below:

- **Age**: The number of subjects > 65 years was too small to draw meaningful conclusions. When ESI/ECI were analysed by age categories, pruritus and anemia were higher in the >45≤ 65 years age group of TMC435 treated patients. A higher incidence of dyspnea is reported in simeprevir treated patients in the subset of subjects >45 years compared to placebo (16% vs 9.1%, respectively), although the reason for the finding remains unclear.
- **Race**: The number of Asian and black subjects in both treatment groups was too small to draw meaningful conclusions.
- **Body Mass Index (BMI):** Trends towards more TMC435-related events in the lower BMI category were observed with respect to the occurrence of anaemia, increased bilirubin and rash.
- **Renal Impairment:** The safety and efficacy of simeprevir have not been studied in HCV infected patients with severe renal impairment or end-stage renal disease, including patients requiring dialysis. However, contraindications/warnings adopted for PegIFN and RBV with reference to their use in renally impaired patients should always be considered in light of the combination therapy.
- **METAVIR Fibrosis Score:** Overall, TMC435 did not seem to significantly impact the occurrence of AEs in a stage-dependent manner. When ESI/ECI are analysed individually, it is noted that TMC435 effect on the occurrence of increased bilirubin and anaemia is significantly higher in patients with F4 fibrosis (for increased bilirubin: delta TMC435 vs PBO = 4% in F0-F2, 2.6% in F3 and 12.9% in F4; for anaemia 1.9% in F0-F2, 1.9% in F3 and 8.1% in F4).
- **Advanced Liver Disease:** The safety of TMC435 has not been studied in HCV infected patients with moderate or severe hepatic impairment (Child-Pugh class B or C).Only 3 subjects included had moderate hepatic impairment (Child-Pugh B classification) and patients with decompensated liver disease were excluded. Therefore safety data in patients other than mild hepatic impairment are sparse. Study C113 shows that that degree of liver dysfunction has a significant impact on simeprevir pharmacokinetics, particularly in patients with severe hepatic failure. Dose adjustment may be considered in severe hepatic failure.

Serious adverse event / deaths / other significant events

Serious adverse events

The incidence of SAEs was overall low. During the first 12 weeks phase, SAEs were reported in 2.0% of TMC435/PR arms and in 2.5% of subjects on placebo/PR arms. SAEs reported in more than 1 subject in each treatment group, except for depression, syncope, photosensitivity reaction (each in 2 TMC435-treated subjects), and anaemia (in 2 subjects on placebo).

The TMC435/PBO-related SAE reported were: major depression (1 TMC435-treated subject, very likely related to PegIFN, doubtfully related to RBV), photosensitivity reaction (2 TMC435-treated subjects; 1 possibly related to PegIFN/RBV, 1 not related to PegIFN/RBV), and anaemia (1 subject on placebo, not related to PegIFN, very likely related to RBV).

Not unexpectedly, the incidence tended to increase with longer treatment exposure. Not unexpected SAE have been identified. It is noted that most SAEs were reported by only one subject; SAEs reported by more than one subject in simeprevir treated patients were depression, syncope and photosensitivity reactions (all in 2 patients).

Deaths

There were 4 deaths occurring throughout the entire treatment phase, all in simeprevir treated patients from phase IIb/III trials. None of them were reported during the first 12 weeks phase. Moreover, in none of the 4 cases, the deaths were considered related by investigators to simeprevir and only in one case the event was doubtfully related to Peg-IFN.

Adverse Events of Interest

Based on nonclinical findings for TMC435 and known toxicity profiles for other PIs, PegIFN and RBV, a number of AEs and laboratory abnormalities were predefined to be of special interest (i.e., hepatobiliary AEs) or clinical interest (i.e. pruritus, rash, anemia, photosensitivity conditionsand cardiac AEs). The number of subjects experiencing these events during the first 12 weeks and the entire treatment phase is reported in the table below:

Table 25. Number (%) of subjects with events of special / clinical interest; ITT (primary pooling)

	First 12 Weeks Phase		Entire Treatment Phase	
	PBO	TMC435 150 mg	PBO	TMC435 150 mg
Analysis Set: ITT	397	781	397	781
Events of special interest				
Increased bilirubin	11 (2.8%)	62 (7.9%)	12 (3.0%)	64 (8.2%)
Events of clinical interest				
Rash (Any Type)	67 (16.9%)	181 (23.2%)	99 (24.9%)	218 (27.9%)
Photosensitivity conditions	2 (0.5%)	26 (3.3%)	2 (0.5%)	26 (3.3%)
Pruritus	59 (14.9%)	172 (22.0%)	99 (24.9%)	217 (27.8%)
Neutropenia	60 (15.1%)	129 (16.5%)	88 (22.2%)	164 (21.0%)
Anemia	43 (10.8%)	105 (13.4%)	91 (22.9%)	150 (19.2%)

Subjects are counted only once for any given event, regardless of the number of occurring PTs.

In the dose-response pooling, a trend for a higher incidence of increased bilirubin and anaemia with increasing simeprevir plasma exposure is observed. Consistently, this observation is also found in the incidence of the laboratory abnormality hyperbilirubinemia (TMC435 150 mg group (46.1%) vs TMC435 100 mg group (38.6%) and TMC435 75 mg group (17.0%)).

The treatment duration pooling showed that the incidence of the ECIs rash (any type), pruritus, neutropenia, and anaemia was higher in the TMC435 150 mg groups with longer treatment durations.

Increased Bilirubin

Increases in bilirubin levels are the most salient issue of the safety profile of simeprevir , as the addition of simeprevir to PR clearly increases the risk of experiencing an increased in bilirrubin levels. During the first 12 weeks phase, the incidence of increased bilirubin was higher in TMC435-treated subjects than in subjects on placebo: 7.9% vs 2.8%.

The most frequently reported PTs during the first 12 weeks phase were hyperbilirubinemia (3.7% of simeprevir-treated subjects and 2.0% of subjects on placebo) and blood bilirubin increased (3.5% and 0.8%, respectively). During the first 12 weeks phase, the PT blood bilirubin unconjugated increased was reported in 4 (0.5%) simeprevir-treated subjects and 1 (0.3%) subject on placebo. The PT bilirubin conjugated increased was reported in 2 (0.3%) simeprevir-treated subjects and in no subjects on placebo.

An analysis of the severity of bilirubin changes according to different cut-off points shows that the majority of the changes where below the <2 x ULN cut-off. The highest proportion of subjects with total bilirubin >2 x ULN (6% vs 3.1%) or > 3 ULN (1.4% vs 0.3%) was observed at week 1 and subsequently decreases. The proportion of simeprevir-treated subjects with direct/indirect bilirubin ratio >1 was the highest at Week 8 (4.6%). After completion of simeprevir dosing, the proportion of subjects with increased bilirrubin and direct/indirect bilirubin ratio >1 decreased and no relevant difference was observed with subjects on placebo after Week 16.

No cases of drug induced liver injury consistent with Hy's law were identified (ALT or AST $\geq$ 3 x ULN with concomitant or subsequent total bilirubin $\geq$ 2 x ULN within 30 days and with the maximum alkaline phosphatase value in the 30-day period <2 x ULN).

In the secondary pooling, there were 17 simeprevir treated patients meeting the laboratory criteria for ALT or AST $\geq$ 3 x ULN with concomitant or subsequent total bilirubin $\geq$ 2 x ULN within 30 days. The majority of these patients had increase values at baseline. Very few (9) simeprevir treated patients with a total bilirubin increase of >2 x ULN had a concomitant or subsequent increase in the coagulability parameter international normalized ratio (INR) of >1.1 x ULN, with a maximum increase from baseline in INR of 0.4. The patients with bilirubin increases did not have increases in ALT.

Rash

Rash (any type) was more frequently observed in TMC435-treated patients than in those on PBO. TMC435-treated patients, only 2 subjects reported rash as SAE, 5 patients developed rash grade 3 and 6 patients discontinued all study drugs, or only TMC435, due to rash occurrence. Although a higher rate of simeprevir treated patients experienced an event of rash during therapy compared with placebo treated patients, most of them were mild and the majority did not lead to

discontinuations. Nevertheless, dose adjustments of simeprevir/placebo were not allowed during the conduct of the studies. In case of severe reaction, the study drugs should permanently discontinued.

Photosensitivity Conditions

The incidence of TMC435/PBO-related photosensitivity conditions was 2.8% in TMC435-treated subjects and 0.3% in subjects on placebo. Two TMC435-treated patients had TMC435/PBO-related events reported as SAEs (both photosensitivity reaction leading to hospitalisation).

Pruritus

Pruritus was significantly more frequent in TMC435-treated than in PBO-treated patients (22% vs 14.9%, AE occurrence). However, there was only 1 grade 3 event, which prompted discontinuation of all study drugs. It is noted that the incidence of pruritus in TMC435-treated patients approaches that observed in PBO-treated ones as soon as the 12 weeks phase ends, while the prevalence of pruritus declines gradually in these patients, suggesting a slower time to resolution.

Dyspnoea

During the first 12 weeks phase, the incidence of dyspnoea was higher in TMC435-treated subjects than in subjects on placebo (11.8% vs 7.6%). Only grade 1 and 2 events were reported and there were no events leading to discontinuation of any of the study drugs. In subjects aged >45 years, dyspnoea was reported by 16.4% of TMC435-treated patients and by 9.1% of PBO-treated ones. Hence, dyspnoea deserves special attention since the mechanisms subtending its occurrence are not clear in particular in >45 years old patients.

Because of the majority of these adverse events were grade 1 or 2, no additional investigations (i.e. chest x-ray, spirometry blood gas analysis, echocardiography or other cardio-respiratory function tests) were performed.

Laboratory findings

Overall, data on selected laboratory findings by worst grade are of reassurance. TMC435 treatment, when compared to PBO, seems to not significantly impact any of the laboratory parameters with the exception of bilirubin and ALP levels. Increased levels of bilirubin were already discussed in the previous section.

ALP increases while on TMC435 treatment were generally mild and more frequent in those patients with a concurrent elevation in direct bilirubin levels compared to those without it (37% Vs 27%). It is noted that, during the first 12 weeks of treatment, mean ALP levels increased in TMC435-treated patients while were substantially unaffected in PBO-treated ones, suggesting an impact of TMC435 on this parameter. This was not true for GGT levels.

Safety in special populations

HCV-HIV co-infected subjects

Overall, total percentages of AEs and of AEs at least possibly related to TMC435 were similar to those observed in HCV mono-infected patients. However, in HCV-HIV co-infected patients a

significantly higher percentage of worst grade 3 or 4 AEs (30.2%) with respect to HCV mono-infected ones (22.9% in the analysis of the primary pooling) was observed.

With respect to the minority of patients not on HAART, patients on HAART showed higher percentages of grade 3 or 4 AEs, of SAEs, and of AEs leading to permanent stop of any of the study drugs. This finding was expectable since patients on HAART were exposed to the concurrent toxicities of the other antiviral agents.

Table 26. Adverse Event Summary Table; ITT (Study C212, Overall Population)

	Week 24 Interim Analysis		**Week 60 Primary Analysis**	
	TMC435 150 mg 12 Wks PR 24/48			
n/N (%)	TMC435/PR Phase	Entire Treatment Phase	TMC435/PR Phase	Entire Treatment Phase
Analysis set: ITT	106	106	106	106
Any AE	102 (96.2)	103 (97.2)	102 (96.2)	103 (97.2)
Most frequent AEs by PT or grouped term during the TMC435 + PR phase (ie, in >25% of subjects), n (%)				
Fatigue	43 (40.6)	48 (45.3)	43 (40.6)	48 (45.3)
Headache	29 (27.4)	33 (31.1)	30 (28.3)	35 (33.0)
Nausea	28 (26.4)	29 (27.4)	27 (25.5)	30 (28.3)
Neutropenia	26 (24.5)	32 (30.2)	27 (25.5)	33 (31.1)
Event of special interest[c]				
Increased bilirubin	5 (4.7)	5 (4.7)	5 (4.7)	5 (4.7)
Events of clinical interest[c]				
Rash (any type)	18 (17.0)	20 (18.9)	18 (17.0)	20 (18.9)
Pruritus	21 (19.8)	21 (19.8)	21 (19.8)	21 (19.8)
Photosensitivity conditions	2 (1.9)	2 (1.9)	2 (1.9)	2 (1.9)
Neutropenia	29 (27.4)	38 (35.8)	30 (28.3)	39 (36.8)
Anemia	22 (20.8)	33 (31.1)	22 (20.8)	35 (33.0)
Worst grade 3 or 4 AE	32 (30.2)	45 (42.5)	35 (33.0)	49 (46.2)
Worst grade 3	26 (24.5)	37 (34.9)	29 (27.3)	41 (38.7)

Worst grade 4	6 (5.7)	8 (7.5)	6 (5.7)	8 (7.5)
At least possibly related to TMC435	5 (4.7)	5 (4.7)	3 (2.8)	3 (2.8)
Treatment-related AE	101 (95.3)	103 (97.2)	101 (95.3)	103 (97.2)
At least possibly related to TMC435	69 (65.1)	70 (66.0)	70 (66.0)	71 (67.0)
Any AE with fatal outcome	0	0	0	0
Any SAE	5 (4.7)	10 (9.4)	6 (5.7)	11 (10.4)
At least possibly related to TMC435	1 (0.9)	1 (0.9)	1 (0.9)	1 (0.9)
AE leading to permanent stop[a]	5 (4.7)	5 (4.7)	5 (4.7)	5 (4.7)
TMC435[b]	4 (3.8)	4 (3.8)	4 (3.8)	4 (3.8)
TMC435 only	1 (0.9)	1 (0.9)	1 (0.9)	1 (0.9)
TMC435 + PegIFN	0	0	0	0
TMC435 + RBV	0	0	0	0
TMC435, PegIFN and RBV	3 (2.8)	3 (2.8)	3 (2.8)	3 (2.8)

Permanent stop of at least one drug. Allocation of an AE that led to permanent stop of study drug(s) to a treatment phase is based on the onset date of the AE.

Without regard to PegIFN and RBV.

For definitions and grouped terms of ESI/ECIs, see TMC435/C0000006/Mod2.7.4/Section 1.6.5.1.

Source: Mod5.3.5.2/C212-TLR-IA-W24 and Mod5.3.5.1/C212-W60-CSR

Genotype 4 HCV infected subjects, HPC3011 study

The interim data from HPC 3011 study submitted in the initial application suggested that no relevant differences (12 weeks phase) were noted in the safety profile of TMC435 in HCV genotype 4 infected subjects when compared to that in HCV genotype 1 infected subjects.

Table 27. Adverse Event Summary Table; ITT (HPC3011)

Table 28.	Table 29. Interim Analysis Submitted in Initial Application		*Table 30.* Current Interim Analysis Table 31.	
	TMC435 150 mg 12 Wks PR 24/48			
n (%)	TMC435/PR Phase	Entire Treatment Phase	TMC435/PR Phase	Entire Treatment Phase
Analysis set: ITT	107	107	107	107
Any AE	105 (98.1)	106 (99.1)	105 (98.1)	107 (100.0)
Most frequent AEs by PT during the TMC435/PR phase (ie, in >25% of subjects), n (%)				
Influenza-like illness	48 (44.9)	50 (46.7)	49 (45.8)	51 (47.7)
Asthenia	43 (40.2)	43 (40.2)	45 (42.1)	48 (44.9)
Fatigue	37 (34.6)	38 (35.5)	37 (34.6)	38 (35.5)
Worst grade 3 or 4 AE	6 (5.6)	7 (6.5)	6 (5.6)	8 (7.5)
Worst grade 3	5 (4.7)	6 (5.6)	5 (4.7)	7 (6.5)
Worst grade 4	1 (0.9)	1 (0.9)	1 (0.9)	1 (0.9)
At least possibly related to TMC435	3 (2.8)	3 (2.8)	3 (2.8)	3 (2.8)
Treatment-related AE	104 (97.2)	105 (98.1)	104 (97.2)	106 (99.1)
At least possibly related to TMC435	81 (75.7)	81 (75.7)	80 (74.8)	80 (74.8)
At least possibly related to RBV	94 (87.9)	96 (89.7)	93 (86.9)	95 (88.8)
At least possibly related to PegIFN	103 (96.3)	104 (97.2)	103 (96.3)	105 (98.1)
Any AE with fatal outcome	0	0	0	0
Any SAE	4 (3.7)	4 (3.7)	5 (4.7)	7 (6.5)
At least possibly related to TMC435	0	0	0	0
AE leading to permanent stop[a]	1 (0.9)	1 (0.9)	1 (0.9)	3 (2.8)
TMC435[b]	1 (0.9)	1 (0.9)	1 (0.9)	1 (0.9)
TMC435 only	0	0	0	0
TMC435 and PegIFN	0	0	0	0
TMC435 and RBV	1 (0.9)	1 (0.9)	1 (0.9)	1 (0.9)
TMC435, PegIFN and RBV	0	0	0	0
PegIFN and/or RBV	1 (0.9)	1 (0.9)	1 (0.9)	3 (2.8)
PegIFN only	1 (0.9)	1 (0.9)	1 (0.9)	1 (0.9)
RBV only	0	0	0	1 (0.9)
PegIFN and RBV	0	0	0	1 (0.9)
Event of special interest[c]				
Increased bilirubin	2 (1.9)	2 (1.9)	2 (1.9)	2 (1.9)
Events of clinical interest[c]				
Rash (any type)	14 (13.1)	20 (18.7)	14 (13.1)	24 (22.4)
Pruritus	20 (18.7)	25 (23.4)	22 (20.6)	33 (30.8)
Photosensitivity conditions	0	0	0	0
Neutropenia	5 (4.7)	6 (5.6)	5 (4.7)	7 (6.5)
Anemia	9 (8.4)	11 (10.3)	10 (9.3)	18 (16.8)

AE: adverse events; PT: preferred term; SAE: serious adverse event

[a] Permanent stop of at least one drug. Allocation of an AE that led to permanent stop of study drug(s) to a treatment phase is based on the onset date of the AE.

[b] Without regard to PegIFN and RBV.

[c] For definitions and grouped terms of ESI/ECIs, see Mod2.7.4/Summary of Clinical Safety/Sec1.6.5.1.

Source: Mod5.3.5.2/HPC3011-TLR-IA2-17Jan2013; Mod5.3.5.2/HPC3011-TLR-IA3-Oct2013

Inteferon-free regimens (HPC2002)

The combination of simeprevir and sofosbuvir was generally safe and well tolerated. The overall incidence of AEs was 92.6% and 90.3% in the 24-week groups with and without RBV, respectively, and 85.2% and 71.4% in the 12-week groups with and without RBV, respectively. Most AEs (77.2%) were grade 1 or grade 2 in severity. Overall, 3 subjects (1.8%; all in the 24-week groups)

had a total of 4 SAEs during treatment (injury, anemia, retinal tear, visual impairment). Apart from anemia, none of these serious events was considered related to treatment. The subject with injury (grade 4) died on Day 42 while on treatment. The subject with anemia (grade 1) died of ischemic stroke on Day 215 during post-treatment follow-up. The ischemic stroke was considered not related to study treatment. A listing of the AEs for subjects with a fatal event is provided in Table 24. Overall, 4 subjects (2.4%) (all in a 24-week group) stopped all treatment due to an AE (injury, blood creatine phosphokinase increased, aggression, renal failure). The injury and renal failure was considered as not related to any of the study medications by the investigators. The event of aggression was considered to be possibly related to simeprevir and sofosbuvir and doubtfully related to ribavirin by the investigator. The AE of blood creatine phosphokinase increased was considered to be doubtfully related to simeprevir and sofosbuvir by the investigator.

Table 32. Listing of Adverse Events for Subjects with a Fatal Adverse Event (Study HPC2002; Cohort 1 and Cohort 2)

Cohort	Treatment	Unique Subject Identifier	Age/Gender	Adverse Event Preferred Term/ Reported Term	Day of Onset/ Duration	Toxicity Grade Causality (T/S/R)[a]	Action Taken (T/S/R)[b] Outcome[c]
1	TMC435/ PSI-7977/ RBV 24 Weeks	TMC435 HPC2002-1095	57 years old Male	Anaemia Anemia	Day 20 36 days	Grade 1 NR/PRB/NR	NCHG/NCHG/ NCHG REC/RES
				Ischaemic stroke Ischemic Cerebrovascular Accident	Day 215 6 days	Grade 3 NR/NR/NR	NA/NA/NA FATAL
2	TMC435/ PSI-7977/ RBV 24 Weeks	TMC435 HPC2002-2120	62 years old Male	Sunburn Erythema Ears (Suntan)	Day 27 16 days	Grade 1 NR/NR/NR	NCHG/NCHG/ NCHG NREC/NRES
				Injury Trauma	Day 42 1 days	Grade 4 NR/NR/NR	WTHDR/ WTHDR/ WTHDR FATAL

T: TMC435; P: PSI-7977; R: ribavirin
Causality (NR: Not related; DBT: Doubtful; POS: Possible; PRB: Probable; VL: Very likely)
Action Taken (NCHG: Dose not changed; INC: Dose increased; RED: Dose reduced; INT: Dose interrupted; WTHDR: Dose withdrawn; UNK: Unknown; NA: Not applicable)
Outcome (REC/RES: Recovered/Resolved; NREC/NRES: Not recovered/Not resolved; REC/RESSEQ: Recovered/Resolved with sequelae; FATAL: Fatal; UNK: Unknown)
Adverse events are coded using MedDRA version 14.1.

The most frequently reported AEs (in >15% of subjects overall) were fatigue (29.9%) and headache (19.8%). Fatigue was somewhat more common in the 24-week groups (32.3% to 37.0%) than in the 12-week groups (24.1-25.0%). AEs of clinical interest, in particular bilirubin increase, rash, and anemia, were more common with the RBV-containing regimen than with the RBV-sparing regimen (see Table 25).

For 5 (3.0%) subjects “sunburn” was reported. This preferred term is not yet included in the grouped term photosensitivity conditions in Table 25 for the present interim analysis, but will be included in the final analysis.

Table 33. Adverse Events of Interest (Study HPC2002; Cohort 1 and Cohort 2)

	TMC435 PSI-7977 RBV	TMC435 PSI-7977	TMC435 PSI-7977 RBV	TMC435 PSI-7977
n/N (%)	24 Wks	24 Wks	12 Wks	12 Wks
Analysis set: ITT	54	31	54	28
Events of special interest				
Increased bilirubin	6 (11.1)	1 (3.2)	5 (9.3)	0
Events of clinical interest				
Rash (any type)	9 (16.7)	3 (9.7)	9 (16.7)	2 (7.1)
Pruritus (any type)	9 (16.7)	1 (3.2)	5 (9.3)	4 (14.3)
Photosensitivity conditions	1 (1.9)	1 (3.2)	1 (1.9)	0
Neutropenia	0	1 (3.2)	0	0
Anemia	14 (25.9)	1 (3.2)	7 (13.0)	0

Subjects are counted only once for any given event, regardless of the number of times they actually reported the same event. Adverse events are coded using MedDRA version 14.1.
Increased bilirubin includes MedDRA Preferred Terms: Bilirubin conjugated abnormal, Bilirubin conjugated increased, Bilirubin excretion disorder, Bilirubinuria, Blood bilirubin abnormal, Blood bilirubin increased, Blood bilirubin unconjugated increased, Hyperbilirubinemia, Icterus increased index, Jaundice, Jaundice cholestatic, Jaundice extrahepatic obstructive, Jaundice hepatocellular, Ocular icterus, Urine bilirubin increased, Yellow skin
Rash (any type) includes MedDRA High Level Terms: Erythemas, Papulosquamous conditions, Rashes, eruptions and exanthems NEC, Photosensitivity conditions, MedDRA SMQ Severe cutaneous adverse reaction: narrow scope and selected terms of the broad scope
Pruritus (any type) includes MedDRA High Level Term: Pruritus NEC
Photosensitivity conditions includes MedDRA High Level Term: Photosensitivity conditions
Neutropenia includes MedDRA Preferred Terms: Neutropenia, Neutrophil count decreased
Anemia includes MedDRA Preferred Terms: Anaemia, Haemoglobin decreased, Haemolytic anemia

Discontinuation due to adverse events

In the primary pooling, during the first 12 weeks phase, TMC435/PBO (without regard to PegIFN/RBV) was discontinued due to an AE in 14 subjects (1.8%) of TMC435-treated subjects and in 5 (1.3%) of subjects on placebo. By PT, the most frequent AE leading to discontinuation of TMC435/PBO was rash, reported in 5 (0.6%) subjects.

2.6.1. Discussion on clinical safety

The addition of simeprevir to a standard peg-IFN +RBV antiviral regimen leads to an increase in certain adverse events primarily bilirubin, rash and pruritus. However, this increased risk does not translate into a higher incidence of serious adverse events or treatment discontinuations.

Table 34. AEs in the first 12 weeks of treatment

AEs in the first 12 weeks	TMC435 150 mg 12 weeks	PBO
Any AE	95.3%	94.7%
SAEs	2%	2.5%
Worst grade 3 or 4 AEs	22.9%	24.7%
AEs leading to permanent stop of any of the study drugs	2.6%	4.5%

Increases in bilirubin levels are the most salient issue of the safety profile of simeprevir as the addition of simeprevir to PR clearly increases the risk of experiencing an increment in bilirubin levels. Apparently, bilirubin increments were not associated with mean increases in transaminases. In 12 out of 27 simeprevir treated patients who did experience an increase in maximum alkaline phosphatase, this was associated with increased direct bilirubin but the majority of these patients had increased values at baseline. In different single and repeat- dose toxicity studies in mice, rats and dogs, increases in bilirubin was associated with concomitant ALT, AST and/or alkaline phosphatase (ALP) elevations. However, no cases of drug induced liver injury consistent with Hy's law were identified in simeprevir clinical studies. In addition, very few (9) simeprevir treated patients with a total bilirubin increase had a concomitant or subsequent increase in the coagulability parameter international normalized ratio (INR), with a maximum increase from baseline in INR of 0.4. Overall, the data are quite reassuring. In any case, the addition of

simeprevir to PR clearly increases the risk of experiencing an increased in bilirubin levels. This is reflected in the SmPC.

The cause of rash and pruritus are unknown. The Applicant has clarified if there was any correlation between these two ECIs and circulating levels of bile acids. Indeed, if so, these two AEs could be potentially prevented. The potential relevance of the inhibition of the hepatic uptake and biliary efflux of taurocholate, pointing out that the inhibition should not be linked to hepatotoxicity. In vitro data suggest that simeprevir may increase the serum levels of bile acids, which may explain and correlate to pruritus. Unfortunately, serum levels of bile acids were not monitored. The Applicant states that the lack of correlation between ALP increases and pruritus argues against a role of bile acids in the pathogenesis of pruritus in simeprevir-treated patients and, mainly, that recent evidence from literature does not support a causative role of bile acids in the development of pruritus. The Applicant concludes that there is no scientific evidence supporting consideration of bile acid levels in the management of pruritus on treatment with simeprevir combination therapy. The CHMP agreed that there is not sufficient evidence supporting monitoring and eventually treating elevated serum bile acid levels in simeprevir-treated patients developing pruritus. As this was the measure implemented during clinical studies, it has been included in the SmPC a warning recommending simeprevir interruption in case of severe rash adverse event.

A higher incidence of dyspnoea is observed in simeprevir older patients (>45 years) when compared to older patients on placebo (16.4% vs 9.1% respectively), while there was no difference between treatment groups in younger patients (<45). Overall, the reason for the finding of increased rates of dyspnea, especially in patients aged >45 years in the simeprevir group remains unclear. The increased rate of dyspnea associated with simeprevir treatment has been reflected in the SmPC and will be followed at post approval (PSUR).

The lack of data in patients with advanced liver disease are reflected in the SmPC.

Two TMC435-treated patients had TMC435/PBO-related events reported as SAEs both for photosensitivity reaction leading to hospitalization. Cutaneous photosensitizing potential of TMC435 was assessed in study C215. Due to the higher incidence reported in simeprevir arms, TMC435 was not associated with a delayed photosensitizing effect. Nevertheless, relevant information is reflected in the SmPC including precautionary measure to reduce the risk of photosensitivity reactions.

For the remaining adverse events identified as “of clinical interest” (anemia, neutropenia) no major objections were identified.

With regard to the safety in special populations, the safety profile of simeprevir appears to be similar in patients with advanced fibrosis compared to patients without advanced fibrosis, with only a higher frequency of increased bilirubin and anaemia reported in the F4 score group. This is based on a very limited number of patients with advance fibrosis or cirrhosis. The applicant has provided the mean TMC435 plasma concentration according to the different stages of fibrosis. It seems likely that the higher TMC435 plasma concentrations contribute, at least in part, to the higher observed deltas for anemia and hyperbilirubinemia in the TMC435-treated cirrhotic population when compared to placebo. This information is reflected in the the SmPC.

The number of patients > 65 years was too small to draw meaningful conclusions. No data is available on patient over the age of 73 years. It should be noted that, in the primary pooling,

anaemia was reported in 8 of the 21 TMC435 treated patients >65 years (38%) with respect to only 1 of the 8 patients >65 years on PBO, suggesting a possible age-related effect of TMC435 on this parameter. The same trend was observed for pruritus. No other age-related effects of TMC435 were revealed. No dose adjustment is recommended in this population.

Other subpopulations

HCV/HIV co- infected patients

Considered as SOCs, most of AEs were more frequent in HCV-HIV co-infected population than in HCV mono-infected patients. In particular, remarkable differences were: infections and infestations, blood and lymphatic tissue disorders, psychiatric disorders, musculoskeletal and connective tissue, gastrointestinal disorders, nervous system disorders. Although the lack of placebo in co-infected patients does not allow a definite evaluation, most of these differences are probably related to the lower tolerability of pegylated interferon/ribavirin in co-infected patients and it is very unlikely that a significant part of these differences depend on an increased toxicity of TMC435 in co-infected patients.

Overall the safety profile between mono and co-infected patients is mostly overlapping with some expected differences related to the underlined infection i.e. hematological toxicity but no new safety signals in HCV/HIC co-infected patients. Since the study is on-going, the Applicant commits to provide the final data (see Section 2.8).

HCV genotype 4 infected patients

The updated interim analyses suggest that the safety in this population is similar to that observed for genotype 1. Since the study is on-going, the Applicant commits to provide the final data (see Section 2.8).

Interferon-free regimen

With regard to use of simprevir in combination with sofosbuvir +/- ribavirin, based on preliminary data of the COSMOS study no relevant safety findings have been identified, apart from those well known to be associated with ribavirin. The Applicant has included safety data on the COSMOS study in the SmPC. Since the study is on-going, the Applicant commits to provide the final data (see Section 2.8).

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Overall, simeprevir was well tolerated when added to PEG/RBV, with very few patients discontinuing due to AEs or suffering SAEs during treatment.

When simeprevir is added to Peg-IFN and RBV, there is an increased risk of developing TEAEs compared with standard of care (difference = 11.7%). An increase in the percentage of patients experiencing some TEAEs as compared to IFN-RBV treated arm were reported, mainly skin and subcutaneous disorders (pruritus and rash); gastrointestinal disorders (nausea); decreased appetite, insomnia, blood and lymphatic system disorders; injury, poisoning and sunburn.

The increased rate of dyspnea associated with simeprevir treatment has been reflected in the SmPC and is going to be followed post approval through Routine Pharmacovigilance activities and reported in the PSUR.The addition of simeprevir to PEG/RBV clearly increases the risk of experiencing an increase in bilirrubin levels and this has been reflected in the SmPC.

The safety profile of simeprevir in special populations, HIV/HCV co-infected patients and GT4 infected patients did not raised specific concerns. With regard to use of simprevir in combination with sofosbuvir +/- ribavirin, no relevant safety findings, apart from those anticipated with ribavirin use, have been identified in the COSMOS study.

Overall, simeprevir appears well tolerated and with an acceptable and manageable safety profile.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

The PRAC considered that the risk management system is acceptable.

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

Summary of Safety Concerns

Important Identified Risks	Photosensitivity conditions
	Rash
Important Potential Risks	Development of drug resistance
Missing Information	Use in children and adolescents (≥3 to <18 years)
	Use in elderly patients (>65 years)
	Use in pregnant or breast-feeding women
	Use in patients with moderate or severe hepatic impairment or decompensated liver disease
	Use in patients with GFR <30 mL/min/1.73 m^2
	Use in organ transplant patients
	Use in HCV/HBV co-infection
	Use in patients previously treated with a HCV protease inhibitor or other direct-acting antivirals

	Drug-drug interactions
	OLYSIO + medicinal products other than peginterferon alfa and ribavirin

HCV=hepatitis C virus; HBV=hepatitis B virus; GFR=glomerular filtration rate

- **Pharmacovigilance plans**

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Trial C212/ Interventional clinical trial Phase III open-label study to evaluate the safety, tolerability and efficacy of TMC435 plus PegIFNα-2a (Pegasys®) and ribavirin (Copegus®) triple therapy in chronic hepatitis C genotype 1 infected subjects who are co-infected with human immunodeficiency virus type 1 (HIV-1) Category 3	To evaluate the durability of SVR and sequence changes in HCV RNA in case of treatment failure in HCV/HIV co-infected subjects.	Important Potential Risk/Development of drug resistance	Started	final report: 3Q2014

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Trial HPC2002/ Interventional clinical trial An exploratory Phase IIa, randomized, open-label trial to investigate the efficacy and safety of 12 weeks or 24 weeks of TMC435 in combination with PSI-7977 with or without ribavirin in chronic hepatitis C genotype 1-infected prior null responders to peginterferon/ribavirin therapy or HCV treatment-naïve subjects Category 3	To evaluate the risk of development of drug resistance associated with a regimen including more than one direct-acting antiviral, without peginterferon alfa and with or without ribavirin. To explore the efficacy and safety of simeprevir in combination with medicinal products other than peginterferon alfa and ribavirin as part of an interferon-free regimen.	Important Potential Risk/Development of drug resistance Missing Information/ OLYSIO + medicinal products other than peginterferon alfa and ribavirin	Started	final report: 1Q2015
Trial HPC3011/ Interventional clinical trial An open-label, single-arm Phase III study to evaluate the efficacy, safety and tolerability of TMC435 in combination with PegIFNα-2a (Pegasys®) and ribavirin (Copegus®) in treatment-naïve or treatment-experienced, chronic hepatitis C virus genotype-4 infected subjects Category 3	To evaluate the durability of SVR and sequence changes in HCV RNA in case of treatment failure in HCV genotype 4 infected subjects.	Important Potential Risk/Development of drug resistance	Started	final report: 1Q2015

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Trial C213/ Interventional clinical trial A Phase III, open-label trial of TMC435 in combination with peginterferon alfa-2a and ribavirin for HCV genotype-1 infected subjects who participated in the placebo group of a Phase II/III TMC435 study (C201, C205, C206, C208, C216 or HPC3007), or who received short-term (up to 14 days) direct-acting antiviral treatment for hepatitis C infection in a selected Tibotec[b] sponsored Phase I study Category 3	To evaluate the risk of development of drug resistance in the treatment-experienced subjects who were previously treated with a direct-acting antiviral. To evaluate the safety and efficacy of simeprevir 150 mg once daily in combination with peginterferon alfa and ribavirin in subjects who previously received short-term treatment with a direct-acting antiviral.	Important Potential Risk/Development of drug resistance Missing Information/Use in patients previously treated with a HCV protease inhibitor or other direct-acting antivirals	Started	final report: 2Q2016

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Trial HPC3002/ 3-year follow-up trial A prospective 3-year follow-up study in subjects previously treated in a Phase IIb or Phase III study with a TMC435-containing regimen for the treatment of hepatitis C virus (HCV) infection Category 3	To evaluate sequence changes in HCV NS3/4A region over time in subjects who were treated with a simeprevir-containing regimen in a previous Phase 2b or Phase 3 trial and who had confirmed detectable HCV RNA until the last planned visit of that previous trial. To evaluate the frequency of late relapse and sequence changes in the HCV NS3/4A region in subjects with late relapse who had been treated with a simeprevir-containing regimen in a previous Phase 2b or Phase 3 trial and maintained undetectable HCV RNA until the last planned visit of that previous trial.	Important Potential Risk/Development of drug resistance	Started	final report: 3Q2017
In vitro investigation Category 3	To investigate the in vitro inhibition potential of simeprevir on human OCT2, BCRP and OATP1B3.	Missing Information/Drug-drug interactions	Planned	final report: 1Q2015

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Trial HPC3017/ Interventional clinical trial A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of a 12- or 8-Week Treatment Regimen of Simeprevir in Combination with Sofosbuvir in Treatment-Naïve and -Experienced Subjects with Chronic Genotype 1 Hepatitis C Virus Infection Without Cirrhosis Category 3	To evaluate the efficacy and safety of simeprevir in combination with medicinal products other than peginterferon alfa and ribavirin as part of an interferon-free regimen.	Missing Information/ OLYSIO + medicinal products other than peginterferon alfa and ribavirin	Planned	Final report: 3Q2016
Trial HPC3018/ Interventional clinical trial A Phase 3, Multicenter, Open-Label, Single-Arm Study to Investigate the Efficacy and Safety of a 12-Week Regimen of Simeprevir in Combination with Sofosbuvir in Treatment-Naïve or -Experienced Subjects with Chronic Genotype 1 Hepatitis C Virus Infection and Cirrhosis Category 3	To evaluate the efficacy and safety of simeprevir in combination with medicinal products other than peginterferon alfa and ribavirin as part of an interferon-free regimen.	Missing Information/ OLYSIO + medicinal products other than peginterferon alfa and ribavirin	Planned	Final report: 3Q2016

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
A trial/substudy in genotype 4 HCV-infected subjects The safety and efficacy of simeprevir in combination with sofosbuvir in patients infected with genotype 4 is planned to be investigated in a separate study or as an additional cohort in study HPC3018. Category 3	To evaluate the efficacy and safety of simeprevir in combination with medicinal products other than peginterferon alfa and ribavirin as part of an interferon-free regimen.	Missing Information/ OLYSIO + medicinal products other than peginterferon alfa and ribavirin	Planned	Final report: 3Q2016

TMC435=Tibotec Medicinal Compound 435; vs=versus; PegIFNα-2a/2b=peginterferon alfa-2a/2b; HIV-1=human immunodeficiency virus type 1; HCV(-4)=hepatitis C virus (genotype 4); RBV=ribavirin; DAA=direct-acting antiviral; SVR=sustained virologic response

[a] Trial performed under the responsibility of Bristol-Myers Squibb.

[b] Now called Janssen Research & Development.

[c] Trial performed under the responsibility of Idenix Pharmaceuticals.

- **Risk minimisation measures**

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risk:		
Photosensitivity conditions	SmPC Section 4.4 (Special warnings and precautions for use) includes a subsection on photosensitivity, with recommendations on the use of sun protective measures. SmPC Section 4.8 (Undesirable effects) lists photosensitivity reaction as a common adverse reaction to the use of OLYSIO in combination with peginterferon alfa and ribavirin.	None
Rash	SmPC Section 4.4 (Special warnings and precautions for use) includes a subsection on rash. SmPC Section 4.8 (Undesirable effects) lists rash as a very common adverse reaction to the use of OLYSIO in combination with peginterferon alfa and ribavirin.	None
Important Potential Risk:		
Development of drug resistance	SmPC Section 4.2 (Posology and method of administration) contains information on the proper use of OLYSIO and indicates that OLYSIO treatment must be used in combination with other medicinal products for the treatment of chronic hepatitis C and administered for 12 weeks. This section also states that when considering OLYSIO combination treatment with peginterferon alfa and ribavirin in HCV genotype 1a patients, patients should be tested for the presence of virus with the NS3 Q80K polymorphism before starting treatment. SmPC Section 4.4 (Special warnings and precautions for use) clearly states that OLYSIO must not be administered as monotherapy and informs on the effect of the presence of a baseline Q80K polymorphism on SVR when treating patients with OLYSIO in combination with other medical products. SmPC Section 5.1 (Pharmacodynamic properties) discusses resistance in cell culture and in clinical trials, persistence of resistance-associated substitutions, effect of baseline HCV polymorphisms on treatment response and cross-resistance.	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Missing Information:		
Use in children and adolescents (≥3 to <18 years)	SmPC Section 4.2 (Posology and method of administration) and Section 5.2 (Pharmacokinetic properties) state that the pharmacokinetics, safety and efficacy of OLYSIO in children aged below 18 years have not yet been established. No data are available. SmPC Section 5.1 (Pharmacodynamic properties) contains information on the deferral which was granted by EMA for the obligation to submit the results of trials with OLYSIO in subsets of the paediatric population from 3 years to less than 18 years of age in the treatment of chronic viral hepatitis C.	None
Use in elderly patients (>65 years)	SmPC Section 4.2 (Posology and method of administration) and Section 5.2 (Pharmacokinetic properties) state that there are limited data on the safety and efficacy of OLYSIO in patients older than 65 years. No dose adjustment of OLYSIO is required in elderly patients. Section 4.2 (Posology and method of administration) states that tare no safety and efficacy data of OLYSIO in patients over the age of 75 years. SmPC Section 5.2 (Pharmacokinetic properties) states that age (18-73 years) had no clinically meaningful effect on the pharmacokinetics of simeprevir.	None
Use in pregnant or breast-feeding women	SmPC Section 4.4 (Special warnings and precautions for use) and 4.6 (Fertility, pregnancy and lactation) state that the contraindications and warnings regarding pregnancy, breast-feeding and contraception requirements applicable to the coadministered products also apply to OLYSIO combination treatment. Section 4.6 (Fertility, pregnancy and lactation) indicate that there are no adequate and well-controlled trials with OLYSIO in pregnant women. Studies in animals have shown reproductive effects. OLYSIO should only be used during pregnancy or in women of childbearing potential if the benefit justifies the risk. Female patients of childbearing potential must use an effective form of contraception. It is also stated that extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients and information on the appropriate contraception to be used is provided. It is stated that a decision must be made whether to	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	discontinue breast-feeding or to discontinue/abstain from OLYSIO therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.	
Use in patients with moderate or severe hepatic impairment or decompensated liver disease	SmPC Section 4.2 (Posology and method of administration), Section 4.4 (Special warnings and precautions for use), and section 5.2 (Pharmacokinetic properties) state that no dose adjustment of OLYSIO is necessary in patients with mild or moderate hepatic impairment (Child-Pugh class A or B). Simeprevir exposure is significantly increased in subjects with severe hepatic impairment (Child-Pugh class C) and no dose recommendation can be given for those patients. The safety and efficacy of OLYSIO have not been studied in HCV-infected patients with moderate or severe hepatic impairment (Child-Pugh class B or C); therefore particular caution is recommended when prescribing OLYSIO to HCV-infected patients with moderate or severe hepatic impairment. Reference is made to the respective SmPCs of the medicinal products used in combination with OLYSIO.	None
Use in patients with GFR <30 mL/min/1.73 m^2	SmPC Section 4.2 (Posology and method of administration) and section 5.2 (Pharmacokinetic properties) state that no dose adjustment of OLYSIO is required in patients with mild or moderate renal impairment. Increased simeprevir exposures have been observed in individuals with severe renal impairment. OLYSIO has not been studied in HCV-infected patients with severe renal impairment (creatinine clearance below 30 mL/min) or end stage renal disease, including patients requiring haemodialysis. As exposure may be increased in HCV-infected patients with severe renal impairment, caution is recommended when prescribing OLYSIO to these patients. As simeprevir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis. Reference is made to the respective SmPCs of the medicinal products used in combination with OLYSIO regarding the use in subjects with renal impairment.	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Use in organ transplant patients	SmPC Section 4.4 (Special warnings and precautions for use) states that the safety and efficacy of OLYSIO have not been studied in organ transplant patients. SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction) provides information on the concomitant use of OLYSIO with immunosuppressants.	None
Use in HCV/HBV co-infection	SmPC Section 4.4 (Special warnings and precautions for use) states that the safety and efficacy of OLYSIO for the treatment of HCV infection in patients co-infected with HBV have not been studied.	None
Use in patients previously treated with a HCV protease inhibitor or other direct-acting antivirals	SmPC Section 4.4 (Special warnings and precautions for use) states that there are no clinical data on the use of OLYSIO in re-treating patients who have failed an HCV NS3/4A protease inhibitor-based therapy.	None
Drug-drug interactions	SmPC Section 4.4 (Special warnings and precautions for use) states that coadministration of OLYSIO with substances that moderately or strongly induce or inhibit cytochrome P450 3A (CYP3A4) is not recommended as this may lead to significantly lower or higher exposure of simeprevir, respectively. SmPC Section 4.5 (Interactions with other medicinal products and other forms of interactions) lists drugs for which coadministration with OLYSIO should be used with caution; is not recommended; requires specific monitoring; or requires dose adjustments.	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
OLYSIO + medicinal products other than peginterferon alfa and ribavirin	SmPC Section 4.1 (Therapeutic indications) states that OLYSIO is indicated, in combination with other medicinal products, for the treatment of chronic hepatitis C in adult patients. Cross-reference is made to Sections 4.2, 4.4 and 5.1 where additional information regarding the use of OLYSIO is provided Section 4.4 (Special warnings and precuations for use) states that interferon-free regimens with simeprevir have not been investigated in Phase 3 studies. The optimal regimen and treatment duration have not been established. Interferon-free therapy with OLYSIO should only be used in patients who are intolerant to or ineligible for interferon therapy, and are in urgent need of treatment. OLYSIO should only be coadministered with other direct acting antiviral medicinal products if the benefits are considered to outweigh the risks based upon available data. There are no data to support the coadministration of OLYSIO and telaprevir or boceprevir. These HCV protease inhibitors are anticipated to be cross-resistant, and co-administration is not recommended.	None

HCV=hepatitis C virus; HBV=hepatitis B virus; CYP=cytochrome P450; GFR=glomerular filtration rate; SmPC=Summary of Product Characteristics; EU-European Union; PBRER= Periodic Benefit-Risk Evaluation Report

The CHMP endorsed this advice without changes.

2.9. 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

Chronic hepatitis C virus infection is an important public health problem and a major cause of end-stage liver disease and hepatocellular carcinoma .

Simeprevir is a selective inhibitor of the HCV NS3/4A protease. The Applicant has conducted a comprehensive clinical program to characterize the efficacy and safety of simeprevir in combination with PegIFN/RBV in the treatment of chronic HCV infection. The clinical development program mainly comprised 5 main clinical trials, which focused on genotype 1 chronically infected patients:

- Phase IIb studies: C205 in naïve patients and C206 in treatment experienced patients.
- Phase III studies : C208 & C216 in treatment naïve patients and HPC3007 in patients who relapsed after previous PR treatment.

In addition, there are three additional open label phase III studies ongoing: C213, which includes patients who failed PR treatment in the control group of the simeprevir development program, study C212 in patients with HCV genotype 1/HIV-1 co-infection and study HPC3011, with patients with chronic HCV genotype 4.

Furthermore, the Applicant is conducting an IFN-free clinical programme, which includes study HPC2002 (COSMOS), an on-going Phase IIa that enrolled mostly PEG/RBV treatment-experienced patients who are being treated with simeprevir in combination with sofosbuvir (with or without RBV). Additional phase 3 clinical developments is planned to further characterise the safety and efficacy of IFNfree-regimens with simeprevir in combination with sofosbuvir, as well as in other combinations.

As discussed in the introduction, the CHMP considers that there exist a sufficient rational evidence for indicating the HCV medicines for use "*in combination with other medicinal products*". The particular information for each compound, which is needed for rational regimen selection, should be provided in the relevant sections of the SmPC (i.e. mainly 4.2, 4.5, 5.1) as appropriate.

Hence, based on the above the following indication is proposed for simeprevir:

"OLYSIO is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adult patients (see sections 4.2, 4.4 and 5.1).

For hepatitis C virus (HCV) genotype specific activity, see Sections 4.4 and 5.1."

Benefits

Beneficial effects

HCV G1 patients treated with simeprevir+PEG/RBV:

Treatment naïve and prior relapsers

Based on the results from the 3 phase III studies, it can be concluded that the addition of simeprevir to SOC therapy provides a significant gain in SVR12 and SVR24 in patient with HCV genotype 1 either treatment naïve as well as relapsers. Differences in the SVR12 rate between simeprevir 150mg (during 12 weeks) + SOC therapy and placebo were both statistically significant and clinically relevant across all core clinical studies. For naïve patients, SVR12 was achieved in 80.4% of patients in the TMC435/PR group compared with 50.0% of patients in the PBO/PR group. SVR24 rates showed similar rates (82.2% vs 50.5%). In patients who relapsed to previous SOC treatment, SVR12 was achieved in 79.2% of patients in the TMC435/PR group compared to 36.8% of patients in the PBO/PR arm. SVR24 rates showed similar rates (78.3% vs 31.3%). Fixed 24-week PR treatment duration was proposed and endorsed by the CHMP provided that patients with Gt1a Q80K are excluded (based on baseline Q80K polymorphisms screening).

G1 HCV Partial and null responders

Partial and null responders to PEG/RBV were only studied in phase IIb study C206. This study included two different doses (100 and 150 mg qd) and different simeprevir treatment durations (PR was given on fixed 48 weeks duration). The results showed that the difference in SVR24 rate between each simeprevir dose and treatment duration group individually and placebo was statistically significant. Viral breakthrough and viral relapse data, showed that longer treatment duration was not associated with any additional benefits in terms of SVR12 rates, and therefore are supportive of the proposed treatment regimen (Fixed 48 weeks duration consisting on 12 weeks of triple therapy followed by 36 weeks of PR). Overall, in the simeprevir 150 mg qd dose treated patients (irrespective of simeprevir treatment duration), results from C206 also indicate that the addition of TMC435 to SOC therapy results in an increase in SVR12 when compared to PEG/RBV therapy (51% vs. 18.8% for prior null responders, 75.4% vs 8.7% for prior partial responders). In HPC3007, SVR rates were also higher than the comparator (79.2% vs. 36.8% for SVR12, 78.3% vs. 31.3% for SVR24). Data in prior non responder patients generated in studies C206 and C212 (HCV genotype 1/HIV-1 co-infected patients) in combination with indirect evidence from an analysis conducted in treatment-naïve patients with combinations of unfavorable baseline characteristics, are considered adequate to support the use of simeprevir in the prior non-responder population. Fixed treatment duration (48 weeks) was proposed and endorsed by the CHMP. Additionally, relapse rates and on-treatment failures were lower in TMC435/PR treated patients compared to SOC, for naïve and previously treated patients.

HIV-HCV coinfected patients with GT1 infection

Study C212 results in co-infected patients indicate that on-treatment response parameters are similar to those observed in HCV G1 mono-infected , as are available interim SVR data and support the recommended conditions for use in co-infected patients as establish in the SmPC. Since the study is on-going, the Applicant commits to provide the final data .

Genotype 4 HCV patients

In-vitro and in-vivo virological response and clinical virology data, along with the preliminary efficacy data, are supportive of the efficacy of simeprevir in the HCV genotype 4 infected population. Study HPC3011 show consistent results compared to those of Genotype 1 infected population and support the recommended conditions for use in Genotype 4 infected patients as establish in the SmPC. Since the study is on-going, the Applicant commits to provide the final data.

Use in combination with sofosbuvir+/- ribavirin.

Data from the on-going HPC2002 (COSMOS) study show convincing efficacy results in prior null -responders to PEG/RBV without advanced of fibrosis, as well as in patients with advanced fibrosis that were either prior null responders to PEG/RBV or treatment naïve.

In Cohort 1, the SVR12 rates in the 24-week treatment groups were 79% (19/24) for the simeprevir with sofosbuvir with ribavirin treatment group and 93% (14/15) in the simeprevir with sofosbuvir without ribavirin treatment group. In Cohort 2, the SVR12 rates in the 24-week treatment groups were 93% (28/30) for the simeprevir with sofosbuvir with ribavirin treatment group and 100% (16/16) in the simeprevir with sofosbuvir without ribavirin treatment group. Results from the COSMOS study support the use in patients infected with HCV genotype 1 with/without cirrhosis. Overall, due to absence of phase III data, the CHMP is of the opinion to limit

the target population to patients intolerant to or ineligible for IFN therapy and in urgent need of treatment.

In the COSMOS study, efficacy with 12 weeks of therapy was very high also in patients with compensated cirrhosis. Hence, it is the recommended duration. However, while patients with advanced liver fibrosis are more vulnerable to experience AEs and longer treatment duration is expected to be less well-tolerated, longer treatment duration, up to 24 weeks, may be considered on an individual basis.

Data from the COSMOS study does not indicate that RBV contributes to higher SVR rates. However, the available evidence is limited at this stage. Hence, until further data are available, ribavirin could be added to the treatment combination based on a clinical assessment of each individual patient.

Evidence from the COSMOS study is indicative that the combination of simeprevir+sofosbuvir (+/- ribavirin) demonstrates very high efficacy rates in patients infected with HCV genotype 1. While there are no data on the combination of simeprevir+sofosbuvir (+/- ribavirin) in genotype 4, sofosbuvir is as effective in genotype 4 as in genotype 1. Furthermore, the efficacy of simeprevir has been roughly similar against genotypes 1 and 4in vitro, in short term monotherapy, and when used in other combinations. Therefore, it is considered, the additive efficacy demonstrated by the combination of simeprevir + sofosbuvir (+/- ribavirin) in genotype 1 can be bridged to patients with genotype 4 infection. The CHMP therefore recommends the use of sofosbuvir+simeprevir in genotype 4 patients that are not eligible for interferon therapy and that are in urgent need of treatment.. Of note, the public health importance of an interferon free treatment alternative for European patients with genotype 4 infection is considerable and the medical need urgent in patients with advanced liver disease.

Uncertainty in the knowledge about the beneficial effects.

Efficacy in non-responder patients

The efficacy of simeprevir/PR treatment in non-responder patients has not been evaluated in any of the pivotal trials. Partial and null responders were only studied in the phase IIb dose-finding study (C206). This study included, regardless the simeprevir dose and total duration of treatment, a total of 137 prior partial responders and 101 prior null responders and showed a relevant increase in SVR for both simeprevir dose groups compared to placebo. Viral breakthrough and viral relapse data showed that longer treatment duration was not associated with any additional benefits in terms of higher SVR12 rates and therefore supported the dosing recommendation.

Concerning treatment failure, the data show that most of the virological breakthroughs were reported during the first 12 weeks of treatment or within those, which were reported after week 12, there was already evidence of treatment failure, suggesting again that longer treatment with simeprevir does not prevent virological breakthrough.

Genotype 1a and Q80K polymorphism at baseline

Other important limitation is that SVR rates for patients with HCV genotype 1a and Q80K polymorphism at baseline were consistently lower across all core studies (when compared with non-Q80K polymorphism patients and non HCV G 1a patients) and even comparable to those in the

placebo group in study C205. The virology analyses of clinical studies in treatment-naïve and treatment experienced confirm the impact of baseline polymorphism Q80K on treatment outcome. In addition, the following points were considered:

- *In vitro*, the presence of the Q80K polymorphism is consistently associated with rise high EC_{50} values,
- Both site-directed mutants and recombinant chimeras of genotype 1a carrying the NS3 sequence with the Q80K mutation are less sensitive to TMC435,
- Excepting C206 and C216 clinical trials, lower virologic response rates and higher viral relapse and on-treatment failure rates were observed in TMC435/PR-treated HCV genotype 1a infected patients with a Q80K polymorphism compared with patients without Q80K at baseline,
- Slower decay in viral load after starting treatment was observed in patients carrying the Q80K polymorphisms.

In conclusion only Q80K polymorphisms present in 13.7% HCV genotype 1 infected patients appears to impact on the virological response to TMC435. The adequacy of treating patients with HCV genotype 1a and Q80K polymorphism with simeprevir + PEG/RBV has been questioned, since the benefit of adding simeprevir therapy seems only marginally better than PEG/RBV therapy alone. Clear recommendations for baseline Q80K polymorphism screening of HCV genotype 1a patients prior to starting triple therapy with simeprevir, as well as indications on the clinical management of these patients in locations without access to the baseline testing have been included in the SmPC. In the presence of the Q80K mutation or when this testing is not available, alternative treatments for patients with HCV genotype 1a should be considered.

In addition the data from the COSMOS study tend to indicate that Q80K might also negatively impact the response rate (although to a lesser extent) when simeprevir is used in combination with sofosbuvir (10-15% lower rate of response was observed in G1a with vs without Q80K in COSMOS study), though data are limited. The uncertainties surrounding the impact of the presence of Q80K polymorphism on simeprevir SVR when simeprevir is used in other treatment combinations than with PEG/RBV remains and this has been reflected in the SmPC.

Interferon-free regimens

Regarding the use of simeprevir + sofosbuvir (+/- ribavirin), available data from the on-going study HPC2002 (COSMOS), shows very convincing efficacy results. Based on the available data, dosing recommendations for patients infected with HCV genotype 1 and 4 with/without cirrhosis are included in the SmPC. Due to absence of phase III data, the CHMP primarily recommends this combination for patients intolerant to or ineligible for IFN therapy.

Risks

Unfavourable effects

Overall, simeprevir was well tolerated when added to PEG/RBV, with very few patients discontinuing due to AEs or suffering SAEs during treatment.

When simeprevir is added to PEG/RBV PEG/RBV , there is an increased risk of developing TEAEs compared with standard of care (difference = 11.7%). An increase in the percentage of patients

experiencing any TEAEs as compared to IFN-RBV treated arm were reported, mainly skin and subcutaneous disorders (pruritus and rash); gastrointestinal disorders (nausea); decreased appetite, insomnia, blood and lymphatic system disorders; injury, poisoning and sunburn.

The increased rate of dyspnea associated with simeprevir treatment has been reflected in the SmPC and is going to be followed post approval through Routine Pharmacovigilance activities and reported in the PSUR.

Rash has been observed with simeprevir combination treatment. The cause of rash and pruritus are unknown. In case of severe rash, simeprevir and other co administered medicinal products for the treatment of CHC should be discontinued. Photosensitivity reactions have been observed with simeprevir. Relevant information is reflected in the SmPC including precautionary measure to reduce the risk of photosensitivity reactions.

The addition of simeprevir to PEG/RBV clearly increases the risk of experiencing an increase in bilirubin levels and this has been reflected in the SmPC.

In 36.7 % of patients (66/180) emerging viral resistance mutations were still detected at the end of study HPC3002 (on-going long term follow-up study). Median follow-up time at the EOS visit from the time of failure was 28.4 weeks. Data on longer term follow up are required to properly assess the frequency of resistant variants declining over time. The Applicant has committed to present the results once available.

Uncertainty in the knowledge about the unfavourable effects

Overall, the incidences of AEs are lower than those previously reported with patients treated with PEG/RBV. In the simeprevir clinical trials, both treatment arms were well tolerated.

The number of patients > 65 years was too small to draw meaningful conclusions. No data is available on patient over the age of 73 years. This information is reflected in the SmPC.

With regard to the safety in special populations, the safety profile of simeprevir appears to be similar in patients with advanced fibrosis compared to patients without advanced fibrosis, with only a higher frequency of increased bilirubin and anaemia reported in the METAVIR F4group. This is based in a very limited number of patients with advance fibrosis or cirrhosis. The applicant has provided the mean simeprevir plasma concentration according to the different stages of fibrosis. It seems likely that the higher TMC435 plasma concentrations contribute, at least in part, to the higher observed deltas for anemia and hyperbilirubinemia in the TMC435-treated cirrhotic population when compared to placebo. This information is reflected in the the SmPC.

Regarding HIV/HCV co-infected patients, the data suggest that the safety profile of TMC435 is similar as in Hepatitis C chronic mono-infected patients. Overall, the safety profile between mono and co-infected patients is mostly overlapping but no new safety signals in HIV/HCV co-infected patients. Since the study is on-going, the Applicant commits to provide the final data.

The available interim data from HPC3011 study suggest that no relevant differences were noted in the safety profile of TMC435 in HCV genotype 4 infected patients when compared to that in HCV genotype 1 infected patients. Since the study is on-going, the Applicant commits to provide the final data.

With regard to use of simprevir in combination with sofosbuvir +/- ribavirin, based on preliminary data of the COSMOS study no relevant safety findings have been identified, apart from those expected with the use of ribavirin. The Applicant has included safety data on the COSMOS study in the SmPC. Since the study is on-going, the Applicant commits to provide the final data.

Benefit-risk balance

Importance of favourable and unfavourable effects

Simeprevir is a selective protease inhibitor belonging to the same pharmacotherapeutic class of boceprevir, and telaprevir. Simeprevir has shown a significant improvement of SVR in naïve (32% of improvement) and relapsers (57% of improvement) infected with genotype 1, compared to placebo, when used as an add-on to PEG/RBV. Results are also relevant for null and partial responders. Appropriate and well substantiated treatment recommendations for simeprevir and background PEG/RBV treatment combination are proposed for the different populations studied.

In HIV/HCV co-infected patients with genotype 1 infection and in patients with HCV genotype 4 infection rates of SVR12 consistent with those seen in mono-infected patients. The CHMP is of the opinion that the available data support the treatment recommendations in combination with PR in these populations. Since these studies are on-going, the Applicant commits to provide the final data.

Data from the study HPC2002 (COSMOS) shows convincing efficacy results in prior non-responders with or without advanced fibrosis, that were either null responders to PEG/RB or treatment naïve. The CHMP is of the opinion that these data support the treatment recommendations for the use of simeprevir + sofosbuvir (+/- ribavirin) in patients infected with HCV genotype 1 and 4 with/without cirrhosis who intolerant to or ineligible for IFN therapy. Since the study is on-going, the Applicant commits to provide the final data.

The presence of the Q80K mutation at baseline has a clear impact on virologic response. Clear recommendation for baseline Q80K polymorphism screening of HCV genotype 1a patients prior to startingtherapy with simeprevir with PEG/RBV has been included in the SmPC. In the presence of the Q80K mutation or when this testing is not available, alternative treatments for patients with HCV genotype 1a should be considered.

From the safety point of simeprevir seems to be well tolerated, with very few discontinuations due to AEs and a low incidence of SAEs.

Benefit-risk balance

The efficacy of simeprevir in the treatment of HCV patients appears well demonstrated in genotype 1 chronically infected patients either naïve or who relapsed to previous treatment with peginterferon and ribavirin and in previous non responder patients (partial and null).

Available efficacy data of simeprevir in other subgroup of patients, such as HIV co-infected patients or HCV G4 infected patients are supportive of the efficacy in these populations.

In addition, the available data support the treatment recommendations for the use of simeprevir + sofosbuvir (+/- ribavirin) in patients infected with HCV genotype 1 and 4 with/without cirrhosis who are intolerant to or ineligible for IFN therapy.

Overall, simeprevir appears well tolerated and with an acceptable and manageable safety profile.

Discussion on the benefit-risk balance

The overall benefit risk balance is considered positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Olysio in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adult patients is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal products subject to restricted medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

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

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that simeprevir is qualified as a new active substance.