17 December 2015
EMA/807529/2015
Procedure Management and Committees Support Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

INCIVO

telaprevir

Procedure no: EMEA/H/C/002313/P46/023

Note

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

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1. Introduction

On October 5th, 2015, the MAH submitted the final report of a paediatric study, VX-11-950-118, for INCIVO, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The study was part of a PIP. The study was terminated early because it was determined that, given the rapid development in the Hepatitis C field of IFN-free regimens, telaprevir with Peg IFN and RBV did not represent a meaningful therapeutic benefit and was unlikely to be used in pediatric patients

2.2. Information on the pharmaceutical formulation used in the studies

The marketed film coated tablet and a new chewable formulation have been used in the clinical study.

2.3. Clinical aspects

2.3.1. Introduction

The pediatric development program of telaprevir included the Phase 2 Study VX11-950-118 (118), designed to assess the appropriate dose of telaprevir and the benefit/risk of INCIVO in the treatment of chronic hepatitis C in children above 3 years of age and adolescents. Prior to the initiation of Study 118, no clinical studies with telaprevir were conducted in the pediatric population. The study was stopped once all ongoing subjects in Part A of the study had reached SVR12, or discontinued the study earlier.

The applicant wants to submit the results available but does not aim for any changes in the SPC.

The MAH submitted final reports for:

- Study VX11-950-118 (Study 118); A Two-Part, Open-Label, Single-Arm Phase 1/2 Study of Safety, Pharmacokinetics, and Efficacy of Telaprevir in Combination With Peginterferon alfa-2b and Ribavirin in Pediatric Subjects Aged 3 to 17 Infected With Genotype 1 Hepatitis C Virus

- Study VX11-950-022 (Study 22); A Phase 1, Randomized, Open-label, Single-Dose, Crossover, Relative Bioavailability, and Food-Effect Study of a Pediatric Chewable Tablet Formulation Relative to a 375-mg Core Tablet Formulation of Telaprevir in Healthy Adult Subjects

2.3.2. Clinical studies

Study 118

Description

Methods

Objectives

Part A

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Primary Objectives:

- To evaluate the short-term safety of telaprevir in combination with Peg-IFN and RBV (Peg-IFN/RBV) in treatment-naïve pediatric subjects without cirrhosis
- To evaluate the PK and determine the appropriate dose of telaprevir in combination with Peg-IFN/RBV in treatment-naïve pediatric subjects without cirrhosis

Secondary Objective:

- To evaluate the efficacy of telaprevir in combination with Peg-IFN/RBV in treatment-naïve pediatric subjects without cirrhosis

Part B

Primary Objective:

- To evaluate the safety of telaprevir in combination with Peg-IFN/RBV in treatment-naïve and peginterferon/RBV treatment-experienced pediatric subjects with or without cirrhosis

Secondary Objectives:

- To evaluate the efficacy of telaprevir in combination with Peg-IFN/RBV in treatment-naïve and peginterferon/RBV treatment-experienced pediatric subjects with or without cirrhosis
- To evaluate the PK of telaprevir in combination with Peg-IFN/RBV in treatment-naïve and peginterferon/RBV treatment-experienced pediatric subjects with or without cirrhosis

Study design

The study was designed as an open-label, single arm, 2-part (Part A and Part B) study. The study was to include at least 120 pediatric subjects (at least 30 subjects without cirrhosis in Part A and at least 90 subjects with or without cirrhosis in Part B), balanced by age groups, and including at least 25 subjects who had prior treatment with Peg-IFN/RBV. The study was to be conducted in 2 parts (Part A and Part B). In both parts, subjects were to be enrolled into 3 age-based cohorts (13-17 years; 7-12 years; and 3-6 years).

Treatments

All subjects were to receive telaprevir in combination with Peg IFN/RBV for 12 weeks followed by Peg IFN/RBV for an additional 12 or 36 weeks, depending on the subject's prior treatment status, liver disease status, and individual on-treatment virologic response in the study. Treatment-naïve and prior relapse subjects who achieved an extended rapid virologic response (eRVR, defined as undetectable HCV ribonucleic acid (RNA) at both Weeks 4 and 12) and did not have cirrhosis were to receive a total of 24 weeks of treatment. All other subjects were to receive a total of 48 weeks of treatment.

Interim analysis of Day 7 PK data was performed for each cohort to evaluate the need for telaprevir dose adjustment before enrollment of the next younger cohort. The telaprevir dose was to be adjusted if the area under the concentration versus time curve from the time of dosing to 24 hours (AUC0-24h) in less than 2/3 of the subjects was between 57600 ng•h/mL (estimated 25th percentile in adults) and 138000 ng•h/mL (twice the estimated 50th percentile in adults).

Subjects in Cohorts 2 and 3 received a chewable tablet (see study22 below) developed for use in children. For subjects in Cohort 1 (13 to 17 years old), film-coated tablets were used; individual subjects could receive the pediatric chewable tablet if swallowing the film-coated tablet was not feasible. The initial dose of telaprevir was 14 to 18 mg/kg bid (rounded up to the nearest achievable dose using whole tablets; maximum 1125 mg) depending on age group and formulation as follows:

- For Cohort 1, ages 13 through 17 years: 15 mg/kg bid as film-coated tablets or 14 mg/kg bid as chewable tablets
- For Cohort 2, ages 7 through 12 years: 16 mg/kg bid as chewable tablets
- For Cohort 3, ages 3 through 6 years: 18 mg/kg bid as chewable tablets

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For all cohorts, Peg-IFN was administered by subcutaneous injection once weekly at a dose of 60 µg/m2. Ribavirin (200-mg capsules or 40-mg/mL solution) was administered orally at 15 mg/kg/day, divided bid, with a total daily maximum dose of 1200 mg. The cohort of subjects aged 13 to 17 years (Cohort 1) started dosing first.

Outcomes/endpoints

Efficacy Assessments
Planned efficacy endpoints were:

- Proportion of subjects who achieved undetectable HCV RNA 12 weeks after the last planned dose of study drug (SVR12)
- Proportion of subjects who achieved undetectable HCV RNA 24 weeks after the last planned dose of study drug (SVR24)
- Proportion of subjects who achieved undetectable HCV RNA at Week 4, at Week 12, at both Weeks 4 and 12 (eRVR), and at the planned EOT
- Proportion of subjects with on-treatment virologic failure, defined as either meeting a futility rule or completing the assigned treatment duration with detectable HCV RNA at the EOT
- Proportion of subjects with virologic relapse, defined as having undetectable HCV RNA at planned EOT followed by detectable HCV RNA after planned EOT

Safety Assessments
Safety was assessed by AEs and serious adverse events (SAEs), clinical laboratory assessments, ECGs, vital signs, physical examinations, and study drug discontinuations or dose modifications.

Results

Recruitment/ Number analysed

Thirteen subjects enrolled in Cohort 1 (13 to 17 years old), 19 subjects in Cohort 2 (7 to 12 years old), and 10 subjects in Cohort 3 (3 to 6 years old), for a total enrollment of 42 subjects in Part A.

Baseline data

Subjects ranged in age from 4 to 13 years at baseline. Twenty-eight subjects (66.7%) were female; 39 subjects (92.9%) were White and 28 subjects were enrolled in the US. All subjects were treatment naïve, and none had previously documented cirrhosis. The majority of subjects (32 subjects, 76.2%) had a baseline HCV RNA viral load of at least 800,000 IU/mL; median log10 viral load was 6.3 IU/mL.

Pharmacokinetics

Serial PK sampling for telaprevir was performed on Day 7 from predose through at least 8 hours after the morning dose. In addition, 2 PK samples, collected at least 1 hour apart within the same dosing interval, were collected Week 2, Week 4, and Week 8. The same format was repeated before enrolling the youngest age group (3 to 6 years; Cohort 3). Due to the premature ending of the study, population PK analysis was not conducted on the sparse samples obtained at Weeks 2, 4, and 8.

A median time of the maximum concentration (tmax) of 4 hours was observed in all 3 cohorts. The mean maximum observed concentration (Cmax) ranged from 4060 ng/mL to 5050 ng/mL and the mean minimum observed concentration (Cmin) ranged from 2190 ng/mL to 2730 ng/mL across cohorts. Relative to the target median adult equivalent AUC0-24h of 69200 h•ng/mL, the estimated AUC0-24h was 15% greater in 13- to 17-year-olds, 21% greater in 7- to 12-year-olds, and 10% greater in 3- to 6-year-olds. No dose adjustment of the telaprevir dose was required in any of the cohorts.

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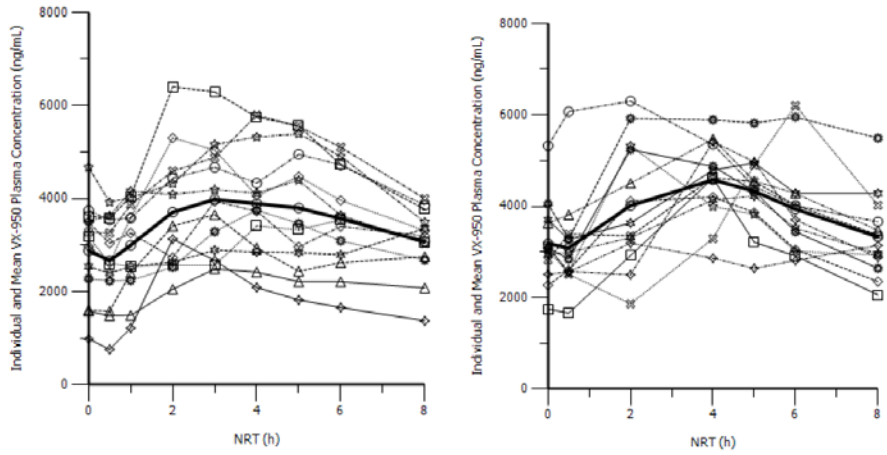
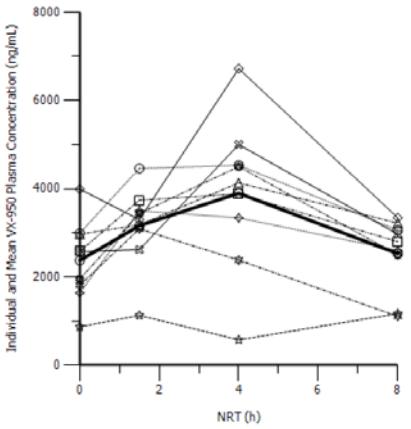
Figure 1 Individual and Mean Telaprevir Plasma Concentrations on Day 7 in Cohort 1 (a) 13-17 Years, (b) 7-12 years and (c)3-6 years

A) **B)**



C)



Pharmacokinetic sampling was only carried out up to 8 hours, therefore, AUC0-12h was calculated by re-specifying predose concentrations as Hour 12 concentrations. To estimate AUC0-24h, AUC0-12h was multiplied by 2. Relative to the target median adult equivalentAUC0-24h of 69200 ng•h/mL, the estimated AUC0-24h was 15% greater in Cohort 1, 21% greater in Cohort 2, and 10% greater in Cohort 3. A quite big part of the subjects had another dose than specified in the protocol. Usually, the actually administered dose was larger than the calculated one. However, there are also patients that received a lower dose than planned.

If a subject did not receive the protocol-specified dose, an adjusted AUC0-24h estimate, AUC0-24h_Adj, was obtained by multiplying the AUC0-24h by an adjustment factor to determine the expected AUC0-24h at the protocol-specified dose. Dose-proportional increases were assumed when calculating the adjustment factor. The PK of telaprevir is not completely linear.

Table 1 Pharmacokinetic Parameters of Telaprevir on Day 7

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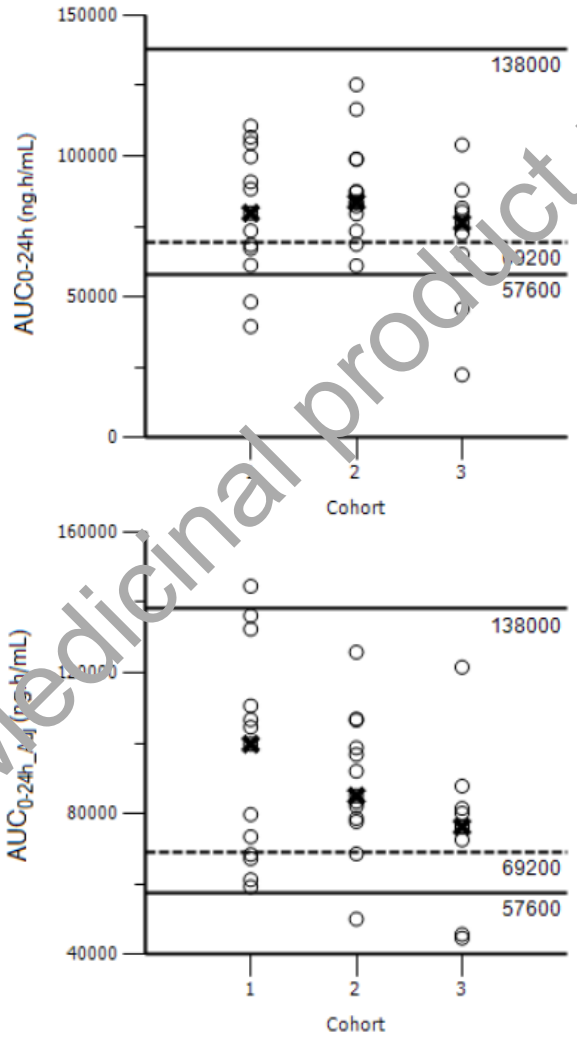
Parameter, units	Statistic	Cohort 1 13-17 Years N = 13	Cohort 2 7-12 Years N = 13	Cohort 3 3-6 Years N = 9
t_{max}, hours	Median (min, max)	4.00 (1.92, 8.00)	4.00 (1.98, 6.02)	4.00 (1.50, 8.00)
C_{max}, ng/mL	Mean (%CV)	4310 (26.9)	5050 (17.5)	4060 (37.0)
C_{min}, ng/mL	Mean (%CV)	2560 (34.1)	2730 (22.0)	2190 (42.5)
$AUC_{0\text{-}tlast}$, ng•h/mL	Mean (%CV)	39900 (28.4)	43300 (21.9)	35300 (34.1)
$AUC_{0\text{-}12h}$, ng•h/mL	Mean (%CV)	39900 (28.4)	44100 (20.5)	35300 (34.1)
	Median (min, max)	39900 (19700, 55300)	41800 (30500, 62700)	38100 (11200, 52000)
$AUC_{0\text{-}24h}$, ng•h/mL	Mean (%CV)	79900 (28.4)	88100 (20.5)	70600 (34.1)
	Median (min, max)	79700 (39500, 111000)	83700 (61100, 125000)	76300 (22300, 104000)
$AUC_{0\text{-}24h\_Adj}$, ng•h/mL	Mean (%CV)	95700 (31.1)	88600 (21.6)	76300 (30.0)
	Median (min, max)	99700 (59200, 145000)	85000 (50100, 126000)	76300 (44600, 122000)

Source: Table 14.4.3
CV: coefficient of variation
Note: Subjects 112001, 112002, 112003 and 602001 had samples collected but not analyzed per Vertex directive due to multiple non-compliance issues.

Figure 2 Individual Distribution of AUC(0-24h) on Day 7 Before (Top) and After (Bottom) Adjustment to Project Exposure at Protocol-Specified Dose



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Assessor´s comment:

The variability on telaprevir exposure is high. However, mean AUC was quite similar between the age ranges. In general Cmax, AUC and Cmin were lower in the age range 3-6 years. The normalization of PK parameters to the protocol specified dose assuming linear PK is not completely supported. However, this will not be further pursued as the applicant has not applied for an SPC change. It is agreed that PK data in does not need to be included the SPC as in this specific case. PK data is usually included in order to help the prescriber being in a situation where the drug has to be used off-label due to lack of suitable treatment options. However, for INCIVO no such need is foreseen. In the future if applicant applied for a variation to perform SPC changed, the SPC wording could be altered showing that PK data in children is sparse but not nonexistent, as implied by the present text in section 4.2: "Paediatric population The safety and efficacy of INCIVO in children aged < 18 years have not yet been established. No data are available."

Efficacy results

Overall, 30 subjects (71.4%) achieved SVR12, including 9 subjects (69.2%) in Cohort 1, 17 subjects (89.5%) in Cohort 2, and 4 subjects (40.0%) in Cohort 3.

- Twelve subjects (28.6%) did not achieve SVR12. Six of these subjects met a futility rule. Of the 6 who did not meet a futility rule, 2 had detectable HCV RNA at 12 weeks after the last planned dose, and 4 had no HCV RNA data at 12 weeks after the last planned dose.
- Twenty-eight subjects (66.7%) achieved eRVR. The proportions of subjects achieving eRVR were similar across age groups.
- Overall, 30 subjects (71.4%) achieved RVR. The proportions of subjects achieving RVR were similar across age groups.
- At baseline, 38 of 41 subjects (93%) had wild-type HCV; 1 subject (2%) had a telaprevir-susceptible variant (I132V); and 2 subjects (5%) had a lower-level telaprevir-resistant variant (R155K).
- The 2 subjects who had lower-level telaprevir-resistant variants at baseline both achieved SVR12. Thus, there was no evidence that the presence of lower-level telaprevir-resistant variants would alter initial antiviral response to telaprevir or preclude successful treatment with telaprevir.
- Six subjects (14.3%) had on-treatment virologic failure due to meeting a futility rule. Four of these 6 subjects had viral sequencing data at the time of virologic failure, and all 4 had higher-level telaprevir-resistant variants (V36M+R155K) observed.
- No virologic relapse was observed during the follow-up period until study termination in the 33 subjects who completed the assigned treatment period and had undetectable HCV RNA at EOT.

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Table 2: Efficacy Results of Study 118

Efficacy Parameter	Cohort 1 13-17 Years N = 13	Cohort 2 7-12 Years N = 19	Cohort 3 3-6 Years N = 10	Total N = 42
Virologic Response				
Subjects with $SVR12_{planned}$, n (%)	9 (69.2)	17 (89.5)	4 (40.0)	30 (71.4)
Subjects with RVR, n (%)	9 (69.2)	14 (73.7)	7 (70.0)	30 (71.4)
Subjects with eRVR, n (%)	8 (61.5)	14 (73.7)	6 (60.0)	28 (66.7)
Subjects without $SVR12_{planned}$, Reasons				
On-Treatment Virologic Failure				
Subjects who met a virologic stopping rule, n (%)	2 (15.4)	1 (5.3)	3 (30.0)	6 (14.3)
Subjects who completed treatment with detectable HCV RNA at planned EOT, n (%)	0	0	0	0
Other Reasons				
Subjects with detectable HCV RNA at 12 weeks after last planned dose[a]	2 (15.4)	0	0	2 (2.4)
Subject with missing HCV RNA at 12 weeks after last planned dose	0	1 (5.3)	3 (30.0)	4 (4.8)

[a] Subjects had missing HCV RNA at EOT.

Assessor's comment

The efficacy of telaprevir in combination with Peg-IFN/RBV in treatment-naïve pediatric subjects without cirrhosis was similar to that in treatment-naïve adults. All subjects with on-treatment virologic failure and available viral sequencing data (n=4) had higher-level telaprevir-resistant variants present.

Safety results

- No subjects died. One subject had an SAE of infection, which occurred more than 6 weeks after the subject finished taking telaprevir.
- Most subjects had at least 1 AE (41 subjects, 97.6%) and at least 1 AE considered related to study drug (40 subjects, 95.2%).
- The most common AEs were headache (30 subjects, 71.4%); pyrexia and vomiting (each in 26 subjects, 61.9%); nausea (17 subjects, 40.5%); and fatigue (15 subjects, 35.7%).
- Most AEs were mild. Three subjects had severe AEs, all of which resolved. The only severe AE that occurred in more than 1 subject was anemia.
- Eleven subjects (26.2%) had AEs in the anemia CMQ. Two subjects (4.8%) had severe AEs in this CMQ. No subjects took erythropoietin or blood transfusions for anemia.
- Seventeen subjects (40.5%) had AEs in the rash CMQ. None of these AEs were considered severe.
- Changes in laboratory parameters were consistent with the known effects of telaprevir/Peg-IFN/RBV treatment.
- There were no clinically significant abnormal ECG findings.

Assessor's comment

No new or unexpected safety signals were observed in this limited sample of children and adolescents.

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Study 22

Methods

Study design

This is a relative bioavailability study and food effect study supporting the use of the chewable tablet in study 118. The study was a randomized, open-label, single-dose, 2-formulation, 6-sequence, 3-period crossover study in 18 healthy adult subjects. A moderate breakfast 533 kcal where of 21g (=35%kcal) from fat was administered 30 minutes before dosing.

Results

Pharmacokinetics

Table 3 Telaprevir Formulations in the Treatment Period

Treatment Designation	Formulation	Total Dose	Dosing Regimen
Treatment R	Reference Formulation 375-mg core tablet	750-mg administered as 2 x 375-mg tablets	fed state (standard normal-caloric meal)
Treatment T	Test Formulation pediatric chewable tablet	750-mg administered as 3 x 250-mg tablets	fed state (standard normal-caloric meal)
Treatment TF	Test Formulation pediatric chewable tablet	750-mg administered as 3 x 250-mg tablets	fasted state

Table 4 Statistical Comparison of Telaprevir Exposures Between the Chewable Formulation Administered in the Fed State (T) and the Core Tablet Formulation Administered in the Fed State (R)

Parameters	Treatment	N	GLS Mean	GLS Mean Ratio[b]	90% CI of GLS Mean Ratio (Lower, Upper)
$AUC_{0-\infty}$ (ng·hr/mL) [a]	R	16	10051.54	-	-
	T	16	11228.99	1.12	0.956, 1.31
AUC_{0-last} (ng·hr/mL)	R	17	9629.72	-	-
	T	16	11037.27	1.15	0.993, 1.32
C_{max} (ng/mL)	R	17	1865.78	-	-
	T	16	2016.28	1.08	0.881, 1.33

[a] N = 16 for Treatment R as values were excluded due to lack of data points in terminal phase for estimation of λ_z. See Section 9.7.1.3.2.

[b] Treatment R (core tablet formulation administered in the fed state) is the reference arm in the denominator

Intake with food with the chewable formulation gave rise to a increase in AUC and Cmax as compared to fasting

Table 5 Statistical Analysis of Food Effect on Telaprevir PK Exposure After Administration of the Pediatric Chewable Formulation in the Fed (T) and Fasted (TF) States

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Parameters	Treatment	N	GLS Mean	GLS Mean Ratio[b]	90% CI of GLS Mean Ratio (Lower, Upper)
$AUC_{0-\infty}$ (ng·hr/mL)[a]	T	16	11228.99	-	-
	TF	13	3996.19	0.356	0.301, 0.421
AUC_{0-last} (ng·hr/mL)	T	16	11037.27	-	-
	TF	15	3746.59	0.339	0.291, 0.396
C_{max} (ng/mL)	T	16	2016.28	-	-
	TF	15	444.86	0.221	0.177, 0.274

Assessor´s comment
The formulations gave raise to similar telaprevir AUC and Cmax under fed conditions. AUC increased by 180%, which seems similar to the food effect observed with the approved tablet formulation if looking at the food interaction information reported in the SPC. INCIVO should be taken with food. The SPC also states: "Taking INCIVO without food or without regard to the dosing interval may result in decreased plasma concentrations of telaprevir which could reduce the therapeutic effect of INCIVO."

2.3.3. Discussion on clinical aspects

The variability on telaprevir exposure is high. Mean AUC was quite similar between the age ranges. However, in general Cmax, AUC and Cmin were lower in the age range 3-6 years. It is agreed that PK data in does not need to be included the SPC as in this specific case, PK data is usually included in order to help the prescriber being in a situation where the drug has to be used off-label due to lack of suitable treatment options. However, for INCIVO no such need is foreseen. Data in adults indicate that the exposure of telaprevir administered as commercial tablet and chewable formulation (used in part of the children) was comparable.

The efficacy of telaprevir in combination with Peg-IFN/RBV in treatment-naïve pediatric subjects without cirrhosis was similar to that in treatment-naïve adults, with an overall SVR12 of 71.4%. Safety outcomes did not reveal any unexpected signals.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

Study 118 was terminated early because it was determined that, given the rapid development in the Hepatitis C field of IFN-free regimens, telaprevir with Peg IFN and RBV did not represent a meaningful therapeutic benefit and was unlikely to be used in pediatric patients.

The exposure of telaprevir was reasonably similar between the studied age ranges albeit somewhat lower in the youngest (3-6 year old) children. No new issues on efficacy or safety with implications for the currently approved indication have arisen from the presented data. No changes of the SPC are needed based on the submitted data. Thus, this report does not have any regulatory consequences.

Recommendation

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled:**

Additional clarifications requested

Not applicable.

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