IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Telaprevir –

Benefit assessment according to § 35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment "Telaprevir – Nutzenbewertung gemäß § 35a SGB V" (Version 1.0; Status: 12.01.2012). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the external expert for his contribution to the dossier assessment. However, he was not involved in the actual preparation of the dossier assessment. Individual sections and conclusions in the dossier assessment therefore do not necessarily reflect his opinion.

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Table of contents

List of tables

List of figures

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AM-NutzenV	Arzneimittel-Nutzenbewertungsverordnung (Regulation for Early Benefit Assessment of New Pharmaceuticals)
cHCV	chronic hepatitis C virus
EQ-5D	EuroQol EQ-5D
eRVR	extended rapid virological response
FSS	Fatigue Severity Scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HIV	human immunodeficiency virus
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PegIFN	pegylated interferon alpha
RBV	ribavirin
RGT	response-guided treatment
RNA	ribonucleic acid
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SSC	special search category
SVR	sustained virological response
TVR	telaprevir
W	(treatment) week

2. Benefit assessment

2.1 Executive summary of the benefit assessment

Background

On 17.10.2011, in accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) wrote to IQWiG to commission the benefit assessment of the drug telaprevir. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company").

Research question

The benefit assessment of telaprevir was carried out on the basis of the approved therapeutic indication for the following research questions:

1) In combination with peginterferon + ribavirin in the response-guided treatment (RGT) regimen versus peginterferon + ribavirin

- In treatment-naïve patients with chronic hepatitis C virus (cHCV) infection (genotype 1) without cirrhosis,
- In previously treated relapsed patients with cHCV infection (genotype 1) without cirrhosis.

2) In combination with peginterferon + ribavirin in a 48-week treatment regimen (48 W) versus peginterferon + ribavirin

- In treatment-naïve patients with cHCV infection (genotype 1) with cirrhosis,
- In previously treated non-responders with cHCV infection (genotype 1) with or without cirrhosis,
- In previously treated relapsed patients with cHCV infection (genotype 1) with cirrhosis.

The population of patients with cHCV infections co-infected with human immunodeficiency virus (HIV) and/or hepatitis B virus (HBV) was excluded in these considerations because from the outset, the company did not include this patient group and made no explicit claim of an added benefit for this population. Instead, in its dossier the company referred to the limited data as well as to ongoing studies in these groups of patients.

Results

A total of 3 relevant studies were available. Two of these studies (ADVANCE, REALIZE) were European approval studies of the company; the G060-A6 study was a Japanese approval study that was not carried out by the company itself. The studies were randomized and active-controlled. The ADVANCE and REALIZE studies were double-blind; the G060-A6 study was open-label. The ADVANCE and the G060-A6 studies compared treatment with telaprevir + peginterferon + ribavirin with treatment with peginterferon + ribavirin in treatment-naïve patients. In the REALIZE study, telaprevir + peginterferon + ribavirin were compared with

peginterferon + ribavirin in previously treated patients (non-responders and relapsed patients). On the basis of these studies (direct comparison) data on 3 of the above-named subindications were available (treatment-naïve without cirrhosis; previously treated – non-responders with or without cirrhosis; previously treated – relapsed patients with cirrhosis). Study data for a further subindication (previously treated – relapsed patients without cirrhosis) were shown only for additional information, because due to the divergent treatment regimen these data could generally not be used for the research question of interest (use of telaprevir in the study population in accordance with the approval status). No adequate data were submitted for the subindication of treatment-naïve patients with cirrhosis or for the patient group with HIV and/or HBV co-infections.

The results for the above-named subindications were as follows:

Treatment-naïve patients without cirrhosis

Two studies (ADVANCE, G060-A6) were available for the assessment of treatment-naïve patients without cirrhosis. The risk of bias in the ADVANCE study was low, both at the study level as well as for most of the individual outcomes. The only exceptions were the outcomes "fatigue" and "health-related quality of life", where the risk of bias was estimated as high. The risk of bias of the G060-A6 study was assessed as high both at the study level and also for the individual outcomes. On the basis of the available evidence (2 studies), in principle proof, e.g. of an added benefit, could be derived from the data - unless outcome-specific aspects weakened the informative value.

Mortality

Due to the low event rate, no statistical analysis of all-cause mortality was conducted. An added benefit of telaprevir for this outcome is not proven.

Morbidity

Sustained virological response as surrogate outcome for hepatocellular carcinoma

The outcome "sustained virological response" (SVR) was considered as adequately valid for use as a surrogate for a patient-relevant outcome (hepatocellular carcinoma [HCC]) that was, however, not recorded in the included studies. Nevertheless, it should be borne in mind that SVR is not formally validated as a surrogate parameter and the assessment of "adequate validity" is based exclusively on data from observational studies, with no consideration of the relationship between effects on the surrogate and effects on the (patient-relevant) outcomes of interest. Account is taken of this increased uncertainty by the rating of the extent of the added benefit (if an added benefit is present, then its extent is rated as "non-quantifiable").

The SVR showed a statistically significant difference in favour of telaprevir. Proof was found that the results differed depending on the baseline viral load (interaction test). In patients with high baseline viral load (HCV-RNA $\geq$ 800,000 IU/ml), the result was statistically significant, whereas in patients with low baseline viral load (HCV-RNA < 800,000 IU/ml) it was not.

Taken as a whole, there is proof of an added benefit of telaprevir for treatment-naïve patients (without cirrhosis) with high baseline viral load. On the other hand, an added benefit of telaprevir for treatment-naïve patients (without cirrhosis) with low baseline viral load is not proven.

Fatigue

The result for fatigue (recorded with the Fatigue Severity Scale [FSS]) was statistically significant in favour of telaprevir. However, due to the size of the effect, a clinically relevant difference could not be assumed. An added benefit of telaprevir for this outcome is not proven.

Health-related quality of life

The result for health-related quality of life (recorded with EQ-5D) was not statistically significant. An added benefit of telaprevir for this outcome is not proven.

Adverse events

At least one adverse event occurred in nearly all patients of both groups. In view of this high event rate, no statistical analysis was carried out for the overall rate of adverse events. The result for serious adverse events, discontinuations due to adverse events and psychiatric events was not statistically significant in each case. Although the result for infections was statistically significantly different, the effect size was too marginal. The infections were almost exclusively non-serious events. Greater/lesser harm from telaprevir is not proven for these 5 outcomes.

For the outcomes “anaemia” and “rash”, the respective meta-analysis of the two studies showed a high degree of heterogeneity. There were statistically significant differences in both studies to the disadvantage of telaprevir for the outcome “anaemia”. For the outcome “rash”, there was a statistically significant difference to the disadvantage of telaprevir in the ADVANCE study, but in contrast there was no statistically significant difference in the G060-A6 study. For both outcomes events were almost exclusively non-serious. Overall, there is proof of greater harm from telaprevir for the outcome “anaemia” and an indication of greater harm from telaprevir for the outcome “rash”.

Treatment-naïve patients with cirrhosis

The company submitted no results for treatment-naïve patients with cirrhosis. Although in the ADVANCE study patients were also investigated who showed cirrhosis at the start of the study, these patients were treated in the study with a treatment regimen that did not correspond to the approval requirements. Furthermore, no separate results were presented for such patients for all relevant outcomes. There was therefore no evaluable data. An added benefit of telaprevir for treatment-naïve patients with cirrhosis is not proven.

Previously treated patients – non-responders with or without cirrhosis

The REALIZE study was available for the assessment of previously treated non-responders with or without cirrhosis. The risk of bias was low both at the study level and for the individual outcomes. On the basis of the available evidence (1 study), in principle (at best) indications, e.g. of an added benefit, could be derived from the data - unless outcome-specific aspects weakened the informative value.

Mortality

Due to the low event rate, no statistical analysis of all-cause mortality was conducted. An added benefit of telaprevir for this outcome is not proven.

Morbidity

Sustained virological response as surrogate outcome for hepatocellular carcinoma

The outcome "SVR" was considered as adequately valid for use as a surrogate for a patient-relevant outcome (HCC) that was, however, not recorded in the included studies. Nevertheless, it should be borne in mind that SVR is not formally validated as a surrogate parameter and the assessment of "adequate validity" is based exclusively on data from observational studies, with no consideration of the relationship between effects on the surrogate and effects on the (patient-relevant) outcomes of interest. Account is taken of this increased uncertainty by the rating of the extent of the added benefit (if an added benefit is present, then its extent is rated as "non-quantifiable").

The SVR showed a statistically significant difference in favour of telaprevir. There was an indication that the results differed depending on cirrhosis status (cirrhosis; no cirrhosis) (interaction test). The result was statistically significant in patients without cirrhosis, but not in those with cirrhosis. The latter led to a weakening of the certainty of results, but not to an overall negation of a possible effect, since the interaction test itself only provided an indication of an effect modification.

Overall there is an indication of an added benefit of telaprevir for previously treated patients (non-responders) without cirrhosis. On the other hand, there is only a hint of an added benefit of telaprevir for previously treated patients (non-responders) with cirrhosis.

Health-related quality of life

The company's dossier contained no evaluable data on health-related quality of life. An added benefit of telaprevir for this outcome is not proven.

Adverse events

The result for the overall rate of serious adverse events, discontinuations due to adverse events, psychiatric events and infections was not statistically significant in each case. Although the result for the overall rate of adverse events was statistically significantly

different, the effect size was too marginal. Greater harm from telaprevir is not proven for these 5 outcomes.

For the outcomes “anaemia” and “rash”, there were statistically significant differences to the disadvantage of telaprevir. For both outcomes these were (almost) exclusively non-serious events. Overall there are indications of greater harm from telaprevir for the outcomes “anaemia” and “rash”.

Previously treated patients – relapsed patients with cirrhosis

The REALIZE study was available for the assessment of previously treated relapsed patients with cirrhosis. The risk of bias was low both at the study level and also for the individual outcomes. On the basis of the available evidence (1 study), in principle (at best) indications, e.g. of an added benefit, could be derived from the data. However uncertainties exist concerning the transferability of the submitted data for the total population of relapsed patients in the approval study, because the proportion of relapsed patients with cirrhosis in this total population was only 20%. The company submitted a corresponding subgroup analysis only for one relevant outcome (SVR). The interaction test between cirrhosis status and treatment effect was not statistically significant for this outcome. The handling of this uncertainty is discussed below in the specific discussion of results.

Mortality

A statistical analysis of all-cause mortality was not performed as no deaths occurred. An added benefit of telaprevir for this outcome is not proven.

Morbidity

Sustained virological response as surrogate outcome for hepatocellular carcinoma

Data on the population of relapsers with cirrhosis were available: the outcome “SVR” was considered as adequately valid for use as a surrogate for a patient-relevant outcome (HCC) that was, however, not recorded in the included studies. Nevertheless, it should be borne in mind that SVR is not formally validated as a surrogate parameter and the assessment of the “adequate validity” is based exclusively on data from observational studies, with no consideration of the relationship between effects on the surrogate parameter and effects on the (patient-relevant) outcomes of interest. Account is taken of this increased uncertainty by the rating of the extent of the added benefit (if an added benefit is present, then its extent is rated as “non-quantifiable”). The SVR showed a statistically significant difference in favour of telaprevir. Overall, there is an indication of an added benefit of telaprevir.

Health-related quality of life

The company’s dossier contained no evaluable data on health-related quality of life. An added benefit of telaprevir for this outcome is not proven.

Adverse events

Only data on the total relapsed population were available for the complex "adverse events". The result for the overall rate of adverse events, discontinuations due to adverse events, rash, psychiatric events and infections was not statistically significant in each case. Although the result for anaemia was statistically significantly different, the effect size was too marginal. Cases of anaemia were almost exclusively non-serious. Greater harm from telaprevir is not proven for these 6 outcomes.

There was a statistically significant difference to the disadvantage of telaprevir for the outcome "serious adverse events". This produces an indication of greater harm from telaprevir for this outcome. Because of the lack of separate data for the population of relapsed patients with cirrhosis, there is admittedly a general uncertainty about the harm from telaprevir in this subindication. However, in the Institute's view, this uncertainty due to missing data should not lead to a non-consideration of the harm factor. The Institute therefore used the above-mentioned results of the total relapsed population when considering harm as a whole.

Previously treated patients – relapsed patients without cirrhosis

The available data of the REALIZE study were only shown as additional information for assessing the previously treated relapsed patients without cirrhosis, because these data originated from a treatment regimen that deviated from the approval requirements. In general, the available data were therefore not suitable to answer the research question of interest (use of telaprevir in this study population in accordance with the approval status).

As also for relapsed patients with cirrhosis, the main findings were that effects in favour of telaprevir regarding the SVR were accompanied by effects to the disadvantage of telaprevir regarding serious adverse events. In summary, an added benefit of telaprevir for relapsed patients without cirrhosis is not proven from the present data. This is essentially explained by the lack of data on the RGT regimen approved for this population. It is pointed out in this regard that approval was given on the basis of the study data submitted by the company for this benefit assessment, but changes were subsequently made in the treatment regimen for this population. Thus there were no data on the current approval status in this population available for the present benefit assessment.

Co-infected (HIV and/or HBV) patients

The company presented no data for the patient group with HIV and/or HBV co-infections included in the above-mentioned subindications. An added benefit of telaprevir is not proven for this patient group and was explicitly not claimed by the company either.

Extent and probability of the added benefit, patient groups with therapeutically important added benefits

Based on the results presented and taking outcome categories and effect sizes into account, the extent and probability of the added benefit of the drug telaprevir is assessed as follows:

For **treatment-naïve patients without cirrhosis,** the results differ depending on the baseline viral load. For **patients with high baseline viral load** there is proof of an added benefit (extent "non-quantifiable") of telaprevir + peginterferon + ribavirin versus peginterferon + ribavirin. For **patients with low baseline viral load** on the other hand, there is an indication of a lesser benefit of telaprevir + peginterferon + ribavirin versus peginterferon + ribavirin.

For **treatment-naïve patients with cirrhosis** an added benefit of telaprevir + peginterferon + ribavirin versus peginterferon + ribavirin is not proven.

For **previously treated non-responders,** the results differ depending on cirrhosis status. For **patients without cirrhosis** there is an indication of an added benefit (extent "non-quantifiable") of telaprevir + peginterferon + ribavirin versus peginterferon + ribavirin. On the other hand, for **patients with cirrhosis** there is a hint of an added benefit (extent "non-quantifiable") of telaprevir + peginterferon + ribavirin versus peginterferon + ribavirin.

For **previously treated relapsed patients with cirrhosis** and **previously treated relapsed patients without cirrhosis**, an added benefit of telaprevir + peginterferon + ribavirin versus peginterferon + ribavirin is not proven.

For the respective patient groups of patients **co-infected with HIV and/or HBV** contained in the above-mentioned subindications, an added benefit of telaprevir + peginterferon + ribavirin versus peginterferon + ribavirin is not proven.

The overall conclusions concerning the extent of added benefit are based on the aggregation of the extents of added benefit derived at the outcome level.

The procedure for deriving the overall conclusion on the added benefit is a proposal from IQWiG. The G-BA decides on the added benefit

2.2 Research question

The company named pegylated interferon alfa (alfa-2a or alfa-2b) in combination with ribavirin as the appropriate comparator therapy (ACT) for the therapeutic indication of genotype 1 cHCV in adult patients with liver disease (including cirrhosis). It therefore adhered to the specification of the G-BA. The benefit assessment of telaprevir was carried out using the ACT specified by the G-BA and named by the company.

With regard to the division of the overall therapeutic indication, genotype 1 cHCV, the assessment applied deviated substantially from the procedure adopted by the company, in particular according to cirrhosis status (see Section 2.7.2.1 of the full dossier assessment). This is because of the approval status of telaprevir. The Institute divided the overall therapeutic indication into 5 subindications in accordance with the approval and assessed them separately (see Table 1).

Table 1: Subindications, treatment regimens and appropriate comparator therapy

	Therapeutic indication of telaprevir (in combination with PegIFN/RBV), division into disease entities/subindications	Approved treatment regimen[a]	Appropriate comparator therapy
1	Genotype 1 chronic HCV infection. treatment-naïve patients without cirrhosis	Response-guided treatment regimen	PegIFN in combination with RBV
2	Genotype 1 chronic HCV infection, treatment-naïve patients with cirrhosis	Treatment regimen with fixed duration of treatment (48 W)	PegIFN in combination with RBV
3	Genotype 1 chronic HCV infection, previously treated patients – non-responders with or without cirrhosis	Treatment regimen with fixed duration of treatment (48 W)	PegIFN in combination with RBV
4	Genotype 1 chronic HCV infection, previously treated patients – relapsed patients with cirrhosis	Treatment regimen with fixed duration of treatment (48 W)	PegIFN in combination with RBV
5	Genotype 1 chronic HCV infection, previously treated patients – relapsed patients without cirrhosis	Response-guided treatment regimen	PegIFN in combination with RBV
a: Information as per approval text according to Summary of Product Characteristics [1]. HCV: hepatitis C virus, PegIFN: pegylated (Peg)interferon alfa, RBV: ribavirin, W: treatment weeks			

Patients who showed co-infections with HIV and/or HBV, are, in both cases, excluded from these assessments. Here, the Institute concurs with the approach adopted by the company, which did not include these patient groups from the outset and made no explicit claim of an added benefit for this population. Instead, in its dossier the company referred to the limited data as well as to ongoing studies in these groups of patients.

The assessment was undertaken with respect to patient-relevant outcomes, with a surrogate outcome used for the assessment of liver-related late complications. Only direct comparative randomized controlled trials were included in the assessment.

Further information about the research question can be found in Module 3, Section 3.1 and Module 4, Section 4.2.1 of the dossier and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information/steps:

- Studies completed by the company up to 01.09.2011 on telaprevir in genotype 1 cHCV infection (study list of the company).
- Results of a search in trial registries for studies on telaprevir in cHCV infections (last search 19.04.2011, searches by the company).

- The Institute's own searches for studies on telaprevir using the inclusion criteria chosen by the company to check the company's search results up to 03.11.2011. This process identified no additional relevant study.
- Checks of the study pool named by the company using the inclusion criteria.

The study pool resulting from these steps differed substantially from that of the company. The study pool presented by the company contains a total of 8 studies, of which 5 did not however meet the inclusion criteria (especially the division of subindication and treatment regimen according to approval status) (see 2.7.2.3.1 of the full dossier assessment). That left 3 studies included in the assessment, but on the basis of these studies, data were not available for all subindications (see Section 2.3.1).

Further information about the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.7.2.1 and 2.7.2.3.1 of the full dossier assessment.

2.3.1 Studies included

With regard to the division of the overall therapeutic indication, in particular according to cirrhosis status, the assessment deviated substantially from the procedure adopted by the company. This is because the approval requirements stipulate different treatment regimens for the affected patient groups (see Section 2.7.2.1 of the full dossier assessment for an overview of the subindications). The company's assessment is based on the results on a division of the overall therapeutic indication cHCV (treatment-naïve, previously treated) according to treatment experience and a further division of the therapeutic indication of the previously treated patients (relapsed, non-responders). However, there was no separate allocation of subindication and approved treatment regimen.

In the available studies, the required treatment regimens were only partly investigated and separate data were not available for all subindications.

The studies listed in the following table were included in the benefit assessment.

Table 2: Study pool

	Study category		
Subindication Study	**Pivotal study for approval of the drug to be assessed (yes/no)**	**Sponsored study[a] (yes/no)**	**Third-party study (yes/no)**
Treatment-naïve patients without cirrhosis			
ADVANCE (VX07-950-108)	yes	yes	no
G060-A6	yes[b]	no	yes
Treatment-naïve patients with cirrhosis			
	No study submitted		
Previously treated patients – non-responders with or without cirrhosis			
REALIZE (VX-950-TiDP24-C216)	yes	yes	no
Previously treated patients – relapsers with cirrhosis			
REALIZE (VX-950-TiDP24-C216)	yes	yes	no
Previously treated patients – relapsers without cirrhosis			
	No study submitted[c]		

a: Study for which the company was sponsor, or in which the company was otherwise financially involved.
b: For the regulatory authorities in Japan.
c: Only a supplementary consideration of the REALIZE (VX-950-TiDP24-C216) study (study not included) took place for this subindication, because the treatment regimen investigated deviated from the approval requirement (see Section 2.7.2.3.1 of the full dossier assessment).

Two studies (ADVANCE und G060-A6) were included for the assessment of telaprevir (TVR) in combination with peginterferon alfa und ribavirin (PegIFN/RBV) in treatment-naïve patients without cirrhosis in direct comparison with PegIFN/RBV. The other 2 studies (PROVE 1 and PROVE 2) submitted by the company were not taken into consideration, because the study populations were treated with a treatment regimen that did not correspond to the approval requirements.

No relevant studies were submitted for the assessment of TVR in combination with PegIFN/RBV in treatment-naïve patients with cirrhosis in direct comparison with PegIFN/RBV.

One study (REALIZE) was included for the assessment of TVR in combination with PegIFN/RBV in previously treated non-responders (with or without cirrhosis) and in previously treated relapsed patients with cirrhosis in direct comparison with PegIFN/RBV. A further study submitted by the company on previously treated patients (PROVE 3) was not taken into account because the study population was treated with a treatment regimen that did not correspond with the approval requirements for the above-named subindications.

The company submitted 2 already mentioned studies (REALIZE and PROVE 3) for the assessment of TVR in combination with PegIFN/RBV in previously treated relapsed patients without cirrhosis in direct comparison with PegIFN/RBV. Neither study is suitable for

inclusion because the respective study population was treated with a treatment regimen that does not correspond to the approval requirements. The REALIZE study - anyway already included – is additionally shown for this population. In general, the available studies were not however suitable to answer the research question of interest (use of telaprevir in this study population in accordance with the approval status).

No studies with HIV- or HBV-co-infected patients were available for any of the named subindications. The company excluded these patient groups from its assessment and explicitly claimed no added benefit for them.

Section 2.6 contains a list of data sources named by the company for the studies included in the assessment.

Further information about the results of information retrieval and the resulting study pool can be found in Module 4, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier and in Section 2.7.2.3 of the full dossier assessment.

2.3.2 Study characteristics

Table 3 and Table 4 describe the studies used for the benefit assessment. Two studies (ADVANCE, REALIZE) were European approval studies of the company; Study G060-A6 was a Japanese approval study that was not carried out by the company itself.

As already described in Section 2.3.1 about the study pool, the company presented data on 3 relevant subindications: treatment-naïve without cirrhosis (ADVANCE, G060-A6), previously treated – non-responders with and without cirrhosis (REALIZE) and previously treated – relapsed patients with cirrhosis (REALIZE). The data used for previously treated – relapsed patients without cirrhosis (REALIZE) were only considered as an addition.

For these subindications the approval status specifies the following treatment regimens for the use of telaprevir:

For **treatment-naïve patients without cirrhosis,** a treatment regimen is specified that was investigated in the ADVANCE study as RGT (only one study arm with telaprevir was relevant and corresponded to the approval requirements). Here patients were divided on the basis of the HCV-RNA serum concentration into early responders (eRVR+) and late responders (eRVR–) and, in the case of an early response, the total treatment period was shortened from 48 to 24 weeks. In the Japanese approval study G060-A6, no RGT regimen was investigated, but a fixed treatment period of 24 weeks. Nevertheless, an adequate proportion of patients were treated in this study in accordance with the approval status, because more than 80% of the study population were early responders, who, according to the approval requirements, are to be treated for a total period of 24 weeks.

For **previously treated non-responders (with and without cirrhosis)** a treatment regimen is specified that was investigated in the approval study REALIZE as treatment with a fixed treatment period of 48 weeks.

For **previously treated relapsed patients with cirrhosis** a treatment regimen is specified that was investigated in the approval study REALIZE as treatment with a fixed treatment period of 48 weeks. However, the proportion of relapsers with cirrhosis is only 20% of the relapser total population. Conclusions for relapsed patients with cirrhosis are therefore to be reached depending on the data availability for this subgroup.

According to the approval status, an RGT regimen is specified for **previously treated relapsed patients without cirrhosis** that was not investigated in the approval study REALIZE additionally shown here. According to the RGT regimen, patients were to be divided on the basis of the HCV-RNA serum concentration into early responders (eRVR+) and late responders (eRVR–) and, in the case of an early response, the total treatment period was to be shortened from 48 to 24 weeks. In the REALIZE study, a treatment regimen with a fixed treatment period of 48 weeks was investigated. The proportion of relapsers without cirrhosis was 80% of the relapser total population and 35% of this total population were late responders. Accordingly, only a maximum of 35% of relapsers without cirrhosis were treated in accordance with the approval status, i.e. with a long treatment period. The available data were therefore not suitable to answer the research question of interest (use of telaprevir in this study population in accordance with the approval status).

Table 3 shows the characteristics of the studies and Table 4 the characteristics of the interventions.

Table 3: Characteristics of the included studies

Study	Study design	Population	Interventions (number of randomized patients)	Duration of study	Location and period of study	Primary outcome; secondary outcomes[a]
Treatment-naïve patients without cirrhosis						
ADVANCE	RCT, double-blind*, parallel	Adults (18–70 years) with cHCV infection (genotype 1), compensated liver disease (including cirrhosis), without previous treatment of the disease with an approved therapy	**Group 1[b]:** T8W/PR (n=364)[d] **Group 2[c]:** T12W/PR24W or T12W/PR48W response-guided treatment (RGT) (n=363)[d] **Group 3:** Pbo/PR48W (n=361)[d]	**Group 2:** Telaprevir 12 weeks with PegIFN/RBV for 24 or 48 weeks; Follow-up observation: 24, 48 or 60 weeks **Group 3:** Placebo 12 weeks with PegIFN/RBV for 48 weeks; Follow-up observation: 24, 48 or 60 weeks	Study centres in 3 geographical regions (i.e. North America, Europe and other). Period 03/2008–05/2010	Primary: proportion of patients with undetectable plasma HCV-RNA 24 weeks after planned end of treatment (SVR) Secondary: all-cause mortality, health-related quality of life, fatigue, adverse events
G060-A6	RCT , open label, parallel	Adults (20–65 years) with cHCV infection (genotype 1), compensated liver disease (without cirrhosis), without previous treatment with IFN or PegIFN	**Group 1:** T12W/PR24W (n=126) **Group 2:** PR48W (n=63)	**Group 1:** Telaprevir 12 weeks with PegIFN/RBV for 24 weeks; Follow-up observation: 24 weeks **Group 2:** PegIFN/RBV for 48 weeks; Follow-up observation: 24 weeks	Japan (7 centres, 41 institutions) Period 11/2008–08/2010	Primary: proportion of patients with undetectable plasma HCV-RNA 24 weeks after actual end of treatment (or discontinuation) (SVR) Secondary: all-cause mortality, adverse events

(continued on next page)

Table 3: Characteristics of the included studies (continued)

Study	Study design	Population	Interventions (number of randomized patients)	Duration of study	Location and period of study	Primary outcome; secondary outcomes[a]
Previously treated patients – non-responder and/or relapsers with/without cirrhosis						
REALIZE	RCT, double-blind, parallel	Adults (18–70 years with cHCV infection (genotype 1), compensated liver disease (including cirrhosis), unsuccessfully previously treated with PegIFN/RBV: relapsers or non-responders	**Group 1[c]:** T12W/PR48W (n=266; Relapsers: n=145; with cirrh.: n=28; without cirrh.: n=117; Non-responders: n=121) **Group 2[b]:** T12W/DSPR48W (n=264) **Group 3:** Pbo/PR48W (n=132; Relapsers: n=68; with cirrh.: n=15; without cirrh.: n=53; Non-responders: n=64)[d]	**Group 1:** PegIFN/RBV for 48 weeks with telaprevir for 12 weeks (then placebo 4 weeks); Follow-up observation: 24 weeks **Group 2:** PegIFN/RBV for 48 weeks with placebo 4 weeks, then telaprevir 12 weeks (delayed start of treatment) **Group 3:** PegIFN/RBV for 48 weeks with placebo for 16 weeks; Follow-up observation: 24 weeks	105 centres in 17 countries: Argentina, Australia, Austria, Belgium, Brazil, Canada, Switzerland, Germany, Spain, France, United Kingdom, Israel, Italy, The Netherlands, Poland, Sweden, USA Period 09/2008–07/2010	Primary: proportion of patients with undetectable plasma HCV-RNA 24 weeks after planned end of treatment (SVR) Secondary: all-cause mortality, health-related quality of life, adverse events

a: Extracted primary outcome criteria contain information with no consideration of relevance for this benefit assessment. Extracted secondary outcome criteria contain exclusively information on the relevant available outcomes for this benefit assessment.
b: Arm not relevant for the assessment and no longer shown in the following tables.
c: Treatment regimen relevant and/or additionally shown for the assessment.
d: FAS analysis: all randomized patients who received at least one dose of a study medication.
*: The masking of the treated persons to the group allocation was lifted for early responders (eRVR+) under T-treatment in Week 24.
cHCV: hepatitis C virus (chronic infection); DS: delayed start of treatment; eRVR+: non-detectable HCV-RNA in Weeks 4 and 12; HCV-RNA: hepatitis C virus ribonucleic acid; IFN: interferon alfa; Pbo: placebo; PegIFN: peginterferon alfa; PR: peginterferon alfa + ribavirin; RBV: ribavirin; RCT: randomized controlled trial; SVR: sustained virological response; T: telaprevir; W: treatment week

Table 4: Characteristics of the interventions

Study	Telaprevir + PegIFN/RBV	PegIFN/RBV
Treatment-naïve patients without cirrhosis		
ADVANCE	Telaprevir 750 mg q8h po in Weeks 1-12 + peginterferon alfa-2a 180 µg/week sc in Weeks 1-24 or Weeks 1-48 + ribavirin (depending on body weight) 1000-1200 mg q12h po in Weeks 1-24 *or* Weeks 1-48 *Specification of the total treatment period:* 24 weeks in patients with eRVR+ 48 weeks in patients with eRVR–	Placebo q8h po in Weeks 1-12 + peginterferon alfa-2a 180 µg/Week sc in Weeks 1-48 + ribavirin (depending on body weight) 1000-1200 mg q12h po in Weeks 1-48
G060-A6	Telaprevir 750 mg q8h po in Weeks 1-12 + peginterferon alfa-2b, 1250-1739 µg (1.5 µg/kg) per week sc in Weeks 1-24 + ribavirin (depending on body weight) 600 to 1000 mg q12h po in Weeks 1-24	Peginterferon alfa-2b 1250-1739 µg (1.5 µg/kg) per week sc in Weeks 1-48 + ribavirin (depending on body weight) 600 to 1000 mg q12h po in Weeks 1-48
Previously treated patients – non-responder and/or relapsers with/without cirrhosis		
REALIZE	Telaprevir 750 mg q8h po in Weeks 1-12 + placebo q8h po in Weeks 13-16 + peginterferon alfa-2a 180 µg/Week sc in Weeks 1-48 + ribavirin (depending on body weight) 1000 or 1200 mg q12h po in Weeks 1-48	Placebo q8h po in Weeks 1-16 + peginterferon alfa-2a 180 µg/Week sc in Weeks 1-48 + ribavirin (depending on body weight) 1000 or 1200 mg q12h po in Weeks 1-48

eRVR+: non-detectability of HCV-RNA in Weeks 4 and 12; eRVR–: detectable HCV-RNA in Weeks 4 or 12; HCV-RNA: hepatitis C virus ribonucleic acid; PegIFN: peginterferon alfa; po: per oral; RBV: ribavirin; sc: subcutaneous

The two European approval studies ADVANCE and REALIZE were randomized, active-controlled and double-blind, and enrolled adult patients with genotype 1 cHCV infection. ADVANCE only considered treatment-naïve patients and REALIZE only patients previously unsuccessfully treated with PegIFN/RBV, i.e. patients who had not responded adequately to a prior treatment (non-responders: categorized into partial and null responders) or who had suffered a relapse (relapsers). The total duration of treatment in the ADVANCE study was 24 or 48 weeks (RGT) and led to an unmasking of the study personnel to the group allocation for early responders (eRVR+) under telaprevir treatment in Week 24. The total treatment period in the REALIZE study was 48 weeks. The group allocation in the two studies was stratified according to the baseline viral load (HCV-RNA < 800,000 IU/mL or ≥ 800,000 IU/mL). In addition, in the ADVANCE study patients were stratified according to genotype 1 variants, whereas stratification in the REALIZE study was according to virological response to a previous PegIFN/RBV treatment (non-responders or relapsed patients). In the REALIZE study, patients within the stratum of non-responders were additionally stratified according to partial or null response. Of the total of 1095 randomized patients in the ADVANCE study, 365 were assigned to the control arm (Pbo/PR48), and 365 patients to the relevant telaprevir-RGT arm. Of the 663 patients randomized for the REALIZE study, 133 were assigned to the

control arm (Pbo/PR48) and 266 patients to the relevant telaprevir arm (fixed treatment period of 48 weeks). For its analysis, the company reported the number of patients who received at least one dose of the study medication, which reduced the number of patients in the ADVANCE study by 4 (n = 361) and in the RGT arm by 2 (n = 363). In the REALIZE study, only the number of patients in the control arm was reduced by 1 (n = 132). The proportion of patients without cirrhosis in the total population was considerably in the majority, with over 90% (ADVANCE) and approx. 75% (REALIZE). The primary and secondary outcomes were similar in the two studies with the focus on the SVR.

The Japanese approval study G060-A6 was randomized, active-controlled and open-label, and enrolled treatment-naïve adult patients with genotype 1 cHCV infection; patients with cirrhosis were excluded. The total treatment period was 24 weeks. The method used in the study for (ostensibly randomized) group allocation of patients remains unclear (see Section 2.7.2.4.2 of the full dossier assessment). Of the total of 189 randomized patients, 63 were assigned to the control arm (PR48) and 126 patients to the telaprevir arm. The primary and secondary outcomes were similar to those of the two European approval studies, with the focus on the SVR.

In all 3 studies, patients were treated with the triple combination TVR + PegIFN/RBV in the first 12 weeks. In the G060-A6 study this was followed by treatment with PegIFN/RBV for a further 12 weeks (total duration of treatment 24 weeks), whereas in the REALIZE study, treatment comprised a further 36 weeks with PegIFN/RBV (total duration of treatment 48 weeks). In the ADVANCE study, patients were divided on the basis of the HCV-RNA serum concentration (at Weeks 4 and 12) into early responders (eRVR+) and late responders (eRVR–) and, depending on this response, were treated with PegIFN/RBV either for a further 12 weeks (early responders: total duration of treatment 24 weeks) or 36 weeks (late responders: total duration of treatment 48 weeks). In the respective control arms of all 3 studies, patients were treated with the combination treatment PegIFN/RBV for 48 weeks. The ADVANCE and REALIZE studies were placebo-controlled for the telaprevir treatment, whereas this was not the case in the open-label G060-A6 study.

Table 5 shows the characteristics of the patients in the studies included.

Table 5: Characteristics of the study populations

Study Group	N[a]	Age in years (mean)	Gender w/m (%)	Ethnicity Caucasians/ other (%)	Cirrhosis/ no cirrhosis (%)	HCV RNA < 800,000/ ≥ 800,000 IU/ml (%)
Treatment-naïve patients without cirrhosis						
ADVANCE[b]						
TVR + PegIFN/RBV (RGT)	363	47	41 / 59	90 / 10	6 / 94	23 / 77
PegIFN/RBV	361	47	42 / 58	88 / 12	6 / 94	23 / 77
G060-A6						
TVR + PegIFN/RBV	126	51	48 / 52	0 / 100[c]	0 / 100	14[d] / 86[d]
PegIFN/RBV	63	52	48 / 52	0 / 100[c]	0 / 100	14[d] / 86[d]
Previously treated patients – total population						
REALIZE						
TVR + PegIFN/RBV	266	51	31 / 69	92 / 8	27 / 73	11 / 89
PegIFN/RBV	132	50	33 / 67	89 / 11	23 / 77	14 / 86
Previously treated patients – non-responders						
REALIZE						
TVR + PegIFN/RBV	121	50	30 / 70	94 / 6	36 / 64	6 / 94
PegIFN/RBV	64	49	34 / 66	88 / 12	23 / 77	9 / 91
Previously treated patients – relapsers with/without cirrhosis[e]						
REALIZE						
TVR + PegIFN/RBV	145	51	32 / 68	91 / 9	19 / 81	14 / 86
PegIFN/RBV	68	51	32 / 68	90 / 10	22 / 78	18 / 82

a: FAS analysis: all randomized patients, who received at least one dose of the study medication.

b: Data of the total study population are used for conclusions for treatment-naïve patients without cirrhosis.

c: Japanese patient population.

d: The subgroup with a baseline viral load < 800,000 IU/ml comprised the subgroup defined in the study with a baseline viral load < 1,000,000 IU/ml and the subgroup with a baseline viral load ≥ 800,000 IU/ml comprised the subgroups defined there with a baseline viral load ≥ 1,000,000 IU/ml.

e: No separate data available for relapsed patients with/without cirrhosis.

FAS: Full Analysis Set; HCV: hepatitis C virus; IU: international units; PegIFN: peginterferon alfa; RBV: ribavirin; RNA: ribonucleic acid; TVR: telaprevir

Within the total populations of the individual studies, there were no substantial divergences between the treatment groups regarding age or gender. The patients were on average 47 to 52 years old. In the European approval studies ADVANCE and REALIZE, the clear majority of patients were of Caucasian origin, whilst the study population of the Japanese approval study G060-A6 was exclusively Japanese. The majority of patients investigated in the studies showed no cirrhosis; fewer patients in ADVANCE had cirrhosis (approx. 6%) than in REALIZE (approx. 27%). No patients with cirrhosis were enrolled in the G060-A6 study. Among the treatment-naïve population there was a higher proportion of patients with low baseline viral load (ADVANCE) compared to the previously treated population (REALIZE).

The classification high/low baseline viral load was defined slightly differently in the G060-A6 study than in the two other studies.

The risk of bias at the study level is shown in Table 6.

Table 6: Risk of bias at the study level

Study	Random sequence generation	Allocation concealment	Blinding		Selective reporting	Other sources of bias	Risk of bias at the study level
			Participants	Personnel			
Treatment-naïve patients without cirrhosis							
ADVANCE	yes	yes	yes	yes*	no	no	low
G060-A6	unclear	unclear	no	no	no	no	high
Previously treated patients – non-responders or relapsers with/without cirrhosis							
REALIZE	yes	yes	yes	yes	no	no	low
*: The masking of the group allocation was lifted for early responders under telaprevir treatment in Week 24.							

The risk of bias at the study level for the ADVANCE and REALIZE studies was rated as low. This concurs with the company's assessment. The risk of bias at the study level for the open-label G060-A6 study was rated as high, which deviated from the company's assessment.

Further information about the study design, study populations and risk of bias at the study level for the direct comparisons can be found in Module 4 Sections 4.3.1.2.1 and 4.3.1.2.2 of the dossier and in Sections 2.7.2.2, 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.

2.4 Results concerning added benefit

The following patient-relevant outcomes were included in this assessment (for more detailed reasoning, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality (all-cause mortality)
- Fatigue
- Health-related quality of life
- Adverse events
  - Overall rate of adverse events (AEs)
  - Overall rate of serious adverse events (SAEs)
  - Overall rate of adverse events that led to treatment discontinuation (discontinuations due to AEs)
  - Specific adverse events, anaemia

- Specific adverse events, rash
- Specific adverse events, psychiatric events
- Specific adverse events, infections

In addition, the following outcome was taken into consideration as a surrogate parameter (for detailed description see Section 2.4.1 as well as Section 2.7.2.9.4 of the full dossier assessment):

- Sustained virological response (SVR)

The company also included the outcomes "fatigue" (named by the company as defining quality of life), "health-related quality of life", "AEs", "SAEs", "discontinuations due to AEs", "anaemia", "rash" and "SVR" in the assessment. The remaining outcomes were additionally included by the Institute to enable a comprehensive assessment of the added benefit (see here also Section 2.7.2.4.3 of the full dossier assessment).

Table 7 shows for which outcomes data were available in the studies included. Table 8 describes the risk of bias for these outcomes.

Table 7: Matrix of outcomes, data availability

Outcome / Study	Overall mortality	SVR	Fatigue	Health-related quality of life	Adverse events	Serious adverse events	Discontinuation due to adverse events	Specific adverse events: anaemia	Specific adverse events: rash	Specific adverse events: psychiatric events	Specific adverse events: infections
Treatment-naïve patients without cirrhosis											
ADVANCE	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
G060-A6	yes	yes	no	no	yes	yes	yes	yes[a]	yes	yes	yes
Previously treated patients – non-responders or relapsers with/without cirrhosis											
REALIZE	yes	yes	no[b]	no[b]	yes	yes	yes	yes	yes	yes	yes

a: Outcome with limitations regarding the definition, but this is used in the dossier assessment.

b: Despite data being available in principle, the outcome could not be used for the dossier assessment, because the proportion of evaluated patients was <70%.

SVR: sustained virological response

Table 8: Risk of bias at the study and outcome levels

Outcome / Study	Study level	All-cause mortality	SVR	Fatigue	Health-related quality of life	Adverse events	Serious adverse events	Discontinuation due to adverse events	Specific adverse events: anaemia	Specific adverse events: rash	Specific adverse events: psychiatric events[a]	Specific adverse events: infections[a]
Treatment-naïve patients without cirrhosis												
ADVANCE	low	low	low	high[d]	high[d]	low	low	low	low	low	low	low
G060-A6	high	high[c]	high[c]	-[b]	-[b]	high[c]	high[c]	high[c]	high[c]	high[c]	high[c]	high[c]
Previously treated patients – non-responders or relapsers with/without cirrhosis												
REALIZE	low	low	low	-[b]	-[b]	low	low	low	low	low	low	low

a: The assessment of the risk of bias of the outcome was undertaken solely by the Institute, because the outcome was considered in addition to those included by the company.

b: Outcome was not recorded/(adequately) reported; for reasons see Table 7 and Section 2.7.2.4.2 of the full dossier assessment.

c: Assessment of the risk of bias at the study level: high.

d: Patients not taken into account in the assessment (proportion not considered) >10%.

SVR: sustained virological response

Apart from the partly unused data on fatigue and health-related quality of life, an overall good availability of outcomes can be assumed for the direct comparison of TVR + PegIFN/RBV and PegIFN/RBV in treatment-naïve patients without cirrhosis, previously treated non-responders, relapsers with cirrhosis and relapsers without cirrhosis (see Table 7).

The choice of outcome for the present assessment differs substantially from the company's procedure, which used further outcomes for the assessment (e.g. relapse rate, early virological response [RVR, eRVR], further AEs, see Section 2.7.2.4.3 of the full dossier assessment). Moreover, the Institute included additional outcomes for the present assessment.

There was a high risk of bias at the study level in the G060-A6 study because of the lack of blinding together with the unclear masking of the group allocation. Therefore a relevant bias for the outcomes recorded in the study cannot be ruled out. Hence, a high risk of bias was assumed for all the outcomes. This deviates from the company's assessment (low risk of bias at the study and outcome level). In the ADVANCE study, more than 10% of the randomized patients were missing in the analysis for the outcomes "fatigue" and "health-related quality of life", which is why the risk of bias for these outcomes in rated as high. This again deviates from the company's assessment. For the REALIZE study more than 30% of the randomized patients were missing in the analysis of the outcomes "fatigue" and "health-related quality of life". The Institute rated the data as not valid and they were not included in the benefit assessment. This deviates from the assessment of the company, which used these data for the assessment. There was a low risk of bias for all of the further outcomes with evaluable data included by the company. This concurs with the company's assessment. The additional outcomes of the ADVANCE and REALIZE studies included for this assessment by the Institute were likewise rated as having a low risk of bias; for the additional outcomes of the G060-A6 study the risk of bias was rated as high.

Further information about the choice of outcome, risk of bias at the outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier and in Sections 2.7.2.2, 2.7.2.4.2, 2.7.2.4.3, 2.7.2.8 and 2.7.9.4 of the full dossier assessment.

2.4.1 Results on treatment-naïve patients without cirrhosis

Table 9 summarizes the results on the comparison of telaprevir (TVR) + PegIFN/RBV (RGT) and PegIFN/RBV in treatment-naïve patients without cirrhosis.

The data correspond to those submitted by the company on the outcomes to be considered and the outcomes added by the Institute. The numbers from the dossier were also supplemented by the Institute's calculations on relative risks, where these were not given in the dossier (shown with footnotes).

Table 9: Results from studies on the comparison TVR + PegIFN/RBV (RGT) vs. PegIFN/RBV for treatment-naïve patients without cirrhosis

Outcome[a] Study	**Telaprevir + PegIFN/RBV (RGT)**		**PegIFN/RBV**		**Telaprevir + PegIFN/RBV (RGT) vs. PegIFN/RBV**	
	Total N	**Events N (%)**	**Total N**	**Events N (%)**	**RR [95% CI][b]**	**p-value**
Overall mortality						
ADVANCE	363	2 (< 1)	361	1 (< 1)	not applicable[c]	
G060-A6	126	0 (0)	63	0 (0)	not applicable[c]	
Meta-analysis					not applicable[c]	
Sustained virological response (SVR)[d]						
ADVANCE	363	271 (75)	361	158 (44)	not applicable*	
G060-A6	126	92 (73)	63	31 (49)	not applicable*	
Meta-analysis					not applicable*	
	Total N	**Value in Week 72 (M ± SD)**	**Total N**	**Value in Week 72 (M ± SD)**	**Mean difference [95% CI]**	**p-value**
Fatigue (FSS)[g]						
ADVANCE[h]	289	2.6 (1.67)	296	2.9 (1.77)	-0.30 [-0.58; -0.02] -0.17 [-0.34; -0.01][i]	0.035[j]
Health-related quality of life (EQ-5D)[k]						
ADVANCE[h]	287	0.90 (0.17)	296	0.87 (0.21)	0.03 [0.00; 0.06]	0.059[j]
	Total N	**Events N (%)**	**Total N**	**Events N (%)**	**RR [95% CI][b]**	**p-value**
Adverse events (AEs)						
ADVANCE	363	361 (99)	361	354 (98)	not applicable[l]	
G060-A6	126	126 (100)	63	63 (100)	not applicable[l]	
Meta-analysis					not applicable[l]	
Serious adverse events (SAEs)						
ADVANCE	363	33 (9)	361	24 (7)	1.37 [0.83; 2.27]	0.233[e]
G060-A6	126	15 (12)	63	6 (10)	1.25 [0.51; 3.07]	0.728[e]
Meta-analysis					1.34 [0.86; 2.08]	0.195[f]
Treatment discontinuations due to adverse events						
ADVANCE	363	36 (10)	361	26 (7)	1.38 [0.85; 2.23]	0.214[e]
G060-A6	126	21 (17)	63	14 (22)	0.75 [0.41; 1.37]	0.394[e]
Meta-analysis	Heterogeneity: Q = 2.39, df = 1. p = 0.122, I^2 = 58.1%					

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Table 9: Results from studies on the comparison TVR + PegIFN/RBV (RGT) vs. PegIFN/RBV for treatment-naïve patients without cirrhosis (continued)

Outcome[a] Study	Telaprevir + PegIFN/RBV (RGT)		PegIFN/RBV		Telaprevir + PegIFN/RBV (RGT) vs. PegIFN/RBV	
	Total N	Events N (%)	Total N	Events N (%)	RR [95% CI][b]	p-value
Specific adverse events: anaemia						
ADVANCE	363	148 (41)	361	89 (25)	1.65 [1.33; 2.06]	< 0.001[e]
G060-A6[m]	126	115 (91)	63	46 (73)	1.25 [1.07; 1.47]	< 0.001[e]
Meta-analysis	Heterogeneity: Q = 5.51. df = 1. p = 0.019, I^2 = 81.9%					
of which SAEs						
ADVANCE	363	8 (2)	361	4 (1)	not applicable[c]	
G060-A6[m]	126	2 (2)	63	0 (0)	not applicable[c]	
Meta-analysis					not applicable[c]	
Specific adverse events: rash						
ADVANCE	363	221 (61)	361	172 (48)	1.28 [1.12; 1.46]	< 0.001[e]
G060-A6	126	113 (90)	63	53 (84)	1.07 [0.94; 1.20]	0.308[e]
Meta-analysis	Heterogeneity: Q = 4.95, df = 1. p = 0.026, I^2 = 79.8%					
of which SAEs						
ADVANCE	363	3 (< 1)	361	0 (0)	not applicable[c]	
G060-A6	126	3 (2)	63	0 (0)	not applicable[c]	
Meta-analysis					not applicable[c]	
Specific adverse events: psychiatric events						
ADVANCE	363	207 (57)	361	193 (54)	1.07 [0.94; 1.22]	0.373[e]
G060-A6	126	45 (36)	63	22 (35)	1.02 [0.68; 1.54]	0.953[e]
Meta-analysis					1.06 [0.94; 1.20]	0.342[f]
of which SAEs						
ADVANCE	363	2 (< 1)	361	3 (< 1)	not applicable[c]	
G060-A6	126	1 (< 1)	63	1 (2)	not applicable[c]	
Meta-analysis					not applicable[c]	
Specific adverse events: infections						
ADVANCE	363	103 (28)	361	136 (38)	0.75 [0.61; 0.93]	0.008[e]
G060-A6	126	50 (40)	63	28 (44)	0.89 [0.63; 1.27]	0.608[e]
Meta-analysis					0.79 [0.66; 0.94]	0.010[f]
of which SAEs						
ADVANCE	363	11 (3)	361	5 (1)	2.19 [0.77; 6.23]	0.144[e]
G060-A6	126	3 (2)	63	0 (0)	3.53 [0.19; 67.26]	0.238[e]
Meta-analysis					2.31 [0.86; 6.19]	0.097[f]

(continued on next page)

Table 9: Results from studies on the comparison TVR + PegIFN/RBV (RGT) vs. PegIFN/RBV for treatment-naïve patients without cirrhosis (continued)

Data of the ADVANCE study correspond to the total population, but are used for the population without cirrhosis.

a: FAS analysis for the ADVANCE study: all randomized patients, who received at least one dose of a study medication. Does not apply for outcomes "quality of life" (EQ-5D) and "fatigue" (FSS).

b: Institute's calculation, RR TVR + PegIFN/RBV vs. PegIFN/RBV.

c: Too small a proportion of patients with event (≤ 2%).

d: Roche TaqMan HCV-RNA Assay with a lower limit of quantification of 25 IU/ml and a limit of detection of 10–15 IU/ml.

e: Institute's calculation, unconditional exact test (CSZ method according to [2]).

f: Institute's calculation , meta-analysis, model with random effects (according to DerSimonian and Laird [3])

g: A higher value shows greater impairments due to fatigue.

h: No FAS analysis, but "Observed Cases" analysis.

i: SMD in the form of Hedges' g to assess the relevance of the statistically significant group difference. If the 95% confidence interval for the SMD was not fully below the irrelevance threshold of -0.2, the effect was not regarded as relevant.

j: Institute's calculation, t-test.

k: EQ-5D Valuation Index: a higher value shows a better health status.

l: Too high a proportion of patients with event (≥98%).

m: Outcome with limitations in terms of definition: anaemia according to MedDRA/J PT ("Anaemia").

*: No presentation of the overall effect because of proof of a relevant effect modification by the characteristic "baseline viral load" (see 2.4.1.1).

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; EQ-5D: EuroQol EQ-5D; FAS: Full Analysis Set; FSS: Fatigue Severity Scale; HCV-RNA: hepatitis C virus ribonucleic acid; IU: international units; J: Japan; M: mean; MedDRA: Medical Dictionary for Regulatory Activities; PegIFN: peginterferon alfa; PT: Preferred Terms; RBV: ribavirin; RGT: response-guided treatment regimen; RR: relative risk; SD: standard deviation; SMD: standardized mean difference; SAE: serious adverse event; SVR: sustained virological response 24 weeks after end of treatment; TVR: telaprevir

The submitted data based on the total population of the ADVANCE study were used to assess the treatment-naïve patients without cirrhosis, because the proportion of patients without cirrhosis is over 80% and the risk of a potential restriction of transferability is estimated as acceptable [4]. In the G060-A6 study, only patients without cirrhosis were enrolled. For assessment of the risk of bias at the study and outcome level, see Section 2.7.2.4.2 of the full dossier assessment.

In principle, it is possible to derive proof, e.g. of an added benefit, from the meta-analysis of the 2 submitted studies ADVANCE and G060-A6. This assessment corresponds to that of the company. A possible weakening of proof through outcome-specific aspects is considered separately in the subsequent presentation of the results for the individual outcomes below.

Mortality

The proportion of patients who died under treatment in the two studies did not differ - or not substantially - between TVR + PegIFN/RBV and PegIFN/RBV. However, the very low event rate has to be borne in mind when interpreting this result (no deaths in G060-A6). Therefore

no statistical analyses of these event rates were performed. An added benefit of telaprevir for this outcome is not proven.

Morbidity

Sustained virological response (SVR)

The outcome SVR is not a patient-relevant outcome per se and there are no studies to validate SVR as surrogate outcome. However, results could be used from observational studies that compared the occurrence of late complications in patients who had/had not achieved an SVR (Section 2.7.2.9.4 of the full dossier assessment). These results showed firstly that the risk of occurrence of HCC in patients with SVR was similarly low as in a comparable population without HCV infection. Secondly, the risks for patients with SVR are considerably less compared with patients without SVR and the underlying biological model appeared plausible. Therefore the SVR constitutes an adequately valid surrogate outcome for the occurrence of HCC. Hence, the consideration of SVR in the benefit assessment and the derivation of conclusions regarding added benefit are, in principle, possible.

A higher proportion of the treatment-naïve patients without cirrhosis treated with TVR + PegIFN/RBV achieved an SVR than those treated with PegIFN/RBV. However, during the assessment of subgroup characteristics, there was proof of an effect modification for the characteristic “baseline viral load”. Conclusions about added benefit in terms of this outcome are therefore not possible for the total patient population and must be made on the basis of the subgroups. These subgroup analyses with the related evidence can be found at the end of this section.

Fatigue (FSS)

This outcome was only investigated in the ADVANCE study. The mean total fatigue score after treatment (at Week 72) was lower in the patients treated with TVR + PegIFN/RBV than in those treated with PegIFN/RBV. There was a statistically significant difference in favour of telaprevir.

When considering this outcome, which was defined using a (complex) scale, besides evaluating statistical significance, it is necessary to evaluate the relevance of the effect. Since there are neither scale-specifically validated nor established relevance criteria for group differences, nor responder analyses based on validated and/or established response thresholds, a general statistical parameter had to be used to assess the relevance. In this case, the standardized mean difference (SMD in the form of Hedges’ g) was considered. In accordance with the methods of the Institute [4], an irrelevance threshold of -0.2 was used. If the confidence interval corresponding to the observed effect was fully below this irrelevance threshold, it was assumed that the effect did not lie in a definitely irrelevant region. This was to ensure that the effect can be regarded at least as “small”, with adequate reliability.

Neither the overall estimator nor the upper limit of the confidence interval was below the irrelevance threshold of −0.2, so it cannot be assumed with adequate certainty that a clinically relevant effect is present and an added benefit of telaprevir for this outcome is not proven.

The assessment of this outcome deviates from that of the company (for the Institute's view, which led to the present interpretation of data, see Section 2.7.2.4.3 of the full dossier assessment).

Health-related quality of life (EQ-5D)

This outcome was only investigated in the ADVANCE study. The mean EQ-5D Valuation Indices of the patients in both treatment groups (TVR + PegIFN/RBV and PegIFN/RBV) of the ADVANCE study after treatment (at Week 72) did not differ substantially. The result was not statistically significant and hence an added benefit of telaprevir for this outcome is not proven.

Adverse events

Adverse events (overall)

The proportions of patients with adverse events (overall rate) in the two studies did not differ substantially between TVR + PegIFN/RBV and PegIFN/RBV. However, the very high event rate in each of the two treatment groups needs to be considered when interpreting this result. Therefore no statistical analysis of this event rate was undertaken. Greater harm from telaprevir for this outcome is not proven. The company derived greater harm from telaprevir (not explicitly at the outcome level, but overall for adverse events).

Serious adverse events

The proportion of patients with serious adverse events in the two studies did not differ substantially between TVR + PegIFN/RBV and PegIFN/RBV. The result of the meta-analysis was not statistically significant and there was no heterogeneity between the results of the individual studies (Figure 1). Greater harm from telaprevir for this outcome is not proven. The company derived greater harm from telaprevir (not explicitly at the outcome level, but overall for adverse events).

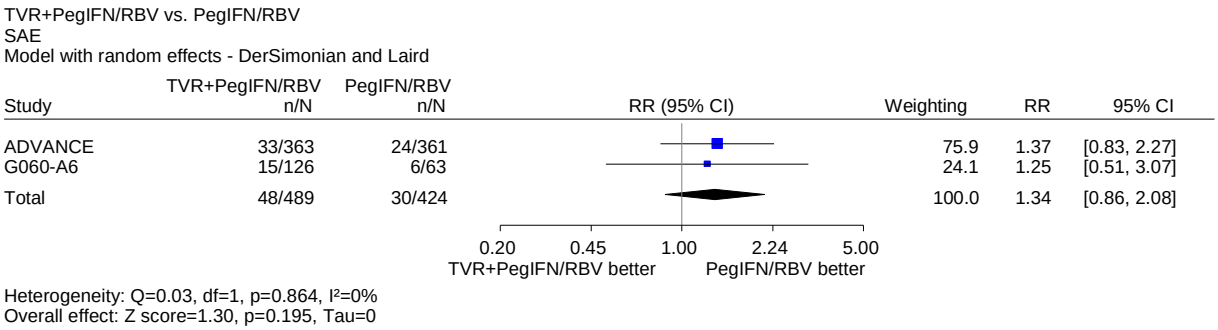

Figure 1: Meta-analysis, TVR + PegIFN/RBV (RGT) vs. PegIFN/RBV, treatment-naïve patients without cirrhosis, serious adverse events

CI: confidence interval; PegIFN: peginterferon alfa; RBV: ribavirin; RGT: response-guided treatment regimen; RR: relative risk; SAE: serious adverse events; TVR: telaprevir

Treatment discontinuations due to adverse events

The proportions of patients with treatment discontinuations due to adverse events did not differ substantially between TVR + PegIFN/RBV and PegIFN/RBV in the two studies. The meta-analysis showed a high heterogeneity ($p < 0.2$), so no overall effect estimator was calculated (Figure 2). A further investigation of heterogeneity was not necessary in this case, because the results of the two individual studies were not statistically significant. Greater harm from telaprevir for this outcome is thus not proven. The company derived greater harm from telaprevir (not explicitly at the outcome level, but overall for adverse events).

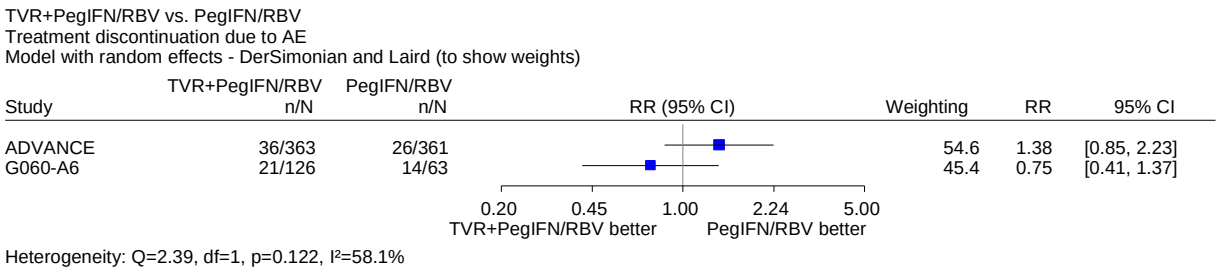

Figure 2: Meta-analysis, TVR + PegIFN/RBV (RGT) vs. PegIFN/RBV, treatment-naïve patients without cirrhosis, treatment discontinuations due to adverse events

AE: adverse events; CI: confidence interval; PegIFN: peginterferon alfa; RBV: ribavirin; RGT: response-guided treatment regimen; RR: relative risk; TVR: telaprevir

Specific adverse events: anaemia

Anaemia occurred more often in treatment-naïve patients without cirrhosis treated with TVR + PegIFN/RBV than in patients given PegIFN/RBV. The meta-analysis showed a high

heterogeneity ($p < 0.2$) and no overall effect estimator was calculated (Figure 3). On the basis of the individual study results there were, however, consistent statistically significant differences to the disadvantage of telaprevir. This produces proof of greater harm from telaprevir. Because of the heterogeneity existing between the individual study results, the extent of the added benefit is determined based on the study with the higher certainty of results (ADVANCE, see Section 2.5.1).

The cases of anaemia were almost exclusively non-serious. No statistical analysis of the low event rates for serious anaemia was undertaken.

The assessment of this outcome corresponds with that of the company, which derived greater harm from telaprevir (not explicitly at the outcome level, but for adverse events as a whole). However the procedure of the company deviated in that the data of the ADVANCE study reported by the company in Modules 1-4 of the dossier referred to the MedDRA Preferred Term "Anaemia", whereas the assessments in this report related to data on the SSC (special search category) "Anaemia". The proportions of patients with events were generally higher in the latter analysis in both treatment groups.

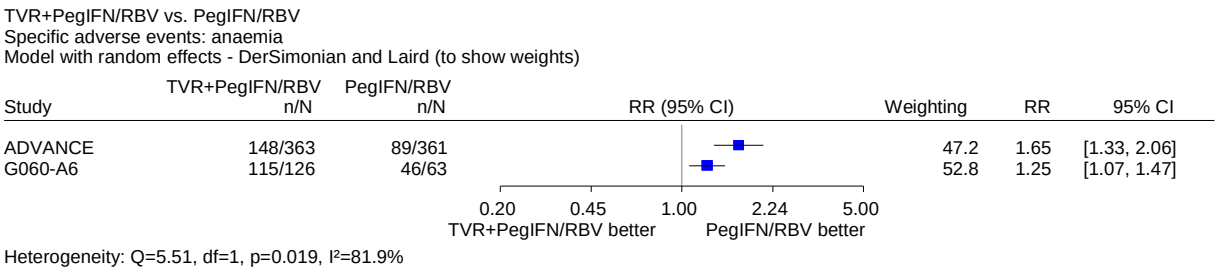

Figure 3: Meta-analysis, TVR + PegIFN/RBV (RGT) vs. PegIFN/RBV, treatment-naïve patients without cirrhosis, specific adverse events: anaemia

CI: confidence interval; PegIFN: peginterferon alfa; RBV: ribavirin; RGT: response-guided treatment regimen; RR: relative risk; TVR: telaprevir

Specific adverse events: rash

Rashes occurred more frequently in the treatment-naïve patients without cirrhosis treated with TVR + PegIFN/RBV than in the patients who received PegIFN/RBV. The meta-analysis showed a high heterogeneity ($p < 0.2$) and no overall effect estimator was calculated (Figure 4). Based on the individual study results, only the ADVANCE study showed a statistically significant difference to the disadvantage of telaprevir. Since this has a higher certainty of results than the G060-A6 study, the result was assessed as an indication of greater harm from telaprevir for this outcome and the extent of added benefit was determined on the basis of this study (see Section 2.5.1).

The rashes that occurred were almost exclusively non-serious. No statistical analysis of the low event rates for serious rashes was carried out.

The assessment of this outcome corresponded to that of the company, which derived greater harm from telaprevir (not explicitly at the outcome level, but for adverse events as a whole). However the procedure of the company deviated in that the data of the ADVANCE and G060-A6 studies reported by the company in Modules 1-4 of the dossier referred to the MedDRA Preferred Terms "Rash" and/or "Exanthema", whereas the assessments in this report related to data on the SSC (special search category) "Rash". The proportions of patients with events were generally higher in the latter analysis in both treatment groups.

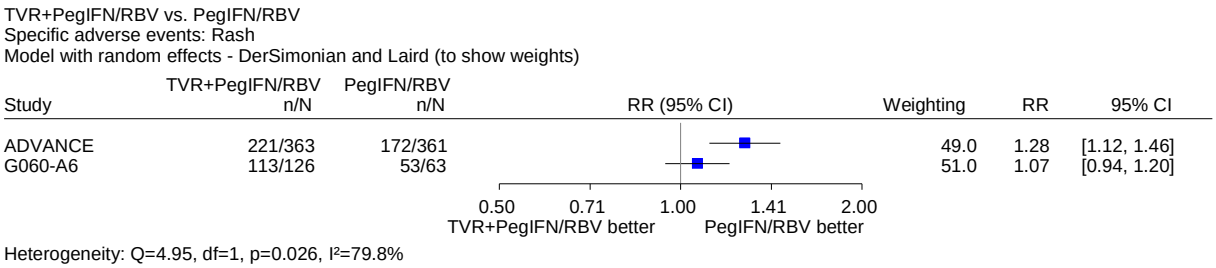

Figure 4: Meta-analysis, TVR + PegIFN/RBV (RGT) vs. PegIFN/RBV, treatment-naïve patients without cirrhosis, specific adverse events: rash

CI: confidence interval; PegIFN: peginterferon alfa; RBV: ribavirin; RGT: response-guided treatment regimen; RR: relative risk; TVR: telaprevir

Specific adverse events: psychiatric events

The proportions of patients with adverse psychiatric events did not differ substantially between TVR + PegIFN/RBV und PegIFN/RBV in the two studies. The overall effect of the meta-analysis was not statistically significant and there was no heterogeneity (Figure 5). Hence greater harm from telaprevir for this outcome is not proven. The company derived greater harm from telaprevir (not explicitly at the outcome level, but for adverse events as a whole).

The psychiatric events were almost exclusively non-serious. No statistical analysis of the low event rates for serious psychiatric events was carried out.

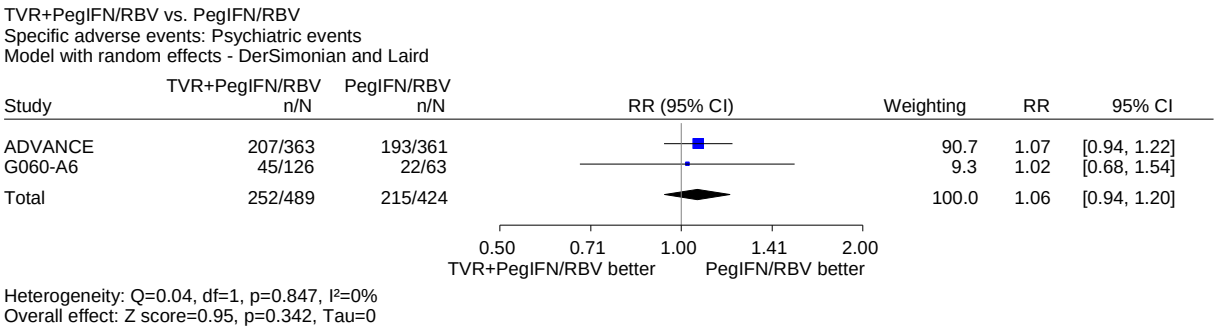

Figure 5: Meta-analysis, TVR + PegIFN/RBV (RGT) vs. PegIFN/RBV, treatment-naïve patients without cirrhosis, specific adverse events: psychiatric events

CI: confidence interval; PegIFN: peginterferon alfa; RBV: ribavirin; RGT: response-guided treatment regimen; RR: relative risk; TVR: telaprevir

Specific adverse events: infections

Infections occurred more often in the treatment-naïve patients without cirrhosis treated with PegIFN/RBV than in the patients who received TVR + PegIFN/RBV. The overall effect of the meta-analysis was statistically significant, and there was no heterogeneity between the results of the individual studies. However, because of the small effect size (confidence interval for RR not fully below 0.9; see Section 2.5.1) there is no proof of a lesser harm in favour of telaprevir. The company derived greater harm from telaprevir (not explicitly at the outcome level, but for adverse events as a whole).

The infections that occurred were mostly non-serious. The analysis of the serious events of this category showed no statistically significant difference.

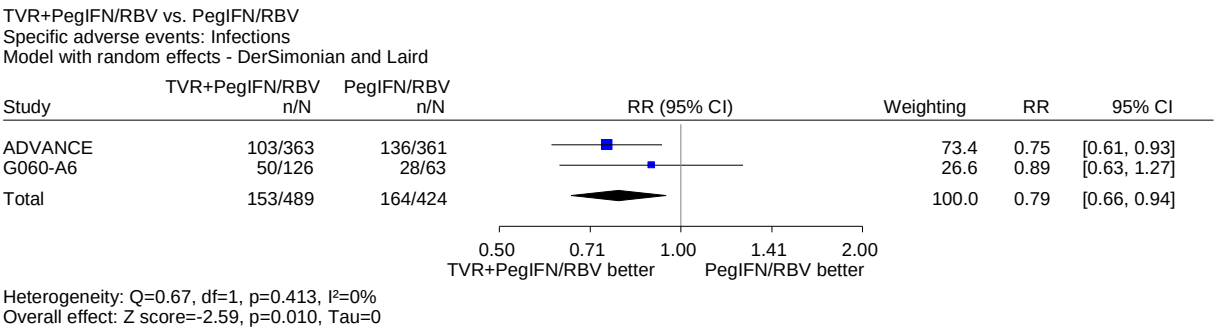

Figure 6: Meta-analysis, TVR + PegIFN/RBV (RGT) vs. PegIFN/RBV, treatment-naïve patients without cirrhosis, specific adverse events: infections

CI: confidence interval; PegIFN: peginterferon alfa; RBV: ribavirin; RGT: response-guided treatment regimen; RR: relative risk; TVR: telaprevir

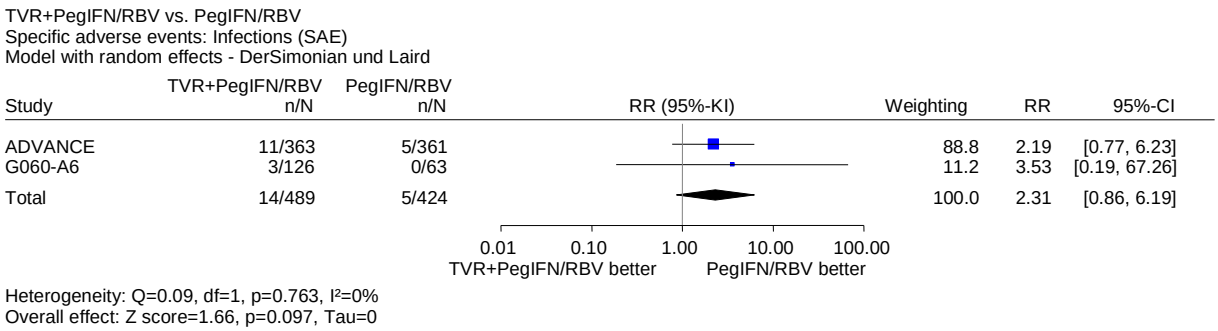

Figure 7: Meta-analysis, TVR + PegIFN/RBV (RGT) vs. PegIFN/RBV, treatment-naïve patients without cirrhosis, particular serious adverse events: infections

CI: confidence interval; PegIFN: peginterferon alfa; RBV: ribavirin; RGT: response-guided treatment regimen; RR: relative risk; TVR: telaprevir

2.4.1.1 Subgroup analysis of baseline viral load

In order to detect a possible effect modification by the stratification characteristic "baseline viral load", results of the treatment comparison between TVR + PegIFN/RBV and PegIFN/RBV in treatment-naïve patients without cirrhosis for the outcome "SVR" were compared between patient groups with low (HCV-RNA < 800,000 IU/ml) and high baseline values (HCV-RNA ≥ 800,000 IU/ml).

The prerequisite for proof of differing effects was a statistically significant homogeneity / interaction test ($p \leq 0.05$). A p-value between 0.05 and 0.2 provided an indication of differing effects.

Meta-analysis of the treatment effects in the corresponding subgroups of the ADVANCE and G060-A6 studies for the outcome SVR produced proof of an effect modification through baseline viral load (< 800,000 IU/ml; ≥ 800,000 IU/ml) and rendered a separate consideration of the results in the two groups necessary.

Table 10 shows the results of this subgroup analysis.

Table 10: Subgroup results of the comparison TVR + PegIFN/RBV vs. PegIFN/RBV in treatment-naïve patients without cirrhosis with high or low baseline viral load for the outcome "SVR"

Subgroup characteristic/treatment		Total n	Events N (%)	RR [95% CI][a]	Interaction test (p-value)[b]
HCV-RNA < 800,000 IU/ml					
ADVANCE	TVR+PegIFN/RBV PegIFN/RBV	82 82	64 (78) 57 (70)	1.12 [0.93, 1.35]	
G060-A6[c]	TVR+PegIFN/RBV PegIFN/RBV	18 9	16 (89) 7 (78)	1.14 [0.78, 1.68]	
Meta-analysis				1.13 [0.95, 1.33]	
HCV-RNA ≥ 800,000 IU/ml					
ADVANCE	TVR+PegIFN/RBV PegIFN/RBV	281 279	207 (74) 101 (36)	2.03 [1.72, 2.41]	
G060-A6[c]	TVR+PegIFN/RBV PegIFN/RBV	108 54	76 (70) 24 (44)	1.58 [1.15, 2.19]	
Meta-analysis	Heterogeneity: Q = 1.82, df = 1, p = 0.178, I^2 = 45.0%				
					p = 0.047

a: Institute's calculation.

b: Interaction test between baseline viral load and treatment effect (meta-regression).

c: The subgroup with a baseline viral load < 800,000 IU/ml included the subgroup defined in Study G060-A6 with a baseline viral load < 1,000,000 IU/ml and the subgroup with baseline viral load ≥ 800,000 IU/ml included the subgroups defined there with a baseline viral load 1,000,000–10,000,000 IU/ml and > 10,000,000 IU/ml.

CI: confidence interval; HCV-RNA: hepatitis C virus ribonucleic acid; IU: international units; PegIFN: peginterferon alfa; RBV: ribavirin; RR: relative risk; SVR: sustained virological response; TVR: telaprevir

In treatment-naïve patients without cirrhosis with low baseline viral load, the proportions of patients who achieved SVR did not differ substantially between TVR + PegIFN/RBV and PegIFN/RBV in the two studies. The overall effect of the meta-analysis was not statistically significant and there was no heterogeneity between the results of the individual studies (Figure 8). An added benefit of telaprevir for treatment-naïve patients without cirrhosis with low baseline viral load is therefore not proven for this outcome.

In treatment-naïve patients without cirrhosis with a high baseline viral load, a higher proportion of patients treated with TVR + PegIFN/RBV reached SVR compared to those who received PegIFN/RBV. However, the meta-analysis showed a high heterogeneity ($p < 0.2$), and therefore no overall effect estimator was illustrated (Figure 8). Nevertheless, on the basis of the individual study results, there were in each case statistically significant differences in favour of telaprevir, so that there is proof of an added benefit of telaprevir for this outcome in treatment-naïve patients without cirrhosis and with high baseline viral load.

However, it should be borne in mind at the outcome level that the SVR as surrogate is not formally validated and the assessment of "adequate validity" is based exclusively on data

from observational studies (see Section 2.7.2.9.4 of the full dossier assessment). Account is taken below of this increased uncertainty by the rating of the extent of the added benefit ("non-quantifiable").

In summary, there is proof of an added benefit of telaprevir for the outcome "SVR" only in treatment-naïve patients without cirrhosis with high baseline viral load. An added benefit of telaprevir is not proven for patients with low baseline viral load. This assessment deviates from that of the company, which derived overall proof of an added benefit and did not differentiate according to baseline viral load.

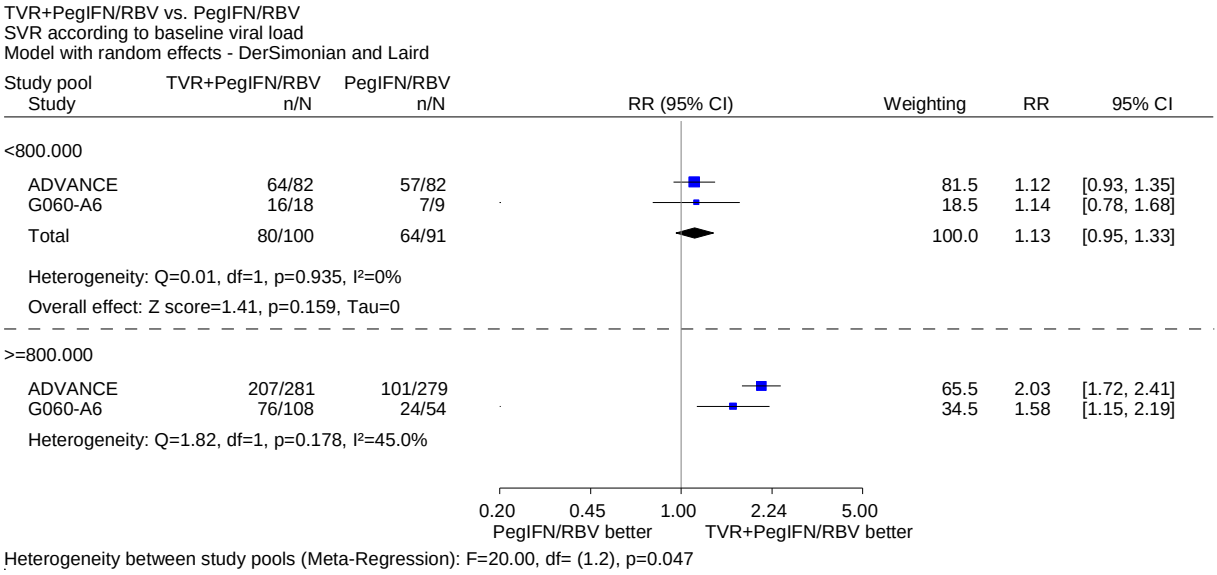

Figure 8: Meta-analysis, TVR + PegIFN/RBV (RGT) vs. PegIFN/RBV, subgroups with low (HCV-RNA < 800,000 IU/ml) and high (HCV-RNA ≥ 800,000 IU/ml) baseline viral load, treatment-naïve patients without cirrhosis, outcome "SVR"

CI: confidence interval; HCV-RNA: hepatitis C virus ribonucleic acid; PegIFN: peginterferon alfa; RBV: ribavirin; RGT: response-guided treatment regimen; RR: relative risk; SVR: sustained virological response; TVR: telaprevir

On the basis of these results, overall conclusions on the added benefit for treatment-naïve patients without cirrhosis must be drawn separately for patients with high and low baseline viral load respectively. However, there were no subgroup data in the dossier on baseline viral load for outcomes other than SVR. Therefore in order to enable an overall consideration of the benefit-harm ratio for the subgroups with low and high baseline viral load, the data of the total population of treatment-naïve patients without cirrhosis (see 2.4.1) were used for these further outcomes. The transferability of this data is limited, less for the group with high viral load (e.g. approx. 77% of the total population of the ADVANCE study had a high viral load), but more for the group with low viral load (only approx. 23% of the total population had a

low viral load). This existing limitation is taken into account in the overall conclusion on added benefit.

2.4.2 Results for treatment-naïve patients with cirrhosis

Although patients with cirrhosis were enrolled in the ADVANCE study (approx. 6%), they were treated with a RGT regimen that did not correspond to the approval requirements for this group of patients. Hence, no evaluable data are available, nor did the company submit further evaluable studies. An added benefit of telaprevir regarding this subindication is therefore not proven. This assessment differs substantially from that of the company, which derived an added benefit for the therapeutic indication in treatment-naïve patients as a whole – and thus implicitly also for patients with cirrhosis.

2.4.3 Results for previously treated patients – non-responders and/or relapsed patients with or without cirrhosis

Table 11 summarizes the results for the comparison of telaprevir (TVR) + PegIFN/RBV and PegIFN/RBV in previously treated patients (non-responders, relapsed patients with or without cirrhosis). The subindications and data on the total study population are shown together in this section to enable the study results to be compared at a glance.

The data correspond to those presented by the company for the outcomes considered and those outcomes added by the Institute. The numbers from the dossier were also supplemented by the Institute's calculations of relative risks, where these were not given in the dossier (identified with footnotes).

Table 11: Study results on the comparison TVR + PegIFN/RBV vs. PegIFN/RBV for previously treated patients (non-responders, relapsed patients with or without cirrhosis)

Outcome[a] **Study**	**Telaprevir + PegIFN/RBV**		**PegIFN/RBV**		**Telaprevir + PegIFN/RBV vs. PegIFN/RBV**	
	Total N	**Events N (%)**	**Total N**	**Events N (%)**	**RR [95% CI][b]**	**p-value[c]**
Overall mortality						
REALIZE						
Total population	266	0 (0)	132	1 (< 1)	not applicable[d]	
Relapsed patients	145	0 (0)	68	0 (0)	not applicable[d]	
without cirrhosis	-	-	-	-		
with cirrhosis	-	-	-	-		
Non-responders	121	0 (0)	64	1 (2)	not applicable[d]	
Sustained virological response (SVR)[e]						
REALIZE						
Total population	266	171 (64)	132	22 (17)	3.86 [2.61; 5.71]	< 0.001
Relapsed patients	145	121 (83)	68	16 (24)	3.55 [2.30; 5.48]	< 0.001
without cirrhosis	117	98 (84)	53	14 (26)	3.17 [2.01; 5.00]	< 0.001
with cirrhosis	28	23 (82)	15	2 (13)	6.16 [1.68; 22.64]	< 0.001
Non-responders	121	50 (41)	64	6 (9)	4.41 [2.00; 9.72]*	< 0.001
Health-related quality of life	No evaluable data available					
Adverse events (AEs)						
REALIZE						
Total population	266	260 (98)	132	126 (96)	1.02 [0.98; 1.07]	0.214
Relapsed patients	145	141 (97)	68	67 (99)	0.99 [0.95; 1.03]	0.622
without cirrhosis	-	-	-	-		
with cirrhosis	-	-	-	-		
Non-responders	121	119 (98)	64	59 (92)	1.07 [0.99; 1.15][f]	0.038
Serious adverse events (SAEs)						
REALIZE						
Total population	266	33 (12)	132	7 (5)	2.34 [1.06; 5.15]	0.027
Relapsed patients	145	23 (16)	68	2 (3)	5.39 [1.31; 22.22]	0.006
without cirrhosis	-	-	-	-		
with cirrhosis	-	-	-	-		
Non-responders	121	10 (8)	64	5 (8)	1.06 [0.38; 2.96]	0.935

(continued on next page)

Table 11: Study results on the comparison TVR + PegIFN/RBV vs. PegIFN/RBV for previously treated patients (non-responders, relapsed patients with or without cirrhosis) (continued)

Outcome[a] Study	Telaprevir + PegIFN/RBV		PegIFN/RBV		Telaprevir + PegIFN/RBV vs. PegIFN/RBV	
	Total N	Events N (%)	Total N	Events N (%)	RR [95% CI][b]	p-value[c]
Treatment discontinuations due to adverse events						
REALIZE						
Total population	266	17 (6)	132	4 (3)	2.11 [0.72; 6.14]	0.171
Relapsed patients	145	10 (7)	68	1 (1)	4.69 [0.61; 35.90]	0.099
without cirrhosis	-	-	-	-		
with cirrhosis	-	-	-	-		
Non-responders	121	7 (6)	64	3 (5)	1.23 [0.33; 4.61]	0.795
Specific adverse events: anaemia						
REALIZE						
Total population	266	91 (34)	132	23 (17)	1.96 [1.31; 2.95]	< 0.001
Relapsed patients	145	54 (37)	68	14 (21)	1.81 [1.08; 3.02]	0.015
without cirrhosis	-	-	-	-		
with cirrhosis	-	-	-	-		
Non-responders	121	37 (31)	64	9 (14)	2.17 [1.12; 4.22]	0.014
of which SAEs						
Total population	266	7 (3)	132	1 (< 1)	3.47 [0.43; 27.94]	0.236
Relapsed patients	145	5 (3)	68	0 (0)	5.20 [0.29; 92.69]	0.127
without cirrhosis	-	-	-	-		
with cirrhosis	-	-	-	-		
Non-responders	121	2 (2)	64	1 (2)	not applicable[d]	
Specific adverse events: rash						
REALIZE						
Total population	266	151 (57)	132	42 (32)	1.78 [1.36; 2.34]	<0.001
Relapsed patients	145	78 (54)	68	29 (43)	1.26 [0.92; 1.73]	0.138
without cirrhosis	-	-	-	-		
with cirrhosis	-	-	-	-		
Non-responders	121	73 (60)	64	13 (20)	2.97 [1.79; 4.93]	<0.001
of which SAEs						
Total population	266	2 (< 1)	132	0 (0)	not applicable[d]	
Relapsed patients	145	2 (1)	68	0 (0)	not applicable[d]	
without cirrhosis	-	-	-	-		
with cirrhosis	-	-	-	-		
Non-responders	121	0 (0)	64	0 (0)	not applicable[d]	

(continued on next page)

Table 11: Study results on the comparison TVR + PegIFN/RBV vs. PegIFN/RBV for previously treated patients (non-responders, relapsed patients with or without cirrhosis) (continued)

Outcome[a] Study	Telaprevir + PegIFN/RBV		PegIFN/RBV		Telaprevir + PegIFN/RBV vs. PegIFN/RBV	
	Total N	Events N (%)	Total N	Events N (%)	RR [95% CI][b]	p-value[c]
Specific adverse events: psychiatric events						
REALIZE						
Total population	266	122 (46)	132	68 (52)	0.89 [0.72; 1.10]	0.321
Relapsed patients	145	65 (45)	68	36 (53)	0.85 [0.63; 1.13]	0.309
without cirrhosis	-	-	-	-		
with cirrhosis	-	-	-	-		
Non-responders	121	57 (47)	64	32 (50)	0.94 [0.69; 1.28]	0.780
of which SAEs						
Total population	266	0 (0)	132	0 (0)	not applicable[d]	
Relapsed patients	145	0 (0)	68	0 (0)	not applicable[d]	
without cirrhosis	-	-	-	-		
with cirrhosis	-	-	-	-		
Non-responders	121	0 (0)	64	0 (0)	not applicable[d]	
Specific adverse events: infections						
REALIZE						
Total population	266	99 (37)	132	47 (36)	1.05 [0.79; 1.38]	0.828
Relapsed patients	145	53 (37)	68	25 (37)	0.99 [0.68; 1.45]	> 0.999
without cirrhosis	-	-	-	-		
with cirrhosis	-	-	-	-		
Non-responders	121	46 (38)	64	22 (34)	1.11 [0.74; 1.66]	0.647
of which SAEs						
Total population	266	6 (2)	132	2 (2)	not applicable[d]	
Relapsed patients	145	3 (2)	68	1 (2)	not applicable[d]	
without cirrhosis	-	-	-	-		
with cirrhosis	-	-	-	-		
Non-responders	121	3 (3)	64	1 (2)	1.59 [0.17; 14.95]	0.727

The data on the total population are given only for reasons of transparency; no conclusions on added benefit are drawn.

-: No data available.

a: FAS analysis: all randomized patients who received at least one dose of a study medication.

b: Institute's calculation, RR TVR + PegIFN/RBV vs. PegIFN/RBV.

c: Own calculation, unconditional exact test CSZ method according to [2]).

d: Too small a proportion of patients with event (≤ 2%).

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Table 11: Study results on the comparison TVR + PegIFN/RBV vs. PegIFN/RBV for previously treated patients (non-responders, relapsed patients with or without cirrhosis) (continued)

e: Roche TaqMan HCV-RNA Assay with a lower limit of quantification of 25 IU/ml and a limit of detection of 10 IU/ml.

f: Institute's calculation, asymptotic discrepancy between p-value (exact) and confidence interval (asymptotic) because of different methods of calculation, p-value is decisive for the assessment, but not for the subsequent evaluation of the extent of the added benefit.

*: Overall effect shown to illustrate that a statistically significant difference is present. Due to an indication of a relevant effect modification by the characteristic "cirrhosis status", the results are considered separately for the respective subgroups (see 2.4.3.1.1).

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; FAS: Full Analysis Set; HCV-RNA: hepatitis C virus ribonucleic acid; PegIFN: peginterferon alfa; RBV: ribavirin; RR: relative risk; SAE: serious adverse event; SVR: sustained virological response 24 weeks after end of treatment; TVR: telaprevir

2.4.3.1 Previously treated patients – non-responders

The data available for the group of non-responders from the REALIZE study were used to assess the non-responders (with or without cirrhosis). See Section 2.7.2.4 of the full dossier assessment for the assessment of the risk of bias at the study and outcome level.

In the Institute's view, the REALIZE study does not meet the particular requirements placed on the derivation of proof from a single study (see Section 2.7.2.8.2 of the full dossier assessment). Hence, at most indications, e.g. of an added benefit, could be derived from the data, unless outcome-specific aspects further weakened the informative value (see also Section 2.7.2.8.1. of the full dossier assessment). This assessment deviates from that of the company, which derived proof of an added benefit (not explicitly at the outcome level, but overall). The possible weakening by outcome-specific aspects is discussed separately below in the presentation of results on the individual outcomes.

Mortality

The proportions of non-responders who died under treatment did not differ substantially between TVR + PegIFN/RBV and PegIFN/RBV. However, the very low event rate should be borne in mind when interpreting the results. No statistical analysis of this event rate was undertaken. An added benefit of telaprevir for this outcome is not proven.

Morbidity

Sustained virological response (SVR)

As already explained in Section 2.4.1, the outcome "SVR" is not a patient-relevant outcome per se and there are no studies to validate SVR as surrogate outcome. However, in the Institute's view, on the basis of a consideration of the results from observational studies, SVR is an adequately valid surrogate outcome for the occurrence of HCC. Hence, the consideration

of SVR in the benefit assessment and the derivation of conclusions regarding added benefit are, in principle, possible.

A higher proportion of the non-responders treated with TVR + PegIFN/RBV achieved a SVR than those treated with PegIFN/RBV. However, during the assessment of subgroup characteristics, there was an indication of an effect modification for the characteristic "cirrhosis status". Conclusions about added benefit in terms of this outcome must therefore be drawn on the basis of subgroups. These subgroup analyses with the related evidence can be found at the end of this section.

Health-related quality of life

The company's dossier contained no evaluable data on health-related quality of life. An added benefit of telaprevir for this outcome is not proven.

Adverse events

The proportion of non-responders with serious adverse events, treatment discontinuations due to adverse events, psychiatric events and infections did not differ substantially between TVR + PegIFN/RBV and PegIFN/RBV. The respective result was not statistically significant and greater harm from telaprevir for these outcomes is not proven. Adverse events (overall rate), anaemia and rash occurred more often in patients treated with TVR + PegIFN/RBV than in those who received PegIFN/RBV. In each case, there was a statistically significant difference to the disadvantage of telaprevir. Due to the small effect size (confidence interval for RR not fully below 0.9; see Section 2.5.3) for the outcome "adverse events" (overall rate) greater harm from telaprevir is not proven. For anaemia and rash there is an indication of greater harm from telaprevir in each case.

The cases of anaemia and rash that occurred were almost exclusively or exclusively non-serious. No statistical analysis of these event rates was undertaken.

Overall, the assessments regarding the specific adverse events corresponded to those of the company, which derived greater harm from telaprevir (not explicitly at the outcome level, but for adverse events as a whole). However the company's procedure deviated in that the data from the REALIZE study reported by the company in its dossier (Module 1-4) referred to the MedDRA Preferred Terms "Anaemia" and "Rash", whereas the assessments in this report concerned data on the SSC (special search category) "Anaemia" and/or "Rash".

2.4.3.1.1 Subgroup analysis on cirrhosis status

In order to detect possible effect differences between patient groups with and without cirrhosis, results of the treatment comparison between TVR + PegIFN/RBV and PegIFN/RBV in non-responders were investigated for the outcome "SVR" regarding a possible effect modification through the cirrhosis status.

The prerequisite for proof of differing subgroup effects was a statistically significant homogeneity / interaction test ($p \leq 0.05$). A p-value between 0.05 and 0.2 provided an indication of differing effects.

The assessment of treatment effects of the corresponding subgroups (cirrhosis; no cirrhosis) through an interaction test provided an indication of an effect modification for the outcome "SVR" through the cirrhosis status.

Table 12 shows the results of the subgroup analysis.

Table 12: Subgroup results for the comparison TVR + PegIFN/RBV vs. PegIFN/RBV in previously treated non-responders with or without cirrhosis for the outcome "SVR"

Subgroup characteristic/Treatment		Total n	Events N (%)	RR [95% CI][a] p-value	Interaction test (p-value)[b]
Non-responders (REALIZE Study)					
Cirrhosis	TVR+PegIFN/RBV PegIFN/RBV	44 15	11 (25) 2 (13)	1.88 [0.47; 7.51] 0.374	0.161
No cirrhosis	TVR+PegIFN/RBV PegIFN/RBV	77 49	39 (51) 4 (8)	6.20 [2.36; 16.28] < 0.001	

a: Institute's calculation.
b: Heterogeneity test (Cochran's Q statistic).
CI: confidence interval; PegIFN: peginterferon alfa; RBV: ribavirin; RR: relative risk; SVR: sustained virological response; TVR: telaprevir

In previously treated non-responders without cirrhosis, a higher proportion of patients treated with TVR + PegIFN/RBV achieved SVR compared with those who received PegIFN/RBV. There was a statistically significant difference in favour of telaprevir (Figure 9). This produces an indication of an added benefit of telaprevir in non-responders without cirrhosis for this outcome.

Although among the previously treated non-responders with cirrhosis a higher proportion of patients treated with TVR + PegIFN/RBV also achieved SVR compared with those given PegIFN/RBV, the difference between the treatment groups was not statistically significant (Figure 9). Since the available data gave only an indication of an interaction, the certainty of the overall result was merely downgraded from "indication" to "hint" because, on the basis of the overall analysis, there was an indication of an added benefit. This produced an overall hint of an added benefit of telaprevir in previously treated non-responders with cirrhosis for this outcome.

However, it should be borne in mind at the outcome level that SVR is not formally validated as surrogate and the assessment of "adequate validity" is exclusively based on data from observational studies (see Section 2.7.2.9.4 of the full dossier assessment). Account is taken

below of this increased uncertainty by the rating of the extent of the added benefit ("non-quantifiable").

In summary, there is an indication of an added benefit of telaprevir for the outcome "SVR" in previously treated non-responders without cirrhosis. For patients with cirrhosis there is a hint of an added benefit of telaprevir. This assessment differs from that of the company, which derived overall proof of an added benefit and did not differentiate according to cirrhosis status.

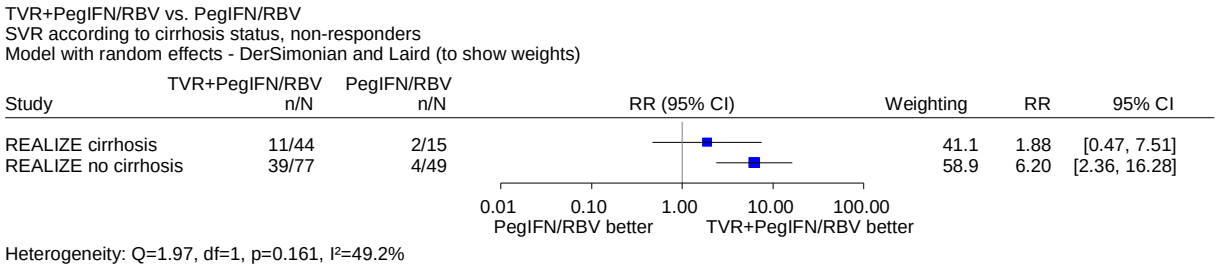

Figure 9: Meta-analysis, TVR + PegIFN/RBV vs. PegIFN/RBV, subgroups with and without cirrhosis, previously treated non-responders, outcome "SVR"

CI: confidence interval; PegIFN: peginterferon alfa; RBV: ribavirin; RR: relative risk; SVR: sustained virological response; TVR: telaprevir

Because of these results, overall conclusions regarding added benefit for previously treated non-responders must be drawn separately for patients with and without cirrhosis. However, there are no subgroup data in the dossier on the cirrhosis status of non-responders for outcomes other than SVR. In order to enable an overall consideration of the benefit-harm ratio for the subgroups with and without cirrhosis, the data of the total population of non-responders (see 2.4.3.1) were used for these further outcomes. The applicability of this data is limited and this is taken into account in the overall conclusion on added benefit.

2.4.3.2 Previously treated patients – relapsed patients with cirrhosis

In the Institute's view, the REALIZE study does not meet the particular requirements placed on the derivation of proof from a single study (see Section 2.7.2.8.1 of the full dossier assessment). Hence, at most indications, e.g. of an added benefit, could be derived from the data. This assessment deviates from that of the company, which derived proof of an added benefit (not explicitly at the outcome level, but overall).

As already addressed in Sections 2.3.2 and 2.7.2.4.1, uncertainties arose concerning the transferability of the submitted data for the total population of relapsed patients in the approval study, because the proportion of relapsed patients with cirrhosis in the total population was only 20% and the company presented an appropriate subgroup analysis only for one relevant outcome (SVR). The interaction test between cirrhosis status and treatment

effect for this outcome was not statistically significant. The handling of this uncertainty is discussed below in the specific discussion of results and may lead to outcome-specific aspects that further weaken the informative value. See Section 2.7.2.4.2 of the full dossier assessment for an assessment of the risk of bias at the study and outcome level.

Mortality

Only data for the total population of relapsed patients were available. Neither patients receiving TVR + PegIFN/RBV nor those receiving PegIFN/RBV died during the study. No statistical analysis of the event rate was undertaken. An added benefit of telaprevir for this outcome is not proven.

Morbidity

Sustained virological response (SVR)

As already explained in Section 2.4.1, the outcome SVR is not a patient-relevant outcome per se and there are no studies to validate SVR as surrogate outcome. However, in the Institute's view, on the basis of a consideration of the results from observational studies, SVR is an adequately valid surrogate outcome for the occurrence of HCC. Hence the consideration of SVR in the benefit assessment and the derivation of conclusions regarding added benefit are, in principle, possible.

For SVR, data for relapsed patients with cirrhosis were available. The proportion of patients who achieved SVR was higher under TVR + PegIFN/RBV than under PegIFN/RBV. There was a statistically significant difference in favour of telaprevir. In summary, there is an indication of an added benefit of telaprevir for this population. This assessment deviates from that of the company, which derived proof of an added benefit.

However, it should be borne in mind at the outcome level that SVR is not formally validated as surrogate and the assessment of "adequate validity" is exclusively based on data from observational studies (see Section 2.7.2.9.4 of the full dossier assessment). Account is taken below of this increased uncertainty by the rating of the extent of the added benefit ("non-quantifiable").

Health-related quality of life

The company's dossier contained no evaluable data on health-related quality of life. An added benefit of telaprevir for health-related quality of life is not proven.

Adverse events

Only data for the total population of relapsed patients were available for the complex "adverse events". The proportion of patients with adverse events (overall rate), treatment discontinuations due to adverse events, rash, psychiatric events and infections did not differ substantially between TVR + PegIFN/RBV and PegIFN/RBV. The respective result was not statistically significant and greater harm from telaprevir for this outcome in the total

population of relapsed patients is not proven. Serious adverse events and anaemia (almost exclusively non-serious) occurred more frequently in the patients treated with TVR + PegIFN/RBV than in those who received PegIFN/RBV. In each case there was a statistically significant difference to the disadvantage of telaprevir. Because of the small effect size (confidence interval for RR not fully below 0.9; see Section 2.5.4) for the total population of relapsed patients, there is no proof of greater harm from telaprevir for the outcome "anaemia". However, there is an indication of greater harm from telaprevir for serious adverse events.

The company's procedure with regard to anaemia deviated in that the data from the REALIZE study reported by the company in Modules 1-4 of its dossier referred to the MedDRA Preferred Term "Anaemia", whereas the assessments in this report concerned data on the SSC (special search category) "Anaemia".

In summary, because of the lack of separate data for relapsed patients with cirrhosis on adverse events, there is a general uncertainty in respect of the harm from telaprevir in this population. In the Institute's view, this uncertainty due to missing data should, however, not lead to a non-consideration of the harm factor. The Institute therefore used the above-mentioned results of the total relapsed population when considering harm as a whole. The resulting assessment corresponds to that of the company, which derived greater harm from telaprevir (not explicitly at the outcome level, but for adverse events as a whole).

2.4.3.3 Previously treated patients – relapsed patients without cirrhosis

According to the approval status, an RGT regimen is specified for previously treated relapsed patients without cirrhosis. In the REALIZE study, a treatment regimen with a fixed treatment period of 48 weeks was investigated and 35% of the total relapsers population were late responders (the proportion of relapsers without cirrhosis was 80% of the total relapsers population). Accordingly, not more than 35% of relapsers without cirrhosis were treated in accordance with the approval status, i.e. (for a longer treatment period), and at least 65% of these patients were treated for too long (not in accordance with the approval status). Taken as a whole, the available results of the REALIZE study were not suitable for answering the research question of interest (use of telaprevir according to approval status in relapsed patients without cirrhosis).

Having said that, the supplementary consideration of the study data produced the following results (reduced to statistically significant differences):

The proportion of relapsed patients without cirrhosis who achieved SVR was higher under TVR + PegIFN/RBV than under PegIFN/RBV. There was a statistically significant difference in favour of telaprevir.

Serious adverse events and anaemia (almost exclusively non-serious) occurred more frequently in patients treated with TVR + PegIFN/RBV than in those given PegIFN/RBV. In each case, there was a statistically significant difference to the disadvantage of telaprevir. Due

to the small effect size (confidence interval for RR not fully below 0.9; see Section 2.5) for the outcome "anaemia", there was no proof of greater harm from telaprevir for this outcome.

As also for relapsed patients with cirrhosis, the main results were that effects in favour of telaprevir regarding the SVR were accompanied by effects to the disadvantage of telaprevir regarding serious adverse events.

In summary, on the basis of the available data, an added benefit of telaprevir for relapsed patients without cirrhosis is not proven.

2.4.4 Results for patients co-infected with HIV and/or HBV

A co-infection with HIV and/or HBV was an exclusion criterion of the ADVANCE, REALIZE and G060-A6 studies. The company submitted no further studies on this population and/or explicitly excluded this research question. An added benefit of telaprevir regarding this patient population is thus not proven for all the previously considered subindications. This assessment corresponds to that of the company, which also derived no added benefit for this group of patients.

Further information about outcome results of the direct comparison can be found in Module 4, Section 4.3.1.3 of the dossier and in Sections 2.7.2.4.3 and 2.7.2.8 of the full dossier assessment.

2.5 Extent and probability of the added benefit

The derivation of the extent and probability of added benefit is presented below for each patient population at the outcome level, taking into account outcome categories and effect sizes. The methods used for this purpose are explained in Appendix A of Benefit Assessment A11-02 [5].

The procedure for deriving the overall conclusion on added benefit based on the aggregation of the conclusions derived at the outcome level is a proposal from IQWiG. The G-BA decides on the added benefit.

2.5.1 Treatment-naïve patients without cirrhosis

2.5.1.1 Evaluation of added benefit at the outcome level

The data presented in Section 2.4.1 produced proof of an added benefit for patients with high baseline viral load; for patients with low baseline viral load, an added benefit was not proven. However, for both groups of patients there was proof and a further indication of greater harm.

An assessment of the extent of the respective added benefit at the outcome level was carried out and is shown in Table 13.

Table 13: Treatment-naïve patients without cirrhosis: TVR + PegIFN/RBV (RGT) vs. PegIFN/RBV – extent of added benefit at the outcome level

	Effect estimator [95% CI] / Proportion of event TVR + PegIFN/RBV vs. PegIFN/RBV / p-value / Probability[a]	**Derivation of extent[b]**
Mortality		
Overall mortality	Not applicable[d] < 1% vs. < 1% Not applicable[d]	Lesser benefit/added benefit not proven.
Morbidity		
HCC, considered via the surrogate SVR[c] **Baseline viral load[i] < 800,000 IU/ml**	No statistically significant difference (SVR).	Outcome category: serious/severe symptoms/late complications Lesser benefit/added benefit not proven.
HCC, considered via the surrogate SVR[c] **Baseline viral load[i] ≥ 800,000 IU/ml**	Non-quantifiable. Probability: "proof"	Outcome category: serious/severe symptoms/late complications Added benefit, extent: "non-quantifiable".
Tiredness FSS	MD -0.30 [-0.58; -0.02] p = 0.035 SMD -0.17 [-0.34; -0.01][k]	Lesser benefit/added benefit not proven.
Health-related quality of life		
EQ-5D	MD 0.03 [0.00; 0.06] p = 0.059	Lesser benefit/added benefit not proven.
Adverse events		
AEs	Not applicable[e] 99% vs. 98% Not applicable[e]	Greater/lesser harm not proven.
SAEs	RR 1.34 [0.86; 2.08] 10% vs. 7% p=0.195	Greater/lesser harm not proven.
Discontinuation due to AEs[h]	RR 1.38 [0.85; 2.23] 10% vs. 7% p = 0.214	Greater/lesser harm not proven.
Anaemia[h]	RR 1.65 [1.33; 2.06][f] RR 0.60 [0.49; 0.75][g] 41% vs. 25% p < 0.001 Probability: "proof"	Outcome category: non-serious / non-severe adverse events $CI_o < 0.8$ Greater risk of harm, extent: "considerable"
Rash[h]	RR 1.28 [1.12; 1.46][f] RR 0.78 [0.683; 0.897][g] 61% vs. 48% p < 0.001 Probability: "indication"	Outcome category: non-serious / non-severe adverse events $0.8 \leq CI_o < 0.9$ Greater risk of harm, extent: "minor"

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Table 13: Treatment-naïve patients without cirrhosis: TVR + PegIFN/RBV (RGT) vs. PegIFN/RBV – extent of added benefit at the outcome level (continued)

	Effect estimator [95% CI] / Proportion of event TVR + PegIFN/RBV vs. PegIFN/RBV / p-value / Probability[a]	**Derivation of extent[b]**
Psychiatric events	RR 1.06 [0.94; 1.20] 52% vs. 51% p = 0.342	Greater/lesser harm not proven.
Infections	RR 0.79 [0.66; 0.94] 31% vs. 39% p = 0.010	Outcome category: non-serious / non-severe adverse events $CI_o \geq 0.90$ Greater/lesser harm not proven.[j]

a: Probability, if statistically significant differences are present that exceed a marginal extent.

b: Estimations of effect size are made depending on outcome category with different limits based on upper limit of the confidence interval (CI_0).

c: The SVR was assessed as an adequately valid surrogate for a patient-relevant outcome (HCC) in order to be considered in the benefit assessment (for detailed reasoning, see Section 2.7.2.9.4 of the full dossier assessment).

d: Too small a proportion of patients with event (≤ 2%).

e: Too high a proportion of patients with event (≥ 98%).

f: Proportion of events TVR+PegIFN/RBV vs. PegIFN/RBV.

g: Proportion of events PegIFN/RBV vs. TVR+PegIFN/RBV (effect direction reversed to enable derivation of extent of added benefit).

h: Effect estimator, p-values and proportion of events refer to the study with higher certainty of result (ADVANCE) due to greater heterogeneity between individual results of the studies included in the assessment.

i: Splitting of population due to a proof of an interaction and effect modification by the respective characteristic.

j: Because the upper limit of the confidence interval is above the specified threshold of 0.90.

k: SMD in the form of Hedges' g to assess relevance of the statistically significant group difference. If the 95% confidence interval for the SMD is not fully below the irrelevance threshold of -0.2, the effect was regarded as not relevant.

AE: adverse event; CI: confidence interval; CI_o: upper confidence interval; EQ-5D: EuroQol EQ-5D; FSS: Fatigue Severity Scale; HCC: hepatocellular carcinoma; MD: mean difference; PegIFN: peginterferon alfa; RBV: ribavirin; RGT: response-guided treatment regimen; RR: relative risk; SAE: serious adverse event; SMD: standardized mean difference; SVR: sustained virological response; TVR: telaprevir; vs.: versus

On the basis of the data presented in the dossier, the extent of the added benefit measured in respect of HCC (on the basis of the adequately valid, but not formally validated surrogate SVR) cannot be quantified. Hence, it can also not be classified into one of the categories for the extent of added benefit, i.e. it remains unclear whether the identified added benefit should be classed as "minor", "considerable" or "major". According to the legislation, in situations where, on the basis of the scientific data, uncertainty prevails concerning the classification of the extent of the added benefit, the term "non-quantifiable" must be applied as the assessment category (see Regulation for Early Benefit Assessment of New Pharmaceuticals (AM-NutzenV) Section 5, subsection 7).

2.5.1.2 Overall conclusion on added benefit for treatment-naïve patients without cirrhosis with high baseline viral load

The summary of results that determine the overall conclusion on added benefit is shown in Table 14.

Table 14: Treatment-naïve patients without cirrhosis with high baseline viral load – overall conclusion on added benefit

Positive effects	Negative effects
Proof of an added benefit – extent: "non-quantifiable" (serious complications: HCC, considered via the surrogate SVR).	Proof of greater harm – extent: "considerable" (non-serious adverse events: anaemia). Indication of greater harm – extent: "minor" (non-serious adverse events: rash).
HCC: hepatocellular carcinoma; SVR: sustained virological response	

Taken as a whole (Table 14), positive and negative results of equal certainty (proof) remain. On the side of added benefit, on the basis of the available data, the extent is "non-quantifiable"; on the side of greater harm, the extent is "considerable". Because the added benefit is non-quantifiable, it is not possible to state definitively whether a downgrading of the extent regarding added benefit would be reasonable. But the question arises as to whether the negative effects entirely outweigh the positive. However, the notion that the proof of greater harm through the non-serious adverse events (rash, anaemia) would fully outweigh the proof of added benefit in terms of the serious late complication (HCC) seems inappropriate.

In summary, there is proof of an added benefit (extent "non-quantifiable") of TVR + PegIFN/RBV over the ACT PegIFN/RBV for treatment-naïve patients without cirrhosis with high baseline viral load.

2.5.1.3 Overall conclusion on added benefit for treatment-naïve patients without cirrhosis with low baseline viral load

The summary of results that determine the overall conclusion on added benefit is shown in Table 15.

Table 15: Treatment-naïve patients without cirrhosis with lower baseline viral load – overall conclusion on added benefit

Positive effects	Negative effects
-	Proof of greater harm – extent: "considerable" (non-serious adverse events: anaemia). Indication of greater harm – extent: "minor" (non-serious adverse events: rash).

Taken as a whole (Table 15), only negative results remain and the extent "considerable" is reached. In accordance with the Regulation for Early Benefit Assessment of New Pharmaceuticals (AM-NutzenV), this results in a lesser benefit of telaprevir. However, it

should be borne in mind when determining the related certainty of result that, on the one hand, it does not appear appropriate not to use the results on adverse events for the subgroup of patients with low baseline viral load, only because no subgroup analyses for this group are available (see Section 2.4.1.1). On the other hand, this group only accounts for approx. 23% of the total population and therefore it likewise appears less than appropriate to derive a proof for the subgroup from the data of the total population as a whole.

In summary, there is an indication of a lesser benefit of TVR + PegIFN/RBV versus the ACT PegIFN/RBV for treatment-naïve patients without cirrhosis with lower baseline viral load.

2.5.2 Treatment-naïve patients with cirrhosis

As described in Section 2.4.2, there are no usable data for treatment-naïve patients with cirrhosis.

The added benefit of TVR + PegIFN/RBV over the ACT PegIFN/RBV for the subindication of treatment-naïve patients with cirrhosis is not proven.

2.5.3 Previously treated patients – non-responders with and without cirrhosis

2.5.3.1 Evaluation of added benefit at the outcome level

The data presented in 2.4.3.1 for previously treated non-responders without cirrhosis produced an indication of an added benefit; for patients with cirrhosis, there was a hint of an added benefit. For both groups of patients there were indications of greater harm.

An assessment of the extent of the respective added benefit at the outcome level is shown in Table 16.

Table 16: Previously treated patients – non-responders: TVR + PegIFN/RBV vs. PegIFN/RBV – extent of added benefit at the outcome level

	Effect estimator [95% CI] / Proportion of event TVR + PegIFN/RBV vs. PegIFN/RBV / p-value / Probability[a]	**Derivation of extent[b]**
Mortality		
All-cause mortality	Not applicable[d] 0% vs. 2% Not applicable[d]	Lesser benefit/added benefit not proven.
Morbidity		
HCC, considered via the surrogate SVR[c] **Subgroup:** **with cirrhosis[g]**	Non-quantifiable. Probability: "hint"	Outcome category: serious/severe symptoms/late complications Added benefit, extent: "non-quantifiable".
HCC, considered via the surrogate SVR[c] **Subgroup:** **without cirrhosis[g]**	Non-quantifiable. Probability: "indication"	Outcome category: serious/severe symptoms/late complications Added benefit, extent: "non-quantifiable".
Health-related quality of life		
	No evaluable data available.	Lesser benefit/added benefit not proven.
Adverse events		
AEs	RR 1.07 [0.99; 1.15][e] RR 0.94 [0.87; 1.01][f] 98% vs. 92% p = 0.038	Outcome category: non-serious / non-severe adverse events $CI_o \geq 0.9$ Greater/lesser harm not proven.[h]
SAEs	RR 1.06 [0.38; 2.96] 8% vs. 8% p = 0.935	Greater/lesser harm not proven.
Discont. due to AEs	RR 1.23 [0.33; 4.61] 6% vs. 5% p = 0.795	Greater/lesser harm not proven.
Anaemia	RR 2.17 [1.12; 4.22][e] RR 0.46 [0.24; 0.89][f] 31% vs. 14% p=0.014 Probability: "indication"	Outcome category: non-serious/non-severe adverse events $0.8 \leq CI_o < 0.9$ Greater risk of harm, extent: "minor".
Rash	RR 2.97 [1.79; 4.93][e] RR 0.34 [0.20; 0.56][f] 60% vs. 20% p < 0.001 Probability: "indication"	Outcome category: non-serious/non-severe adverse events $CI_o < 0.8$ Greater risk of harm, extent: "considerable".

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Table 16: Previously treated patients – non-responders: TVR + PegIFN/RBV vs. PegIFN/RBV – extent of added benefit at the outcome level (continued)

	Effect estimator [95% CI] / Proportion of event TVR + PegIFN/RBV vs. PegIFN/RBV / p-value / Probability[a]	**Derivation of extent[b]**
Psychiatric events	RR 0.94 [0.69; 1.28] 47% vs. 50% p = 0.780	Greater/lesser harm not proven.
Infections	RR 1.11 [0.74; 1.66] 38% vs. 34% p = 0.647	Greater/lesser harm not proven.

a: Probability, if statistically significant differences are present that exceed a marginal extent.

b: Estimations of effect size are made depending on outcome category with different limits based on upper limit of the confidence interval (CIo).

c: The SVR was assessed as an adequately valid surrogate for a patient-relevant outcome (HCC), in order to be considered in the benefit assessment (for detailed reasoning, see Section 2.7.2.9.4 of the full dossier assessment).

d: Too small a proportion of patients with event (≤ 2%).

e: Proportion of event TVR+PegIFN/RBV vs. PegIFN/RBV.

f: Proportion of event PegIFN/RBV vs. TVR+PegIFN/RBV (effect direction reversed to enable derivation of extent of added benefit).

g: Splitting of population due to an indication of an interaction and effect modification by the respective characteristic.

h: Because the upper limit of the confidence interval is above the specified threshold of 0.90.

AE: adverse event; CI: confidence interval; CIo: upper confidence interval; HCC: hepatocellular carcinoma; PegIFN: peginterferon alfa; RBV: ribavirin; RR: relative risk; SAE: serious adverse event; SVR: sustained virological response; TVR: telaprevir; vs.: versus

On the basis of the data presented in the dossier, the extent of the added benefit measured in respect of HCC (on the basis of the adequately valid, but not formally validated surrogate SVR) cannot be quantified. Hence, it can also not be classified in one of the categories for the extent of added benefit, i.e. it remains unclear whether the identified added benefit should be classed as “minor”, “considerable” or “major”. According to the legislation, in situations where, on the basis of the scientific data, uncertainty prevails concerning the classification of the extent of the added benefit, the term “non-quantifiable” must be applied as assessment category (see Regulation for Early Benefit Assessment of New Pharmaceuticals [AM-NutzenV] Section 5, subsection 7).

2.5.3.2 Overall conclusion on added benefit for previously treated non-responders without cirrhosis

The summary of results that determine the overall conclusion on added benefit is shown in Table 17.

Table 17: Previously treated non-responders without cirrhosis – overall conclusion on added benefit

Positive effects	Negative effects
Indication of an added benefit – extent: "non-quantifiable" (serious late complications: HCC, considered via the surrogate SVR).	Indication of greater harm – extent: "minor" (non-serious adverse events: anaemia). Indication of greater harm – extent: "considerable" (non-serious adverse events: rash).
HCC: hepatocellular carcinoma; SVR: sustained virological response	

Taken as a whole (Table 17), positive and negative results of equal certainty (indication) remain. On the side of added benefit, on the basis of the available data, the extent is "non-quantifiable"; on the side of greater harm, the extent "considerable" is achieved. Because the added benefit is non-quantifiable, it is not possible to state definitively whether a downgrading of the extent regarding added benefit would be reasonable. But the question arises whether the negative effects entirely outweigh the positive. However, the notion that the indications of greater harm through the non-serious adverse events (rash, anaemia) would fully outweigh the indication of added benefit in terms of the serious late complication (HCC) seems inappropriate.

In summary, there is an indication of an added benefit (extent "non-quantifiable") of TVR + PegIFN/RBV over the ACT PegIFN/RBV for previously treated non-responders without cirrhosis.

2.5.3.3 Overall conclusion on added benefit for previously treated non-responders with cirrhosis

The summary of results that determine the overall conclusion on added benefit is shown in Table 18.

Table 18: Previously treated non-responders with cirrhosis – overall conclusion on added benefit

Positive effects	Negative effects
Hint of an added benefit – extent: "non-quantifiable" (serious late complications: HCC, considered via the surrogate SVR).	Indication of greater harm – extent: "minor" (non-serious adverse events: anaemia). Indication of greater harm – extent: "considerable" (non-serious adverse events: rash).
HCC: hepatocellular carcinoma; SVR: sustained virological response	

Taken as a whole (Table 18), positive and negative results of differing certainty remain. On the side of the added benefit there was a hint of added benefit; the extent on the basis of the available data was "non-quantifiable". On the side of the greater harm, there were indications in each case, and the extent "considerable" was achieved. Because the added benefit is non-quantifiable, it is not possible to state definitively whether a downgrading of the extent

regarding added benefit would be logical. However the question arises as to whether the negative effects entirely outweigh the positive.

As already addressed in Section 2.4.3.1.1, because of the lack of available data for all outcomes apart from SVR, the data of the total population of previously treated non-responders had to be used. Admittedly, it seems inappropriate not to use the results on adverse events for this reason. However, it seems equally inappropriate that the indications of greater harm through the non-serious adverse events (rash, anaemia) fully outweigh a hint of an added benefit in terms of the serious late complication (HCC).

In summary, there is hint of an added benefit (extent "non-quantifiable") of TVR + PegIFN/RBV over the ACT PegIFN/RBV for previously treated non-responders with cirrhosis.

2.5.4 Previously treated patients – relapsed patients with cirrhosis

2.5.4.1 Evaluation of added benefit at the outcome level

The data presented in Section 2.4.3.2 produced an indication of an added benefit as well as an indication of greater harm for relapsed patients with cirrhosis.

An assessment of the extent of the respective added benefit at the outcome level was carried out and is shown in Table 19.

Table 19: Previously treated patients – relapsed patients with cirrhosis: TVR + PegIFN/RBV vs. PegIFN/RBV – extent of added benefit at the outcome level

	Effect estimator [95% CI] / Proportion of event TVR + PegIFN/RBV vs. PegIFN/RBV / p-value / Probability[a]	**Derivation of extent[b]**
Mortality		
All-cause mortality	Not applicable[d] 0% vs. 0% Not applicable[d]	Lesser benefit/added benefit not proven.
Morbidity		
HCC, considered via the surrogate SV^{Rc}	Non-quantifiable. Probability: "indication"	Outcome category: serious/severe symptoms/late complications Added benefit, extent: "non-quantifiable".
Health-related quality of life		
	No evaluable data available.	Lesser benefit/added benefit not proven.
Adverse events[g]		
AEs	RR 0.99 [0.95; 1.03] 97% vs. 99% p = 0.622	Greater/lesser harm not proven.
SAEs	RR 5.39 [1.31; 22.22][e] RR 0.19 [0.05; 0.76][f] 16% vs. 3% p = 0.006 Probability: "indication"	Outcome category: serious/severe adverse events $0.75 \leq CI_o < 0.90$ Greater harm, extent: "considerable".
Discont. due to AEs	RR 4.69 [0.61; 35.90] 7% vs. 1% p = 0.099	Greater/lesser harm not proven.
Anaemia	RR 1.81 [1.08; 3.02] [e] RR 0.55 [0.33; 0.92] [f] 37% vs. 21% p = 0.015	Outcome category: non-serious/non-severe adverse events $CI_o \geq 0.90$ Greater/lesser harm not proven.[h]
Rash	RR 1.26 [0.92; 1.73] 54% vs. 43% p = 0.138	Greater/lesser harm not proven.
Psychiatric events	RR 0.85 [0.63; 1.13] 45% vs. 53% p = 0.309	Greater/lesser harm not proven.
Infections	RR 0.99 [0.68; 1.45] 37% vs. 37% p = 0.999	Greater/lesser harm not proven.

(continued on next page)

Table 19: Previously treated patients – relapsed patients with cirrhosis: TVR + PegIFN/RBV vs. PegIFN/RBV – extent of added benefit at the outcome level (continued)

a: Probability provided, if statistically significant differences are present that exceed a marginal extent.

b: Estimations of effect size are made depending on outcome category with different limits based on upper limit of the confidence interval (CI_o).

c: The SVR was assessed as an adequately valid surrogate for a patient-relevant outcome (HCC), in order to be considered in the benefit assessment (for detailed reasoning , see Section 2.7.2.9 of the full dossier assessment).

d: Too small a proportion of patients with event (≤ 2%).

e: Proportion of events TVR+PegIFN/RBV vs. PegIFN/RBV.

f: Proportion of events PegIFN/RBV vs. TVR+PegIFN/RBV (effect direction reversed to enable derivation of extent of added benefit).

g: When considering the harm side in the overall picture, the results of the total population of relapsed patients were used because separate data on relapsed patients with cirrhosis were not available. In the Institute's view, this could not lead to a non-consideration of the harm side.

h: Because the upper limit of the confidence interval is above the specified threshold of 0.90.

AE: adverse event; CI: confidence interval; CI_o: upper confidence interval; HCC: hepatocellular carcinoma; PegIFN: peginterferon alfa; RBV: ribavirin; RR: relative risk; SAE: serious adverse event; SVR: sustained virological response; TVR: telaprevir; vs.: versus

On the basis of the data presented in the dossier, the extent of the added benefit measured in respect of HCC (on the basis of the adequately valid, but not formally validated surrogate SVR) cannot be quantified. Hence, it can also not be classified into one of the categories for the extent of added benefit, i.e. it remains unclear whether the identified added benefit should be classed as "minor", "considerable" or "major". According to the legislation, in situations where, on the basis of the scientific data, uncertainty prevails concerning the classification of the extent of the added benefit, the term "non-quantifiable" must be applied as the assessment category (see Regulation for Early Benefit Assessment of New Pharmaceuticals (AM-NutzenV) Section 5, subsection 7).

2.5.4.2 Overall conclusion on added benefit for previously treated relapsed patients with cirrhosis

The summary of results that determine the overall conclusion on added benefit is shown in Table 20.

Table 20: Previously treated relapsed patients with cirrhosis – overall conclusion on added benefit

Positive effects	**Negative effects**
Indication of an added benefit – extent: "non-quantifiable" (serious late complications: HCC, considered via the surrogate SVR).	Indication of greater harm – extent: "considerable" (serious/severe adverse events: SAEs).
HCC: hepatocellular carcinoma; SAE: serious adverse event; SVR: sustained virological response	

Taken as a whole (Table 20), positive and negative results of equal certainty (indication) remain. On the side of the added benefit the extent on the basis of the available data is “non-quantifiable”. On the side of the greater harm, the extent “considerable” was achieved. Because the added benefit is non-quantifiable, it is not possible to state definitively whether a downgrading of the extent regarding added benefit would be reasonable. However, the question arises as to whether the negative effects entirely outweigh the positive. In the Institute’s view, because of the contrary indication of considerable greater harm in terms of serious adverse events, the indication of an added benefit of non-quantifiable extent regarding serious late complications is, however, questioned.

In summary, an added benefit of TVR + PegIFN/RBV over the ACT PegIFN/RBV for previously treated relapsed patients with cirrhosis is not proven.

2.5.5 Previously treated patients – relapsed patients without cirrhosis

As described in Section 2.3.1, there were no studies included in the assessment for relapsed patients without cirrhosis and hence no usable data were available.

The main result of the additionally presented REALIZE study is that – as also in relapsed patients with cirrhosis – there were effects in favour of telaprevir in terms of SVR and to the disadvantage of telaprevir regarding serious adverse events.

In summary, an added benefit of TVR + PegIFN/RBV over the ACT PegIFN/RBV for relapsed patients without cirrhosis is not proven. This is largely because of the lack of data for the approved RGT treatment regimen for this population. It is pointed out here that approval was granted on the basis of the study data presented by the company for this benefit assessment, but changes in the treatment regimen were subsequently made for this population. Thus, there are no data on the current approval status in this population available for the present benefit assessment.

2.5.6 Patients co-infected with HIV and/or HBV

As described in Section 2.4.4, there are no usable data for patients co-infected with HIV and/or HBV and the company also explicitly claims no added benefit for these groups of patients.

The added benefit of TVR + PegIFN/RBV over the ACT PegIFN/RBV for the patient population co-infected with HIV and/or HBV is not proven for any of the above-mentioned subindications.

2.5.7 Extent and probability of the added benefit - summary

The extent and probability of the added benefit compared with the ACT for the various subindications of telaprevir are summarized below:

Table 21: Telaprevir: extent and probability of the added benefit

	Therapeutic indication of telaprevir + PegIFN/RBV, disease entities / subindications*	**Appropriate comparator therapy**	**Extent and probability of the added benefit**
1	Genotype 1 chronic HCV infection. Treatment-naïve patients without cirrhosis	PegIFN/RBV	
1a	high baseline viral load		Proof of an added benefit of telaprevir (extent "non-quantifiable")
1b	low baseline viral load		Indication of a lesser benefit of telaprevir
2	Genotype 1 chronic HCV infection. Treatment-naïve patients with cirrhosis	PegIFN/RBV	Added benefit not proven.
3	Genotype 1 chronic HCV infection. Previously treated non-responders	PegIFN/RBV	
3a	without cirrhosis		Indication of an added benefit of telaprevir (extent "non-quantifiable")
3b	with cirrhosis		Hint of an added benefit of telaprevir (extent "non-quantifiable")
4	Genotype 1 chronic HCV infection. Previously treated relapsed patients with cirrhosis	PegIFN/RBV	Added benefit not proven.
5	Genotype 1 chronic HCV infection. Previously treated relapsed patients without cirrhosis	PegIFN/RBV	Added benefit not proven.
Subdivisions 1–5 arise from the approval requirements for the therapeutic indication and/or the treatment regimen. Subdivisions a–b arise because the data provide proof and/or an indication of a relevant effect modification. *: The population of patients co-infected with HIV and/or HBV is excluded in each case because the company did not include this group of patients in the assessment from the outset. The conclusions therefore apply only to patients without co-infections. The added benefit is not proven for HIV and/or HBV co-infected patients. HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; PegIFN: pegylated (Peg)Interferon alfa; RBV: ribavirin			

This overall assessment deviates substantially from that of the company, which claimed proof of a major added benefit for all patients except the co-infected patients. The assessment regarding the co-infected patients corresponds with that of the company, which did not derive any added benefit for this group of patients.

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier and in Section 2.7.2.8 of the full dossier assessment

2.6 List of included studies

ADVANCE

Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011; 364(25): 2405-2416.

Vertex Pharmaceuticals. A phase 3 study of telaprevir in combination with Pegasys and Copegus in treatment-naive subjects with genotype 1 HCV [online]. In: Clinicaltrials.gov. 22.06.2011 [Accessed on: 20.12.2011].
URL: http://clinicaltrials.gov/ct2/show/NCT00627926.

Vertex Pharmaceuticals, Tibotec. Module 2.7 clinical summary: 2.7.3 summary of clinical efficacy for telaprevir in subjects with hepatitis C; addendum [unpublished]. 2011.

Vertex Pharmaceuticals, Tibotec. A phase 3 study of 2 dose regimens of telaprevir in combination with peginterferon alfa-2a (Pegasys) and ribavirin (Copegus) in treatment-naive subjects with genotype 1 chronic hepatitis C: study VX07-950-108; clinical study report [unpublished]. 2010.

Vertex Pharmaceuticals, Tibotec. A phase 3 study of 2 dose regimens of telaprevir in combination with peginterferon alfa-2a (Pegasys) and ribavirin (Copegus) in treatment-naive subjects with genotype 1 chronic hepatitis C: study VX07-950-108; clinical trial protocol [unpublished]. 2009.

Vertex Pharmaceuticals, Tibotec. A phase 3 study of 2 dose regimens of telaprevir in combination with peginterferon alfa-2a (Pegasys) and ribavirin (Copegus) in treatment-naive subjects with genotype 1 chronic hepatitis C: study VX07-950-108; patient-reported outcomes report [unpublished]. 2010.

G060-A6

Kondo K. Efficacy and safety of MP-424/peginterferon alfa-2b/ribavirin combination in treatment-naive patients with chronic hepatitis C [online]. In: Clinicaltrials.gov. 06.03.2011 [Accessed on: 20.12.2011]. URL: http://clinicaltrials.gov/ct2/show/NCT00780416.

Kumada H, Toyota J, Okanoue T, Chayama K, Tsubouchi H, Hayashi N. Telaprevir with peginterferon and ribavirin for treatment-naive patients chronically infected with HCV of genotype 1 in Japan. J Hepatol 2011; 56(1): 78-84.

Mitsubishi Tanabe Pharma. Verification study of MP-424 targeting chronic hepatitis C (initial treatment): combination study with peginterferon alfa-2b (genetic recombination) and ribavirin; study G060-A6; summary report [unpublished]. 2010.

REALIZE

Tibotec. A randomized, double-blind, placebo-controlled, phase III trial of 2 regimens of telaprevir (with and without delayed start) combined with pegylated interferon alfa-2a (Pegasys) and ribavirin (Copegus) in subjects with chronic genotype 1 hepatitis C infection who failed prior pegylated interferon plus ribavirin treatment: study VX-950-TiDP24-C216; patient-reported outcomes report [unpublished]. 2010.

Tibotec. A randomized, double-blind, placebo-controlled, phase III trial of 2 regimens of telaprevir (with and without delayed start) combined with pegylated interferon alfa-2a (Pegasys) and ribavirin (Copegus) in subjects with chronic genotype 1 hepatitis C infection who failed prior pegylated interferon plus ribavirin treatment: study VX-950-TiDP24-C216; clinical research report [unpublished]. 2010.

Tibotec. A randomized, double-blind, placebo-controlled, phase III trial of 2 regimens of telaprevir (with and without delayed start) combined with pegylated interferon alfa-2a (Pegasys) and ribavirin (Copegus) in subjects with chronic genotype 1 hepatitis C infection who failed prior pegylated interferon plus ribavirin treatment: study VX-950-TiDP24-C216; revised clinical trial protocol [unpublished]. 2009.

Tibotec. VX-950-TiDP24-C216: a safety and efficacy study of telaprevir in chronic, genotype 1, hepatitis C patients that failed previous standard treatment [online]. In: Clinicaltrials.gov. 18.07.2011 [Accessed on: 20.12.2011].
URL: http://clinicaltrials.gov/ct2/show/NCT00703118.

Vertex Pharmaceuticals, Tibotec. Module 2.7 clinical summary: 2.7.4 summary of clinical safety for telaprevir in subjects with hepatitis C [unpublished]. 2011.

Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S et al. Telaprevir for retreatment of HCV infection. N Engl J Med 2011; 364(25): 2417-2428.

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(please see full dossier assessment for full reference list)

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