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List of abbreviations

Abbreviation	Meaning
CHC	chronic hepatitis C
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HIV	human immunodeficiency virus
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IU	international units
NICE	National Institute for Health and Care Excellence
PEG	peginterferon alfa
RBV	ribavirin
RCT	randomized controlled trial
SIM	simeprevir
SVR 24	sustained virologic response 24 weeks after the end of treatment

1 Background

On 6 October 2014 the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A14-18 (benefit assessment of simeprevir) [1].

In the commenting procedure on the assessment of simeprevir, the pharmaceutical company (hereinafter referred to as "the company") submitted further data in its comment to the G-BA [2] that went beyond the information in the dossier [citation]. These were the following analyses:

- historical comparison including the TMC435-TiDP16-C212 study in chronic hepatitis C (CHC) genotype 1 patients with human immunodeficiency virus (HIV) coinfection
- historical comparison including the RESTORE study in CHC genotype 4 patients

The G-BA commissioned IQWiG to assess these analyses subsequently submitted.

In the following Chapter 2 the analyses subsequently submitted are assessed in Sections 2.1 and 2.2. A summarizing assessment and presentation of whether the analyses subsequently submitted change the conclusions of the original benefit assessment A14-18 can be found in Section 2.3.

The responsibility for the present assessment and its result lies solely with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

2.1 Assessment of the historical comparison in CHC genotype 1 patients with HIV coinfection

In its dossier from 21 May 2014, the company included the one-arm TMC435-TiDP16-C212 study (hereinafter referred to as "study C212") with simeprevir (SIM) + peginterferon alfa (PEG) + ribavirin (RBV) in treatment-naive and treatment-experienced CHC genotype 1 patients with HIV coinfection in the benefit assessment (see Appendix A for characteristics of the study). The added benefit of SIM + PEG + RBV was not proven in this patient population, however, because the company presented no data on the comparator therapy PEG + RBV that were systematically searched for and assessed [1].

For its comment, the company searched for randomized controlled trials (RCTs), uncontrolled (one-arm) clinical studies and observational studies (cohort studies) in which treatment-naive or treatment-experienced adult patients with CHC genotype 1 infection and HIV coinfection were treated with PEG + RBV. From the studies identified, the company used study arms in which patients were treated with peginterferon alfa-2a and ribavirin and compared the results with the C212 study results [2]. This approach represents an unadjusted historical comparison.

The unadjusted historical comparison presented by the company was unsuitable to draw robust conclusions on the comparison of SIM + PEG + RBV and PEG + RBV in patients with CHC genotype 1 and HIV coinfection.

Information retrieval

The company exclusively conducted a bibliographical literature search to identify studies for its historical comparison. The company did not conduct the search in trial registries required in accordance with the dossier template. Hence the information retrieval conducted by the company for the historical comparison did not fulfil the dossier requirements for information retrieval for "further investigations".

Suitability and similarity of the studies included

In its bibliographical search, the company identified 11 studies, from which it included a total of 12 study arms in the comparison with its one-arm study C212. PEG + RBV were not used in compliance with the approval in 7 of these 12 study arms (treatment duration too short and/or insufficient dosage of ribavirin). The company described this problem too and presented an analysis of the remaining 5 study arms for the sustained virologic response 24 weeks after the end of treatment (SVR 24), which it rated as sensitivity analysis. The company also included the patients who were not treated in compliance with the approval in its main analysis. This main analysis is not further commented on.

Further consideration of the similarity of the studies in the present addendum is limited to the 5 studies with approval-compliant use of PEG + RBV (Murphy 2011 [3], Rivero-Juarez 2014 [4], Rodriguez-Torres 2012 [5], Torres-Cornejo 2014 [6], Tural 2008 [7]). The patients'

age and the proportion of male patients in these study arms were comparable with the patient characteristics of the C212 study. Information on the proportion of patients with high viral load (> 800 000 international units [IU]/mL) was only available for 2 of the 5 study arms (Rodriguez-Torres 2012: 80%, Torres-Cornejo 2014: 73%), these values are marginally below the ones of the C212 study (86%). Greater differences between the patient populations occurred with regard to the stage of the liver disease. Whereas the proportion of patients with cirrhosis was comparable in the studies C212 (13%) and Rodriguez-Torres 2012 (12%), the proportion of patients with very advanced liver disease was higher in the Torres-Cornejo study (39% METAVIR score F4). From the studies Rivero-Juarez 2014 and Tural 2008, only information on the METAVIR score F3-F4 were available. For Rivero-Juarez 2014 (51%), these were considerably, and for Tural 2008 (38%) slightly above the information provided for the C212 study (33%). The influence of these differences on the comparison of the SVR 24 remains unclear.

Assessment of the SVR rates and the results on adverse events

An SVR 24 of 22% to 50% was observed in the 5 study arms with approval-compliant use of PEG + RBV. The SVR 24 in the C212 study was 73%. The difference between the SVR 24 under PEG + RBV and under SIM + PEG + RBV did not meet the criteria for a “dramatic effect” [8], i.e.it was not so large that it could no longer be explained by the influence of confounders alone in the present naive comparison of treatment arms.

Only occasional information on adverse events was available in the studies with PEG + RBV. The overall rate of adverse events and serious adverse events was only available in the Rodriguez-Torres 2012 study (96% and 17% of patients with event in the study arm with approval-compliant use), study discontinuation due to adverse event was only reported in Torres-Cornejo 2014 (16% of the patients). In the C212 study, an adverse event was reported in 98% of the patients, a serious adverse event in 10%, and discontinuation due to adverse events in 5%. No robust conclusions on the comparison of PEG + RBV with SIM + PEG + RBV can be drawn based on these data.

2.2 Assessment of the historical comparison in CHC genotype 4 patients

In its dossier from 21 May 2014, the company included the one-arm RESTORE study with SIM + PEG + RBV in treatment-naive and treatment-experienced CHC genotype 4 patients in the benefit assessment (see Appendix B for characteristics of the study). The added benefit of SIM + PEG + RBV was not proven in this patient population, however, because the company presented no data on the comparator therapy PEG + RBV that were systematically searched for and assessed [1].

In its comment, the company presented a so-called “matching-adjusted indirect comparison” based on a systematic literature search. It compared the results of the RESTORE study with individual arms of the studies it included [2].

Information retrieval

For its comment, the company used a systematic literature search, which was conducted for a dossier for the English National Institute for Health and Care Excellence (NICE), and supplemented this with a handsearch in conference proceedings and health technology assessment websites. This search did not fulfil the requirements for the dossier and is unsuitable to ensure the completeness of the search result.

The search in bibliographical databases presented by the company did not meet the requirements described in the dossier templates because the result of the bibliographical literature search, which was conducted in November 2013, was not sufficiently up to date. Moreover, the company did not conduct the search in trial registries required according to the dossier templates. In addition, the company claimed in its comment to use the bibliographical literature search to search for clinical studies in general. However, the search strategy in MEDLINE is unsuitable to completely identify one-arm studies too. The fact that 2 of the 5 studies included by the company were not identified by this search strategy made this particularly clear.

The company's approach on the comparison of SIM + PEG + RBV and PEG + RBV is not further commented on because of the serious deficiencies in information retrieval.

The comparison presented by the company was unsuitable to draw robust conclusions on the comparison of SIM + PEG + RBV and PEG + RBV in CHC genotype 4 patients.

2.3 Summarizing assessment

The documents subsequently submitted by the company with the comments do not change the result of the benefit assessment of simeprevir (dossier assessment A14-18 [1]). This applies both to genotype 1 patients with HIV coinfection and to genotype 4 patients.

3 References

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Appendix A – Information on the TMC435-TiDP16-C212 study

Table 1: Characteristics of study TMC435-TiDP16-C212: SIM + PEG + RBV (patients with HIV coinfection)

Study	Study design	Population	Interventions (number of treated patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
TMC435-TiDP16-C212	open-label, multicentre	Adult (18-70 years) patients with confirmed chronic HCV infection (genotype 1) and HIV coinfection plasma HCV RNA > 10 000 IU/mL at screening treatment-naive patients or patients pretreated with PEG + RBV (at least one treatment cycle)	SIM + PEG + RBV (N = 106)	Treatment duration: SIM simeprevir: 12 weeks PEG + RBV: 24 or 48 weeks (response-guided) follow-up until week 48 or 72	Canada, France, Germany, Great Britain, Portugal, Puerto Rico, Spain, United States 9/2011-8/2013	Primary: proportion of patients with SVR 12 Secondary: patients with SVR 24, adverse events

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes exclusively contain information on the relevant available outcomes for this benefit assessment.

HCV: hepatitis C virus; HIV: human immunodeficiency virus; IU: international units; N: number of randomized patients; PEG: peginterferon alfa; RBV: ribavirin; RNA: ribonucleic acid; SIM: simeprevir; SVR: sustained virologic response

Table 2: Characteristics of the interventions in study TMC435-TiDP16-C212: SIM + PEG + RBV (patients with HIV coinfection)

Study	**SIM + PEG + RBV**	**Concomitant medication**
TMC435-TiDP16-C212	Week 1-12: Simeprevir orally 150 mg once daily + PEG subcutaneously 180 µg once weekly + RBV 1000 or 1200 mg/day orally (depending on body weight: < 75 kg = 1000 mg/day; ≥ 75 kg = 1200 mg/day), divided into 2 doses/day Week 13-24 or 13-48 (response-guided): PEG + RBV, same dosage as week 1-12	Prohibited at any time point: ▪ any other anti-HCV treatments Prohibited from 30 days before screening until the end of the study: ▪ all investigational drugs and medical devices Prohibited from screening until the end of the study: ▪ immunomodulators, all herbal anti-HCV drugs or HCV-specific dietary supplements Prohibited during the treatment phase: ▪ CYP3A4 inducers ▪ CYP3A4 inhibitors ▪ CYP3A4 substrates with low therapeutic indices ▪ CYP1A2 substrates with low therapeutic indices ▪ CYP2C8 substrates with low therapeutic indices
CYP: cytochrome P450; HCV: hepatitis C virus; HIV: human immunodeficiency virus; PEG: peginterferon alfa; RBV: ribavirin; SIM: simeprevir		

Table 3: Characteristics of the study population in study TMC435-TiDP16-C212: SIM + PEG + RBV (patients with HIV coinfection)

Study group	N	Age [years] mean (SD)	Sex [F/M[%	Fibrosis score[a] %	Cirrhosis[b] [with/without] %	Genotype [1a/1b/1d] %	Viral load [≤ 800 000/ > 800 000] %	Ethnicity [white/black/ other] %	Study discon-tinuations n (%)
TMC435-TiDP16-C212	106	46.6 (8.11)	15.1/84.9	F0: 10.4 F1: 25.4 F2: 31.3 F3: 19.4 F4: 13.4	13.1/86.9	82.1/17.0/0.9	14.2[c]/85.8	82.1/14.2/3.8[c]	9 (8.5)

a: N = 67, no results on the METAVIR score were available for 37 patients.
b: N = 99, no results on the METAVIR score were available for 7 patients.
c: Institute's calculation for others.
F: female; HIV: human immunodeficiency virus; M: male; N: number of randomized (or included) patients; n: number of patients with event; PEG: peginterferon alfa; RBV: ribavirin; SD: standard deviation; SIM: simeprevir

Appendix B – Information on the RESTORE study

Table 4: Characteristics of the RESTORE study included: SIM + PEG + RBV (patients with HCV genotype 4)

Study	Study design	Population	Interventions (number of treated patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
RESTORE	Open-label, multicentre	Adult (18-70 years) patients with confirmed chronic HCV infection (genotype 4) plasma HCV RNA > 10 000 IU/mL at screening treatment-naive patients or patients pretreated with PEG + RBV (at least one treatment cycle)	SIM + PEG + RBV (N = 107)	Treatment duration: SIM simeprevir: 12 weeks PEG + RBV: 24 or 48 weeks (response-guided) follow-up until week 48 or 72	Belgium, France 3/2012-3/2014	Primary: proportion of patients with SVR 12 Secondary: proportion of patients with SVR 24, adverse events

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes exclusively contain information on the relevant available outcomes for this benefit assessment.

HCV: hepatitis C virus; IU: international units; N: number of randomized patients; PEG: peginterferon alfa; RBV: ribavirin; RNA: ribonucleic acid; SIM: simeprevir; SVR: sustained virologic response

Table 5: Characteristics of the interventions in the RESTORE study: SIM + PEG + RBV (patients with HCV genotype 4)

Study	**SIM + PEG + RBV**	**Concomitant medication**
RESTORE	Week 1-12: Simeprevir orally 150 mg once daily + PEG subcutaneously 180 µg once weekly + RBV 1000 or 1200 mg/day orally (depending on body weight: < 75 kg = 1000 mg/day; ≥ 75 kg = 1200 mg/day), divided into 2 doses/day Week 13-24 or 13-48 (response-guided): PEG + RBV, same dosage as week 1-12	Prohibited at any time point: ▪ any other anti-HCV treatments Prohibited from 30 days before screening until the end of the study: ▪ all investigational drugs and medical devices ▪ nitazoxanide ▪ praziquantel Prohibited from screening until the end of the study: ▪ immunomodulators ▪ substances that stimulate blood production Prohibited during the treatment phase: ▪ CYP3A4 inducers ▪ CYP3A4 inhibitors ▪ CYP3A4 substrates with low therapeutic indices Use only with caution, i.e. lowest possible dosage and observation of adverse events: ▪ analgesics, calcium channel blockers, lipid-lowering drugs, phosphodiesterase-5 inhibitors, sedatives, buprenorphine
CYP: cytochrome P450; HCV: hepatitis C virus; PEG: peginterferon alfa; RBV: ribavirin; SIM: simeprevir		

Table 6: Characteristics of the study population in the RESTORE study: SIM + PEG + RBV (patients with CHC genotype 4)

Study group	N	Age [years] mean (SD)	Sex [F/M] %	Fibrosis score %	Cirrhosis [with/without] %	Viral load [≤ 800 000/ > 800 000] %	Ethnicity [white/black/ other] %	Study discontinuations n (%)
RESTORE	107	49.6 (8.35)	21.5/78.5	F0-F1: 32.7 F2: 24.0 F3: 14.4 F4: 28.8	ND	40.2[a]/59.8	72.0/28.0/0	0 (0)

a: Institute's calculation.

CHC: chronic hepatitis C; F: female; M: male; N: number of randomized (or included) patients; n: number of patients with events; ND: no data; PEG: peginterferon alfa; RBV: ribavirin; SD: standard deviation; SIM: simeprevir