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Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
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)
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
SVR	sustained virologic response
SVR 24	sustained virologic response measured 24 weeks after the end of treatment

1 Background

On 13 June 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 A14-05 (benefit assessment of sofosbuvir [1]).

In the commenting procedure on the assessment of sofosbuvir, as Appendix 1 of its comment, the pharmaceutical company (hereinafter abbreviated to "the company") submitted further data to the G-BA [2] that went beyond the information in the dossier [3]. These were the following analyses:

- historical comparison including the P7977-1910 study in treatment-naive genotype 1 patients with human immunodeficiency virus (HIV) coinfection
- supplementation of the historical comparison in treatment-naive genotype 1 patients
- additional analyses on the outcomes of adverse events (AEs) of the FISSION study (treatment-naive genotype 2 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 to 2.3. A summarizing assessment and presentation of whether the analyses subsequently submitted change the conclusions of the original benefit assessment A14-05 can be found in Section 2.4.

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 treatment-naive genotype 1 patients with HIV coinfection

The company presented an unadjusted indirect comparison for treatment-naive genotype 1 patients with HIV coinfection in Section 1.1 of the documents subsequently submitted with its comment [2]. The company did not submit these data in the original dossier because, according to the company, the final results of the study with sofosbuvir (study P7977-1910 [4]) relevant for this were not yet available at the time the dossier was submitted.

The unadjusted historical comparison presented by the company was unsuitable.

Information retrieval inadequate

According to the company, it limited the choice of the studies on the comparator therapy to those studies it had already identified for the original dossier [3] (for the assessment in genotype 2 or 3 patients with HIV coinfection). As described in dossier assessment A14-05, the search conducted by the company was incomplete because it used different inclusion criteria for the intervention (sofosbuvir) and the comparator therapy, and only included study arms from randomized controlled trials (RCTs) for the comparator therapy to "reduce the number of hits". There was therefore a systematic difference between the underlying data of the intervention and the one of the comparator therapy, and the unadjusted indirect comparison presented by the company was incomplete.

Additionally it should be noted that the company not even considered the search step it had corrected for treatment-naive genotype 1 patients in the comments (secondary selection of the search result from trial registries, see Section 2.2) for the comparison now presented. The company did not justify this inconsistent approach.

Contents of included studies not sufficiently similar

The company also included studies with patients with other genotypes than genotype 1 [4-7]. For the comparator therapy this was already clear from the fact that the underlying data only consisted of studies the company had used for the assessment of genotype 2 and 3 patients in the original dossier. The company presented no analyses for genotype 1 alone. For the P7977-1910 study included by the company, it was evident from the documents submitted by the company that the patients for whom no sustained virologic response (SVR) measured 24 weeks after the end of treatment (SVR 24) was reached, all had genotype 1, which is the one of interest [4].

Moreover, patients with cirrhosis were sometimes also included in the studies on the comparator therapy [7-9], whereas these were excluded from the study with sofosbuvir. The company presented no analyses for patients without cirrhosis alone.

Finally, on the side of the comparator therapy the company also included studies in which the dose range for ribavirin (and partially also for peginterferon) partly did not concur with the Summary of Product Characteristics (SPC) valid in Germany, so that underdosage was possible [5,7,9]. The company presented no analyses in which underdosage of the comparator therapy was excluded.

Assessment of the SVR rates and the results on adverse events

The SVR rates differed considerably in the studies on the comparator therapy presented by the company. It ranged from approximately 45% (Sulkowski 2013b [7]) to approximately 22% (Rodriguez-Torres 2012 [8]). This difference was of a magnitude the company called "dramatic effect" (relative risk [RR] at least 2). This clearly shows that the definition of a dramatic effect chosen by the company is unsuitable overall, but also specifically for the present research question. However, the clear heterogeneity within the study pool on the comparator therapy also shows that in the present case the result can depend to an important degree on other factors than the treatment applied. A high threshold for the derivation of an added benefit based on the unadjusted indirect comparison is therefore necessary. In relation to the threshold used and justified in the dossier assessment A14-05 [1], there was no dramatic effect between sofosbuvir and the comparator therapy.

Also with regard to AEs, there were mostly large differences between the studies on the comparator therapy. However, the clear heterogeneity within the study pool on the comparator therapy again shows that in the present case the result can depend to an important degree on other factors than the treatment applied. Moreover, the company did not consider the differences in treatment duration between the studies on sofosbuvir and those on the comparator therapy: The same problem occurs that was mentioned in dossier assessment A14-05 [1] in the assessment of the FISSION study on genotype 2, and which the company addressed with the analyses in Section 1.3 of the documents presented with its comment (see Section 2.3). It remained unclear why the company addressed this point in the assessment on genotype 2, but not in the assessment on genotype 1, and hence was inconsistent in its approach. In relation to the threshold described and justified in the dossier assessment A14-05 [1], there was also no dramatic effect for most AE outcomes between sofosbuvir and the comparator therapy. The only exception was the difference described by the company for serious AEs (SAEs). However, this might be caused by the fact that the sofosbuvir study with a total of 23 patients was too small to detect possible SAEs. In the 2 larger studies on sofosbuvir with patients of the same genotype (but without HIV coinfection), under an identical therapeutic regimen, SAEs occurred in 1.2% (NEUTRINO study [10]) and 3.9% (ATOMIC study [11]) of the patients.

2.2 Assessment of the amendments to the historical comparison in treatment-naive genotype 1 patients without cirrhosis

The company presented amendments to the unadjusted indirect comparison in treatment-naive genotype 1 patients in Section 1.2 of the documents subsequently submitted with its comment

[2]. This was an expansion with studies on the comparator therapy that were excluded in the dossier due to the study type (no RCTs) and due to the application, which was not compliant with the approval. Both aspects were addressed in the dossier assessment A14-05 [1]. The analyses now presented by the company are still unsuitable for the benefit assessment, however.

Information retrieval still insufficient

According to the company, it conducted the amendment with studies of other study types, and with those that did not use the investigated drugs in compliance with the approval, exclusively on the basis of the original search in trial registries. However, this was only one part of the total search. The company completely disregarded the bibliographic search, which was the part that produced the considerably greater number of hits. On the one hand, it would have needed to change this search in order not to exclude non-randomized studies by the search itself from the outset. On the other hand, it would have needed to completely reselect the search result to also consider studies it had excluded based on the abstract because of the study type or the approval status.

Overall, there was therefore still a systematic difference between the underlying data of the intervention (sofosbuvir) and the comparator therapy. The company presented an incomplete unadjusted indirect comparison and justified the limitation with the effort involved (“to reduce the number of hits” [3]). The (reduced) effort alone is no sufficient justification if it cannot be explained that the studies that were not considered had no influence on the result. The company did not provide such proof.

Inclusion of studies without sufficient evaluation with regard to contents

It was pointed out in the dossier assessment A14-05 that the company’s conclusions on the relevance of individual studies with the triple therapy were contradictory. On the one hand, the company named any deviation from the dosage approved according to the SPC as a reason for exclusion (this was not consistently implemented, however). On the other hand, it justified the choice of the ACT with the results of the benefit assessments on the triple therapy with boceprevir and telaprevir respectively and the related G-BA decisions. In these benefit assessments however, the deviations from the approval status were evaluated with regard to contents, and the studies with negligible deviations were not excluded [12,13]. In the dossier assessment A14-05 on sofosbuvir it is therefore noted [1]: “The inclusion criterion of a use of the treatments that is not in accordance with the approval is basically acceptable. However, it must be examined whether deviations from the approval-compliant use limit the interpretability of the data."

In the documents subsequently submitted in the comment, the company only conducted an inadequate evaluation with regard to contents of any deviations. At first the company also included studies in which treatment deviated from the approval status. It then conducted sensitivity analyses in which those studies were excluded in which ribavirin was underdosed. However, it did not consider further important deviations relevant for the assessment,

particularly not those that were already addressed in the benefit assessments on the triple therapy and resulted in the exclusion of individual studies or study arms. For example, the company included arm C from the SPRINT-2 study, although it was excluded with justification from the assessment A11-17 on boceprevir because no response-guided treatment regimen was investigated [12].

Further inclusion criteria still partly inadequate

It was pointed out in the dossier assessment A14-05 that the exclusion of studies that only report results either on genotype 1a or on genotype 1b is inadequate. The company did not correct this erroneous exclusion of studies in the documents subsequently submitted although the research question comprised both subgenotypes.

It was also noted in the dossier assessment A14-05 that only patients without cirrhosis are relevant for the comparison with the triple therapy. However, in the supplementary analyses the company also considered studies in which patients with cirrhosis were included, although the company itself talked of a "historical comparison in treatment-naive patients with chronic hepatitis C by genotype 1 without cirrhosis". As patients with cirrhosis, particularly under triple therapy, have a considerably lower SVR rate, the SVR rates for patients without cirrhosis are underestimated in the consideration of the total population of the studies. Most studies presented by the company also included patients with cirrhosis. Their proportion was between approximately 5% and approximately 15%.

Assessment of the SVR rates and the results on adverse events

The SVR rates differed considerably in the studies on the comparator therapy presented by the company. It ranged from approximately 40% (Group A of the study Poordad 2013 [14]) to approximately 92% (Group A of the ILLUMINATE study [15]). This difference was of a magnitude the company called "dramatic effect" (RR at least 2).

Also with regard to AEs, there were considerable differences between the studies on the comparator therapy. This also applies to the overall rate of SAEs in particular. The company again used an inconsistent approach in the present research question because it did not address the differences in treatment duration between the studies on sofosbuvir and those on the comparator therapy.

Overall, in relation to the threshold described and justified in the dossier assessment A14-05, there was no dramatic effect both for the SVR rate and the individual AE outcomes between sofosbuvir and the comparator therapy.

2.3 Assessment of the data on adverse events for treatment-naive genotype 2 patients subsequently submitted

The company presented supplementary analyses on AE outcomes of the FISSION study in Section 1.3 of the documents subsequently submitted with its comment [2].

In the analyses from Section 1.3.1 of the company's documents, the frequencies of AEs are compared that occurred in the period of 12 weeks + 30 days (treatment arm sofosbuvir + ribavirin) and in the period of 24 weeks + 30 days (treatment arm peginterferon alfa + ribavirin). Besides an analysis in which only patients were considered who received at least one study medication (safety analysis), 2 further analyses were available, in which all randomized patients were considered. In these analyses, either "no event" (imputation strategy 1) or "1 event" (imputation strategy 2) was assumed for all patients of the treatment arm sofosbuvir + ribavirin who discontinued treatment already before administration of the first medication. For the control treatment peginterferon alfa + ribavirin, "no event" was assumed for the respective patients [16]. These additional analyses with imputation methods were not conducted for the outcomes "death" and "SAEs".

In Section 1.3.1.1 of the company's documents, 2 analyses of the frequencies of AEs, in which only the period of 12 weeks after the start of treatment were considered, were presented besides another presentation of the results of the safety analyses (see above). Again, for patients who discontinued treatment already before administration of the first medication, either "no event" or "1 event" was assumed in the treatment arm sofosbuvir + ribavirin, and "no event" was assumed in the treatment arm peginterferon alfa + ribavirin. These additional analyses were not conducted for the outcomes "death" and "SAEs".

All participants of the study, independent from their genotype, were considered in the analyses presented by the company. The patients in the FISSION study mostly had genotype 2 or 3: Of the patients who received at least 1 study medication, 71.9% had genotype 3, and 27.5% had genotype 2. Based on the information provided by the company, it can be assumed that the hepatitis C virus genotype has an influence on the frequency of AEs. Even if this assumption applied to side effects from treatment (for which the company presented no evidence), this would be no sufficient justification for the effects on AEs not depending from the genotype. This is because, besides "actual" side effects, the recording of AEs also documents other AEs such as those that are caused by the disease itself. Hence the result of an analysis of the total population cannot be transferred to the subpopulation of genotype 2 patients without the appropriate evidence. As the analyses in Section 1.3.1 and the analyses in Section 1.3.1.1 of the company's documents were conducted for the total population, their results cannot be used for the benefit assessment of a genotype 2 population.

It should be noted as additional information that the company's approach is not comprehensible because the problem of the missing analyses according to genotype was pointed out in dossier assessment A14-05 [1]. The company only selectively addressed some of the aspects pointed out in the dossier assessment with this submission of the analyses, but still provided no complete data base, although it would have been possible for the company. There is still no list of the individual AEs that occurred in genotype 2 patients and no subgroup analyses on AEs for genotype 2 patients.

2.4 Summarizing assessment

The documents subsequently submitted as Appendix 1 with the comment do not change the result of the benefit assessment (dossier assessment A14-05 [1]). This applies for treatment-naive genotype 1 patients with HIV coinfection, for treatment-naive genotype 1 patients without HIV coinfection, and for treatment-naive genotype 2 patients without HIV coinfection.

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