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(Addendum to Commission A14-31)[1]

Addendum

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[2] Due to legal data protection regulations, employees have the right not to be named.

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HCV	hepatitis C virus
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
MAIC	matching-adjusted indirect comparison
RNA	ribonucleic acid
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
SVR	sustained virologic response

1 Background

On 13 January 2015, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A14-31 (Daclatasvir – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

With its comment, the pharmaceutical company (hereinafter referred to as "the company") presented results on the ALLY 3 study (AI444218) in patients with genotype 3 [2]. The company had designated this study as "ongoing" in the original dossier [3]. Moreover, the company presented additional sensitivity analyses on sustained virologic response (SVR) for the AI444042 study in treatment-naive patients with genotype 4 with its comment [2].

The G-BA therefore commissioned IQWiG to assess the data and analyses of the ALLY 3 study and the sensitivity analyses for the AI444042 study.

The responsibility for the present assessment and the results of the assessment lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

With its comment, the company presented results on the ALLY 3 study (AI444218) in patients with genotype 3 and additional sensitivity analyses on the outcome "SVR" for the AI444042 study in treatment-naive patients with genotype 4 [2].

The assessment of the ALLY 3 study can be found in the following Section 2.1. The additional analyses on the AI444042 study are assessed in the subsequent Section 2.2. Section 2.3 summarizes whether, and, if any, which conclusions of the original dossier assessment A14-31 were changed by the newly submitted data.

2.1 Assessment of the ALLY 3 study (genotype 3)

Data and analyses presented on the ALLY 3 study

The company did not present the analyses on the ALLY 3 study in accordance with the G-BA's methodological requirements. It did not describe the design of the ALLY 3 study in detail in the dossier or in its comment. The company also presented no information on baseline data of the study population and on the operationalization of the individual outcomes in the dossier or in the comment. Finally, the company also only provided an incomplete report of the results on the ALLY 3 study in its comment. Some of the missing data can be found in further documents submitted with the comment or with the original dossier ("top-line results" [4] and study protocol [5] of the ALLY 3 study).

Assessment of the ALLY 3 study

The ALLY 3 study was an open-label, uncontrolled study in which treatment-naive and treatment-experienced genotype 3 patients with or without cirrhosis were included. All patients were treated for 12 weeks and in combination with sofosbuvir. Hence the treatment deviated substantially from the recommendations on treatment regimens and treatment duration of daclatasvir, which specify a combination therapy with sofosbuvir and ribavirin over a period of 24 weeks for genotype 3 patients with compensated cirrhosis and for treatment-experienced patients [6]. According to the Summary of Product Characteristics (SPC) of daclatasvir, there is no treatment recommendation for treatment-naive patients without cirrhosis [6]. Moreover, the ALLY 3 study provided no results in comparison with the ACT because of the uncontrolled design (see below for the matching-adjusted indirect comparison [MAIC] additionally presented by the company).

Overall, the ALLY 3 study is unsuitable for conclusions on the added benefit of daclatasvir. Regardless of this, the results on the SVR and on adverse events (AEs), serious AEs (SAEs) and discontinuations due to AEs are presented in Appendix A as additional information.

Additional information on the MAIC with the ALLY 3 study

In its comment, the company referred to its MAIC analysis, in which, among other things, the results of the ALLY 3 study were compared with results from studies on the combination therapy of peginterferon and ribavirin in genotype 3.

Since the ALLY 3 study is unsuitable for the assessment of the added benefit of daclatasvir (see above), the MAIC analysis presented by the company is also unsuitable already for this reason. Regardless of this, the company also provided no comprehensible processing of this analysis in its comment. Important deficiencies regarding the methods and the presentation of the analysis could be inferred from the Appendix [7] submitted with the comment, however, which is why the MAIC analysis is unsuitable for the assessment of the added benefit also for these reasons. In particular, there was no search in trial registries, the search was not documented in a comprehensible way (no information on search interfaces, no search strategies adapted to interfaces or databases, no listing of the references excluded in the full text screening with reasons for exclusion) and the inclusion and exclusion criteria were not adequate (see comments on the MAIC in genotype 1 in dossier assessment A14-31 [1]).

2.2 Sensitivity analyses on the outcome "SVR" of the AI444042 study (treatment-naive genotype 4 patients)

Necessity of the sensitivity analyses

In the AI444042 study on the comparison of daclatasvir + peginterferon alfa-2a + ribavirin versus peginterferon alfa-2a + ribavirin (+ placebo) in treatment-naive genotype 4 patients, unsuitable criteria for treatment discontinuation were chosen in the control arm, which may have led to an underestimation of the SVR rate [1]. Hence sensitivity analyses on the outcome "SVR" were conducted in dossier assessment A14-31 to check the robustness of the effect, which showed that the result to the advantage of daclatasvir was not robust [1].

In its comment, the company argued that the criteria for treatment discontinuation in the AI444042 study were adequate and referred to the corresponding guideline recommendations [8]. However, the studies on this topic used in the guideline were almost exclusively conducted in genotype 1 patients, and correspondingly the recommendation in the guideline cited by the company also refers to genotype 1 patients [8]. The company's rationale can therefore not raise doubts about the necessity of sensitivity analyses due to unsuitable treatment criteria.

Assessment of the sensitivity analyses newly submitted by the company with the comment

Regardless of its rationale described above, the company presented sensitivity analyses on the outcome "SVR 24 weeks after the end of treatment (SVR 24)" with its comment, which, from the company's point of view, support the result in favour of daclatasvir (Table 5 in the company's comment [2]). The company conducted each of its analyses twice. For the intervention arm with daclatasvir, the analyses were once based on 82, and once on 83 patients, because one patient had discontinued the study already before the first treatment. Hereinafter only the analyses are considered in which all 83 randomized patients were included in the daclatasvir arm because all randomized patients should be considered in the framework of an adequate intention to treat (ITT) analysis, and because, when using the correction of variance (see below), there was no qualitative difference between these 2 approaches in any case.

In contrast to the approach in dossier assessment A14-31, the company used no correction of variance in the calculation of the treatment effect (data-set re-sizing approach). It justified this with the use of comparably high response probabilities for the missing values in the control group and with conservative rounding of the patient numbers. This justification is insufficient and was also not supported by any reference by the company. A correction of variance according to [9] is necessary also for the sensitivity analyses presented by the company. Hence hereinafter only the treatment effects under consideration of the correction of variance are considered.

The following Table 1 shows the analyses presented in dossier assessment A14-31 and presented by the company with the comment, using the approach described above.

Table 1: Sensitivity analyses with different imputation strategies for missing values for the outcome "SVR 24" in the AI444042 study (treatment-naive genotype 4 patients)

Outcome type of analysis **analysis**	**DCV + PEG + RBV**		**PLC + PEG + RBV**		**DCV + PEG + RBV vs. PLC + PEG + RBV**
	N	**Patients with events n (%)**	**N**	**Patients with events n (%)**	**RR [95% CI]; p-value[a]**
SVR 24					
Sensitivity analyses					
Imputation strategy 1/ sensitivity analysis 3 of the company[b]	83	- (83.7)	42	- (60.7)	1.38 [1.01; 1.89]; 0.045
Imputation strategy 2[c]	83	- (77.1)	42	- (60.7)	1.27 [0.92; 1.75]; 0.147
Imputation strategy 3[d]	83	- (88.0)	42	- (73.8)	1.19 [0.94; 1.51]; 0.146
Sensitivity analysis 1 of the company[e]	83	- (83.1)	42	- (57.1)	1.45 [1.04; 2.04]; 0.029
Sensitivity analysis 2 of the company[f]	83	- (86.5)	42	- (60.7)	1.42 [1.04; 1.94]; 0.026
Sensitivity analysis 4 of the company[g]	83	- (80.4)	42	- (60.7)	1.32 [0.96; 1.82]; 0.084
Reference values					
Without imputation of missing values	74	64 (86.5)	28	17 (60.7)	1.42 [1.04; 1.94]; 0.026[h]
Missing = failure	83	64 (77.1)	42	17 (40.5)	1.91 [1.30; 2.80]; 0.0010[h]

a: Unless stated otherwise: Institute's calculation, asymptotic. The variances were adapted according to the data-set re-sizing approach (approach W3 in [9]). The patient numbers are not rounded, but the exact percentage proportions are maintained. There may be slight deviations in point estimates because the company rounded the patient numbers in its own analyses. In the present case however, these deviations did not influence the overall conclusion.
b: In both arms, missing values were imputed with the risk observed in the control group (60.7%).
c: In the PLC + PEG + RBV arm, missing values were imputed with the risk observed in the control group (60.7%). In the DCV + PEG + RBV arm, missing values were assumed as non-responders.
d: In both arms, missing values were assumed as responders.
e: "Individual medically plausible assessment" according to the company's definition (corresponding to a risk of 55.6% in the DCV + PEG + RBV arm, and 50.0% in the PLC + PEG + RBV arm); see also text below.
f: In both arms, missing values were imputed with the risk observed in the respective group (86.5% in the DCV + PEG + RBV arm, and 60.7% in the PLC + PEG + RBV arm).
g: In the DCV + PEG + RBV arm, missing values were imputed with half the risk observed in the control group (corresponding to 30.35%); in the PLC + PEG + RBV arm, with the risk observed in the control group (60.7%).
h: Information from the company's comment [2].
CI: confidence interval; DCV: daclatasvir; N: number of analysed patients; n: number of patients with event; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RR: relative risk; SVR 24: sustained virologic response 24 weeks after the end of treatment; vs.: versus

No new findings resulted from the sensitivity analysis 2 presented by the company. In this analysis, the missing values were imputed with the respective risk observed so that the result did not differ from the analysis without imputation of missing values.

The sensitivity analysis 4 presented by the company showed no statistically significant result and confirmed the doubt regarding the robustness of the result. However, in this analysis the missing values in the daclatasvir arm were imputed with half the risk observed in the control group (30.35%), for which the company presented no meaningful explanation in its comment.

The sensitivity analysis 1 presented by the company showed a statistically significant result in favour of daclatasvir. According to the company, it had conducted an "individual medically plausible assessment" for this analysis using the hepatitis C virus (HCV) ribonucleic acid (RNA) measurements available until the study discontinuation. However, the company's approach did not solve the problem of the shorter treatment duration because in premature treatment discontinuation in particular it is unclear whether an SVR is achieved in case of sufficiently long treatment or not. Instead, considering the patients who had discontinued the study, but in whom the treatment itself had been complete, might provide additional findings. Such a consideration is possible on the basis of the documents subsequently submitted by the company with the comments [10]. It could be inferred from the company's documents that treatment was complete in 0 patients in the daclatasvir arm and in 4 patients in the control arm. HCV RNA measurements 12 weeks or more after the end of treatment were also available for these 4 patients, the result of which can be used with sufficient certainty for the assessment of the response. According to the findings, 1 of the 4 patients is to be rated as responder because the last HCV RNA measurement was below the limit of detection. In 3 of the 4 patients, the measurement was markedly above the limit of detection, which is why these are to be rated as non-responders [10].

This resulted in a corrected SVR rate for the control group of 56.3% (18 of 32 patients). The following Table 2 shows the results of both sensitivity analyses from dossier assessment A14-31, which had raised doubts about the robustness of the effect in favour of daclatasvir (in each case no statistically significant result) under consideration of these findings.

Table 2: Sensitivity analyses for the outcome "SVR 24" in the AI444042 study under consideration of the findings on the SVR 12

Outcome type of analysis **analysis**	**DCV + PEG + RBV**		**PLC + PEG + RBV**		**DCV + PEG + RBV vs. PLC + PEG + RBV**
	N	**Patients with events n (%)**	**N**	**Patients with events n (%)**	**RR [95% CI]; p-value[a]**
SVR 24					
Sensitivity analyses					
Imputation strategy 2[b]	83	- (77.1)	42	- (56.3)	1.37 [0.99; 1.91]; 0.061
Imputation strategy 3[c]	83	- (88.0)	42	- (66.7)	1.32 [1.02; 1.71]; 0.036
Reference value					
Without imputation of missing values	74	64 (86.5)	32	18 (56.3)	1.54 [1.12; 2.11]; 0.008

a: Unless stated otherwise: Institute's calculation, asymptotic. The variances were adapted according to the data-set re-sizing approach (approach W3 in [9]). In the correction of variance, patient numbers are not rounded, but the exact percentage proportions are maintained.
b: In the PLC + PEG + RBV arm, missing values were imputed with the risk observed in the control group (56.3 %). In the DCV + PEG + RBV arm, missing values were assumed as non-responders.
c: In both arms, missing values were assumed as responders.
CI: confidence interval; DCV: daclatasvir; N: number of analysed patients; n: number of patients with event; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RR: relative risk; SVR 24: sustained virologic response 24 weeks after the end of treatment; vs.: versus

Under consideration of the additional information, the result in imputation strategy 3 (all patients with missing values are rated as responders) is statistically significant. Hence the only remaining not statistically significant result is the analysis with imputation strategy 2, which represents the most conservative approach (all patients with missing values in the daclatasvir arm are rated as non-responders; for the control arm, the observed risk is assumed). Under consideration of the information on HCV RNA measurements subsequently submitted, the results on the SVR 24 were therefore considered to be sufficiently robust, even though they are still subject to great uncertainty. As a result, the AI444042 study is suitable for the benefit assessment of daclatasvir in treatment-naive genotype 4 patients.

As described in dossier assessment A14-31, the results of the AI444042 study on AEs, SAEs and discontinuations due to AEs were only interpretable to a limited extent [1]. The result was not statistically significant for any of the 3 outcomes (see Table 20 of dossier assessment A14-31 [1]). The biasing elements in favour of daclatasvir (shorter observation period in the daclatasvir arm) were accompanied by the ones in favour of the control group (unduly reduced treatment duration). Overall, no doubts were raised about the advantage of daclatasvir in the outcome "SVR 24" by the results on AEs, SAEs and discontinuations due to AEs. However, the results of the AI444042 study were so uncertain overall that no more than hints of an added benefit of daclatasvir could be derived.

Extent of added benefit

The extent of added benefit is unquantifiable for the outcome "SVR 24". This is because, on the one hand, SVR 24 is to be considered a surrogate outcome of hepatocellular carcinoma [1], and on the other, because the effect on the outcome "SVR 24" itself could not be estimated precisely in the present situation because of the high number of missing values.

Overall, a hint of a non-quantifiable added benefit of daclatasvir in comparison with the ACT for treatment-naive genotype 4 patients resulted from the AI444042 study.

2.3 Summary

The data and analyses of the ALLY 3 study in genotype 3 patients presented by the company did not change the conclusion of dossier assessment A14-31.

The documents on the outcome "SVR 24" subsequently submitted by the company for the AI444042 study changed the conclusions of dossier assessment A14-31 in so far as the results on the SVR 24 were considered to be sufficiently robust, even though still subject to high uncertainty, and that the AI444042 study is therefore suitable for the benefit assessment of daclatasvir in treatment-naive genotype 4 patients. Overall, a hint of a non-quantifiable added benefit of daclatasvir in comparison with the ACT for treatment-naive genotype 4 patients resulted from the AI444042 study.

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Appendix A – Results from the ALLY 3 study

Table 3: Results (dichotomous outcomes) – daclatasvir/sofosbuvir, ALLY 3 study

Outcome	Patients with events n (%)			
	Treatment-naive		Treatment-experienced	
	patients with cirrhosis N = 19	patients without cirrhosis N = 75	patients with cirrhosis N = 13	patients without cirrhosis N = 34
SVR 12	11 (57.9)	73 (97.3)	9 (69.2)	32 (94.1)
AEs	13 (68.4)	51 (68.0)	10 (76.9)	28 (82.4)
SAEs	0 (0)	1 (1.3)	0 (0)	0 (0)
Discontinuation due to AEs	0 (0)	0 (0)	0 (0)	0 (0)

AE: adverse event; N: number of analysed patients; n: number of patients with event; SAE: serious adverse event; SVR 12: sustained virologic response 12 weeks after the end of treatment