IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Belatacept
(Addendum to Commission A15-25)[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
CKD	chronic kidney disease
ECD	extended criteria donor
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GFR	glomerular filtration rate
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MMF	mycophenolate mofetil
PTDM	post-transplant diabetes mellitus
SAE	serious adverse event
SCD	standard criteria donor
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 24 November 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 A15-25 (Belatacept – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

In its written comments [2], the pharmaceutical company (hereinafter referred to as "the company") submitted supplementary information, which went beyond the information provided in the dossier, to prove the added benefit. This information concerns the proportion of patients in the studies included who had treatment that was not in compliance with the approval, analyses for the assessment of the risk of bias of the analyses on the proportion of patients with renal insufficiency in chronic kidney disease (CKD) stage 4/5, and time-adjusted analyses on adverse events (AEs). The G-BA therefore commissioned IQWiG with the assessment of the time-to-event analyses and the sensitivity analyses on the data of the studies BENEFIT and BENEFIT-EXTENT, particularly regarding the certainty of conclusions/risk of bias of the results.

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 Risk of bias

2.1 Study level

In benefit assessment A15-25 [1], the risk of bias at study level in the extension phase (after month 36) was rated as high for both studies included (IM103008 and IM103027; hereinafter referred to as "BENEFIT" and "BENEFIT-EXT". The reason for this assessment was that discontinuation or dose reduction of corticosteroids as well as substitution of mycophenolate mofetil (MMF) with sirolimus or azathioprine if the patients did not tolerate therapeutic MMF doses were possible in the extension phase. There was no information on the number of patients who received this treatment, which was not compliant with the approval.

In its comment, the company subsequently submitted data on the number of patients affected by the deviations mentioned (see Table 1). These data show that only few patients overall received treatment that was not compliant with the approval: MMF was substituted or the corticosteroid dose was reduced or discontinued in about 5% and about 3% respectively of the patients in the studies BENEFIT and BENEFIT-EXT (see right column of Table 1). There was no relevant difference between the respective treatment arms in both studies.

Hence overall it cannot be assumed that this deviation from the approval had a relevant influence on the study results of the extension phase. Based on the data subsequently submitted by the company, the risk of bias at study level for the time after 36 months was therefore rated as low.

Categorizing the risk of bias at study level as low had no influence on the derivation of the added benefit of belatacept. The reason for this is that there was a high outcome-specific risk of bias for the individual outcomes of the studies BENEFIT and BENEFIT-EXT because of the different observation periods between the treatment arms with informative censoring as well as a high proportion of missing values in the analyses.

Table 1: Characteristics of the study populations (extension phase) – RCT, direct comparison: belatacept vs. ciclosporin A

Study Group	N	MMF substitution[a] n (%)	Steroid reduction[b] n (%)	MMF substitution[a] or steroid reduction[b] n (%)
BENEFIT				
Belatacept	165	5 (3.0)	3 (1.8)	8 (4.8)
Ciclosporin A	137	1 (0.7)	6 (4.4)	7 (5.1)
BENEFIT-EXT				
Belatacept	113	3 (2.7)	0 (0)	3 (2.7)[c]
Ciclosporin A	90	0 (0)	3 (3.3)	3 (3.3)

a: MMF substituted with azathioprine or sirolimus.
b: Dosage < 2.5 mg/day or discontinuation.
c: According to the data subsequently submitted by the company: 6 (5.3%). However, since according to the company, 3 patients received MMF substitution and no patient had steroid reduction or discontinuation, a total number of 3 patients with treatment that is not compliant with the approval is assumed.
MMF: mycophenolate mofetil; N: number of randomized patients at the start of the extension phase; n: number of patients with event; RCT: randomized controlled trial; vs.: versus

2.2 Outcome level – outcome "renal insufficiency CKD stage 4/5"

The risk of bias for the outcome "renal insufficiency CKD stage 4/5" was rated as high in benefit assessment A15-25 [1]. This classification for the 36-month period was based on the fact that data of a relevant proportion of patients (> 10 %) were not included in the analyses for this outcome. For the 84-month period, this classification was particularly due to the potentially different observation periods between the treatment groups with informative censoring. Moreover, patients in whom no renal function using the glomerular filtration rate (GFR) was recorded were formally included in this survival time analysis, but no additional information was actually included in this analysis. Hence the actual proportion of patients who were not considered in the analysis was high.

The company agreed that there was a risk of bias for this outcome. However, the company presented different sensitivity analyses with its comment on benefit assessment A15-25 [2]. Based on these analyses, the company concluded that the estimation of the direction and extent of the risk of bias does not lead to a downgrading of the reliability of the conclusions for the outcome "renal insufficiency CKD stage 4/5".

The analyses submitted by the company did not refer to the outcome "renal insufficiency CKD stage 4/5" relevant for the benefit assessment. All analyses were conducted on the basis of continuous GFR measurements. The analyses of these measurements allowed no conclusions on the outcome of interest "renal insufficiency CKD stage 4/5" and are therefore not further commented on.

In summary, the data presented by the company did not change the assessment of a high risk of bias for the outcome “renal insufficiency CKD stage 4/5” at month 36 and month 84.

3 Analysis of the results using survival time analyses and subgroup analyses

3.1 Survival time analyses for the outcomes "SAEs", "PTDM", "malignancies" and "infections"

Regarding the different observation periods in the treatment arms, it was noted in benefit assessment A15-25 [1] that incidence densities for the analysis of AEs theoretically are only an option for exponentially distributed survival times. In practice, however, these can often be considered to be a suitable approximation for the analysis of the time to event in rare events and short observation periods. Due to the common events, however, this precondition was not met for the outcomes "serious adverse events (SAEs)", "post-transplant diabetes mellitus (PTDM)", "malignancies" and "infections".

To account for the different observation periods, the company presented survival time analyses for the outcomes "SAEs", "PTDM", "malignancies" and "infections" at month 84 for the studies BENEFIT and BENEFIT-EXT with the comments [2]. The corresponding results for both studies are summarized in Table 2.

Table 2: Results (survival time analysis, month 84) – RCT, direct comparison: belatacept vs. ciclosporin A

Outcome category	Belatacept		Ciclosporin A		Belatacept vs. ciclosporin A
Outcome Study	N	Event rate % [95% CI][a]	N	Event rate % [95% CI][a]	HR [95% CI]; p-value
Adverse events					
SAEs					
BENEFIT	226	71.1 [64.8; 77.2]	221	80.1 [73.9; 85.6]	0.74 [0.60; 0.93]; 0.008
BENEFIT-EXT	175	92.7 [87.5; 96.3]	184	87.9 [82.0; 92.7]	1.02 [0.82; 1.27]; 0.870
Total				Heterogeneity[b]: Q = 3.93; df = 1; p = 0.048; I^2 = 74.5%	
PTDM					
BENEFIT	226	8.3 [5.3; 12.9]	221	9.3 [6.1; 14.0]	0.85 [0.45; 1.60]; 0.604
BENEFIT-EXT	175	11.3 [7.2; 17.5]	184	11.0 [6.6; 18.0]	1.12 [0.57; 2.20]; 0.743
Total					0.96 [0.61; 1.53]; 0.879[b]
Malignancies					
BENEFIT	226	10.3 [6.6; 16.0]	221	15.9 [10.8; 22.9]	0.58 [0.32; 1.07]; 0.079
BENEFIT-EXT	175	20.6 [14.3; 29.1]	184	23.0 [15.6; 33.2]	0.87 [0.51; 1.50]; 0.620
Total					0.73 [0.49; 1.09]; 0.126[b]
Infections					
BENEFIT	226	93.5 [89.1; 96.6]	221	90.8 [84.2; 95.4]	1.00 [0.82; 1.22]; 0.990
BENEFIT-EXT	175	91.8 [85.1; 96.3]	184	100 [NC; NC]	0.89 [0.71; 1.11]; 0.293
Total					0.95 [0.82; 1.10]; 0.488[b]

a: Institute's calculation.
b: Institute's calculation from meta-analysis (see Appendix A).
CI: confidence interval; HR: hazard ratio; N: number of analysed patients; NC: not calculable; PTDM: post-transplant diabetes mellitus; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The pooled analysis showed no statistically significant difference between the treatment groups for each of the outcomes “PTDM”, “malignancies” and “infections”.

The combined consideration of the results of both studies provided proof of heterogeneity ($p < 0.05$) for the outcome “SAEs”. In accordance with the approach in benefit assessment A15-25 [1], the results were therefore considered at the individual study level.

A statistically significant difference between the treatment arms was shown here in the BENEFIT study (patients with standard criteria donor [SCD] transplant), but not for the BENEFIT-EXT study (patients with extended criteria donor [ECD] transplant).

This resulted in a hint of lesser harm of belatacept in comparison with ciclosporin A for the outcome “SAEs” in patients with SCD transplant. However, an effect modification by the characteristic “region” was shown for the results of these patients (see Section 3.2). The subgroup analyses resulted in a statistically significant difference in favour of belatacept in European patients with SCD transplant. Hence there was still a hint of lesser harm of belatacept in comparison with ciclosporin A in patients with SCD transplant.

Greater or lesser harm from belatacept in comparison with ciclosporin A is not proven for patients with ECD transplant (study BENEFIT-EXT).

3.2 Subgroup analyses

It was noted in benefit assessment A15-25 that the company only presented the interaction tests for the subgroup characteristic “region” (North America, South America, Asia/Pacific, each versus Europe), but not the effect estimates for both studies in the respective subgroup. Besides the interaction tests the company additionally presented in its comment the results of the subgroup analyses (based on survival time analyses), with missing information on heterogeneity of the effects in the included study pool within a subgroup (e.g. Europe). These could be calculated on the basis of the data submitted by the company, however.

The examination of the data submitted by the company had consequences for the derivation of the added benefit only for the outcome “SAEs”. The pooled analysis of both studies resulted in proof of heterogeneity ($p < 0.05$) between the studies BENEFIT and BENEFIT-EXT (see Table 3 and Figure 1) for Europe, the region of interest. The results were therefore considered at the individual study level.

There was a statistically significant difference in favour of belatacept in the BENEFIT study, and therefore for SCD patients. This advantage for this patient group was also shown in the region of South America (but not North America and Asia). This resulted in a hint of a lesser harm from belatacept than from ciclosporin A with the extent “considerable” for patients with SCD transplant.

There was no statistically significant difference between the treatment groups in the BENEFIT-EXT study, and therefore for ECD patients, in each of the regions Europe, South

America and North America. Hence greater or lesser harm from belatacept in comparison with ciclosporin A is not proven.

The derivation of a hint of considerable added benefit for the outcome "SAEs" in patients with SCD transplant did not change the conclusions on the added benefit because an indication of considerable added benefit of belatacept (irrespective of the donor type) had already been determined in benefit assessment A15-25.

Table 3: Subgroups (survival time analyses, month 84) – RCT, direct comparison: belatacept vs. ciclosporin A

Outcome	**Belatacept**		**Ciclosporin A**		**Belatacept vs. ciclosporin A**	
Characteristic **Subgroup** **Study**	**N**	**Event rate % [95% CI][a]**	**N**	**Event rate % [95% CI][a]**	**HR [95% CI]**	**p-value**
Serious adverse events						
Region						
Asia/Pacific						
BENEFIT	33	72.6 [56.1; 87.0]	34	82.2 [65.8; 93.7]	0.89 [0.51; 1.55]	0.669
BENEFIT-EXT				–[b]		
Europe						
BENEFIT	60	74.8 [62.9; 85.3]	54	93.0 [81.7; 98.4]	0.53 [0.35; 0.80]	0.002
BENEFIT-EXT	85	95.1 [88.0; 98.6]	88	96.8 [86.8; 99.7]	0.94 [0.68; 1.29]	0.687
North America						
BENEFIT	96	68.4 [58.3; 78.0]	98	70.7 [60.6; 80.2]	0.90 [0.64; 1.28]	0.564
BENEFIT-EXT	41	90.2 [74.7; 98.1]	46	94.9 [82.0; 99.4]	0.65 [0.41; 1.04]	0.072
South America						
BENEFIT	36	70.0 [53.8; 84.6]	33	84.9 [69.9; 94.9]	0.53 [0.31; 0.93]	0.025
BENEFIT-EXT	47	91.5 [81.4; 97.3]	50	74.3 [61.2; 85.7]	1.46 [0.93; 2.28]	0.096
Total					Interaction:	0.956[c]
Asia/Pacific					NC	
Europe					Heterogeneity: Q = 4.53; df = 1; p = 0.033; I^2 = 77.9%[c]	
North America					0.80 [0.59; 1.09]	0.150[c]
South America					Heterogeneity: Q = 7.66; df = 1; p = 0.006; I^2 = 86.9 %[c]	

a: Institute's calculation.
b: According to information provided by the company, only one patient in the IM103027 study was in the subgroup "Asia/Pacific".
c: Institute's calculation from meta-analysis (see Figure 1).
CI: confidence interval; HR: hazard ratio; N: number of analysed patients; NC: not calculated; RCT: randomized controlled trial; vs.: versus

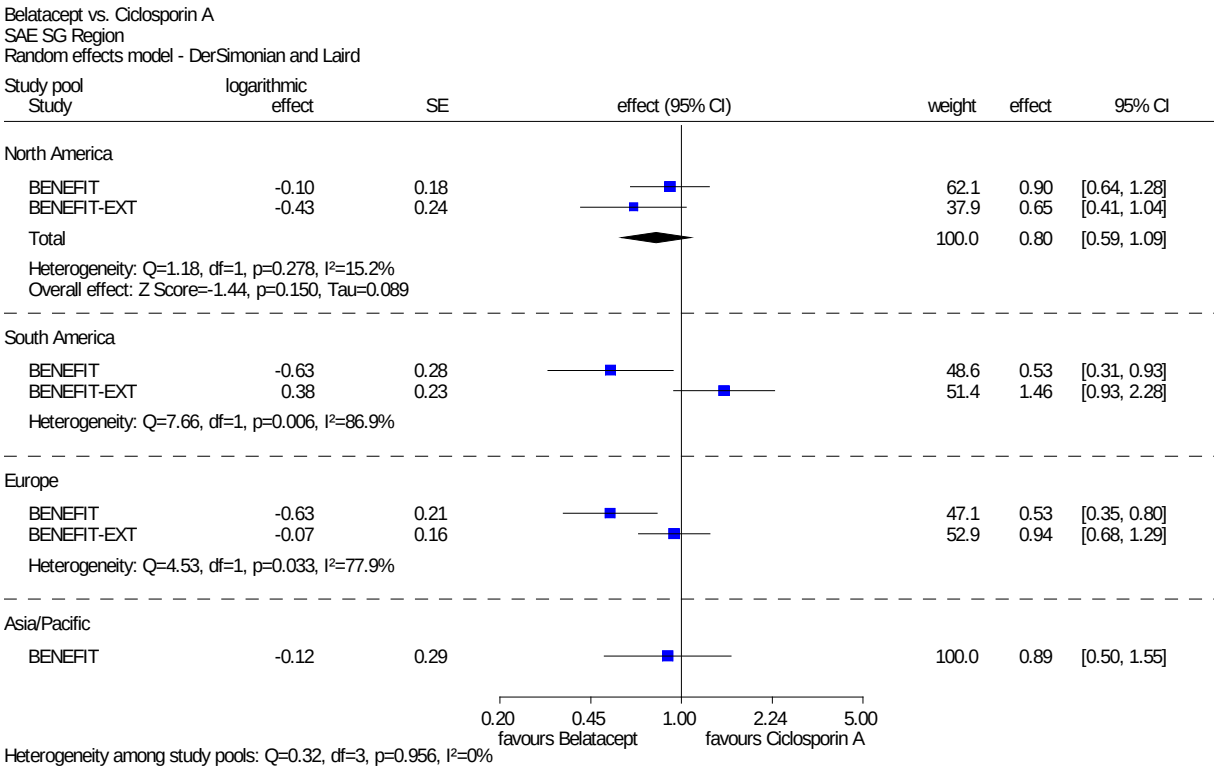

Figure 1: Meta-analysis, SAEs by region, belatacept vs. ciclosporin A

4 Summary

The following changes for benefit assessment A15-25 [1] resulted from the data submitted by the company:

- rating of the risk of bias at study level for the time after 36 months as low
- for the outcome SAEs: hint of lesser harm with considerable extent from belatacept in comparison with ciclosporin A for patients with SCD transplant

As described in Sections 2.1 and 3.2, the changes mentioned had no consequences for the overall conclusion on the added benefit of belatacept.

5 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Belatacept: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A15-25 [online]. 13 October 2015 [accessed: 27 November 2015]. (IQWiG-Berichte; Volume 330). URL: https://www.iqwig.de/download/A15-25_Belatacept_Nutzenbewertung-35a-SGB-V.pdf.

2. Bristol-Myers Squibb. Stellungnahme zum IQWiG-Bericht Nr. 330: Belatacept; Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A15-25. 2015: [Soon available under https://www.g-ba.de/informationen/nutzenbewertung/178/#tab/beschluesse in the document "Zusammenfassende Dokumentation"].

Appendix A – Figures of the meta-analyses of the studies BENEFIT and BENEFIT-EXT

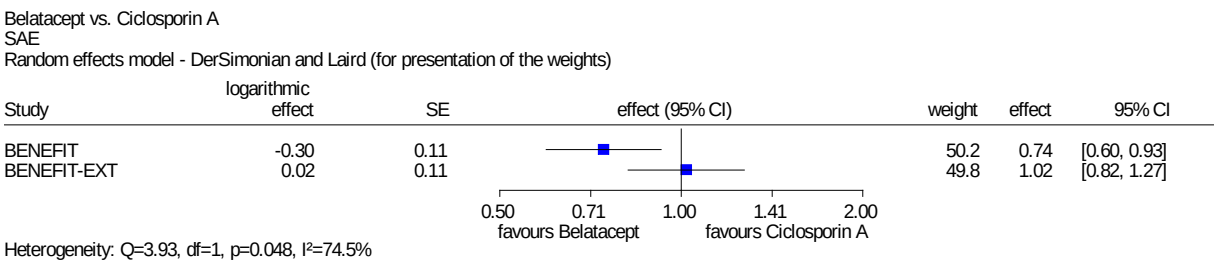

Figure 2: Meta-analysis, SAEs, belatacept vs. ciclosporin A

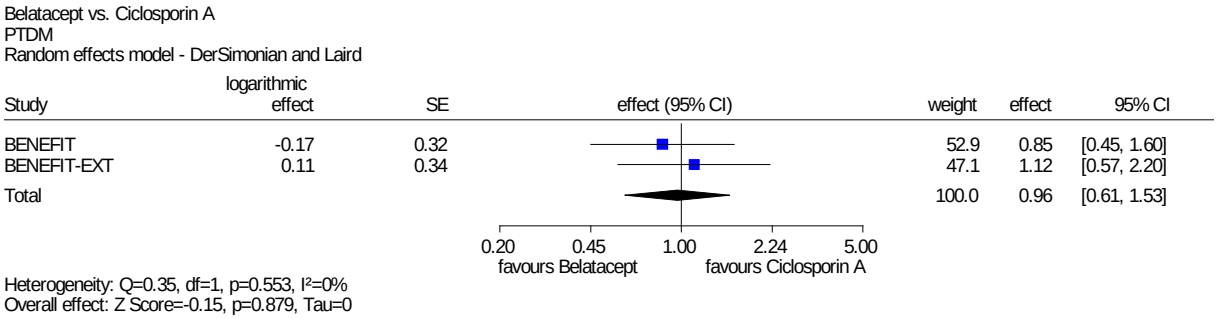

Figure 3: Meta-analysis, PTDM, belatacept vs. ciclosporin A

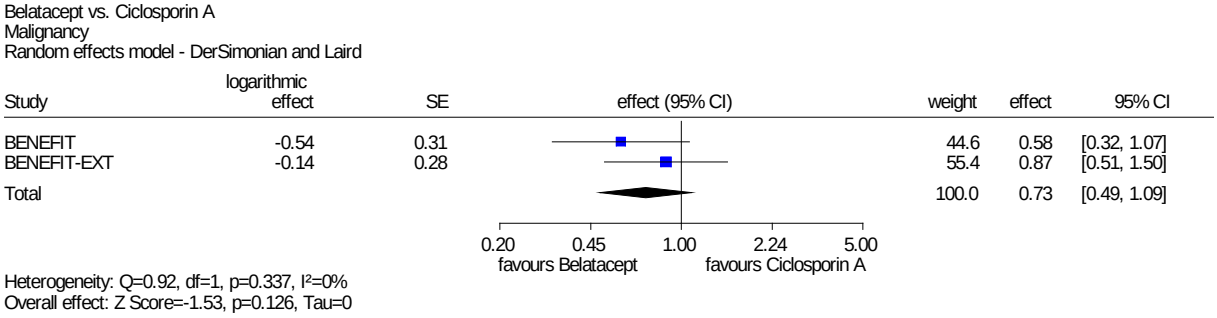

Figure 4: Meta-analysis, malignancy, belatacept vs. ciclosporin A

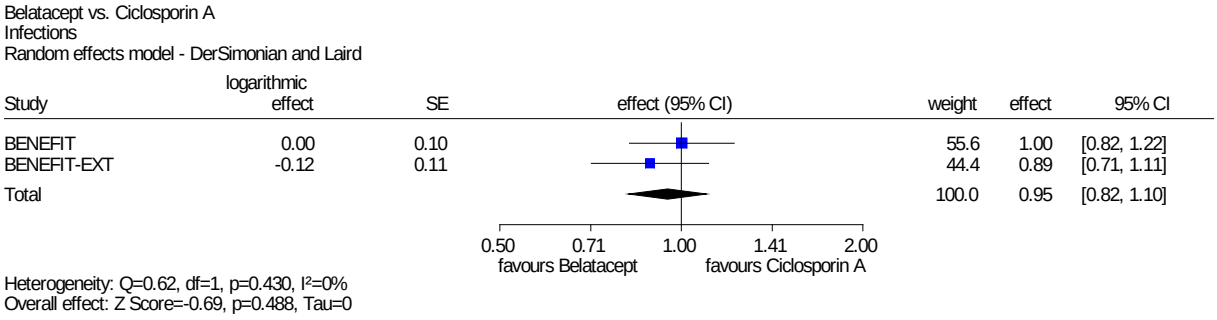

Figure 5: Meta-analysis, infections, belatacept vs. ciclosporin A