IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A15-25

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Belatacept – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 October 2015). 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.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Belatacept – Benefit assessment according to §35a Social Code Book V

Commissioning agency:
Federal Joint Committee

Commission awarded on:
2 July 2015

Internal Commission No.:
A15-25

Address of publisher:
Institute for Quality and Efficiency in Health Care
Im Mediapark 8 (KölnTurm)
50670 Cologne
Germany

Tel.: +49 (0)221 – 35685-0
Fax: +49 (0)221 – 35685-1
E-Mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

- Reinhart T. Grundmann, District Hospitals Altötting-Burghausen, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

IQWiG employees involved in the dossier assessment[2]:

- Stefan Kobza
- Catharina Brockhaus
- Andreas Gerber-Grote
- Wolfram Groß
- Gloria Hanke
- Ulrike Lampert
- Regine Potthast
- Beate Wieseler

Keywords: belatacept, kidney transplantation, benefit assessment

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

Table of contents

List of tables[3]

Page

[3] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CI	confidence interval
CKD	chronic kidney disease
CSR	clinical study report
EBV	Epstein-Barr virus
ECD	extended criteria donor
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
LI	less intensive
LOCF	last observation carried forward
MI	more intensive
MMF	mycophenolate mofetil
PRA	panel reactive antibodies
PTDM	post-transplant diabetes mellitus
PTLD	post-transplant lymphoproliferative disorder
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SCD	standard criteria donor
SF-36	Short Form (36) Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug belatacept. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 2 July 2015.

The company submitted a first dossier of the drug to be evaluated on 16 January 2012 for the early benefit assessment. In this procedure, by decision of 5 July 2012, the G-BA limited its decision until 5 July 2015.

Research question

The aim of this report is to assess the added benefit of belatacept compared with ciclosporin A in combination with corticosteroids and mycophenolate mofetil (MMF) as the appropriate comparator therapy (ACT) for prophylaxis of graft rejection in adults receiving a renal transplant.

In its choice of the ACT, the company followed the G-BA's specification.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. Only randomized controlled trials (RCTs) of direct comparison were included in the assessment.

Results

Study pool

Data suitable for the benefit assessment were available for the included studies BENEFIT and BENEFIT-EXT. For these studies, the dossier from 16 January 2012 for the first benefit assessment of belatacept (Commission A12-03) already contained results on data cut-offs, which the company supplemented with additional analyses in its dossier from 2 July 2015 (see below). Moreover, the company presented results on new data cut-offs for both studies in this dossier.

Unless stated otherwise, the following information applies equally to both studies (BENEFIT and BENEFIT-EXT).

Study characteristics

Both studies were randomized, multicentre, active-controlled approval studies. Their long-term extension phase (hereinafter referred to as "extension phase") started immediately 36 months after transplantation (hereinafter referred to as "month 36"). According to the company, patients could be treated in this extension phase up to 84 months after their

transplantation (hereinafter referred to as "month 84"). The company stated that it had ended the study with submission of the dossier. Adult recipients (≥ 18 years) receiving a renal transplant from a standard criteria donor (SCD) (study BENEFIT), or from an extended criteria deceased donor (ECD) (study BENEFIT-EXT) were included. Treatment was conducted de novo, i.e. without previous switching from a different immunosuppressive drug.

No blinding was conducted for the treatment comparison relevant for this benefit assessment.

The company presented a total of 6 data cut-offs for the studies. The data cut-offs from the clinical study report (CSRs) at 12, 24 and 36 months after transplantation had already been available for the first assessment of belatacept, in which the assessment of the added benefit was primarily based on the data cut-off of the CSR at month 36. The analyses at month 36 in Module 4 A were based on the current database, which, according to the company, contained information on individual patients subsequently added, so that 2 data cut-offs were available on month 36. In case of deviations between information in Module 4 A and the CSR at month 36 resulting from this, the data from the CSR were used for the present benefit assessment.

For the current benefit assessment, subgroup analyses at month 36 were available for the first time. These subgroup analyses were therefore used as supplementary information to the first assessment of belatacept.

Since immunosuppressant therapy after organ transplantation is a long-term treatment, from the 2 last data cut-offs (60 months after transplantation [hereinafter referred to as "month 60"] and month 84), the data cut-off at month 84 was used in the current benefit assessment to assess the added benefit.

The company additionally presented sensitivity analyses for the data cut-off at month 36 to clarify the question of transferability of the study results to the actual health care setting in Germany, which were therefore assessed.

Risk of bias

Both studies had a low risk of bias at study level until month 36. The risk of bias at study level in the extension phase (after month 36) was rated as high.

The risk of bias for all outcomes at month 84, which was relevant for the benefit assessment, was rated as high.

Hence no more than an indication, e.g. of an added benefit, could be derived from both studies for the total population. No more than hints could be derived in the consideration of individual populations.

Results

The results presented below refer to the data cut-off at month 84, which was relevant for the benefit assessment.

Mortality

There was no statistically significant difference between the treatment groups for any of the 2 studies. Hence for mortality there was no hint of an added benefit of belatacept in comparison with ciclosporin A; an added benefit is therefore not proven.

Morbidity

For the composite outcome "death or graft loss", a statistically significant difference between the treatment arms was shown for the BENEFIT study (patients with SCD transplant), but not for the BENEFIT-EXT study (patients with ECD transplant). This resulted in a hint of an added benefit of belatacept in comparison with ciclosporin A for this outcome in patients with SCD transplant. For patients with ECD transplant, there was no hint of an added benefit; an added benefit is not proven for these patients.

For the outcome "renal insufficiency in chronic kidney disease (CKD) stage 4/5", a statistically significant difference in favour of belatacept was shown for both studies. Statistically significant effects in the same direction and of comparable magnitude were observed in both studies. The available data allowed a joint interpretation of the results of patients with SCD and ECD transplant. Hence for this outcome, an indication of added benefit of belatacept in comparison with ciclosporin A resulted from the 2 studies for patients with renal transplant (irrespective of the donor type).

For the outcomes "graft loss", "post-transplant diabetes mellitus", "cardiorenal morbidity and mortality" as well as "cardiovascular morbidity and mortality", no statistically significant difference between the treatment groups was shown in the individual studies or in the meta-analysis. Hence there was no hint of an added benefit of belatacept in comparison with ciclosporin A for these outcomes; an added benefit is therefore not proven.

Health-related quality of life

No data on health-related quality of life at month 84 were available. Overall, there was therefore no hint of an added benefit of belatacept in comparison with ciclosporin A for health-related quality of life; an added benefit is therefore not proven.

Adverse events

For the outcome "serious adverse events (SAEs)", no statistically significant difference between the treatment groups at month 84 was shown for any of the 2 studies. Hence greater or lesser harm from belatacept in comparison with ciclosporin A is not proven.

For the outcome "discontinuation due to adverse events (AEs)", the data at month 84 presented did not refer to the intention to treat (ITT) population. Since no evaluable data were

available on this outcome for this time point relevant for the assessment, greater or lesser harm from belatacept in comparison with ciclosporin A for this outcome is not proven.

There was no statistically significant difference between the treatment groups for the outcomes "infections" "malignancies" and "post-transplant lymphoproliferative disorder (PTLD)" in the individual studies or in the meta-analysis. Hence greater or lesser harm from belatacept in comparison with ciclosporin A for these outcomes is not proven.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

Table 2 presents a summary of the extent and probability of the added benefit of belatacept.

Table 2: Belatacept – extent and probability of added benefit

Therapeutic indication	Appropriate comparator therapy[a]	Extent and probability of added benefit
Prophylaxis of graft rejection and the maintenance of renal function in adults receiving a renal transplant[b]	The appropriate comparator therapy for the initial maintenance therapy is ciclosporin in combination with corticosteroids and mycophenolate mofetil for the prophylaxis of graft rejection and the maintenance of renal function in adults receiving a renal transplant. The drugs should be given in the approved dosages and customized for the individual patient.	Indication of considerable added benefit
a: Presentation of the appropriate comparator therapy specified by the G-BA. b: These data apply only to patients who received an initial treatment with belatacept (de novo), but not to patients switched to belatacept, because the therapeutic indication of belatacept is restricted to recipients of renal transplants with de novo treatment. G-BA: Federal Joint Committee		

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

[4] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit). For further details see [1,2].

2.2 Research question

The aim of this report is to assess the added benefit of belatacept compared with ciclosporin A in combination with corticosteroids and MMF as the ACT for prophylaxis of graft rejection in adults receiving a renal transplant.

In its choice of the ACT, the company followed the G-BA's specification.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. Only RCTs of direct comparison were included in the assessment.

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on belatacept (status: 11 May 2015)
- bibliographical literature search on belatacept (last search on 8 April 2015)
- search in trial registries for studies on belatacept (last search on 8 April 2015)

To check the completeness of the study pool:

- search in trial registries for studies on belatacept (last search on 16 July 2015)

One additional relevant study (IM103100) was identified from the check.

2.3.1 Studies included

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

Table 3: Study pool – RCT, direct comparison: belatacept vs. ciclosporin A

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
IM103008 (BENEFIT)[b]	Yes	Yes	No
IM103027 (BENEFIT-EXT)[b]	Yes	Yes	No
IM103100[c]	Yes	Yes	No

a: Study for which the company was sponsor, or in which the company was otherwise financially involved.
b: Hereinafter referred to as "BENEFIT" and "BENEFIT-EXT".
c: This study is not presented in the following tables because no characteristics and no results for the subpopulations treated in compliance with the approval were available separately; see Appendix A of the full dossier assessment for more information.
RCT: randomized controlled trial; vs.: versus

Data suitable for the benefit assessment were available for the included studies BENEFIT and BENEFIT-EXT. For these studies, the dossier from 16 January 2012 for the first assessment of belatacept (Commission A12-03 [3]) already contained results on data cut-offs, which the company supplemented with additional analyses in its dossier from 2 July 2015 (see Section 2.3.2). Moreover, the company presented results on new data cut-offs for both studies in this dossier.

Deviating from the company's approach, the IM103100 study was additionally included. The company presented no analyses on the subpopulations relevant for the benefit assessment for this study. The number of patients relevant for this benefit assessment who were not considered because of this only constituted about 12% of the patients to be considered, however. A benefit assessment only based on the studies BENEFIT and BENEFIT-EXT therefore appeared acceptable and was conducted.

Section 2.6 contains a reference list for the studies included.

2.3.2 Study characteristics

Table 4 and Table 5 describe the studies used for the benefit assessment.

Table 4: Characteristics of the studies included – RCT, direct comparison: belatacept vs. ciclosporin A

Study	Study design	Population	Interventions (number of randomized patients)[a]	Study duration	Location and period of study	Primary and secondary outcomes[b]
BENEFIT	RCT, partially blinded[c], parallel	Adult recipients (≥ 18 years) of renal transplants from donors classified according to standard criteria (SCDs), de novo[d] treatment	Belatacept MI (N = 219)[e] belatacept LI (N = 226) ciclosporin A (N = 221)	Screening: ▪ living donor: uncertain time point before transplantation ▪ postmortem donor: briefly before transplantation Treatment phase: 36 months or transition to the extension phase[f]	104 study centres in Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, France, Germany, Hungary, India, Israel, Italy, Mexico, Poland, Sweden, Switzerland, Spain, South Africa, Turkey, USA 1/2006–7/2010 (36-month phase), 1/2006–6/2014 (data cut-off at month 84)	Primary: composite outcome on patient and graft survival; renal function; acute rejection reaction Secondary: all-cause mortality, graft loss, renal insufficiency in CKD stage 4/5, cardiovascular morbidity and mortality, health-related quality of life, cardiorenal diseases, adverse events, PTLD, PTDM, malignancies, infections

(continued)

Table 4: Characteristics of the studies included – RCT, direct comparison: belatacept vs. ciclosporin A (continued)

Study	Study design	Population	Interventions (number of randomized patients)[a]	Study duration	Location and period of study	Primary and secondary outcomes[b]
BENEFIT-EXT	RCT, partially blinded[c], parallel	Adult recipients (≥ 18 years) of renal transplants from donors classified according to extended criteria (ECDs), de novo treatment	Belatacept MI (N = 184)[e] belatacept LI (N = 175) ciclosporin A (N = 184)	Screening: uncertain time point before transplantation Treatment phase: 36 months or transition to the extension phase[f]	79 study centres in Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Czech Republic, France, Germany, Hungary, Italy, Norway, Poland, Sweden, Spain, South Africa, United Kingdom, USA 3/2005–6/2010 (36- month phase), 3/2005–5/2014 (data cut-off at month 84)	Primary: composite outcome on patient and graft survival; renal function Secondary: all-cause mortality, graft loss, renal insufficiency in CKD stage 4/5, cardiovascular morbidity and mortality, health-related quality of life, cardiorenal diseases, adverse events, PTLD, PTDM, malignancies, infections

a: Patients in whom a transplantation was carried out.
b: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
c: Study for the comparison of belatacept versus ciclosporin A non-blinded.
d: 3.1% of the patients received no de novo treatment with belatacept.
e: The arm is not relevant for the assessment and is no longer shown in the next tables (MI regimen not approval-compliant).
f: After check of certain inclusion criteria and patient's informed consent, participation in extension phase until market entry of belatacept in the country where the patients were enrolled in the study, or until change of study type, or until the company stopped the development of belatacept in this therapeutic indication.
CKD: chronic kidney disease; ECD: extended criteria donor; LI: lower dose of belatacept; MI: more intensive dose of belatacept; N: number of randomized patients; PTDM: post-transplant diabetes mellitus; PTLD: post-transplant lymphoproliferative disorder; RCT: randomized controlled trial; SCD: standard criteria donor; vs.: versus

Table 5: Characteristics of the interventions – RCT, direct comparison: belatacept vs. ciclosporin A

Study	Belatacept	Ciclosporin A	Prior and concomitant medication
BENEFIT	**Month 0–3:** belatacept 10 mg/kg IV on days 1, 5 and in weeks 2, 4, 8 and 12 **From month 4:** belatacept 5 mg/kg IV every 4 weeks	**Daily starting dose:** ciclosporin A oral 7 ± 3 mg/kg (4–10 mg/kg) **Month 1:** dose adjustment to 150–300 ng/mL **From month 2:** dose adjustment to 100–250 ng/mL	Concomitant medication: ▪ induction therapy with basiliximab: 20 mg IV on day of transplant and 4 days post-operatively ▪ MMF: 2 g/day oral in divided doses[a] ▪ corticosteroids (starting dose 500 mg IV preoperatively; then decreasing to a dose of at least 2.5 mg/day oral up to day 15)[b] Non-permitted concomitant medication: ▪ current use of immunosuppressants (e.g. methotrexate, infliximab, etanercept) due to other therapeutic indications such as an autoimmune disorder or presence of a concomitant disease that might be expected to require treatment with immunosuppressants in the course of the study ▪ immunosuppressants and corticosteroids deviating from the ones specified in the protocol ▪ live vaccines
BENEFIT-EXT	**Month 0–3:** belatacept 10 mg/kg IV on days 1, 5 and in weeks 2, 4, 8 and 12 **From month 4:** belatacept 5 mg/kg IV every 4 weeks	**Daily starting dose:** ciclosporin A oral 7 ± 3 mg/kg (4–10 mg/kg) **Month 1:** dose adjustment to 150–300 ng/mL **From month 2:** dose adjustment to 100–250 ng/mL	Concomitant medication: ▪ induction therapy with basiliximab: 20 mg IV on day of transplant and 4 days post-operatively ▪ MMF: 2 g/day oral in divided doses[a] ▪ corticosteroids (starting dose 500 mg IV preoperatively; then decreasing to a dose of at least 2.5 mg/day oral up to day 15)[b] Non-permitted concomitant medication: ▪ current use of immunosuppressants (e.g. methotrexate, infliximab, etanercept) due to other therapeutic indications such as an autoimmune disorder or presence of a concomitant disease that might be expected to require treatment with immunosuppressants in the course of the study ▪ immunosuppressants and corticosteroids deviating from the ones specified in the protocol ▪ live vaccines

a: Until month 36, dosage was reduced in case of intolerance, or administration of MMF was temporarily discontinued. In the extension phase (after month 36), sirolimus and azathioprine were allowed to be administered as a substitute in case of MMF intolerance. In the belatacept arm, this approach deviates from the SPC, and in the ciclosporin A arm, from the ACT specified by the G-BA. It was not clear from the dossier how many patients were affected by this deviation.
b: In the extension phase (after month 36), the dose could be further reduced or corticosteroids could be discontinued at the investigator's discretion. In the belatacept arm, this approach deviates from the SPC, and in the ciclosporin A arm, from the ACT specified by the G-BA. It was not clear from the dossier how many patients were affected by this deviation.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IV: intravenous; MMF: mycophenolate mofetil; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; vs.: versus

Study design

Unless stated otherwise, the following information applies equally to both studies (BENEFIT and BENEFIT-EXT).

Both studies were randomized, multicentre, active-controlled approval studies. Their long-term extension phase (hereinafter referred to as "extension phase") started immediately 36 months after transplantation (hereinafter referred to as "month 36"). According to the company (Module 4 A, Table 4-9), patients could be treated in this extension phase up to 84 months after their transplantation (hereinafter referred to as "month 84"). The company stated that it had ended the study with submission of the dossier. Adult recipients (≥ 18 years) receiving a renal transplant from an SCD (study BENEFIT), or from an ECD (study BENEFIT-EXT) were included. Treatment was conducted de novo, i.e. without previous switching from a different immunosuppressive drug.

Besides the approval-compliant belatacept arm with lower dosage of belatacept (less intensive, LI) relevant for the benefit assessment, both studies also included another belatacept arm with a more intensive (MI) dosage, which does not comply with the approval, and which is therefore not shown below.

The blinding related solely to the belatacept arms and is thus of no significance for this assessment. No blinding was conducted for the treatment comparison relevant for this benefit assessment.

Primary outcomes were renal function, acute rejection reaction and the composite outcome "death or graft loss".

The enrolment and randomization of patients took place before renal transplantation. Randomization was conducted in a ratio of 1:1:1 (ciclosporin A : belatacept LI : belatacept MI), stratified by study centre. In study BENEFIT, initially 461 patients (belatacept LI: 230 patients; ciclosporin A: 231 patients) and in study BENEFIT-EXT 385 patients (belatacept LI: 193 patients, ciclosporin A: 192 patients) were randomized into treatment arms of relevance for this benefit assessment. Only patients in whom a renal transplant was carried out were included in the benefit assessment (BENEFIT: belatacept LI 226 patients; ciclosporin A 221 patients; BENEFIT-EXT: belatacept LI 175 patients; ciclosporin A 184 patients).

Administration of the drugs used in the studies (ciclosporin A and belatacept, each in combination with MMF and corticosteroids) was conducted before transition to the extension phase without relevant deviation from the requirements of the respective Summary of Product Characteristics (SPC) and package information leaflet [4,5]. The initial ciclosporin A dose of 7 ± 3 mg/kg (4 to 10 mg/kg) was below the dose of 10 to 15 mg/kg recommended in the SPC [5] (for the relevance of these limitations, see Section 2.7.2.1 of the full dossier assessment). Deviating from the SPC, the initial dose could partly be administered only after transplantation. For medical reasons, this was considered to be understandable and without

important influence on the benefit assessment. Subsequent doses were adjusted on the basis of the serum concentration of ciclosporin A; the first serum level measurement took place on day 5 after transplantation.

In the extension phase, in case of MMF intolerance, sirolimus and azathioprine were allowed to be administered as a substitute, and corticosteroids were allowed to be administered at doses below the minimum dose or discontinued. In the belatacept arm, this approach deviates from the SPC [4], and in the ciclosporin A arm, from the ACT specified by the G-BA. It was not clear from the dossier how many patients were affected by this deviation. This limitation is discussed in Section 2.7.2.3.2 of the full dossier assessment.

Current use of immunosuppressants or expected use of immunosuppressants during study participation due to other therapeutic indications as well as immunosuppressants and corticosteroids deviating from the ones specified in the protocol, and administration of live vaccines were not allowed.

Duration of follow-up

Table 6 shows the planned duration of follow-up of the patients for the individual outcomes.

Table 6: Planned duration of follow-up – RCT, direct comparison: belatacept vs. ciclosporin A

Study **Outcome category** **Outcomes**	**Planned follow-up**
BENEFIT	
Mortality and morbidity[a]	Under treatment until month 84 until month 36 also after treatment discontinuation; after month 36 (in the extension phase) only until the time point of treatment discontinuation
Health-related quality of life (SF-36)	Under treatment until month 60 until month 36 also after treatment discontinuation; after month 36 (in the extension phase) only until the time point of treatment discontinuation
Adverse events	
AEs, discontinuation due to AEs, SAEs	under treatment until month 84 in case of treatment discontinuation until 8 weeks after treatment discontinuation
malignancies, PTLD, serious infections, pulmonary oedema, cardiac failure, nonfatal myocardial infarction, stroke, revascularization (surgical or percutaneous) as well as SAEs for which the investigator assumes an association with the investigational drug	Under treatment until month 84 until month 36 also after treatment discontinuation; after month 36 (in the extension phase) until 8 weeks after treatment discontinuation
BENEFIT-EXT	
Mortality and morbidity[a]	Under treatment until month 84 until month 36 also after treatment discontinuation; after month 36 (in the extension phase) only until the time point of treatment discontinuation
Health-related quality of life (SF-36)	Under treatment until month 60 until month 36 also after treatment discontinuation; after month 36 (in the extension phase) only until the time point of treatment discontinuation
Adverse events	
AEs, discontinuation due to AEs, SAEs	Under treatment until month 84 in case of treatment discontinuation until 8 weeks after treatment discontinuation
malignancies, PTLD, serious infections, pulmonary oedema, cardiac failure, nonfatal myocardial infarction, stroke, revascularization (surgical or percutaneous) as well as SAEs for which the investigator assumes an association with the investigational drug	Under treatment until month 84 until month 36 also after treatment discontinuation; after month 36 (in the extension phase) until 8 weeks after treatment discontinuation

a: This outcome category includes all-cause mortality, graft loss, composite outcome "death or graft loss", PTDM, composite outcome "cardiovascular morbidity and mortality", composite outcome "cardiorenal morbidity and mortality" and renal insufficiency in CKD stage 4/5.

AE: adverse event; CKD: chronic kidney disease; PTDM: post-transplant diabetes mellitus; PTLD: post-transplant lymphoproliferative disorder; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form (36) Health Survey (questionnaire on health-related quality of life); vs.: versus

Until month 36, data on mortality and morbidity as well as on health-related quality of life and on selected outcomes on harm were recorded in case of discontinuation of the study medication (hereinafter referred to as “treatment discontinuation”). In the subsequent extension phase, in case of treatment discontinuation, data on mortality and morbidity were recorded at the time point of discontinuation. Health-related quality of life was documented until the time point of discontinuation, but no later than month 60; and AEs were recorded until 8 weeks after treatment discontinuation.

Dates of analysis

The company presented a total of 6 data cut-offs for the studies. The data cut-offs from the CSRs at 12, 24 and 36 months after transplantation had already been available for the first assessment of belatacept [3], in which the assessment of the added benefit was primarily based on the data cut-off of the CSR at month 36. The analyses at month 36 in Module 4 A were based on the current database, which, according to the company, contained information on individual patients subsequently added, so that 2 data cut-offs, which deviated from each other, were available on month 36. The changes in the data base at month 36 were not clear from the dossier (see Section 2.7.2.4.3 of the full dossier assessment). In case of deviating information between Module 4 A and the CSR at month 36, the data from the CSR were therefore used for the present benefit assessment.

For the current benefit assessment, subgroup analyses at month 36 were available for the first time. These subgroup analyses were therefore used as supplementary information to the first assessment of belatacept.

Since immunosuppressant therapy after organ transplantation is a long-term treatment, from the 2 last data cut-offs (60 months after transplantation [hereinafter referred to as “month 60”] and month 84), the data cut-off at month 84 was used in the current benefit assessment to assess the added benefit.

The company additionally presented sensitivity analyses for the data cut-off at month 36 to clarify the question of transferability of the study results to the actual health care setting in Germany, which were therefore assessed.

Patient characteristics

Table 7 shows the characteristics of the patients in the studies included.

Table 7: Characteristics of the study populations – RCT, direct comparison: belatacept vs. ciclosporin A

		Patient characteristics							Donor characteristics	
Study Group	**N**	**Age [years] mean (SD)**	**Sex [F/M] %**	**Number of previous trans-plantations 1-2/missing n (%)**	**EBV status positive n (%)**	**Ethnicity [white/black/ native American Alaskans/ Asian/other] %**	**Study discontin-uations n (%)**	**Treatment discontin-uations n (%)**	**Living/ deceased donors (%)**	**Cold ischaemia time [hours] living/deceased mean (SD)**
BENEFIT										
Belatacept	226	43 (13)	35/65	5 (2.2)/3 (1.3)	199 (88.1)[a]	59/10/2/13/16	36 months: 13 (5.8) 84 months: –[b]	36 months: 56 (24.8) 84 months: 89 (39.4)[a]	57.1[a]/42.9	1.3 (1.6)[c]/16.7 (6.4)
Ciclosporin A	221	44 (14)	25/75	9 (4.1)/4 (1.8)	184 (83.3)[a]	63/8/1/12/17	36 months: 19 (8.8) 84 months: –[b]	36 months: 72 (33.5) 84 months: 129 (58.4)[a]	56.1[a]/43.9	1.5 (2.8)[d]/16.7 (5.7)
BENEFIT-EXT										
Belatacept	175	56 (12)	26/74	not applicable[e]	145 (82.9)[a]	77/14/1/2/7	36 months: 18 (10.3) 84 months: –[b]	36 months: 60 (34.5) 84 months: 91 (52)[a]	0.6/99.4[a, f]	–/21.2 (8.0)
Ciclosporin A	184	56 (12)	37/63	not applicable[e]	153 (83.2)[a]	75/12/0/2/11	36 months: 25 (14.0) 84 months: –[b]	36 months: 79 (44.1) 84 months: 128 (69.6)[a]	0/100	–/19.4 (7.4)

a: Institute's calculation.
b: No information at the time point 84 months.
c: No information on cold ischaemia times in 2 cases.
d: No information on cold ischaemia times in 3 cases.
e: Previous transplantation was an exclusion criterion in study BENEFIT-EXT.
f: Consideration of one case of a living donor because of a protocol infringement; no information on cold ischaemia time in this case.
EBV: Epstein-Barr virus; F: female; M: male; N: number of randomized (or included) patients; n: number of patients with event; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Within the studies, there were no important deviations between the treatment arms for the patient characteristics "age", "sex", "Epstein-Barr virus (EBV) status" and "ethnicity". In both studies however, the proportions of treatment discontinuations differed between the treatment arms (both at month 36 and at month 84). Potential differences in observation duration, which need to be considered in the assessment of the risk of bias at outcome level, resulted from this, particularly in the extension phase (see Section 2.7.2.4.2 of the full dossier assessment).

Contrary to the company's statement, further differences between the 2 study populations resulted from the donor criteria that differed between the studies (see study design); the age of the patients included in the BENEFIT-EXT study was higher than in the BENEFIT study, for example. Moreover, the proportion of deceased donors and cold ischaemia times were lower in study BENEFIT than in study BENEFIT-EXT (Table 7).

Table 8 shows the risk of bias at study level.

Table 8: Risk of bias at study level – RCT, direct comparison: belatacept vs. ciclosporin A

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
Until month 36							
BENEFIT	Yes	Yes	No	No	Yes	Yes	Low
BENEFIT-EXT	Yes	Yes	No	No	Yes	Yes	Low
After month 36							
BENEFIT	Yes	Yes	No	No	Yes	No[a]	High
BENEFIT-EXT	Yes	Yes	No	No	Yes	No[a]	High

a: In the extension phase (after month 36), corticosteroids were discontinued or given at a reduced dose in an unknown number of patients. Moreover, MMF was substituted with sirolimus or azathioprine when patients did not tolerate therapeutic MMR doses in an unknown number of patients in the extension phase. It is therefore unknown how large the proportions of patients are who were no longer treated in compliance with the ACT specified by the G-BA or with the belatacept approval in the extension phase, and whether these proportions differed between the treatment arms to a relevant degree.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; MMF: mycophenolate mofetil; RCT: randomized controlled trial; vs.: versus

Both studies had a low risk of bias at study level until month 36. This partly concurs with the company's assessment, which assessed the risk of bias at study level as low, irrespective of the documentation time. Deviating from the company's assessment, the risk of bias at study level was considered high in the extension phase (after month 36) because in the extension phase, corticosteroids were discontinued or given at a reduced dose in an unknown number of

patients. Moreover, MMF was substituted with sirolimus or azathioprine when patients did not tolerate therapeutic MMR doses in an unknown number of patients in the extension phase. It is therefore unknown how large the proportions of patients are who were no longer treated in compliance with the ACT specified by the G-BA or with the belatacept approval in the extension phase, and whether these proportions differed between the treatment arms to a relevant degree.

Limitations resulting from the open-label study design are described in Section 2.4 with the outcome-specific risk of bias.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - graft loss
  - composite outcome: death or graft loss
  - composite outcome: cardiorenal morbidity and mortality (consisting of the individual components “death”, “graft loss”, “nonfatal myocardial infarction” and “stroke”)
  - composite outcome: cardiovascular morbidity and mortality (consisting of the individual components “adjudicated cardiovascular death”, “ischaemic stroke” and “revascularization”)
  - renal insufficiency in CKD stage 4/5
  - post-transplant diabetes mellitus (PTDM)
- Health-related quality of life
  - Short Form (36) Health Survey (SF-36)
- Adverse events
  - overall rate of SAEs
  - discontinuation due to AEs
  - infections
  - malignancies
  - PTLD

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.7.2.4.3 of the full dossier assessment).

Table 9 shows for which outcomes data were available in the studies included.

Table 9: Matrix of outcomes – RCT, direct comparison: belatacept vs. ciclosporin A

Study	Outcomes												
	All-cause mortality	**Graft loss**	**Death or graft loss**	**Cardiorenal morbidity and mortality[a]**	**Cardiovascular morbidity and mortality[b]**	**Renal insufficiency in CKD stage 4/5**	**PTDM**	**Health-related quality of life (SF-36)**	**SAEs**	**Discontinuation due to AEs**	**Infections**	**Malignancies**	**PTLD**
BENEFIT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes[c]	Yes	Yes[d]	Yes	Yes	Yes
BENEFIT-EXT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes[c]	Yes	Yes[d]	Yes	Yes	Yes

a: Composite outcome consisting of the following individual components: death, graft loss, nonfatal myocardial infarction, stroke.
b: Composite outcome consisting of the following individual components: adjudicated cardiovascular death, myocardial infarction, ischaemic stroke, revascularization (surgical or percutaneous; consisting of the following PTs at month 84 mentioned by the company, which partly deviate from the MedDRA PTs at month 36 and for which the corresponding PTs in MedDRA versions 13 or higher are unknown: BENEFIT: carotid angioplasty, carotid stent implantation, carotid endarterectomy, coronary angioplasty, coronary stent implantation, coronary artery bypass; BENEFIT-EXT: coronary angioplasty, coronary stent implantation, coronary artery bypass, coronary revascularization).
c: Contrary to Module 4 A (Table 4-9) only recorded until month 60.
d: Analyses at month 36 were available separately for study and treatment discontinuation; analyses at month 84 refer only to the population transitioned to the extension phase and are therefore not evaluable.
AE: adverse event; CKD: chronic kidney disease; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; PTDM: post-transplant diabetes mellitus; PTLD: post-transplant lymphoproliferative disorder; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form (36) Health Survey (questionnaire on health-related quality of life); vs.: versus

2.4.2 Risk of bias

The company presented assessments of the risk of bias at outcome level irrespective of the documentation time, implicating that there was no difference in risk of bias between the documentation times. This assessment was not followed (see Section 2.7.2.4.2 of the full dossier assessment for detailed reasons).

To be able to assess the subgroup analyses at month 36 presented by the company in supplementation of the first assessment of belatacept [3], the risk of bias at this

documentation time was evaluated. Additionally, the risk of bias was assessed for the relevant outcomes at month 84 because this was the basis for the current benefit assessment.

Table 10 shows the risk of bias for the relevant outcomes at month 36.

Table 10: Risk of bias at study and outcome level – RCT, month 36, direct comparison: belatacept vs. ciclosporin A

Study		Outcomes												
	Study level	All-cause mortality	Graft loss	Death or graft loss	Cardiorenal morbidity and mortality[a]	Cardiovascular morbidity and mortality[b]	Renal insufficiency in CKD stage 4/5	PTDM	Health-related quality of life (SF-36)	SAEs	Discontinuation due to AEs[c]	Infections	Malignancies	PTLD
BENEFIT	L	L	L	L	L	L	H[d]	L	H[d, e]	L	L	H[f]	L	L
BENEFIT-EXT	L	L	L	L	L	L	H[d]	L	H[d, e]	L	L	H[f]	L	L

a: The risk of bias of the individual components (death, graft loss, nonfatal myocardial infarction, stroke) of this outcome is identical.
b: The risk of bias of the individual components (adjudicated cardiovascular death, myocardial infarction, ischaemic stroke, revascularization [surgical or percutaneous]) of this outcome is identical.
c: Analyses at month 36 are available separately for study and treatment discontinuation due to AEs.
d: High risk of bias because the proportion of missing values is > 10%.
e: Subjective outcome in open-label study design.
f: These were mainly non-serious infections, the documentation of which as AEs has subjective components. Hence in the open-label study design, this leads to a high risk of bias.

AE: adverse event; CKD: chronic kidney disease; H: high; L: low; PTDM: post-transplant diabetes mellitus; PTLD: post-transplant lymphoproliferative disorder; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

At month 36, data were available in the dossier for all outcomes considered to be relevant for the assessment. Deviating from the company's assessment, the risk of bias for the outcome "infections" was rated as high. The fact that at month 36 the majority of the infections documented as AEs were non-serious was decisive, so that their recording in an open-label study design was rated as potentially highly biased. Due to the subjective component, the risk of bias for the outcome "health-related quality of life (SF-36)" was also rated as high. This concurs with the company's assessment. However, the company did not consider that the risk of bias for this outcome was to be rated as high also because of a relevant proportion of missing values of over 10%. The company also did not consider the proportion of missing values of over 10% for the outcome "renal insufficiency in CKD stage 4/5". Deviating from the company's assessment, the risk of bias of this outcome was therefore rated as high.

Table 11 shows the risk of bias for the relevant outcomes at month 84.

Table 11: Risk of bias at study and outcome level – RCT, month 84, direct comparison: belatacept vs. ciclosporin A

Study	Study level	Outcomes												
		All-cause mortality	Graft loss	Death or graft loss	Cardiorenal morbidity and mortality[a]	Cardiovascular morbidity and mortality[b]	Renal insufficiency in CKD stage 4/5	PTDM	Health-related quality of life (SF-36)	SAEs	Discontinuation due to AEs	Infections	Malignancies	PTLD
BENEFIT	H	H[c]	H[c]	H[c]	H[c]	H[c]	H[c]	H[d]	–[e]	H[d]	–[f]	H[d]	H[d]	H[d]
BENEFIT-EXT	H	H[c]	H[c]	H[c]	H[c]	H[c]	H[c]	H[d]	–[e]	H[d]	–[f]	H[d]	H[d]	H[d]

a: No data available for the individual components "nonfatal myocardial infarction" and "stroke".
b: No data available for the individual components (cardiovascular death, myocardial infarction, ischaemic stroke, revascularization [surgical or percutaneous]) of this outcome.
c: High risk of bias at outcome level due to high risk of bias at study level (see Table 8) and due to potential differences in observation duration between the treatment groups in informative censoring.
d: High risk of bias at outcome level due to high risk of bias at study level (see Table 8) and due to unclear proportion of missing values imputed with the LOCF strategy, and due to potential differences in observation duration between the treatment groups.
e: Outcome not recorded at this time point.
f: Analyses relate only to the population transitioned to the extension phase and are therefore not evaluable.
AE: adverse event; CKD: chronic kidney disease; H: high; LOCF: last observation carried forward; PTDM: post-transplant diabetes mellitus; PTLD: post-transplant lymphoproliferative disorder; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form (36) Health Survey (questionnaire on health-related quality of life); vs.: versus

No data on the outcome "health-related quality of life" at month 84 were available. For the outcome "discontinuation due to AEs", analyses were only available for the population transitioned to the extension phase; these analyses were therefore not evaluable. These outcomes could therefore not be used for the present benefit assessment. There was a high risk of bias for all further outcomes relevant for the assessment due to the potential differences in observation duration between the treatment groups in informative censoring or an unclear proportion of missing values, which were imputed with the last observation carried forward (LOCF) strategy. This assessment deviated from that of the company (see Section 2.7.2.4.2 of the full dossier assessment for a detailed justification). Irrespective of the documentation time, the company rated the risk of bias as high only for the outcome "health-related quality of life" relevant for the assessment (see above).

2.4.3 Results

The company presented analyses at month 36 (see Section 2.3.2) on the comparison of belatacept with ciclosporin A in adult recipients of renal transplants with de novo treatment. The results are summarized in Table 12 and Table 13. Deviating from the company's approach, not the data presented in Module 4 A were used for these tables, but those of the corresponding CSRs at month 36, which partly deviate from the information provided in Module 4 A. A detailed justification of this approach can be found in Section 2.7.2.4.3 of the full dossier assessment, comments on results.

Since belatacept is only approved for patients with positive EBV serostatus, analyses for these subpopulations in both studies were preferred. The CSRs at month 36 contained the corresponding data for the outcomes "AEs", "SAEs", "infections" and "PTLD". Deviating from the information provided in Module 4 A, Table 12 therefore contains the analyses only for patients with positive EBV serostatus for these outcomes.

Only data at month 84 were relevant for the derivation of an added benefit. The results are summarized in Table 14. Relative risks (RRs) at month 84 were used for the following outcomes: PTDM, SAEs, infections, malignancies and PTLD (see Section 2.7.2.4.2 of the full dossier assessment for reasons). This deviated from the company's approach, which chose the incidence density ratio of the events as effect estimates at month 84 for the derivation of the added benefit in the dossier.

Where necessary, the data from the company's dossier were supplemented by the Institute's calculations. The figures of the corresponding meta-analyses with indication or proof of outcome-specific heterogeneity between the studies can be found in Appendix B of the full dossier assessment.

An overview of the most common AEs, discontinuations due to AEs, and SAEs at month 36 can be found in Appendix C of the full dossier assessment. These data were not available at month 84.

Table 12: Results (dichotomous outcomes, month 36) – RCT, direct comparison: belatacept vs. ciclosporin A

Outcome category Outcome Study	Belatacept N	Belatacept Patients with event n (%)	Ciclosporin A N	Ciclosporin A Patients with event n (%)	Belatacept vs. ciclosporin A RR [95% CI]; p-value
Mortality					
All-cause mortality					
BENEFIT	226	10 (4.4)	221	15 (6.8)	0.65 [0.30; 1.42]; 0.281
BENEFIT-EXT	175	15 (8.6)	184	17 (9.2)	0.93 [0.48; 1.80]; 0.824
Total					0.80 [0.48; 1.32]; 0.386[a]
Morbidity					
Graft loss					
BENEFIT	226	9 (4.0)	221	10 (4.5)	0.88 [0.36; 2.12]; 0.776
BENEFIT-EXT	175	21 (12.0)	184	23 (12.5)	0.96 [0.55; 1.67]; 0.885
Total					0.94 [0.59; 1.50]; 0.785[a]
Death or graft loss					
BENEFIT	226	18 (8.0)	221	25[b] (11.3)	0.70 [0.40; 1.25]; 0.233
BENEFIT-EXT	175	31 (17.7)	184	37[b] (20.1)	0.88 [0.57; 1.35]; 0.563
Total					0.81 [0.58; 1.15]; 0.240[a]
Cardiorenal morbidity and mortality[c]					
BENEFIT	226	24 (10.6)	221	26 (11.8)	0.90 [0.54; 1.52]; 0.701
BENEFIT-EXT	175	33 (18.9)	184	38 (20.7)	0.91 [0.60; 1.39]; 0.670
Total					0.91 [0.66; 1.26]; 0.567[a]
Nonfatal myocardial infarction					
BENEFIT	226	4 (1.8)	221	3 (1.4)	1.30 [0.30; 5.76][a]
BENEFIT-EXT	175	2 (1.1)	184	4 (2.2)	0.53 [0.10; 2.83][a]
Total					0.88 [0.29; 2.67]; 0.816[a]
Stroke					
BENEFIT	226	2 (0.9)	221	1 (0.5)	1.96 [0.18; 21.41][a]
BENEFIT-EXT	175	0 (0)	184	2 (1.1)	0.21 [0.01; 4.35][a]
Total					0.78 [0.09; 6.84]; 0.824[a, d]

(continued)

Table 12: Results (dichotomous outcomes, month 36) – RCT, direct comparison: belatacept vs. ciclosporin A (continued)

Outcome category Outcome Study	Belatacept N	Belatacept Patients with event n (%)	Ciclosporin A N	Ciclosporin A Patients with event n (%)	Belatacept vs. ciclosporin A RR [95% CI]; p-value
Cardiovascular morbidity and mortality					
BENEFIT	226	11 (4.9)	221	12 (5.4)	0.90 [0.40; 1.99][a]
BENEFIT-EXT	175	7 (4.0)	184	11 (6.0)	0.67 [0.27; 1.69]; 0.394
Total					0.79 [0.43; 1.45]; 0.447[a]
Myocardial infarction					
BENEFIT	226	4 (1.8)	221	3 (1.4)	1.30 [0.30; 5.76][a]
BENEFIT-EXT	175	2 (1.1)	184	4 (2.2)	0.53 [0.10; 2.83][a]
Total					0.88 [0.29; 2.67]; 0.816[a]
Ischaemic stroke					
BENEFIT	226	1 (0.4)	221	1 (0.5)	0.98 [0.06; 15.54][a]
BENEFIT-EXT	175	0 (0)	184	1 (0.5)	0.35 [0.01; 8.54][a]
Total					0.63 [0.08; 5.10]; 0.665[a, d]
Cardiovascular death					
BENEFIT	226	5 (2.2)	221	6 (2.7)	0.81 [0.25; 2.63][a]
BENEFIT-EXT	175	4 (2.3)	184	4 (2.2)	1.05 [0.27; 4.14][a]
Total					0.91 [0.37; 2.21]; 0.831[a]
Revascularization					
BENEFIT	226	5 (2.2)	221	4 (1.8)	1.22 [0.33; 4.49][a]
BENEFIT-EXT	175	2 (1.1)	184	3 (1.6)	0.70 [0.12; 4.14][a]
Total					1.01 [0.35; 2.88]; 0.990[a]
Renal insufficiency in CKD stage 4/5					
BENEFIT	190[e]	19 (10.0)	171[e]	35 (20.5)	0.49 [0.29; 0.82][a]
BENEFIT-EXT	155[e]	42 (27.1)	143[e]	63 (44.1)	0.62 [0.45; 0.84]; 0.003
Total					0.58 [0.44; 0.76]; < 0.001[a]
PTDM					
BENEFIT	168[f]	11 (6.5)	162[f]	18 (11.1)	0.59 [0.29; 1.21][a]
BENEFIT-EXT	136[f]	13 (9.6)	118[f]	11 (9.3)	1.03 [0.48; 2.20][a]
Total					0.77 [0.44; 1.32]; 0.333[a]
Adverse events					
AEs[g]					
BENEFIT	202	202 (100)	184	182 (98.9)	
BENEFIT-EXT	156	155 (99.4)	168	168 (100)	

(continued)

Table 12: Results (dichotomous outcomes, month 36) – RCT, direct comparison: belatacept vs. ciclosporin A (continued)

Outcome category Outcome Study	Belatacept N	Belatacept Patients with event n (%)	Ciclosporin A N	Ciclosporin A Patients with event n (%)	Belatacept vs. ciclosporin A RR [95% CI]; p-value
Adverse events					
SAEs[g]					
BENEFIT	202	116 (57.4)	184	121 (65.8)	0.87 [0.75; 1.02][a]
BENEFIT-EXT	156	123 (78.8)	168	133 (79.2)	1.00 [0.89; 1.11][a]
Total					Heterogeneity: Q = 1.93; df = 1; p = 0.164; I^2 = 48.3%[a]
Discontinuation due to AEs[h]					
BENEFIT	226	16 (7.1)	221	31 (14.0)	0.50 [0.28; 0.90][a]
BENEFIT-EXT	175	36 (20.6)	184	44 (23.9)	0.86 [0.58; 1.27]; 0.448
Total					Heterogeneity: Q = 2.29; df = 1; p = 0.130; I^2 = 56.4%[a]
Infections[g]					
BENEFIT	202	172 (85.1)	184	148 (80.4)	1.06 [0.97; 1.16][a]
BENEFIT-EXT	156	131 (84.0)	168	138 (82.1)	1.02 [0.93; 1.13][a]
Total					1.04 [0.97; 1.11]; 0.234[a]
Malignancies					
BENEFIT	226	10 (4.4)	221	12 (5.4)	0.81 [0.36; 1.85][a]
BENEFIT-EXT	175	15 (8.6)	184	19 (10.3)	0.83 [0.44; 1.58][a]
Total					0.82 [0.50; 1.37]; 0.454[a]
PTLD[g]					
BENEFIT	202	2 (1.0[i])	184	0 (0)	4.56 [0.22; 94.29][a]
BENEFIT-EXT	156	1 (0.6[i])	168	0 (0)	3.23 [0.13; 78.69][a]
Total					3.87 [0.43; 34.86]; 0.227[a, d]

a: Institute's calculation from meta-analysis.
b: One patient with unknown status was imputed as event.
c: The composite outcome "cardiorenal morbidity and mortality" consists of the individual components "graft loss", "nonfatal myocardial infarction", "stroke" and "death".
d: In addition, the POR in rare events (≤ 1%) was calculated by the Institute if the observed POR depending on the respective group size rate and a 1.1 times tolerated deviation was between the maximum effect sizes indicated in Brockhaus 2014 [6] Table III. No qualitative differences were found.
e: Number of patients recorded in the analysis on the renal function cGFR.
f: Number of patients who had no diabetes mellitus at the start of the study.
g: For this outcome, the CSRs contained analyses on patients with positive Epstein-Barr virus serostatus; these analyses are preferred and presented instead of the information provided in Module 4 A.
h: Treatment discontinuation due to AEs.
i: Institute's calculation.

AE: adverse event; cGFR: calculated glomerular filtration rate; CI: confidence interval; CKD: chronic kidney disease; N: number of analysed patients; n: number of patients with (at least one) event; POR: Peto odds ratio; PTDM: post-transplant diabetes mellitus; PTLD: post-transplant lymphoproliferative disorder; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 13: Results (continuous outcomes, month 36) – RCT, direct comparison: belatacept vs. ciclosporin A

Outcome category Outcome Study	Belatacept			Ciclosporin A			Belatacept vs. ciclosporin A
	N[a]	Baseline values mean (SD)	Adjusted change month 36 mean[b] (SE)	N[a]	Baseline values mean (SD)	Adjusted change month 36 mean[b] (SE)	Mean difference[b] [95% CI]; p-value
Health-related quality of life							
SF-36: physical sum score							
BENEFIT	203	42.7 (8.98)	6.5 (0.61)	190	42.3 (9.06)	4.9 (0.63)	1.6 [-0.2; 3.3]; 0.077
BENEFIT-EXT	143	43.2 (8.35)	3.0 (0.76)	145	43.4 (8.18)	0.4 (0.75)	2.6 [0.5; 4.7]; 0.015
Total							2.01 [0.67; 3.35]; 0.003[c] Hedges' g: 0.21 [0.06; 0.36]
SF-36: mental sum score							
BENEFIT	203	44.2 (12.93)	5.1 (0.73)	190	44.2 (12.30)	2.6 (0.76)	2.5 [0.4; 4.5]; 0.019 Hedges' g: 0.22 [0.03; 0.42][d]
BENEFIT-EXT	143	46.7 (12.40)	1.6 (0.86)	145	45.1 (12.13)	1.8 (0.85)	-0.2 [-2.5; 2.2]; 0.892
Total							Heterogeneity: Q = 2.88; df = 1; p = 0.090; I^2 = 65.3%[c]

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: Unless stated otherwise, LOCF analysis of the ITT population.
c: Institute's calculation from meta-analysis.
d: Calculation from meta-analysis based on the unadjusted values at the time point 36 months.
CI: confidence interval; ITT: intention to treat; LOCF: last observation carried forward; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SF-36: Short Form (36) Health Survey (questionnaire on health-related quality of life); vs.: versus

Table 14: Results (dichotomous outcomes, month 84) – RCT, direct comparison: belatacept vs. ciclosporin A

Outcome category Outcome Study	Belatacept N	Belatacept Event rate % [95% CI][a]	Ciclosporin A N	Ciclosporin A Event rate % [95% CI][a]	Belatacept vs. ciclosporin A HR [95% CI][b]; p-value[b]
Mortality					
All-cause mortality					
BENEFIT	226	8.2 [5.0; 13.1]	221	14.4 [9.8; 20.9]	0.55 [0.30; 1.04]; 0.062
BENEFIT-EXT	175	26.7 [20.0; 35.2]	184	22.4 [15.7; 31.4]	1.10 [0.68; 1.80]; 0.692
Total					Heterogeneity: I^2 = 66.2%; tau^2 = 0.159; p = 0.085
Morbidity					
Graft loss					
BENEFIT	226	5.4 [3.0; 9.6]	221	10.2 [6.4; 15.9]	0.55 [0.26; 1.16]; 0.109
BENEFIT-EXT	175	13.6 [9.3; 19.9]	184	19.7 [13.9; 27.6]	0.75 [0.44; 1.30]; 0.306
Total					0.67 [0.43; 1.04]; 0.076
Death or graft loss					
BENEFIT	226	12.8 [8.8; 18.3]	221	21.7 [16.3; 28.7]	0.57 [0.35; 0.93]; 0.023
BENEFIT-EXT	175	34.7 [27.6; 42.9]	184	35.5 [27.9; 44.4]	0.92 [0.63; 1.35]; 0.670
Total					Heterogeneity: I^2 = 56.4%; tau^2 = 0.065; p = 0.13
Cardiorenal morbidity and mortality[c]					
BENEFIT	226	15.4 [11.1; 21.2]	221	22.1 [16.6; 29.1]	0.70 [0.44; 1.11]; 0.127
BENEFIT-EXT	175	36.5 [29.3; 44.8]	184	37.4 [29.6; 46.4]	0.93 [0.64; 1.35]; 0.718
Total					0.83 [0.62; 1.11]; 0.215
Cardiovascular morbidity and mortality[d]					
BENEFIT	226	6.3 [3.7; 10.7]	221	8.9 [5.4; 14.5]	0.74 [0.35; 1.54]; 0.415
BENEFIT-EXT	175	14.6 [9.3; 22.5]	184	12.0 [7.3; 19.6]	0.98 [0.50; 1.93]; 0.961
Total					0.86 [0.52; 1.41]; 0.555
Renal insufficiency in CKD stage 4/5					
BENEFIT	226	25.3 [19.9; 31.9]	221	50.7 [43.6; 58.2]	0.44 [0.32; 0.62]; < 0.001
BENEFIT-EXT	175	58.8 [51.3; 66.4]	184	75.3 [68.4; 81.7]	0.60 [0.46; 0.78]; < 0.001
Total					Heterogeneity: I^2 = 51.5%; tau^2 = 0.025; p = 0.151

(continued)

Table 14: Results (dichotomous outcomes, month 84) – RCT, direct comparison: belatacept vs. ciclosporin A (continued)

Outcome category Outcome Study	Belatacept N	Belatacept Patients with event n (%)	Ciclosporin A N	Ciclosporin A Patients with event n (%)	Belatacept vs. ciclosporin A RR [95% CI][a]; p-value[a]
PTDM					
BENEFIT	168[e]	18 (10.7)	162[e]	20 (12.3)	0.87 [0.48; 1.58]; 0.712
BENEFIT-EXT	136[e]	18 (13.2)	118[e]	16 (13.6)	0.98 [0.52; 1.83]; 0.992
Total					0.92 [0.60; 1.42]; 0.698
Adverse events					
SAEs					
BENEFIT	226	155 (68.6)	221	168 (76.0)	0.90 [0.80; 1.01]; 0.081
BENEFIT-EXT	175	156 (89.1)	184	155 (84.2)	1.06 [0.98; 1.15]; 0.225
Total					Heterogeneity: Q = 5.63; df = 1; p = 0.018; I^2 = 82.2%
Discontinuation due to AEs[f]					
BENEFIT	226	ND	221	ND	
BENEFIT-EXT	175	ND	184	ND	
Total					
Infections					
BENEFIT	226	202 (89.4)	221	186 (84.2)	1.06 [0.99; 1.14]
BENEFIT-EXT	175	151 (86.3)	184	158 (85.9)	1.00 [0.92; 1.09]
Total					1.04 [0.98; 1.10]; 0.195
Malignancies					
BENEFIT	226	19 (8.4)	221	25 (11.3)	0.74 [0.42; 1.31]
BENEFIT-EXT	175	26 (14.9)	184	26 (14.1)	1.05 [0.64; 1.74]
Total					0.90 [0.62; 1.31]; 0.593
PTLD					
BENEFIT	226	2 (0.9)	221	1 (0.5)	1.96 [0.18; 21.41]
BENEFIT-EXT	175	5 (2.9)[g]	184	1 (0.5)	5.26 [0.62; 44.55]
Total					3.39 [0.69; 16.69]; 0.133[h]

(continued)

Table 14: Results (dichotomous outcomes, month 84) – RCT, direct comparison: belatacept vs. ciclosporin A (continued)

a: Institute's calculation.
b: Results from meta-analysis.
c: No data were available at month 84 on the individual components "nonfatal myocardial infarction" and "stroke".
d: No data were available at month 84 on the individual components "cardiovascular death", "myocardial infarction", "ischaemic stroke" and "revascularization".
e: Number of patients who had no diabetes mellitus at the start of the study.
f: Treatment discontinuation due to AEs.
g: Since no analyses were available for patients with positive EBV serostatus, the calculation was conducted across all patients. At least 2 patients were not treated in compliance with the approval because their EBV serostatus was negative. The effect is smaller when only patients treated in compliance with the approval are considered.
h: In addition, the POR in rare events (≤ 1%) was calculated by the Institute if the observed POR depending on the respective group size rate and a 1.1 times tolerated deviation was between the maximum effect sizes indicated in Brockhaus 2004 [6] Table III. No qualitative differences were found.
AE: adverse event; CI: confidence interval; CKD: chronic kidney disease; EBV: Epstein-Barr virus; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; ND: no data; POR: Peto odds ratio; PTDM: post-transplant diabetes mellitus; PTLD: post-transplant lymphoproliferative disorder; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Due to the high risk of bias of all outcomes at month 84 relevant for the assessment, no more than an indication, e.g. of an added benefit, could be derived in the meta-analysis of both study populations. This deviated from the company's assessment, according to which the evidence provided in the case of effects in the same direction are principally suitable to derive proof of added benefit.

In an effect for only one of both donor criteria subgroups (subgroup SCD corresponds to the population of the BENEFIT study; subgroup ECD corresponds to the population in the BENEFIT-EXT study), no more than a hint could be derived because such an effect would only be supported by data from a single study. This deviates from the company's assessment, which derived indications of an added benefit in effects for only one of both subgroups.

Unless stated otherwise, the following results refer to month 84 relevant for the derivation of the added benefit.

Mortality

All-cause mortality

Due to an indication of heterogeneity ($0.05 < p \leq 0.2$), the results were considered at the individual study level. No statistically significant difference between the treatment groups was shown for any of the two studies. Hence for mortality there was no hint of an added benefit of belatacept in comparison with ciclosporin A; an added benefit is therefore not proven. This concurs with the company's assessment.

Morbidity

Graft loss

There was no statistically significant difference between the treatment groups in the individual studies or in the meta-analysis. Hence for the outcome "graft loss", there was no hint of an added benefit of belatacept in comparison with ciclosporin A; an added benefit is therefore not proven. This concurs with the company's assessment.

Death or graft loss

For comparisons with the company's assessments, it should be noted that it designated this composite outcome as "patient and graft survival". This designation is inapplicable because the underlying data relate to the number of the events "death or graft loss".

Due to an indication of heterogeneity, the results were considered at the individual study level. A statistically significant difference between the treatment arms was shown here for the BENEFIT study (patients with SCD transplant), but not for the BENEFIT-EXT study (patients with ECD transplant).

This resulted in a hint of an added benefit of belatacept in comparison with ciclosporin A for the composite outcome "death or graft loss" in patients with SCD transplant. The company deviated from this assessment insofar as it derived an indication of an added benefit, not taking into account the risk of bias.

There was no statistically significant difference between the treatment arms for the BENEFIT-EXT study. Hence for the composite outcome "death or graft loss", there was no hint of an added benefit of belatacept in comparison with ciclosporin A for patients with ECD transplant; an added benefit for these patients is therefore not proven. This concurs with the company's assessment.

Renal insufficiency in CKD stage 4/5

Due to an indication of heterogeneity, the results on renal insufficiency in CKD stage 4/5 were first considered at the individual study level. Statistically significant effects in the same direction and of comparable magnitude were observed here in both studies. The available data allowed a joint interpretation of the results of patients with SCD and ECD transplant. Hence for this outcome, an indication of added benefit of belatacept in comparison with ciclosporin A resulted from the 2 studies for patients with renal transplant (irrespective of the donor type).

The company's assessment deviated insofar as it derived proof of added benefit for the total population, not taking into account the high risk of bias. The company conducted no derivation of an added benefit for the individual populations.

Post-transplant diabetes mellitus, cardiorenal morbidity and mortality, cardiovascular morbidity and mortality

For the outcome "PTDM", the composite outcome "cardiorenal morbidity and mortality" as well as the composite outcome "cardiovascular morbidity and mortality", no statistically significant difference between the treatment groups was shown in the individual studies or in the meta-analysis. Hence there was no hint of an added benefit of belatacept in comparison with ciclosporin A for these outcomes; an added benefit is therefore not proven. This concurs with the company's assessment.

Health-related quality of life

No data on health-related quality of life at month 84 were available. The data available at month 60 did not relate to the intention to treat (ITT) population, and therefore cannot be used for the benefit assessment. No added benefit resulted from the data at month 36 (see first assessment of belatacept [3]).

Overall, there was therefore no hint of an added benefit of belatacept in comparison with ciclosporin A for health-related quality of life; an added benefit is therefore not proven. The company deviated from this assessment insofar as it derived a hint of an added benefit for the physical health sum score of the SF-36 questionnaire from the data at months 36 and 60.

Adverse events

Serious adverse events

Due to proof of heterogeneity ($p < 0.05$) at month 84, the results on SAEs were considered at the individual study level. No statistically significant difference between the treatment groups was shown for any of the two studies at month 84. Hence greater or lesser harm from belatacept in comparison with ciclosporin A is not proven. The company deviated from this assessment insofar as it derived an indication of added benefit from the data at month 36 for patients with SCD transplant, irrespective of their EBV serostatus. Taking into account only patients with positive EBV serostatus, this added benefit at month 36 can no longer be derived.

Discontinuation due to adverse events

For comparisons with the company's assessments, it should be noted that it designated this outcome as "study discontinuation due to AEs". This designation is inapplicable because the underlying data relate to treatment discontinuations due to AEs.

In the first assessment of belatacept [3], the results for the outcome "discontinuation due to AEs at month 36" were considered separately for the studies BENEFIT and BENEFIT-EXT because there was an indication of heterogeneity. This resulted in an indication of lesser harm of belatacept in comparison with ciclosporin A exclusively in patients with SCD transplant. The subgroup analyses at month 36 subsequently submitted in the current dossier showed homogeneous results for both studies in the subpopulation of European patients, and in the

pooled analyses a statistically significant advantage of belatacept for the European population of patients receiving a renal transplant irrespective of the donor criterion (see Section 2.4.4.1). This means that the conclusion on the inexistent added benefit based on the outcome "discontinuation due to AEs" in the first assessment of belatacept [3] did not apply to patients with ECD transplant in Europe at month 36. This result underlines the relevance of subgroup analyses for the benefit assessment.

The data presented at month 60 and month 84 did not relate to the ITT population, and therefore cannot be used for the benefit assessment. It therefore remains unclear whether an added benefit exists for patients in Europe in the longterm course.

Since only data at month 84 were used for the current assessment of the added benefit and no evaluable data were available on this time point, greater or lesser harm of belatacept in comparison with ciclosporin A is not proven for the outcome "discontinuation due to AEs". The company deviated from this assessment insofar as it derived an indication of added benefit for patients with SCD transplant using the data at month 36.

Infections, malignancies, post-transplant lymphoproliferative disorder

There was no statistically significant difference between the treatment groups for infections, malignancies and PTLD in the individual studies or in the meta-analysis. Hence greater or lesser harm from belatacept in comparison with ciclosporin A for these outcomes is not proven. This concurs with the company's assessment.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were considered to be relevant for the present benefit assessment:

- age (< 50 years versus ≥ 50 years)
- sex (female versus male)
- number of previous transplantations (0 versus ≥ 1)
- panel reactive antibodies (PRA; < 20% versus ≥ 20%)
- geographical region (North America versus South America versus Europe versus Africa versus Asia/Pacific)
- donor criterion (SCD versus ECD)

2.4.4.1 Month 36

Subgroup analyses were considered at month 36 to supplement the first assessment of belatacept [3]. At this documentation time, the event numbers within Module 5 were contradictory regarding the following outcomes:

- composite outcome “cardiovascular morbidity and mortality”
- PTDM
- infections
- malignancies
- PTLD

The company justified “slight deviations from the respective analyses of the month 36 CSR in rare cases” with presentations in the “current” database, which contained “relevant information on individual patients subsequently added on the outcomes, which had not yet become known when the month 36 CSR became available” (Module 4 A, Section 4.3.1.3). This justification at most concerns the outcomes “infections” and “PTLD”, however, for which there were higher event numbers after the month 36 CSR had become available. For the remaining outcomes mentioned above, the event number was lower after the month 36 CSR had become available. Since the company provided no appropriate justification for these deviations, the subgroup analyses on the outcomes at month 36 listed above were not considered because of the uncertainty of the results.

For the remaining outcomes, hereinafter only results for subgroup characteristics are presented for which there was at least an indication of an effect modification and for which there was a result deviating from the total population regarding statistical significance for at least one of the subgroups. For the continuous outcome “SF-36”, the criterion of clinical relevance (95% confidence interval [CI] of Hedges’ g completely above 0.2) had to be additionally met for at least one subgroup. The figures of the corresponding subgroup analyses can be found in Appendix D of the full dossier assessment. The results on the subgroup characteristic “donor criterion” (SCD versus ECD) are not presented for month 36 because they were already considered in the first assessment of belatacept for the derivation of the added benefit [3].

Table 15: Subgroups (dichotomous outcomes, month 36) – RCT, direct comparison: belatacept vs. ciclosporin A

Outcome Characteristic Subgroup Study	Belatacept N	Belatacept Patients with event n (%)	Ciclosporin A N	Ciclosporin A Patients with event n (%)	Belatacept vs. ciclosporin A RR [95% CI]	Belatacept vs. ciclosporin A p-value
Serious adverse events						
Region[a]						
Africa						
BENEFIT-EXT[b]	1	1 (100)	0	0	NC	NC
Asia/Pacific						
BENEFIT-EXT[b]	1	1 (100)	0	0	NC	NC
Europe						
BENEFIT-EXT[b]	85	70 (82.4)	88	72 (81.8)	1.01 [0.88; 1.16]	0.962[c]
North America						
BENEFIT-EXT[b]	41	29 (70.7)	46	41 (89.1)	0.79 [0.64; 0.99]	0.035[c]
South America						
BENEFIT-EXT[b]	47	39 (83.0)	50	33 (66.0)	1.26 [0.99; 1.59]	0.061[c]
					Interaction:	0.021[d]
Discontinuation due to AEs[e]						
Region						
Africa						
BENEFIT[b]	1	0 (0)	2	1 (50.0)	0.50 [0.04; 7.10]	ND
BENEFIT-EXT[b]	1	0 (0)	0	0 (0)	NC	NC
Asia/Pacific						
BENEFIT[b]	33	2 (6.1)	34	7 (20.6)	0.29 [0.07; 1.31]	
BENEFIT-EXT[b]	1	1 (100)	0	0 (0)	NC	NC
Europe						
BENEFIT[b]	60	4 (6.7)	54	10 (18.5)	0.36 [0.12; 1.08]	ND
BENEFIT-EXT[b]	85	13 (15.3)	88	24 (27.3)	0.56 [0.31; 1.03]	ND
Total					0.51 [0.30; 0.86][d]	0.012[d]
North America						
BENEFIT[b]	96	8 (8.3)	98	11 (11.2)	0.74 [0.31; 1.77]	ND
BENEFIT-EXT[b]	41	9 (22.0)	46	11 (23.9)	0.92 [0.42; 1.99]	ND
Total					0.84 [0.47; 1.49][d]	0.541[d]
South America						
BENEFIT[b]	36	2 (5.6)	33	3 (9.1)	0.61 [0.11; 3.43]	ND
BENEFIT-EXT[b]	47	13 (27.7)	50	9 (18.0)	1.54 [0.73; 3.26]	ND
Total					1.33 [0.67; 2.64][d]	0.421[d]
					Interaction:	0.169[f]

(continued)

Table 15: Subgroups (dichotomous outcomes, month 36) – RCT, direct comparison: belatacept vs. ciclosporin A (continued)

a: Contrary to the results for patients with positive EBV serostatus in Table 12, subgroup analyses were available only for the total populations of both studies.
b: The SCD subgroup corresponds completely to the population of the BENEFIT study; the ECD subgroup corresponds completely to the population of the BENEFIT-EXT study.
c: Institute's calculation, unconditional exact test (CSZ method according to [7]).
d: Calculated from the Institute's meta-analysis.
e: Treatment discontinuation due to AEs.
f: Calculated from the company's meta-analysis.
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; EBV: Epstein-Barr virus; ECD: extended criteria donor; N: number of analysed patients; n: number of patients with (at least one) event; NC: not calculable; ND: no data; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SCD: standard criteria donor; vs.: versus

Adverse events

Serious adverse events

The results for patients with positive EBV serostatus showed heterogeneity between the studies BENEFIT and BENEFIT-EXT for the outcome "SAEs" at month 36 (see Table 12). Since this heterogeneity is also present in the consideration of the total populations (see [3], Table 9), the subgroup analyses that also relate to the total populations were considered. As a result, there was proof of an effect modification by the subgroup characteristic "geographical region" for the outcome "SAEs" for patients with ECD transplant (population of the BENEFIT-EXT study). Taking into account the individual regions, a statistically significant effect in favour of belatacept was shown only for North America. The results on SAEs in the European patient population with ECD transplant did not differ between the treatment arms. Hence this analysis showed no added benefit of belatacept in comparison with ciclosporin A for the outcome "SAEs" in European patients with ECD transplant.

This deviates from the company's approach, which only considered the interaction term across both studies within this subgroup analysis, and did not consider the effects in the subgroups at the individual study level because there was no indication or proof of interaction.

Discontinuation due to adverse events

The results on the outcome "discontinuation due to AEs" were heterogeneous at month 36 in the joint analysis of both studies, BENEFIT and BENEFIT-EXT. The investigation of effect modifiers resulted in an indication of effect modification by the subgroup characteristic "geographical region". Within the subgroup of patients in Europe, the results of both studies were homogeneous and were therefore considered jointly. There was a statistically significant advantage of belatacept in comparison with ciclosporin A for the European population of patients receiving a renal transplant (irrespective of the donor criterion).

This deviated from the company's approach, which considered only effects at the individual study level within this subgroup analysis.

2.4.4.2 Month 84

At month 84, the company presented results on subgroup analyses only for the following outcomes:

- death or graft loss
- renal insufficiency in CKD stage 4/5
- cardiorenal morbidity and mortality

The analyses for these outcomes relate to the subgroup characteristics “age”, “sex” and “region”; no data were available at month 84 for the subgroup characteristic “PRA”. The data presented at month 84 for the subgroup characteristic “region” were not evaluable. The choice of interaction terms at month 84 is commented on in Section 2.7.2.2 of the full dossier assessment (subgroups/effect modifiers).

For the subgroup characteristics “age” and “sex”, no indications or proof of an interaction were available for the composite outcomes “death or graft loss” and “cardiorenal morbidity and mortality” as well as for the outcome “renal insufficiency in CKD stage 4/5” at month 84. It was unknown for all other outcomes included whether effect modifications by subgroup characteristics were present at month 84 because the company presented no corresponding subgroup analyses.

The donor criterion (SCD vs. ECD) was treated as additional subgroup characteristic (see Section 2.4.4). Since the 2 studies differed regarding the donor criterion, the consideration of the individual studies corresponds to the subgroup analysis by donor criterion. Table 16 shows results for the subgroup characteristic “donor criterion” with at least an indication of an effect modification. Indicating the overall estimator, the results serve to supplement the results in Section 2.4.3; in the presence of heterogeneity, the overall estimator was only used to support the derivation of the extent and probability of the added benefit.

In Section 2.4.3, effect modifications by donor criterion were already taken into account by considering the individual study results in case of indications or proof of heterogeneity between the studies. The results presented in Table 16 are therefore not commented on.

Table 16: Subgroups by donor criteria (dichotomous outcomes, 84 months) – RCT, direct comparison: belatacept vs. ciclosporin A

Outcome category Outcome Study (subgroup)[a]	Belatacept N	Belatacept Event rate [95% CI][b]	Ciclosporin A N	Ciclosporin A Event rate [95% CI][b]	Belatacept vs. ciclosporin A HR [95% CI]	 p-value
Mortality						
All-cause mortality					*0.85 [0.58; 1.24]*[c]	*0.399*[c]
BENEFIT (SCD)	226	8.2 [5.0; 13.1]	221	14.4 [9.8; 20.9]	0.55 [0.30; 1.04]	0.062
BENEFIT-EXT (ECD)	175	26.7 [20.0; 35.2]	184	22.4 [15.7; 31.4]	1.10 [0.68; 1.80]	0.692
					Interaction:	0.085
Morbidity						
Death or graft loss					*0.77 [0.57; 1.04]*[c]	*0.082*[c]
BENEFIT (SCD)	226	12.8 [8.8; 18.3]	221	21.7 [16.3; 28.7]	0.57 [0.35; 0.93]	0.023
BENEFIT-EXT (ECD)	175	34.7 [27.6; 42.9]	184	35.5 [27.9; 44.4]	0.92 [0.63; 1.35]	0.670
					Interaction:	0.13
Renal insufficiency in CKD stage 4/5					*0.54 [0.44; 0.66]*[c]	*< 0.001*[c]
BENEFIT (SCD)	226	25.3 [19.9; 31.9]	221	50.7 [43.6; 58.2]	0.44 [0.32; 0.62]	< 0.001
BENEFIT-EXT (ECD)	175	58.8 [51.3; 66.4]	184	75.3 [68.4; 81.7]	0.60 [0.46; 0.78]	< 0.001
					Interaction:	0.151
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI][b]**	**p-value[b]**
Adverse events						
Serious adverse events					*0.98 [0.83; 1.16]*[c]	*0.829*[c]
BENEFIT (SCD)	226	155 (68.6)	221	168 (76.0)	0.90 [0.80; 1.01]	0.081
BENEFIT-EXT (ECD)	175	156 (89.1)	184	155 (84.2)	1.06 [0.98; 1.15]	0.225
					Interaction:	0.018

a: The SCD subgroup corresponds completely to the population of the BENEFIT study; the ECD subgroup corresponds completely to the population of the BENEFIT-EXT study.
b: Institute's calculation.
c: Overall estimator in the presence of heterogeneity; used only to support the derivation of extent and probability of the added benefit.
CI: confidence interval; CKD: chronic kidney disease; ECD: extended criteria donor; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; RCT: randomized controlled trial; RR: relative risk; SCD: standard criteria donor; vs.: versus

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

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

2.5.1 Assessment of added benefit at outcome level

In comparison between belatacept and ciclosporin A, the data presented in Section 2.4 showed a hint of an added benefit (only in patients with SCD transplant) at month 84 for the composite outcome “death or graft loss” for adult recipients of renal transplants with de novo treatment. An indication of an added benefit (both in patients with SCD and in patients with ECD transplant) was shown for the outcome “renal insufficiency in CKD stage 4/5”.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 17).

Table 17: Extent of added benefit at outcome level: belatacept vs. ciclosporin A

Outcome category **Outcome**	**Belatacept vs. ciclosporin A** **Event rate at month 84**[a] **Effect estimate [95% CI]** **p-value** **probability**[b]	**Derivation of extent**[c]
Mortality		
All-cause mortality		
SCD[d]	8.2% vs. 14.4% HR 0.55 [0.30; 1.04] p = 0.062	Lesser benefit/added benefit not proven
ECD[d]	26.7% vs. 22.4% HR 1.10 [0.68; 1.80] p = 0.692	Lesser benefit/added benefit not proven
Morbidity		
Graft loss	5.4-13.6% vs. 10.2-19.7%[e] HR 0.67 [0.43; 1.04] p = 0.076	Lesser benefit/added benefit not proven
Death or graft loss	HR 0.77 [0.57; 1.04] p = 0.082	
SCD[d]	12.8% vs. 21.7% HR 0.57 [0.35; 0.93] p = 0.023 probability: "hint"	Outcome category: mortality/ serious/severe late complications $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
ECD[d]	34.7% vs. 35.5% HR 0.92 [0.63; 1.35] p = 0.670	Lesser benefit/added benefit not proven
Cardiorenal morbidity and mortality	15.4-36.5% vs. 22.1-37.4%[e] HR 0.83 [0.62; 1.11] p = 0.215	Lesser benefit/added benefit not proven
Cardiovascular morbidity and mortality	6.3-14.6% vs. 8.9-12.0%[e] HR 0.86 [0.52; 1.41] p = 0.555	Lesser benefit/added benefit not proven
Renal insufficiency in CKD stage 4/5		
SCD[d]	25.3% vs. 50.7% HR 0.44 [0.32; 0.62] p < 0.001	Outcome category: non-serious/non-severe symptoms[f] $CI_u < 0.80$ added benefit, extent: "considerable"
ECD[d]	58.8% vs. 75.3% HR 0.60 [0.46; 0.78] p < 0.001 probability (under consideration of both studies): "indication"	

(continued)

Table 17: Extent of added benefit at outcome level: belatacept vs. ciclosporin A (continued)

Outcome category **Outcome**	**Belatacept vs. ciclosporin A** **Event rate at month 84**[a] **Effect estimate [95% CI]** **p-value** **probability**[b]	**Derivation of extent**[c]
PTDM	Patients with event: 10.7-13.2% vs. 12.3-13.6%[e] RR: 0.92 [0.60; 1.42] p = 0.698	Lesser benefit/added benefit not proven
Health-related quality of life		
SF-36	Outcome at month 84 not recorded	Lesser benefit/added benefit not proven
Adverse events		
Serious adverse events		
SCD[d]	Patients with event: 68.6% vs. 76.0% RR: 0.90 [0.80; 1.01] p = 0.081	Greater/lesser harm not proven
ECD[d]	Patients with event: 89.1% vs. 84.2% RR: 1.06 [0.98; 1.15] p = 0.225	Greater/lesser harm not proven
Discontinuation due to AEs	No evaluable data	Greater/lesser harm not proven
Infections	Patients with event: 86.3-89.4% vs. 84.2-85.9%[e] RR: 1.04 [0.98; 1.10] p = 0.195	Greater/lesser harm not proven
Malignancies	Patients with event: 8.4-14.9% vs. 11.3-14.1%[e] RR: 0.90 [0.62; 1.31] p = 0.593	Greater/lesser harm not proven
PTLD	Patients with event: 0.9-2.9[g]%[e] vs. 0.5% RR: 3.39 [0.69; 16.69] p = 0.133	Greater/lesser harm not proven

a: Estimated from Kaplan-Meier curve (if no deviating information).
b: Probability given if statistically significant differences are present.
c: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
d: Population divided by donor criteria due to heterogeneity in the meta-analysis of both studies BENEFIT (only patients with SCD transplant) and BENEFIT-EXT (only patients with ECD transplant); the effect estimates presented correspond to the results of individual studies on the respective outcome.
e: Minimum and maximum value at month 84 per treatment arm in the studies included.
f: For reasons, see Section 2.7.2.4.3 of the full dossier assessment.
g: Contains at least 2 patients who were not treated in compliance with the approval because of negative EBV serostatus.

AE: adverse event; CI: confidence interval; CI_u: upper limit of CI; CKD: chronic kidney disease; EBV: Epstein-Barr virus; ECD: extended criteria donor; HR: hazard ratio; PTDM: post-transplant diabetes mellitus; PTLD: post-transplant lymphoproliferative disorder; RR: relative risk; SAE: serious adverse event; SCD: standard criteria donor; SF-36: Short Form (36) Health Survey (questionnaire on health-related quality of life); vs.: versus

2.5.2 Overall conclusion on added benefit

Table 18 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of belatacept in comparison with ciclosporin A

Positive effects	Negative effects
Indication of added benefit – extent "considerable" (non-serious/non-severe symptoms: renal insufficiency in CKD stage 4/5)	–
Patients with SCD transplant ▪ hint of an added benefit – extent: "minor" (mortality/serious/severe late complications: death or graft loss)	–
CKD: chronic kidney disease; SCD: standard criteria donor	

In the overall consideration, positive results in favour of belatacept remain. There is an indication of considerable added benefit of belatacept in comparison with the ACT ciclosporin A for the outcome "renal insufficiency in CKD stage 4/5" for adult recipients of a renal transplant with de novo treatment (irrespective of donor type). In addition, there is a hint of a minor added benefit for the composite outcome "death or graft loss" for the subpopulation with SCD transplant. This result does not lead to a change in the assessment of the added benefit in this subpopulation.

In summary, there is an indication of considerable added benefit of belatacept in comparison with the ACT ciclosporin A for prophylaxis of graft rejection and the maintenance of renal function in adult recipients of renal transplants with de novo treatment.

The result of the assessment of the added benefit of belatacept in comparison with the ACT is summarized in Table 19.

Table 19: Belatacept – extent and probability of added benefit

Therapeutic indication	Appropriate comparator therapy[a]	Extent and probability of added benefit
Prophylaxis of graft rejection and the maintenance of renal function in adults receiving a renal transplant[b]	The appropriate comparator therapy for the initial maintenance therapy is ciclosporin in combination with corticosteroids and mycophenolate mofetil for the prophylaxis of graft rejection and the maintenance of renal function in adults receiving a renal transplant. The drugs should be given in the approved dosages and customized for the individual patient.	Indication of considerable added benefit
a: Presentation of the appropriate comparator therapy specified by the G-BA. b: These data apply only to patients who received an initial treatment with belatacept (de novo), but not to patients switched to belatacept, because the therapeutic indication of belatacept is restricted to recipients of renal transplants with de novo treatment. G-BA: Federal Joint Committee		

This deviates from the company's approach, which derived proof of considerable added benefit of belatacept in recipients of renal transplants with de novo treatment.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.6 List of included studies

BENEFIT

Bristol Myers Squibb. Belatacept evaluation of nephroprotection and efficacy as first-line immunosuppression trial (BENEFIT): revised protocol 05 incorporating protocol amendments 13 (dated 10-Feb-2011) [online]. In: EU Clinical Trials Register. [Accessed: 8 April 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2004-003635-31.

Bristol-Myers Squibb. Belatacept evaluation of nephroprotection and efficacy as first-line immunosuppression (BENEFIT): full text view [online]. In: ClinicalTrials.gov. 5 March 2015 [accessed: 8 April 2015]. URL: http://ClinicalTrials.gov/show/NCT00256750.

Bristol-Myers Squibb. Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT): study IM103008; revised protocol number 05; incorporates amendment(s) 13 [unpublished]. 2011.

Rostaing L, Vincenti F, Grinyo J, Rice KM, Bresnahan B, Steinberg S et al. Long-term belatacept exposure maintains efficacy and safety at 5 years: results from the long-term extension of the BENEFIT study. Am J Transplant 2013; 13(11): 2875-2883.

Vincenti F, Charpentier B, Vanrenterghem Y, Rostaing L, Bresnahan B, Darji P et al. A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study). Am J Transplant 2010; 10(3): 535-546.

Vincenti F, Larsen CP, Alberu J, Bresnahan B, Garcia VD, Kothari J et al. Three-year outcomes from BENEFIT, a randomized, active-controlled, parallel-group study in adult kidney transplant recipients. Am J Transplant 2012; 12(1): 210-217.

BENEFIT-EXT

Bristol-Myers Squibb. Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial - EXTended Criteria Donors (BENEFIT-EXT): study IM103027; revised protocol number 08; incorporates amendment(s) 11 [unpublished]. 2011.

Bristol-Myers Squibb. Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial: EXTended criteria donors (BENEFIT-EXT); revised protocol number 03 incorporating administrative letters # 2, 4 & 5 [online]. In: EU Clinical Trials Register. [Accessed: 8 April 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2004-002974-48.

Bristol-Myers Squibb. Study of belatacept in subjects who are undergoing a renal transplant (BENEFIT-EXT): full text view [online]. In: ClinicalTrials.gov. 6 February 2015 [accessed: 8 April 2015]. URL: http://ClinicalTrials.gov/show/NCT00114777.

Charpentier B, Medina Pestana JO, Del C. Rial M, Rostaing L, Grinyo J, Vanrenterghem Y et al. Long-term exposure to belatacept in recipients of extended criteria donor kidneys. Am J Transplant 2013; 13(11): 2884-2891.

Durrbach A, Pestana JM, Pearson T, Vincenti F, Garcia VD, Campistol J et al. A phase III study of belatacept versus cyclosporine in kidney transplants from extended criteria donors (BENEFIT-EXT study). Am J Transplant 2010; 10(3): 547-557.

Medina Pestana JO, Grinyo JM, Vanrenterghem Y, Becker T, Campistol JM, Florman S et al. Three-year outcomes from BENEFIT-EXT: a phase III study of belatacept versus cyclosporine in recipients of extended criteria donor kidneys. Am J Transplant 2012; 12(3): 630-639.

IM103100

Bristol-Myers Squibb. Study comparing the safety and efficacy of belatacept with that of cyclosporine in patients with a transplanted kidney: full text view [online]. In: ClinicalTrials.gov. 27 November 2013 [accessed: 16 July 2015]. URL: https://ClinicalTrials.gov/show/NCT0003555.

Bristol-Myers Squibb. Study comparing the safety and efficacy of belatacept with that of cyclosporine in patients with a transplanted kidney: study results [online]. In: ClinicalTrials.gov. 27 November 2013 [accessed: 16 July 2015]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00035555.

Vincenti F, Blancho G, Durrbach A, Friend P, Grinyo J, Halloran PF et al. Five-year safety and efficacy of belatacept in renal transplantation. J Am Soc Nephrol 2010; 21(9): 1587-1596.

Vincenti F, Larsen C, Durrbach A, Wekerle T, Nashan B, Blancho G et al. Costimulation blockade with belatacept in renal transplantation. N Engl J Med 2005; 353(8): 770-781.

References for English extract

Please see full dossier assessment for full reference list.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden: Version 4.2. Köln: IQWiG; 2015. URL: https://www.iqwig.de/download/IQWiG_Methoden_Version_4-2.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2 July 2015 [Epub ahead of print].

3. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Belatacept: Nutzenbewertung gemäß §35a SGB V; Dossierbewertung; Auftrag A12-03 [online]. 12 April 2012 [accessed: 18 September 2015]. URL: https://www.iqwig.de/download/A12-03_Belatacept_Nutzenbewertung_35a_SGB_V.pdf.

4. Bristol-Myers Squibb. Nulojix 250 mg Pulver für ein Konzentrat zur Herstellung einer Infusionslösung: Fachinformation [online]. December 2014 [accessed: 23 February 2015]. URL: http://www.fachinfo.de.

5. Novartis Pharma. Sandimmun Weichkapseln: Fachinformation [online]. October 2014 [accessed: 18 May 2015]. URL: http://www.fachinfo.de.

6. Brockhaus AC, Bender R, Skipka G. The Peto odds ratio viewed as a new effect measure. Stat Med 2014; 33(28): 4861-4874.

7. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574.

The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a15-25-belatacept-nutzenbewertung-gemaess-35a-sgb-v-dossierbewertung.6808.html.