IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Belatacept –

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

Extract

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CAN	chronic allograft nephropathy
EBV	Epstein-Barr virus
ECD	extended criteria donors
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GFR	glomerular filtration rate
IQWiG	Institut für Qualität and Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
OR	odds ratio
PRA	panel-reactive antibodies
PTDM	post-transplant diabetes mellitus
PTLD	post-transplant lymphoproliferative disorder
RCT	randomized controlled trial
SAE	serious adverse event
SCD	standard criteria donors
SF-36	Short Form 36
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

On 16.01.2012, in accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) wrote to the Institute for Quality and Efficiency in Health Care (IQWiG) to commission the benefit assessment of the drug belatacept. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company").

Research question

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

The assessment was undertaken with respect to patient-relevant outcomes. Only randomized controlled trials (RCTs) with a direct comparator were included in the assessment.

Results

A total of 2 relevant studies were available. Study IM103008 enrolled patients given a renal transplant from a donor classified according to standard criteria (standard criteria donors, SCD). Study IM103027 enrolled patients given a renal transplant from a deceased donor classified according to extended criteria (extended criteria donors, ECD). Both studies were unblinded for the treatment comparison relevant to this assessment; this was due to the different forms of administration of the drugs (intravenous administration with belatacept, oral administration with ciclosporin A). Treatment duration was 36 months in each study. The 2 belatacept arms included in each study were blinded, of which only one was used in this assessment because of a dosage according to approval status. Data for the maximum study period of the included studies (documentation time 36 months) were considered. The risk of bias of both studies was rated as low both at study level and also for most of the outcomes. The exception was the outcome "health-related quality of life", which, as a subjective outcome, is to be regarded as having an inherently high risk of bias in open-label studies. Both studies were summarized by meta-analysis. If heterogeneity was present, the assessment was carried out at the level of the individual study, i.e. separately for patients given transplants from donors classified according to standard criteria (SCD) or extended criteria (ECD), because these donor criteria were substantially different between the 2 studies. On the basis of the available evidence (2 studies), in principle proof, e.g. of an added benefit, could be derived, unless outcome-specific aspects weakened the informative value.

All-cause mortality

The result of the meta-analysis for the outcome "mortality" was not statistically significant. An added benefit of belatacept for this outcome is not proven. It should be borne in mind that,

due to study duration and the number of enrolled patients, neither study was suitable for demonstrating differences between the treatments with regard to this outcome.

Morbidity

The result of the meta-analyses on the 4 outcomes **"graft loss", the composite outcome "patient and graft survival", "cardiovascular morbidity and mortality"** and the **composite outcome "cardiorenal diseases"** was not statistically significant in each case. An added benefit of belatacept for these outcomes is not proven.

Health-related quality of life

The result of the meta-analysis on the outcome "health-related quality of life" (recorded using Short Form 36, SF-36) was not statistically significant for the sum score "mental health". The result for the sum score "physical health" was statistically significant in favour of belatacept. However, due to the size of the effect, a clinically relevant difference could not be assumed. An added benefit of belatacept for the outcome "health-related quality of life" is therefore not proven.

Adverse events

The result of the meta-analyses for the 5 outcomes **"adverse events", "post-transplant lymphoproliferative disorder" (PTLD), "post-transplant diabetes mellitus" (PTDM), "malignancies"** and **"infections"** was not statistically significant. Greater or lesser harm from belatacept for these outcomes is not proven.

The results for the 2 outcomes **"serious adverse events"** and **"treatment discontinuations due to adverse events"** were not summarized by meta-analysis because of heterogeneity, and thus were considered separately per study. Since the 2 studies differed in respect of the donor criteria applied (IM103008: SCD; IM103027: ECD), separate conclusions were drawn at outcome level for these donor populations. Based on the respective single study results on both outcomes, Study IM103008 showed a statistically significant result in favour of belatacept, whereas the result was not statistically significant for either outcome in Study IM103027. There is an indication of lesser harm from belatacept in patients who received a transplant from a donor classified according to standard criteria (SCD, IM103008) for both outcomes. In the case of patients who received a transplant from a donor classified according to extended criteria, (ECD, IM103027) greater or lesser harm from belatacept for these outcomes is not proven.

Extent and probability of the added benefit, patient groups with therapeutically important added benefit

Based on the results presented, the extent and probability of the added benefit of the drug belatacept is assessed as follows:

For adult **patients who received a renal transplant from a donor classified according to standard criteria (SCD)**, the data produced an indication of lesser harm from belatacept for

the outcomes "serious adverse events" and "treatment discontinuations due to adverse events" respectively. Based on these results, the extent of the respective lesser harm at outcome level was estimated, taking into account outcome categories and effects sizes. Two positive results in favour of belatacept remain, with the extent "minor" and the probability "indication". A decision on balancing of benefits and harms is not required. **In summary for adult patients who received a renal transplant from a donor classified according to standard criteria (SCD), there is an indication of an added benefit (extent "minor") of belatacept over the ACT ciclosporin A.**

For adult **patients, who received a renal transplant from a donor classified according to extended criteria (ECD)**, the data produced no added benefit or greater/lesser harm from belatacept. Neither positive nor negative effects remain from the assessment of added benefit at outcome level. **In summary, for adult patients who received a renal transplant from a donor classified according to extended criteria (ECD), there is no proof of an added benefit of belatacept over the ACT ciclosporin A.**

The procedure for deriving the overall conclusion on the added benefit is a proposal from IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The benefit assessment of belatacept was undertaken according to the following approved therapeutic indication "*prophylaxis of graft rejection in adults receiving a renal transplant*" (Summary of Product Characteristics, SPC [1]). The company designates ciclosporin A as ACT and thus corresponds to the following ACT specified by the G-BA: *"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 who have received a renal transplant. The drugs should be given in the approved dosages and customized for the individual patient"*.

The aim of the present report is therefore to assess the added benefit of belatacept compared to ciclosporin A for the prophylaxis of graft rejection in adults receiving a renal transplant.

The assessment was carried out with respect to patient-relevant outcomes. Only RCTs with a direct comparator were included in the assessment.

Since immunosuppressive treatment following organ transplantation is a long-term therapy, the Institute – in contrast to the company's procedure – considered primarily data at the maximum duration of the included studies (documentation time 36 months). The company additionally used data from these studies at the time of 12 months. For two outcomes (cardiovascular morbidity and mortality, PTDM) there were divergent effects between both documentation times. Since the company did not present any informative data for an assessment of these outcomes over the course of time, only the analysis at 36 months was considered for these outcomes too.

Further information about the research question can be found in Module 3, Section 3.1 and Module 4, Section 4.2.1 of the dossier and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled from the following data:

- Studies on belatacept completed by the company up to 30.11.2011 (study list of the company).
- Results of a search in trial registries for studies on belatacept (last search 19.12.2011, searches by the company).
- The Institute's own searches in trial registries for studies on belatacept to check the search results of the company (search date: 03.02.2012). In addition, the information retrieval by the company was checked using the inclusion criteria specified by the Institute, which deviated substantially from that of the company with respect to the population (taking account of the EBV (Epstein-Barr virus) status according to the approval status).

The result of the check produced no additional relevant studies, but the following deviations from the study pool shown in the company's dossier (3 studies: IM103008, IM103027 and IM103100):

Study IM103100 included by the company was excluded from the benefit assessment because 43% of the enrolled patients had a negative or unknown EBV serostatus. According to the SPC, belatacept is contraindicated in these patients. As the company presented no adequate subgroup analyses on the patients with positive EBV status, this study could not be considered. Hence, only Studies IM103008 and IM103027 are included in the Institute's benefit assessment.

Further information about the inclusion criteria for studies in the benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.3.1 Studies included in the assessment

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

Table 2: Study pool – RCTs with the drug to be assessed, direct comparison belatacept versus 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)	yes	yes	no
IM103027 (BENEFIT-EXT)	yes	yes	no
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. RCT: randomized controlled trial			

Two RCTs (IM103008 and IM103027) could be included in the assessment of belatacept in direct comparison with ciclosporin A in adult renal transplant recipients.

Section 2.6 contains a list of data sources named by the company for the studies included in its assessment.

Further information about the results of information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment.

2.3.2 Study characteristics

Table 3 and Table 4 describe the studies used for the benefit assessment.

Table 3 shows the study characteristics, Table 4 shows the characteristics of the interventions used in the studies.

Table 3: Characteristics of the included studies – belatacept versus ciclosporin A

Study	Study design	Population	Interventions (number of randomized patients)[a]	Duration of study	Location and period of study	Primary outcomes; secondary outcomes[b]
IM103008	Randomized, partially-blinded[c], active-controlled, multicentre, clinical Phase III trial with parallel groups (1:1:1)	Adult *de novo* renal transplant recipients of organs from donors classified according to standard criteria (SCD)	Belatacept MI (n=219)[d] Belatacept LI (n=226) Ciclosporin A (n=221)	3 years with an 8-week follow-up observation period for safety evaluations	104 study centres: Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, France, Germany, Hungary, India, Israel, Italy, Mexico, Poland, Sweden, Switzerland, Spain, South Africa, Turkey, USA January 2006 – July 2010	Primary: 1. Composite outcome (patient and graft survival), 2. Renal function, 3. Acute rejection reaction. Secondary: all-cause mortality, graft loss, cardiovascular morbidity/mortality, cardiorenal diseases, adverse events, post-transplant lymphoproliferative disorder (PTLD), post-transplant diabetes mellitus (PTDM), malignancy, infections
IM103027	Randomized, partially-blinded[c], active-controlled, multicentre, clinical Phase III trial with parallel groups (1:1:1)	Adult *de novo* renal transplant recipients of organs from deceased donors classified according to extended criteria (ECD)	Belatacept MI (n=184)[d] Belatacept LI (n=175) Ciclosporin A (n=184)	3 years with an 8-week follow-up observation period for safety evaluations	79 study centres: Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Czech Republic, France, Germany, Hungary, Italy, Norway, Poland, Sweden, Spain, South Africa, UK, USA March 2005 – June 2010	Primary: 1. Composite outcome (patient and graft survival), 2. Renal function, 3. Acute rejection reaction. Secondary: all-cause mortality, graft loss, cardiovascular morbidity/mortality, cardiorenal diseases, adverse events, post-transplant lymphoproliferative disorder (PTLD), post-transplant diabetes mellitus (PTDM), malignancy, infections

(continued on next page)

Table 3: Characteristics of the included studies – belatacept versus ciclosporin A (continued)

a: Patients in whom a transplantation was carried out.

b: Primary outcomes contain information without consideration of the relevance for this benefit assessment. Extracted secondary outcome criteria contain exclusively information on the relevant available outcomes for this benefit assessment.

c: Study for the comparison of belatacept (LI) versus ciclosporin A non-blinded.

d: Arm not relevant for the assessment and is no longer shown in the next tables (MI regimen not approval-compliant).

ECD: extended criteria donors; LI: lower dose of belatacept (less intensive); MI: more intensive dose of belatacept;
PTDM: post-transplant diabetes mellitus; PTLD: post-transplant lymphoproliferative disorder; SCD: standard criteria donors

Table 4: Characteristics of the interventions – belatacept versus ciclosporin A

Study	Belatacept	Ciclosporin A	Other treatment characteristics
IM103008	**0–1 month:** Belatacept 10 mg/kg i.v. on Days 1, 5 and in Weeks 2, 4 **2–3 months:** i.v. belatacept 10 mg/kg in Weeks 8 and 12 **4–12 months:** Belatacept 5 mg/kg i.v. every 4 weeks	**Initial daily dose:** Ciclosporin A oral 7 ± 3 mg/kg (4–10 mg/kg) **0–1 month:** Dose adjustment to 150–300 ng/ml **2–12 months:** Dose adjustment to 100–250 ng/ml	All patients received: ▪ Induction therapy with basiliximab: 20 mg i.v. on day of transplant and 4 days post-operatively ▪ Mycophenolate mofetil: 2 g/day p.o. in divided doses ▪ Corticosteroids (starting dose 500 mg i.v. preoperatively; then decreasing to a dose of at least 2.5 mg/day oral up to Day 15)
	After Month 12, patients remained until Month 36 on the maintenance dose of the study medication		
IM103027	**0–1 month:** Belatacept 10 mg/kg i.v. on Days 1, 5 and in Weeks 2, 4 **2–3 months:** Belatacept 10 mg/kg i.v. in Weeks 8 and 12 **4–12 months:** Belatacept 5 mg/kg i.v. every 4 weeks	**Initial daily dose:** Ciclosporin A oral 7 ± 3 mg/kg (4–10 mg/kg) **0–1 month:** Dose adjustment to 150–300 ng/ml **2–12 months:** Dose adjustment to 100–250 ng/ml	All patients received: ▪ Induction therapy with basiliximab: 20 mg i.v. on day of transplant and 4 days post-operatively ▪ Mycophenolate mofetil: 2 g/day p.o. in divided doses ▪ Corticosteroids (starting dose 500 mg i.v. preoperatively; then decreasing to a dose of at least 2.5 mg/day oral up to Day 15)
	After Month 12, patients remained on the maintenance dose of the study medication until Month 36		
i.v.: intravenous; p.o.: per os (oral)			

The 2 included studies were the approval studies of the company in patients undergoing renal transplantation. Both studies were randomized, active-controlled and non-blinded in the study arms (belatacept LI and ciclosporin A) to be considered in the benefit assessment. In addition to the belatacept dosage (LI) that corresponded to the approval status and was relevant for the benefit assessment, both studies also included a further belatacept arm with a higher dosage (MI) that did not correspond to the approval status (Table 3, [1]) and is therefore not shown further below. The blinding of the 2 studies related solely to these 2 belatacept arms and is thus of no significance for this assessment. The enrolment and randomization of patients in both studies took place before renal transplantation. In Study IM103008, initially 461 patients (belatacept LI: 230 patients; ciclosporin A: 231 patients) and in der Study IM103027 385 patients (belatacept LI: 193 patients, ciclosporin A: 192 patients) were randomized into the study arms of relevance for this benefit assessment. Only patients in whom a renal transplant was carried out were included in the assessment (IM103008: belatacept LI 226

patients; ciclosporin A 221 patients; IM103027: belatacept LI 175 patients; ciclosporin A 184 patients). The total duration of each study covered a treatment period of 36 months with a follow-up observation period of 8 weeks for the safety evaluations. In addition to the study medication (belatacept or ciclosporin A), all patients received induction therapy with basiliximab as well as mycophenolate mofetil and corticosteroids. After Month 12, the patients remained on the maintenance dose of the study medication until Month 36.

With regard to the comparator intervention, ciclosporin A, it should be noted that the administered initial dose of 7 ± 3 mg/kg (4 to 10 mg/kg) is below the dose named in the SPC of 10 to 14 mg/kg [2]. Subsequent doses were adjusted on the basis of serum concentrations of ciclosporin A; the first serum level measurement took place on Day 5 after transplantation. Contrary to the SPC, the administration of the initial dose could also sometimes be delayed until after the transplantation. Although these procedures differ from the instructions in the SPC for ciclosporin A [2], in the Institute's view they do not represent a relevant limitation. For detailed reasoning, see Section 2.7.2.1 of the full dossier assessment.

Table 5 shows the characteristics of patients in the studies included in the assessment.

Table 5: Characteristics of the study populations – belatacept versus ciclosporin A

Study Group	Patient characteristics					Donor characteristics	
	N[a]	Age [years] mean (SD)	Gender f /m (%)	Number of patients with previous transplan-tation (%)	EBV status positive n (%)	Living/deceased donors (%)	Cold ischaemia time [hours] mean (SD)
IM103008							
Belatacept	226	42.6 (13.4)	35.4 / 64.6	l–2: 5 (2.2) missing: 3 (1.3)	202 (89.4)[b]	57.1 / 42.9	living 1.3 (1.6)[c] deceased 16.7 (6.4)
Ciclosporin A	221	43.5 (14.3)	25.3 / 74.7	l–2: 9 (4.1) missing: 4 (1.8)	184 (83.2)[b]	56.1 / 43.9	living 1.5 (2.8)[d] deceased 16.7 (5.7)
IM103027							
Belatacept	175	56.1 (12.4)	36.3 / 73.7	not applicable[e]	156 (89.1)[b]	0.6 / 99.4[f]	no living donors deceased 21.2 (8.0)[g]
Ciclosporin A	184	55.7 (12.2)	37.0 / 63.0		168 (91.3)[b]	0 / 100	no living donors deceased 19.4 (7.4)[g]

a: Number of randomized patients (ITT population).
b: Percentages self-calculated.
c: No information about cold ischaemia time in 2 cases.
d: No information about cold ischaemia time in 3 cases.
e: Previous transplantation was an exclusion criterion in Study IM103027.
f: Consideration of one case of a living donor because of a protocol infringement; no information about cold ischaemia time in this case.
g: Standard deviation self-calculated
EBV: Epstein-Barr virus; f: female; m: male; N: number of analysed patients; n: number of patients with event; SD: standard deviation

In neither study were there any substantial differences between the treatment groups in terms of age, gender or EBV status. The studies differed in respect of donor criteria. Whereas Study IM103008 enrolled renal transplant recipients of organs from donors classified according to standard criteria (SCD), renal transplant recipients in Study IM103027 received organs from deceased donors classified according to extended criteria (ECD). This results in differences between the 2 study populations; for example the age of the patients enrolled in Study IM103027 is relatively higher than in Study IM103008. The proportion of deceased donors and cold ischaemia times are lower in Study IM103008 than in Study IM103027 (Table 5).

Table 6 shows the risk of bias at study level.

Table 6: Risk of bias at study level – belatacept versus ciclosporin A

Study	Adequate randomization sequence generation	Allocation concealment	Blinding		Selective outcome reporting	Other sources of bias	Risk of bias at study level
			Patient	Treating persons			
IM103008	yes	yes	no	no	no	no	low
IM103027	yes	yes	no	no	no	no	low

The risk of bias at study level was classed as low for both studies. This concurs with the company's assessment.

Further information about the study design, study populations and risk of bias at study level can be found in Module 4, Sections 4.3.1.2.1, 4.3.1.2.2 and 4.3.2.1.2 of the dossier and in Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.

2.4 Results concerning added benefit

This assessment covers the following patient-relevant outcomes (for reasoning, see Sections 2.7.2.2 and 2.7.2.4.3 of the full dossier assessment):

- All-cause mortality
- Graft loss
- Composite outcome: patient and graft survival
- Cardiovascular morbidity and mortality
- Composite outcome: cardiorenal diseases
- Health-related quality of life (SF-36)
- Overall rate of AE
- Overall rate of SAE

- Treatment discontinuations due to AE
- Post-transplant lymphoproliferative disorder (PTLD)
- Post-transplant diabetes mellitus (PTDM)
- Malignancies
- Infections

The Institute chose different patient-relevant outcomes to those of the company, which included further outcomes in Module 4 of its dossier (graft function based on glomerular filtration rate [GFR], chronic allograft nephropathy [CAN] and acute rejection reactions). In addition, the Institute included the following additional outcomes: "composite outcome: cardiorenal diseases", "malignancies", "infections" (for justification of the choice of outcomes by the Institute, see Sections 2.7.2.2. and 2.7.2.4.3 of the full dossier assessment).

Table 7 shows for which outcomes data were available in the studies included. Table 8 describes the risk of bias for these outcomes.

Table 7: Matrix of outcomes – belatacept versus ciclosporin A

Study	All-cause mortality	Graft loss	Patient and graft survival	Cardiovascular morbidity/mortality	Cardiorenal diseases	Health-related quality of life	Overall rate of AE	Overall rate of SAE	Treatment discontinuations due to AE	PTLD	PTDM	Malignancies	Infections
IM103008	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
IM103027	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes

AE: adverse events; PTDM: post-transplant diabetes mellitus; PTLD: post-transplant lymphoproliferative disorder; SAE: serious adverse events

Table 8: Risk of bias at study and outcome level - belatacept versus ciclosporin A

Outcome / Study	Study level	All-cause mortality	Graft loss	Patient and graft survival	Cardiovascular morbidity/mortality	Cardiorenal diseases	Health-related quality of life	Overall rate of AE	Overall rate of SAE	Treatment discontinuations due to AE	PTLD	PTDM	Malignancies	Infections
IM103008	low	low	low	low	low	low	high	low	low	low	low	low	low	low
IM103027	low	low	low	low	low	low	high	low	low	low	low	low	low	low

AE: adverse events; PTDM: post-transplant diabetes mellitus; PTLD: post-transplant lymphoproliferative disorder; SAE: serious adverse events

Good data availability can be assumed for the outcomes considered relevant by the Institute (see Table 7). However, this does not apply to subgroup analyses of the following subgroup characteristics considered to be relevant by the Institute: "age", "gender", "status concerning previous transplantations", and "status concerning panel-reactive antibodies (PRA value)". The company's dossier contained no data on these subgroups (predefined in the study protocol) for the assessment-relevant time of 36 months. The company only submitted subgroup analyses for 12 months. However, a possible effect modification in these analyses was not checked in terms of its transferability to the time of 36 months and therefore these analyses could not be used. Thus, only the subgroup characteristic "donor criterion" could be considered in this assessment, because this could be investigated as part of the evaluation of heterogeneity between the 2 included studies (IM103008: SCD, IM103027: ECD) at the time of 36 months.

The risk of bias at study and outcome level was rated as low for both studies and all outcomes apart from one. The exception is the outcome "health-related quality of life", which as a subjective outcome, is basically to be rated as having a high risk of bias in open-label studies.

This assessment does not concur with that of the company for the outcomes "adverse events", "serious adverse events" and "treatment discontinuations due to adverse events", because the company assessed the risk of bias for these outcomes as high. The Institute rates the risk of bias for these outcomes as low, because an objectifiable component is assumed for these outcomes due to the clear definitions.

Further information about the choice of outcomes and risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

Table 9 and Table 10 summarize the results of the comparison of belatacept versus ciclosporin A in renal transplant patients. Additional outcomes were added to the data from Module 4 of the company's dossier. The Institute undertook meta-analyses (with the remaining 2 studies) for all outcomes to calculate the relative risks.

In the case of very low event rates (event numbers of ≤ 1% in at least 1 cell) per outcome (e.g. PTLD), the Peto OR instead of the relative risk was calculated as effect measure and used for the assessment.

Table 9: Results on mortality, morbidity and adverse events (dichotomous outcomes) – belatacept versus ciclosporin A

Outcome	Belatacept		Ciclosporin A		Belatacept vs. ciclosporin A	
Study	**N**	**Events n (%)**	**N**	**Events n (%)**	**RR [95% CI]**	**p-value[a]**
All-cause mortality						
IM103008	226	10 (4.4)	221	15 (6.8)	0.65 [0.30; 1.42]	0.289
IM103027	175	15 (8.6)	184	17 (9.2)	0.93 [0.48; 1.80]	0.839
Total[b]	401	25 (6.2)	405	32 (7.9)	0.80 [0.48; 1.32]	0.386
Morbidity						
Graft loss						
IM103008	226	9 (4.0)	221	10 (4.5)	0.88 [0.37; 2.12]	0.826
IM103027	175	21 (12.0)	184	23 (12.5)	0.96 [0.55; 1.67]	0.916
Total[b]	401	30 (7.5)	405	33 (8.1)	0.94 [0.59; 1.50]	0.785
Patient and graft survival[c]						
IM103008	226	18 (8.0)	221	25 (11.3)	0.70 [0.40; 1.25]	0.245
IM103027	175	31 (17.7)	184	37 (20.1)	0.88 [0.57; 1.35]	0.583
Total[b]	401	49 (12.2)	405	62 (15.3)	0.81 [0.58; 1.15]	0.240
Cardiovascular morbidity/mortality[d]						
IM103008	226	11 (4.9)	221	12 (5.4)	0.90 [0.40; 1.99]	0.826
IM103027	175	7 (4.0)	184	11 (6.0)	0.67 [0.27; 1.69]	0.476
Total[b]	401	18 (4.5)	405	23 (5.7)	0.79 [0.43; 1.45]	0.447
Cardiorenal diseases[e]						
IM103008	226	24 (10.6)	221	26 (11.8)	0.90 [0.54; 1.52]	0.769
IM103027	175	33 (18.9)	184	38 (20.7)	0.91 [0.60; 1.39]	0.720
Total[b]	401	57 (14.2)	405	64 (15.8)	0.91 [0.66; 1.26]	0.567
Adverse events						
AE						
IM103008	226	225 (99.6)	221	219 (99.1)	1.00 [0.99; 1.02]	0.577
IM103027	175	174 (99.4)	184	184 (100)	0.99 [0.98; 1.01]	0.356
Total[b]	401	399 (99.5)	405	403 (99.5)	1.00 [0.99; 1.01]	0.930
SAE						
IM103008	226	131 (58.0)	221	150 (67.9)	0.85 [0.74; 0.99]	0.031
IM103027	175	139 (79.4)	184	146 (79.3)[f]	1.00 [0.90; 1.11]	1.00
Total[b]				Heterogeneity: Q = 3.34; df = 1; p = 0.068, I^2 = 70.1%		
Treatment discontinuations due to AE						
IM103008	226	16 (7.1)	221	31 (14.0)	0.51 [0.28; 0.90]	0.018
IM103027	175	36 (20.6)[f]	184	44 (23.9)[f]	0.86 [0.58; 1.27]	0.5
Total[b]				Heterogeneity: Q = 2.29; df = 1; p = 0.130. I^2 = 56.4%		

(continued on next page)

Table 9: Results on mortality, morbidity and adverse events (dichotomous outcomes) – belatacept versus ciclosporin A (continued)

Outcome	Belatacept		Ciclosporin A		Belatacept vs. ciclosporin A	
Study	**N**	**Events n (%)**	**N**	**Events n (%)**	**RR [95% CI]**	**p-value[a]**
PTLD incl. extended follow-up						
IM103008	226	2 (0.9)	221	1 (0.5)	1.91 [0.20; 18.46]	0.639
IM103027	175	4 (2.3)[g]	184	1 (0.5)[g]	3.54 [0.61; 20.67]	0.167
Total[b]	401	6 (1.5)	405	2 (0.5)	2.81 [0.70; 11.30][h]	0.146
PTLD during the study						
IM103008	226	2 (0.9)	221	1 (0.5)	1.91 [0.20; 18.46]	0.639
IM103027	175	3 (1.7)[i]	184	0 (0.0)[i]	4.78 [0.67; 34.21]	0.040
Total[b]	401	5 (1.2)	405	1 (0.2)	3.22 [0.73; 14.25][h]	0.123
PTDM						
IM103008	168[j]	11 (6.5)	162[j]	18 (11.1)	0.59 [0.29; 1.21]	0.154
IM103027	136[j]	13 (9.6)	118[j]	11 (9.3)	1.03 [0.48; 2.20]	0.994
Total[b]	304	24 (7.9)	280	29 (10.4)	0.77 [0.44; 1.32]	0.333
Malignancies						
IM103008	226	10 (4.4)	221	12 (5.4)	0.81 [0.36; 1.85]	0.647
IM103027	175	15 (8.6)	184	19 (10.3)	0.83 [0.44; 1.58]	0.588
Total[b]	401	25 (6.2)	405	31 (7.7)	0.82 [0.50; 1.37]	0.454
Infections						
IM103008	226	185 (81.9)	221	176 (79.6)	1.03 [0.94; 1.13]	0.583
IM103027	175	144 (82.3)	184	151 (82.1)	1.00 [0.91; 1.10]	1.00
Total[b]	401	329 (82.0)	405	327 (80.7)	1.02 [0.95; 1.09]	0.638

Information about the definitions of all outcomes can be found in Section 2.7.2.4.3, Table 15 of the full dossier assessment

a: Institute's calculation, unconditioned exact test (CSZ method according to [3]).

b: Institute's calculation, group difference and p-value from a meta-analysis.

c: Definition Module 4 (Section 4.3.1.3.1.3) of the dossier, proportion of patients who died or with graft loss.

d: Definition Module 4 (Section 4.3.1.3.1.8) of the dossier: composite outcome (defined as proportion of patients with adjusted cardiovascular death, adjusted myocardial infarction, adjusted ischaemic stroke or revascularization procedures [surgical or percutaneous]).

e: Definition: proportion of patients who died, with graft loss, non-fatal myocardial infarction, stroke.

f: In deviation from the company's Module 4, the correct data were taken from the study reports.

g: Data Module 4 of the dossier, in each case these took into account an additional case of PTLD that did not occur until after Month 36.

h: Meta-analysis, model with fixed effect for Peto OR for event numbers of 1% and less in at least 1 cell.

i: Data from study report, only PTLD cases that occurred within the study duration of 36 months.

j: Number of patients without diabetes mellitus before transplantation.

AE: adverse events; CI: confidence interval; CSZ: convex, symmetry, z-score; N: number of analysed patients; n: number of patients with event; PTDM: post-transplant diabetes mellitus; PTLD: post-transplant lymphoproliferative disorder; RR: relative risk; SAE: serious adverse events; vs.: versus

Table 10: Results on health-related quality of life (continuous outcomes) – belatacept versus ciclosporin A

Outcome	Belatacept			Ciclosporin A			Belatacept vs. ciclosporin A	
Study	N	Values at start of study mean (SD)	Values at Month 36 mean (SD)	N	Values at start of study mean (SD)	Values at Month 36 mean (SD)	Group difference [CI]	p-value
SF-36 Sum score physical health								
IM103008	203	42.7 (8.98)	49.1 (9.31)	190	42.3 (9.06)	47.4 (9.20)	1.6 [-0.2; 3.3]	0.077
IM103027	143	43.2 (8.35)	46.2 (9.81)	145	43.4 (8.18)	43.7 (10.05)	2.6 [0.5; 4.7]	0.015
Total[a]						Hedges' g:	0.21 [0.06; 0.36]	0.006
SF-36 Sum score mental health								
IM103008	203	44.2 (12.93)	49.1 (10.63)	190	44.2 (12.30)	46.6 (11.71)	2.5 [0.4; 4.5]	0.0186
IM103027	143	46.7 (12.40)	48.2 (11.85)	145	45.1 (12.13)	47.7 (11.43)	-0.2 [-2.5; 2.2]	0.8922
Total[a]						Hedges' g	0.14 [-0.03; 0.32]	0.111

a: Institute's calculation, group difference and p-value from a meta-analysis.
CI: confidence interval; N: number of analysed patients; SD: standard deviation

Supplementary to the results on overall rate of SAE, Table 11 below records the number of patients with specific serious adverse events. All serious adverse events that occurred in at least one study in one of the 2 treatment groups in ≥ 3% of patients are shown.

On inspection of these data it is clear that for the outcome "SAE" – and by analogy, also for the outcomes "AE" and "treatment discontinuations due to AE", – events were recorded that also referred to other outcomes (e.g. graft loss). The event rates for the 3 outcomes "AE", "SAE" and "treatment discontinuations due to AE" were therefore potentially influenced by the benefit of belatacept and ciclosporin A. However, on the basis of the presentation of SAE below, at least an estimate is possible as to whether the result was substantially affected by the recording of these parameters (e.g. graft loss) as SAE. In the Institute's view, the data show that the effect does not solely arise through the representation of potential benefit parameters.

Table 11: Number (%) of patients with SAE with a relative frequency ≥ 3 % in at least one treatment group – belatacept versus ciclosporin A

	Belatacept		Ciclosporin A	
Adverse events SAE[a] Study	**N**	**Patients with events n (%)**	**N**	**Patients with events n (%)**
Urinary tract infection				
IM103008	226	16 (7.1)	221	25 (11.3)
IM103027	175	22 (12.6)	184	18 (9.8)
Cytomegalovirus infection				
IM103008	226	12 (5.3)	221	7 (3.2)
IM103027	175	16 (9.1)	184	12 (6.5)
Pyelonephritis				
IM103008	226	7 (3.1)	221	4 (1.8)
IM103027	175	1 (0.6)	184	9 (4.9)
Pneumonia				
IM103008	226	7 (3.1)	221	10 (4.5)
IM103027	175	4 (2.3)	184	6 (3.3)
Impairment of renal function				
IM103008	226	6 (2.7)	221	3 (1.4)
IM103027	175	3 (1.7)	184	7 (3.8)
Acute renal failure				
IM103008	226	3 (1.3)	221	8 (3.6)
IM103027	175	4 (2.3)	184	8 (4.3)
Renal artery stenosis				
IM103008	226	2 (0.9)	221	2 (0.9)
IM103027	175	5 (2.9)	184	6 (3.3)
Urinary fistula				
IM103008	226	0 (0)	221	0 (0)
IM103027	175	0 (0)	184	6 (3.3)
Diarrhoea				
IM103008	226	7 (3.1)	221	9 (4.1)
IM103027	175	7 (4.0)	184	4 (2.2)
Graft dysfunction				
IM103008	226	7 (3.1)	221	12 (5.4)
IM103027	175	6 (3.4)	184	11 (6.0)
Graft loss				
IM103008	226	1 (0.4)	221	0 (0)
IM103027	175	4 (2.3)	184	6 (3.3)
Renal transplant complication				
IM103008	226	1 (0.4)	221	1 (0.5)
IM103027	175	7 (4.0)	184	7 (3.8)

(continued on next page)

Table 11: Number (%) of patients with SAE with a relative frequency ≥ 3 % in at least one treatment group – belatacept versus ciclosporin A (continued)

Adverse events SAE[a] Study	Belatacept N	Belatacept Patients with events n (%)	Ciclosporin A N	Ciclosporin A Patients with events n (%)
Toxicity of a therapeutic agent				
IM103008	226	0 (0)	221	7 (3.2)
IM103027	175	0 (0)	184	2 (1.1)
Basal cell carcinoma				
IM103008	226	3 (1.3)	221	4 (1.8)
IM103027	175	2 (1.1)	184	6 (3.3)
Fever				
IM103008	226	10 (4.4)	221	11 (5.0)
IM103027	175	9 (5.1)	184	11 (6.0)
Increased blood creatinine				
IM103008	226	10 (4.4)	221	12 (5.4)
IM103027	175	10 (5.7)	184	16 (8.7)
Anaemia				
IM103008	226	2 (0.9)	221	5 (2.3)
IM103027	175	6 (3.4)	184	5 (2.7)
Lymphocele				
IM103008	226	2 (0.9)	221	8 (3.6)
IM103027	175	5 (2.9)	184	10 (5.4)

a: Preferred Term according to the Medical Dictionary for Regulatory Activities (MedDRA).
N: Number of analysed patients; n: number of patients with event; SAE: serious adverse events

The meta-analysis summary of the 2 present studies might allow, in principle, to derive proof, e.g. of an added benefit. This assessment concurs with that of the company. A possible weakening of the certainty of results by outcome-specific aspects is pointed out below in the presentation of the results on the individual outcomes.

All-cause mortality

The meta-analysis for the outcome "all-cause mortality" showed no statistically significant difference between a treatment with belatacept and ciclosporin A. There was no heterogeneity between the individual study results (Figure 1). An added benefit of belatacept for this outcome is not proven. This concurs with the company's assessment. It should be borne in mind that due to study duration and the number of enrolled patients, neither study was suitable for demonstrating differences between the treatments with regard to this outcome.

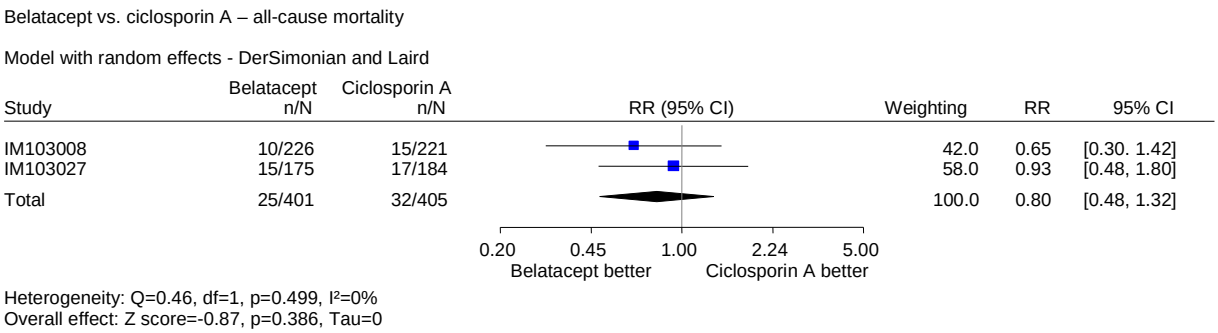

Figure 1: Meta-analysis, belatacept versus ciclosporin A, all-cause mortality, 36 months

CI: confidence interval, RR: relative risk

Morbidity

Graft loss

The meta-analysis for the outcome "graft loss" showed no statistically significant difference between a treatment with belatacept and ciclosporin A. There was no heterogeneity between the individual study results (Figure 2). An added benefit of belatacept for this outcome is not proven. This concurs with the company's assessment.

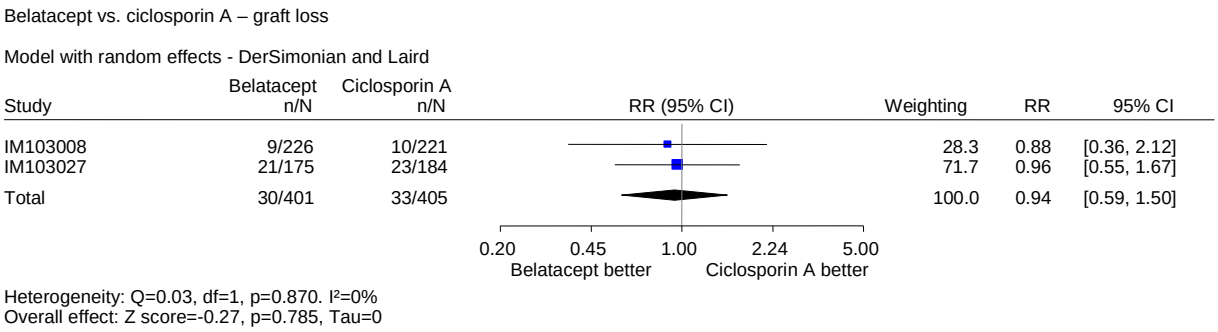

Figure 2: Meta-analysis, belatacept versus ciclosporin A, graft loss, 36 months

CI: confidence interval, RR: relative risk

Composite outcome: patient and graft survival

The meta-analysis for the composite outcome "patient and graft survival" showed no statistically significant difference between a treatment with belatacept and ciclosporin A. There was no heterogeneity between the individual study results (Figure 3). An added benefit of belatacept for this outcome is not proven. This concurs with the company's assessment.

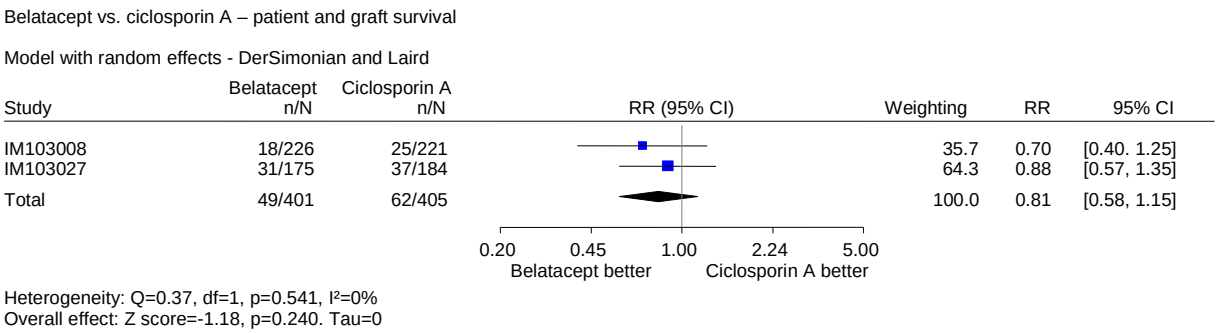

Figure 3: Meta-analysis, belatacept versus ciclosporin A, patient and graft survival, 36 months

CI: confidence interval, RR: relative risk

Cardiovascular morbidity and mortality

The meta-analysis for the outcome "cardiovascular morbidity and mortality" showed no statistically significant difference between a treatment with belatacept and ciclosporin A. There was no heterogeneity between the individual study results (Figure 4). An added benefit of belatacept for this outcome is not proven. In contrast, the company undertook the assessment of this outcome primarily on the basis of data at the documentation time of 12 months and derived proof of a considerable added benefit.

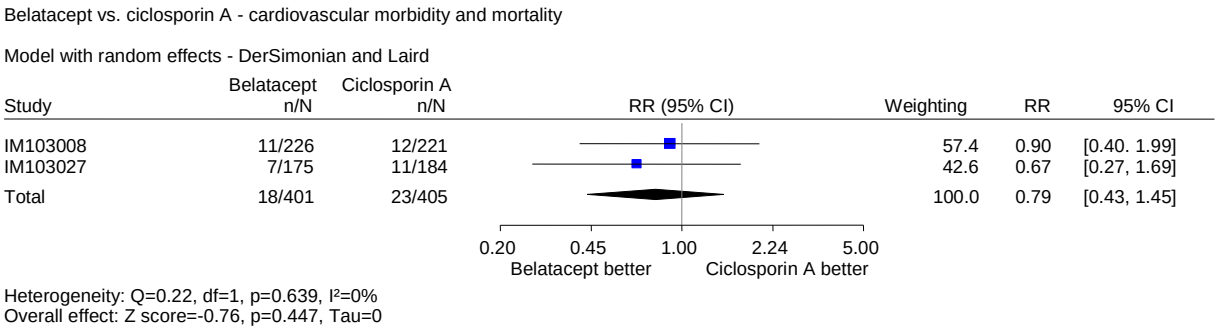

Figure 4: Meta-analysis, belatacept versus ciclosporin A, cardiovascular morbidity or mortality, 36 months

CI: confidence interval, RR: relative risk

Composite outcome: cardiorenal diseases

The meta-analysis for the composite outcome "cardiorenal diseases" showed no statistically significant difference between a treatment with belatacept and ciclosporin A. There was no heterogeneity between the individual study results (Figure 5). An added benefit of belatacept for this outcome is not proven. The company did not consider this outcome in its assessment.

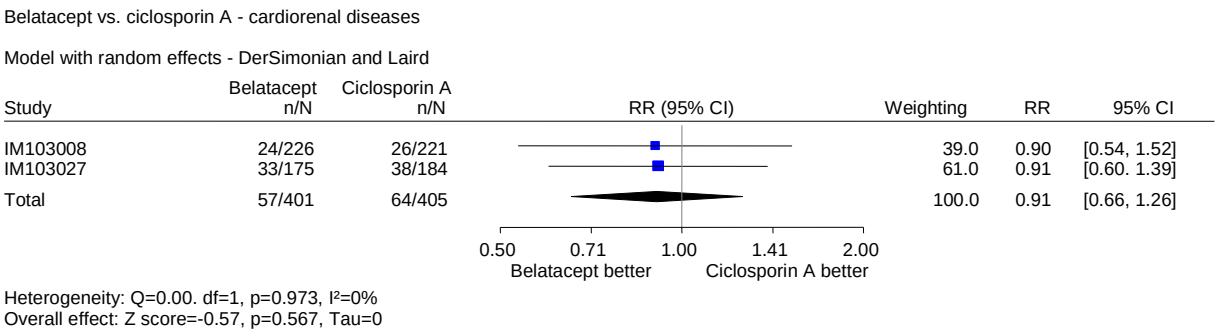

Figure 5: Meta-analysis, belatacept versus ciclosporin A, cardiorenal diseases, 36 months

CI: confidence interval, RR: relative risk

Health-related quality of life

This outcome was measured using the SF-36 questionnaire. Two sum scores, physical and mental health, are produced from the questionnaire items and these scores were investigated separately in the meta-analyses. There was a statistically significant difference in favour of belatacept in the meta-analysis for the sum score "physical health". There was no heterogeneity between the individual study results (Figure 6). When considering this outcome, which was defined using a (complex) scale, it is necessary to evaluate the relevance of the effect as well as the statistical significance. Since neither scale-specific validated or established relevance criteria for group differences nor responder analyses on the basis of validated or established response thresholds existed, a general statistical measure had to be used to assess relevance. In this case, the standardized mean difference (SMD in the form of Hedges' g) was considered. According to the Institute's methods, a value of 0.2 was used as irrelevance threshold [4]. If the confidence interval corresponding to the observed effect was fully above this irrelevance threshold, it was assumed that the effect did not lie in a definitely irrelevant region. This was to ensure that the effect can be regarded with adequate reliability, at least as "small". The effect size for the pooled studies produced a result of 0.21 (95% CI [0.06; 0.36]) points, for which the lower limit of the confidence interval was below 0.2. This means that in this case a clinically relevant effect cannot be assumed with sufficient certainty and an added benefit or greater harm from belatacept for this outcome is not proven. This concurs with the company's assessment.

The result of the meta-analysis for the sum score "mental health" was not statistically significant and there was no substantial heterogeneity between the individual study results (Figure 7). An added benefit of belatacept for this outcome is not proven. This concurs with the company's assessment.

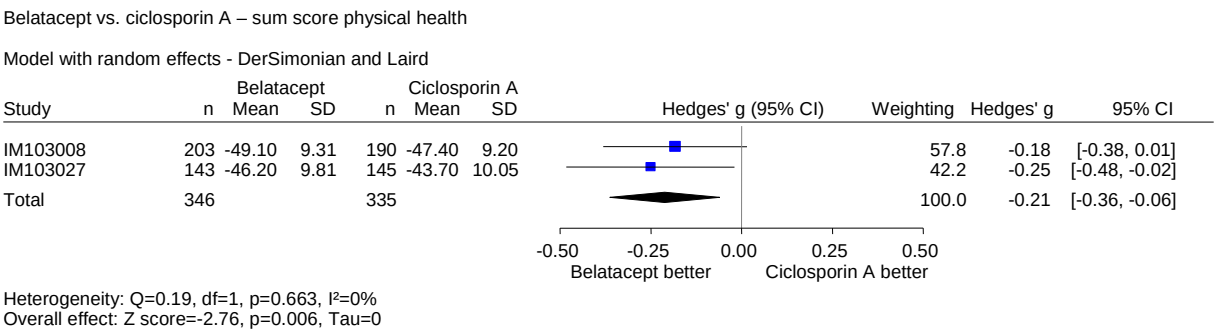

Figure 6: Meta-analysis, belatacept versus ciclosporin A, sum score "physical health", 36 months. The signs of the means were reversed for a uniform presentation of the direction of effect

CI: confidence interval

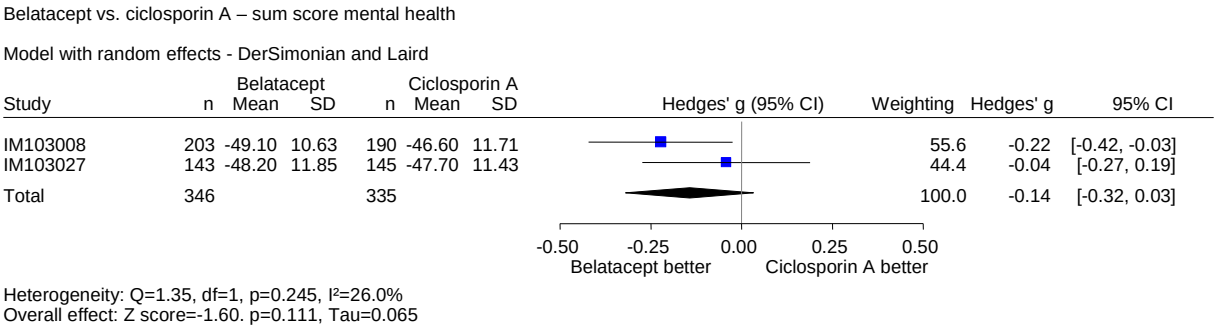

Figure 7: Meta-analysis, belatacept versus ciclosporin A, sum score "mental health", 36 months. The signs of the means were reversed for a uniform presentation of the direction of effect

CI: confidence interval

Adverse events

Overall rate of adverse events (AE)

The meta-analysis for the outcome "overall rate of adverse events" showed no statistically significant difference between a treatment with belatacept and ciclosporin A. There was no heterogeneity between the individual study results (Figure 8). Greater or lesser harm from belatacept for this outcome is not proven. This concurs with the company's assessment.

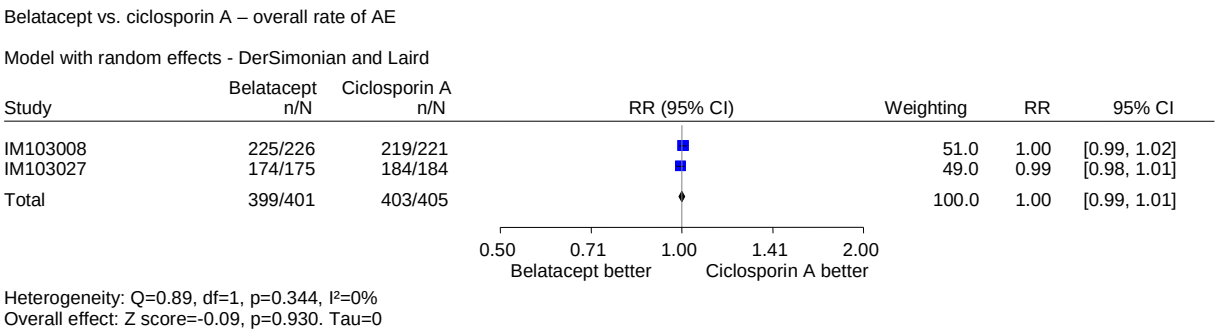

Figure 8: Meta-analysis, belatacept versus ciclosporin A, overall rate of AE, 36 months

CI: confidence interval, RR: relative risk

Overall rate of serious adverse events (SAE)

Due to heterogeneity ($p < 0.2$), the results of serious adverse events were not summarized by meta-analysis and therefore no overall effect estimator was illustrated (Figure 9). If heterogeneity is present, then in the context of this assessment the individual study results are considered. Since the 2 studies differed, in particular in terms of the donor criteria used (IM103008: SCD; IM103027: ECD), separate conclusions are drawn below at outcome level for these donor populations. On the basis of the individual study results, in Study IM103008 there was a statistically significant result in favour of belatacept. In Study IM103027, the rate of serious adverse events under belatacept and ciclosporin A was virtually identical and the result was not statistically significant. There is an indication of lesser harm from belatacept for this outcome in patients who received a renal transplant from a donor classified according to standard criteria (SCD, IM103008). In patients who received a renal transplant from a donor classified according to extended criteria (ECD, IM103027), greater or lesser harm from belatacept for this outcome is not proven. This result concurs, in parts, with the assessment of the company, which here claims an indication of a minor added benefit for the entire population.

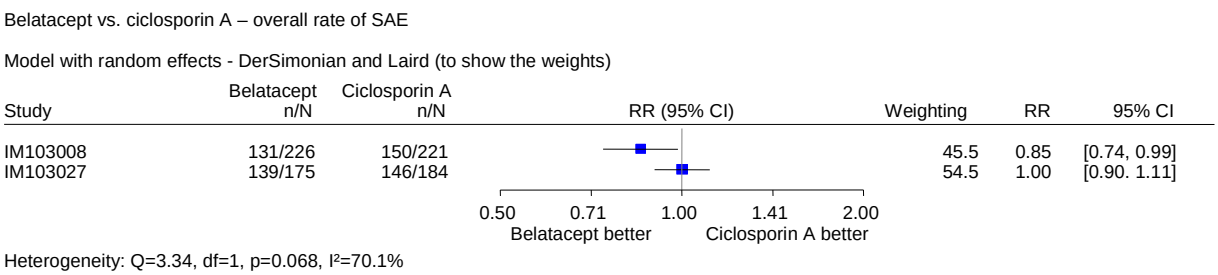

Figure 9: Meta-analysis, belatacept versus ciclosporin A, overall rate of SAE, 36 months

CI: confidence interval, RR: relative risk

Treatment discontinuations due to AE

In both studies, the proportion of patients with adverse events that led to treatment discontinuation differed between belatacept and ciclosporin A. Due to heterogeneity ($p < 0.2$) the results on treatment discontinuations due to AE were not summarized by meta-analysis and therefore no overall effect estimator was illustrated (Figure 10). If heterogeneity is present, then in the context of this assessment, the individual study results are considered. Separate conclusions are drawn below at outcome level for the donor populations SCD and ECD. On the basis of the individual study results, in Study IM103008 there was a statistically significant result in favour of belatacept. In Study IM103027, although the rate of adverse events that led to treatment discontinuation was increased under ciclosporin A, the result was not, however, statistically significant. There is an indication of lesser harm from belatacept in patients given a kidney from a donor classified according to standard criteria (SCD, IM103008) for this outcome. In patients given a kidney from a donor classified according to extended criteria (ECD, IM103027), greater or lesser harm from belatacept for this outcome is not proven. The company derived no added benefit or greater harm from belatacept in respect of this outcome.

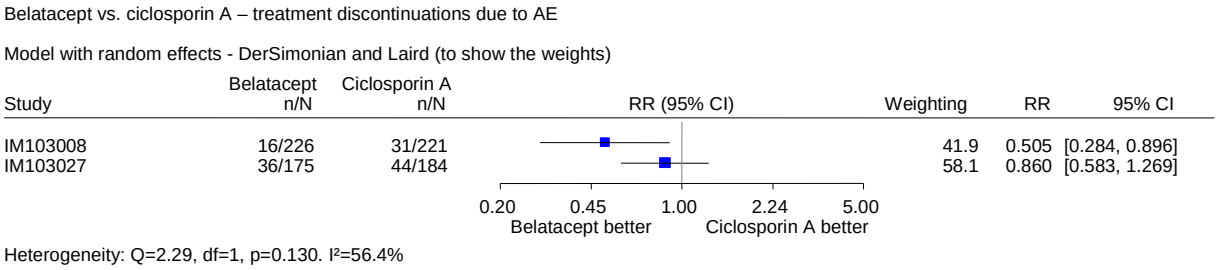

Figure 10: Meta-analysis, belatacept versus ciclosporin A, treatment discontinuations due to AE, 36 months

CI: confidence interval, RR: relative risk

Post-transplant lymphoproliferative disorder (PTLD)

Module 4 of the company's dossier contained an additional case of the outcome "PTLD" in Study IM103027 in both the belatacept and ciclosporin A groups that did not occur until after Month 36. The Institute carried out meta-analyses for both data constellations (with and without these cases). The results of the 2 analyses did not differ substantially from each other. The meta-analysis for the outcome "PTLD" showed no statistically significant difference between a treatment with belatacept and ciclosporin A. There was no heterogeneity between the individual study results (Figure 11 and Figure 12). Greater or lesser harm from belatacept for this outcome is not proven. This concurs with the company's assessment.

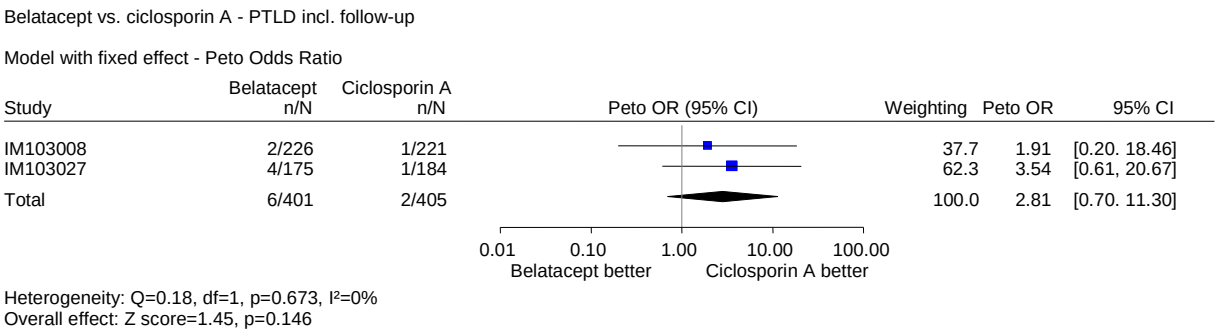

Figure 11: Meta-analysis, belatacept versus ciclosporin A, PTLD, incl. extended follow-up

CI: confidence interval, Peto OR: Peto Odds-Ratio

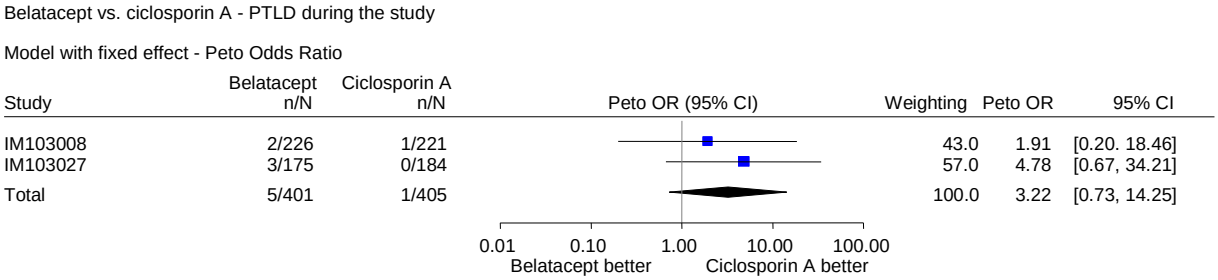

Figure 12: Meta-analysis, belatacept versus ciclosporin A, PTLD, during the study

CI: confidence interval, Peto OR: Peto Odds-Ratio

Post-transplant diabetes mellitus (PTDM)

The meta-analysis for the outcome "PTDM" showed no statistically significant difference between a treatment with belatacept and ciclosporin A. There was no heterogeneity between the individual study results (Figure 13). Greater or lesser harm from belatacept for this outcome is not proven. In contrast, the company undertook the assessment of this outcome primarily on the basis of data at the documentation time of 12 months and derived proof of a considerable added benefit of belatacept.

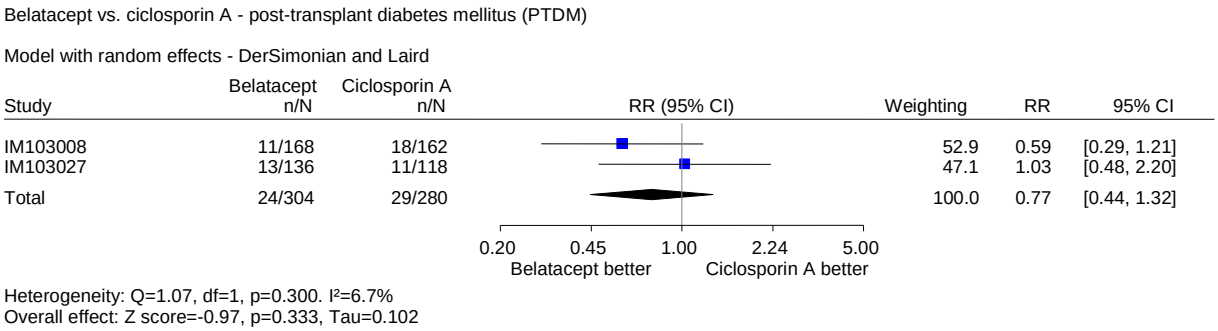

Figure 13: Meta-analysis, belatacept versus ciclosporin A, PTDM, 36 months

CI: confidence interval, RR: relative risk

Malignancies

The meta-analysis for the outcome "malignancies" showed no statistically significant difference between a treatment with belatacept and ciclosporin A. There was no heterogeneity between the individual study results (Figure 14). Greater or lesser harm from belatacept for this outcome is not proven. The company did not consider this outcome in its assessment.

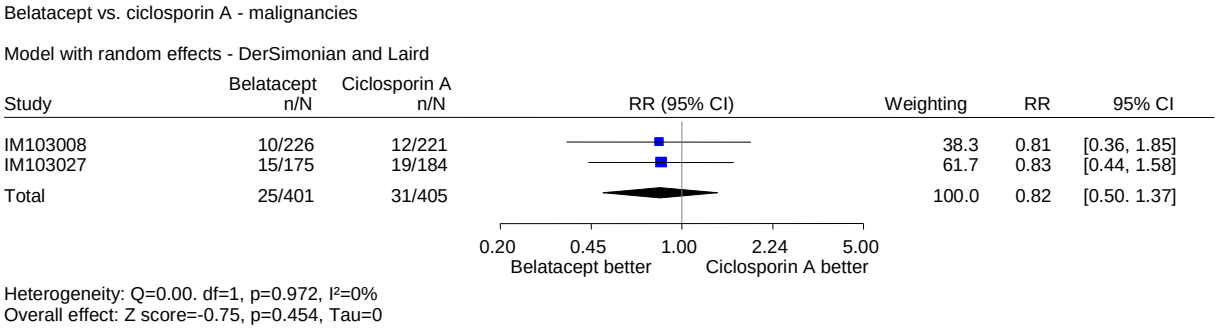

Figure 14: Meta-analysis, belatacept versus ciclosporin A, malignancies, 36 months

CI: confidence interval, RR: relative risk

Infections

The meta-analysis for the outcome "infections" showed no statistically significant difference between a treatment with belatacept and ciclosporin A. There was no heterogeneity between the individual study results (Figure 15). Greater or lesser harm from belatacept for this outcome is not proven. The company did not consider this outcome in its assessment.

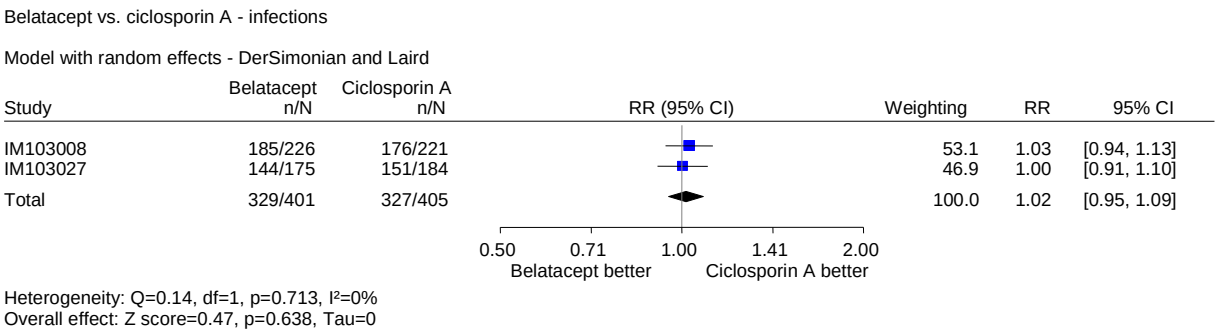

Figure 15: Meta-analysis, belatacept versus ciclosporin A, infections, 36 months

CI: confidence interval, RR: relative risk

Further information about choice of outcome, risk of bias at outcome level and outcome results can be found in Module 4, Sections 4.3.1.2.2 and 4.3.1.3 of the dossier and in Sections 2.7.2.2, 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

2.5 Extent and probability of added benefit

The derivation of extent and probability of the added benefit at outcome level is shown below, taking into account the various outcome categories and effect sizes. The methods used are explained in Appendix A of Benefit Assessment A11-02 [5].

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

2.5.1 Evaluation of added benefit at outcome level

The data presented in Section 2.4 for patients who received the renal transplant from a donor classified according to standard criteria (SCD), produced indications of lesser harm from belatacept in respect of the outcomes “serious adverse events” and “treatment discontinuations due to adverse events”. For patients, who received the renal transplant from a donor classified according to extended criteria (ECD), an added benefit or greater/lesser harm from belatacept was not proven for any of the outcomes investigated.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 12).

Table 12: Belatacept versus ciclosporin A – extent of the added benefit at outcome level

Outcome	Effect estimator [95% CI]/ Proportion of events belatacept vs. ciclosporin A / p-value/probability[a]	Derivation of extent[b]
Mortality		
All-cause mortality	RR 0.80 [0.48; 1.32] 6.2% vs. 7.9% p = 0.386	Lesser benefit/added benefit not proven.
Morbidity		
Graft loss	RR 0.94 [0.59; 1.50] 7.5% vs. 8.1% p = 0.785	Lesser benefit/added benefit not proven.
Composite outcome: patient and graft survival	RR 0.81 [0.58; 1.15] 12.2% vs. 15.3% p = 0.240	Lesser benefit/added benefit not proven.
Cardiovascular morbidity and mortality	RR 0.79 [0.43; 1.45] 4.5% vs. 5.7% p = 0.447	Lesser benefit/added benefit not proven.
Composite outcome: cardiorenal diseases	RR 0.91 [0.66; 1.26] 14.2% vs. 15.8% p = 0.567	Lesser benefit/added benefit not proven.
Health-related quality of life SF-36		
Sum score “physical health”	Hedges’ g 0.21 [0.06; 0.36][c] p = 0.006	Lesser benefit/added benefit not proven.
Sum score “mental health”	Hedges’ g 0.14 [-0.03; 0.32] p = 0.111	Lesser benefit/added benefit not proven.
Adverse events		
Overall rate of AE	RR 1.00 [0.99; 1.01] 99.5% vs. 99.5% p = 0.930	Greater/lesser harm not proven.
Overall rate of SAE SCD[d]	RR 0.85 [0.74; 0.99] 58.0% vs. 67.9% p = 0.031 Probability:” indication”	Outcome category: serious/severe adverse events $0.90 < CI_o < 1.00$ Lesser harm, extent: “minor”.
Overall rate SAE ECD[d]	RR 1.00 [0.90; 1.11] 79.4% vs. 79.3% p = 1.00	Greater/lesser harm not proven.
Treatment discon. due to AE SCD[d]	RR 0.50 [0.28; 0.90] e 7.1% vs. 14.0% p = 0.018 Probability: “indication”	Outcome category: non-serious/non-severe adverse events $0.8 \leq CI_o < 0.9$ Lesser harm, extent: “minor”.
Treatment discon. due to AE ECD[d]	RR 0.86 [0.58; 1.27] 20.6% vs. 23.9% p = 0.5	Greater/lesser harm not proven.

(continued on next page)

Table 12: Belatacept versus ciclosporin A – extent of the added benefit at outcome level (continued)

Outcome	**Effect estimator [95% CI]/ Proportion of events belatacept vs. ciclosporin A / p-value/probability[a]**	**Derivation of extent[b]**
Adverse events		
PTLD	Peto OR 3.22 [0.73; 14.25][f] 1.2% vs. 0.2% p = 0.123	Greater/lesser harm not proven.
PTDM	RR 0.77 [0.44; 1.32] 7.9% vs. 10.4% p = 0.333	Greater/lesser harm not proven.
Malignancies	RR 0.82 [0.50; 1.37] 6.2% vs. 7.7% p = 0.454	Greater/lesser harm not proven.
Infections	RR 1.02 [0.95; 1.09] 82.0% vs. 80.7% p = 0.638	Greater/lesser harm not proven.

a: Probability provided, if statistically significant differences are present.

b: Estimations of effect size are made depending on outcome category with different limits based on upper limit of the confidence interval (CI_o).

c: SMD in the form of Hedges' g to assess the relevance of the statistically significant group difference. If the 95% confidence interval for the SMD is not fully above the irrelevance threshold of 0.2, the effect is regarded as non-relevant.

d: Division of the population according to donor criteria because of heterogeneity in the meta-analysis of the 2 included studies IM103008 (only recipients of SCD kidneys) and IM103027 (only recipients of ECD kidneys). The effect estimators shown correspond to the individual study results for the respective outcome.

e: Precise upper limit of the confidence interval below 0.9 (p-value from meta-analysis = 0.896).

f: Effect estimator for all cases up to the documentation time of 36 months. After this time, 2 further cases occurred. The result of the meta-analysis under consideration of these cases is also not statistically significant.

AE: adverse event; CI: confidence interval; CI_o: upper limit confidence interval; discon.: discontinuation; ECD: extended criteria donors; OR: odds ratio; PTDM: post-transplant diabetes mellitus; PTLD: post-transplant lymphoproliferative disorder; RR: relative risk; SCD: standard criteria donors; SMD: standardized mean difference; SAE: serious adverse event; vs.: versus

2.5.2 Overall conclusion on added benefit

Patients who received a renal transplant from a donor classified according to standard criteria (SCD)

Table 13 summarizes the results considered in the overall conclusion about the extent of added benefit.

Table 13: SCD: Results accompanying the overall conclusion on added benefit – belatacept versus ciclosporin A

Positive effects	Negative effects
Indication of lesser harm – extent: "minor" (serious/severe adverse events: SAE)	
Indication of lesser harm – extent: "minor" (non-serious/non-severe adverse events: treatment discontinuations due to adverse events)	
SCD: standard criteria donors; SAE: serious adverse event	

Taken as a whole, there remain 2 positive results in favour of belatacept with the extent "minor" and the probability "indication". A balancing of benefits and harms is not required.

In summary, for adult patients who received a renal transplant from a donor classified according to standard criteria (SCD), there is an indication of an added benefit (extent "minor") of belatacept over the ACT ciclosporin A.

Patients who received a renal transplant from a donor classified according to extended criteria (ECD)

From the assessment of added benefit at outcome level, there remain neither positive nor negative effects.

In summary, for adult patients who received a renal transplant from a donor classified according to extended criteria (ECD), there is no proof of an added benefit of belatacept over the ACT ciclosporin A.

2.5.3 Extent and probability of added benefit - summary

The overview of the extent and probability of added benefit for the relevant patient populations for the benefit assessment of belatacept compared to the ACT is as follows:

Table 14: Belatacept: extent and probability of added benefit

Population[a]	**Appropriate comparator therapy**	**Extent and probability of the added benefit**
Adult patients who received a renal transplant from a donor classified according to standard criteria (SCD)	Ciclosporin A	Indication of an added benefit (extent: "minor") of belatacept
Adult patients who received a renal transplant from a donor classified according to extended criteria (ECD)	Ciclosporin A	No proof of an added benefit of belatacept
a: These statements apply only to patients who had received an initial treatment with belatacept (*de-novo*), but not to patients switched to belatacept, because the therapeutic indication of belatacept is restricted to patients after *de-novo* renal transplantation. ECD: extended criteria donors; SCD: standard criteria donors		

This overall assessment deviates substantially from that of the company, which claims proof of a considerable added benefit for adults who have received a renal transplant, under consideration of the contraindications and precautions of the belatacept SPC [1].

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier and in Section 2.7.2.8 of the full dossier assessment

2.6 List of included studies

IM103008

Bristol-Myers Squibb. Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT): study IM103008; clinical study report up to month 12 [unpublished]. 2009.

Bristol-Myers Squibb. Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT): study IM103008; clinical study report addendum up to month 24 [unpublished]. 2009.

Bristol-Myers Squibb. Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT): study IM103008; month 36 clinical study report addendum [unpublished]. 2010.

Bristol-Myers Squibb. Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression (BENEFIT) [online]. In: ClinicalTrials.gov. 15.03.2011 [Accessed on: 07.11.2011]. URL: http://www.clinicaltrial.gov/ct2/show/NCT00256750.

Bristol-Myers Squibb. Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression (BENEFIT) [online]. In: WHO International Clinical Trials Registry Platform. 10.08.2010 [Accessed on: 20.12.2011]. URL: http://apps.who.int/trialsearch/Trial.aspx?TrialID=NCT00256750.

Larsen CP, Grinyo J, Medina-Pestana J, Vanrenterghem Y, Vincenti F, Breshahan B et al. Belatacept-based regimens versus a cyclosporine A-based regimen in kidney transplant recipients: 2-year results from the BENEFIT and BENEFIT-EXT studies. Transplantation 2010; 90(12): 1528-1535.

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 2011; 12(1): 210-217.

IM103027

Bristol-Myers Squibb. Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial: EXTended criteria donors (BENEFIT-EXT); study IM103027; clinical study report up to month 12 [unpublished]. 2009.

Bristol-Myers Squibb. Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial: EXTended criteria donors (BENEFIT-EXT); study IM103027; month 24 clinical study report addendum [unpublished]. 2009.

Bristol-Myers Squibb. Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial: EXTended criteria donors (BENEFIT-EXT); study IM103027; month 36 clinical study report addendum [unpublished]. 2010.

Bristol-Myers Squibb. Study of belatacept in subjects who are undergoing a renal transplant (BENEFIT-EXT) [online]. In: ClinicalTrials.gov. 15.03.2011 [Accessed on: 07.11.2011]. URL: http://www.clinicaltrial.gov/ct2/show/NCT00114777.

Bristol-Myers Squibb. Study of belatacept in subjects who are undergoing a renal transplant BENEFIT-EXT [online]. In: WHO International Clinical Trials Registry Platform. 10.08.2010 [Accessed on: 20.12.2011]. URL: http://apps.who.int/trialsearch/Trial.aspx?TrialID=NCT00114777.

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.

Larsen CP, Grinyo J, Medina-Pestana J, Vanrenterghem Y, Vincenti F, Breshahan B et al. Belatacept-based regimens versus a cyclosporine A-based regimen in kidney transplant recipients: 2-year results from the BENEFIT and BENEFIT-EXT studies. Transplantation 2010; 90(12): 1528-1535.

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Please see full dossier assessment for full reference list.

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The full report (German version) is published under www.iqwig.de.