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Belimumab (systemic lupus erythematosus in children and adolescents) –

Addendum to Commission A19-94[1]

Addendum

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Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
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
RCT	randomized controlled trial
SAE	serious adverse event
SELENA	Safety of Estrogens in Lupus Erythematosus – National Assessment
SFI	SELENA-SLEDAI SLE Flare Index
SLE	systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SOC	System Organ Class

1 Background

On 24 March 2020, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A19-94 (Belimumab – Benefit assessment according to §35a Social Code Book V) [1].

The dossier assessment on belimumab concluded that the PLUTO study presented by the pharmaceutical company (hereinafter referred to as "the company") in the dossier [2] was generally suitable for the assessment of the added benefit of belimumab, but that the results of the PLUTO study presented had to be rated as not interpretable for various reasons (type of analyses; implementation of the appropriate comparator therapy [ACT] resulted in unfavourable event; unclear proportion of patients concurring with the target population) [1].

The conclusions drawn in the benefit assessment referred to a subpopulation formed by the company (designated by the company as "ITT-ACT2 population"[2]) because the ACT was best represented in this subpopulation.

The G-BA commissioned IQWiG with the analysis of the results of the ITT-ACT2 population of the PLUTO study under consideration of the information provided in the dossier and of the documents for the relevant subpopulation subsequently requested from the company.

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

[2] The ITT-ACT2 population concurs with the total population of the PLUTO study without the patients who received methotrexate, tacrolimus, leflunomide or mycophenolate.

2 Assessment of the PLUTO study

2.1 Interpretability of the results of the PLUTO study

The PLUTO study was a double-blind randomized controlled trial (RCT) on the comparison of belimumab + individual concomitant medication versus placebo + individual concomitant medication. A total of 93 children and adolescents aged between 5 and < 18 years with active systemic lupus erythematosus (SLE) under pretreatment were included in the study.

In its dossier [2], the company had presented analyses for the total population (= intention to treat [ITT] population) as well as analyses for 2 subpopulations. The benefit assessment considered the ITT-ACT2 population, as the ACT was best represented in this subpopulation. This population concurs with the total population without the patients who received methotrexate, tacrolimus, leflunomide or mycophenolate as concomitant medication in the course of the study. It comprises 21 (belimumab arm) versus 14 (comparator arm) patients.

The study design, the planned interventions and the options for adapting the medication, as well as the characteristics of the ITT-ACT2 population of the PLUTO study considered for the present benefit assessment were already presented in the dossier assessment [1].

Results of the PLUTO study not interpretable on the basis of the available information

Implementation of the appropriate comparator therapy rated as treatment failure or unfavourable event

As described in the benefit assessment of belimumab, one of the reasons for the lack of interpretability was that optimization of individual treatment – and thus the implementation of the ACT – beyond a range of medication described in the study protocol was rated in the study as treatment failure or unfavourable event.

The patients with such adaptations of their medication were rated as non-responders in the analyses for dichotomous outcomes (except adverse events [AEs]). For continuous outcomes, the subsequent values that were no longer recorded were replaced by the last observed value before discontinuation of study participation.

For the outcomes of the categories of morbidity and health-related quality of life, the analyses carried out in this way probably yielded results to the disadvantage of the comparator arm, since, due to the lack of additional therapies (as given in the intervention arm by the additional administration of belimumab), the patients in the comparator arm needed optimizations of their ongoing therapy outside the range of medication described in the study protocol more frequently than in the belimumab arm.

The information on the proportion of the patients with optimization of their ongoing therapy provided in Module 4 A [2] only refers to the total population of the PLUTO study. In this total population, the proportions of patients were 11% in the belimumab arm versus 23% in the comparator arm (6 versus 9 patients).

In the oral hearing on the commenting procedure of belimumab [3], the company explained that this proportion in the ITT-ACT2 population was 5% in the belimumab arm versus 29% in the comparator arm (1 versus 4 patients). In the subpopulation to be considered, the proportion of patients with treatment adaptation rated as treatment failure was therefore of a similar magnitude as in the total population of the PLUTO study, and also higher in the comparator arm than in the belimumab arm. As a result, the results on patient-relevant outcomes of the categories of morbidity and health-related quality of life presented by the company were also not interpretable in a meaningful way.

Flare according to SFI as an example of inadequate operationalization

It was noted in the benefit assessment that some outcomes of the PLUTO study were directly operationalized using the optimization of the concomitant medication (addition/discontinuation of individual drugs and/or dose changes). The outcome "flare according to SELENA-SLEDAI SLE Flare Index" (hereinafter referred to as "flare according to SFI") was named as an example. In this outcome, a flare was defined as the occurrence of one of several components. These components included the increase in the prednisone dose or the addition of new drugs, which concurred with an implementation of the ACT[3].

As described in the benefit assessment, an adequate analysis requires the information on how many of the flares observed in the study were based on characteristic symptoms and not solely on the increase in prednisone dose (or other treatment-related components of this outcome).

After the oral hearing on the commenting procedure of belimumab, the company transmitted a list providing the criteria on the basis of which a severe flare according to SFI was determined for a patient in the ITT-ACT2 population [4]. These are presented in Table 1.

[3] The PLUTO study investigated 2 severity grades of flares: mild/moderate flares and severe flares. Both operationalizations contain almost the same components: increase in prednisone dosage, change in SELENA-SLEDAI score, change in PGA, deterioration of defined symptoms, addition of new drugs. Differences between mild/moderate and severe flares resulted from the threshold values, the type of new drugs used for the treatment of SLE, the symptoms and the hospital admissions.

Table 1: Criteria for a severe flare according to SFI for patients in the ITT-ACT2 population in both study arms of the PLUTO study

Patient No.	Visit of first severe flare	Justification for severe flare	
		Belimumab + concomitant medication	**Placebo + concomitant medication**
1	Week 8	–	▪ Increase of prednisone dosage to more than 0.5 mg/kg/day ▪ Hospitalization due to SLE activity
2[a]	Week 8	–	▪ Change in SELENA-SLEDAI to more than 12 points
3	Week 36	–	▪ Increased daily steroid dose
4	Week 40	–	▪ Increase in PGA score to ≥ 2.5 ▪ Increase of prednisone dosage to more than 0.5 mg/kg/day ▪ New administration of SLE medication due to SLE activity ▪ New symptoms or deterioration of symptoms ▪ Doubling of prednisone dosage or increase of prednisone dosage to > 0.5 mg/kg/day or hospitalization ▪ Change in SELENA-SLEDAI to more than 12 points ▪ Hospitalization due to SLE activity
5[a]	Week 40	▪ Change in SELENA-SLEDAI to more than 12 points	–
6	Week 44	–	▪ Increased dose of anti-malaria medication
7	Week 48	–	▪ New medication (NSAID) for ≥ 1 week after day 309
8	Week 52	▪ Increased daily steroid dose	–

a. Regarding this patient, the company notes that the classification as severe flare was only made on the basis of a change in the SELENA-SLEDAI score to more than 12 points, concurring with the classification according to the original definition of the SFI [5]. However, according to the company, this approach does not concur with the classification of the *modified* SFI in accordance with the study protocol of the PLUTO study [6], according to which flares that only fulfil the criterion of a change to more than 12 points on the SELENA-SLEDAI score are no longer categorized as severe flare in the *modified* SFI.

NSAID: nonsteroidal anti-inflammatory drug; PGA: physician's global assessment; SELENA: Safety of Estrogens in Lupus Erythematosus – National Assessment; SFI: SELENA-SLEDAI SLE Flare Index; SLE: systemic lupus erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index

In a relevant proportion of patients, the increase in medication alone was rated as flare: This applied to 1 of 2 patients in the belimumab arm and to 3 of 6 patients in the comparator arm. Thus, it was unclear for these patients whether the adjustments of therapy were also accompanied by corresponding SLE symptoms. The results on this outcome were therefore not interpretable.

Regarding the criterion of the change in the SELENA-SLEDAI score to more than 12 points, the company additionally noted that this classification was in line with the original definition of the SFI [5]. However, according to the company, this approach did not concur with the classification of the modified SFI in accordance with the study protocol of the PLUTO study [6]. The company stated that the modified SFI did no longer categorize flares that only met the criterion of a change to more than 12 points on the SELENA-SLEDAI score as severe flares. Thus, the change in the SELENA-SLEDAI to more than 12 points was erroneously rated as severe flare in one patient in the belimumab arm and in one patient in the placebo arm.

On the basis of the information provided in Table 1, it is possible to perform analyses of the results on the outcome "SFI" that do not consider those patients who were rated as having a flare only based on an adjustment of the treatment, as well as those patients with a change in the SELENA-SLEDAI score to more than 12 points. The results can be found in Table 8 in Appendix A. These analyses did not show a statistically significant effect between the treatment groups in each case.

Proportion of patients with high disease activity in the PLUTO study

Belimumab is approved for patients with a high degree of disease activity. However, overall, the proportion of patients with high disease activity in the ITT or ITT-ACT2 population of the PLUTO study can only be estimated to a limited extent. Based on the available data it is still unclear whether a relevant proportion of the patients did not exhibit high disease activity at study entry and thus are not part of the target population.

However, the commenting procedure and the oral hearing showed that this did not raise doubts about the general suitability of the PLUTO study and thus of the ITT-ACT2 population.

Conclusion

The assessment of the PLUTO study reached in the benefit assessment also remains under inclusion of the input from the commenting procedure on belimumab. The PLUTO study is principally suitable for the present benefit assessment of belimumab. The results on the outcomes of the categories of morbidity and health-related quality of life are not interpretable due to the type of analyses, however.

This did not apply in the same way to the outcomes on AEs and on the deaths recorded with the AEs. As a result of the exclusion of patients with treatment adjustments beyond the described range of medication, which differed between the treatment arms, relevant AEs in the comparator arm might have been overlooked. In the present situation, in which AEs occurred more frequently in the comparator arm than in the belimumab arm, the additional consideration of AEs that were overlooked in this way would have resulted in even larger effects. The results on AEs were therefore considered usable and their assessment is presented below.

2.2 Results

Risk of bias

As described above, the exclusion of patients with treatment adjustments beyond the described range of medication, which differed between the treatment arms, did not result in the non-interpretability of AE outcomes (and of deaths recorded with the AEs). Nonetheless, the risk of bias for these outcomes was rated as high. This was due to the fact that the proportion of patients in the relevant ITT-ACT2 subpopulation of the PLUTO study with premature discontinuation of the study and therefore incomplete observation was unclear. The respective information is only available for the ITT population. With 9 (22.5%) patients in the belimumab arm and 8 (15.1%) patients, a relevant proportion of this population discontinued the study prematurely.

Results

Table 2 summarizes the results on the comparison of belimumab + individual concomitant medication in comparison with placebo + individual concomitant medication for the treatment of children and adolescents aged 5 to < 18 years with active, autoantibody-positive SLE with a high degree of disease activity (e.g., positive test result for anti-dsDNA antibodies and low complement) despite standard therapy.

Results on further outcomes resulting from the decision on belimumab in SLE in adults [7] and results on further relevant outcomes are presented in Appendix A.

Table 2: Results (dichotomous) – RCT, direct comparison: belimumab + concomitant medication vs. placebo + concomitant medication

Study Outcome category Outcome	Belimumab + concomitant medication		Placebo + concomitant medication		Belimumab + concomitant medication vs. placebo + concomitant medication
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
PLUTO					
Mortality					
All-cause mortality	21	0 (0.0)	14	0 (0.0)	Not calculable
Morbidity and health-related quality of life					
				No usable data	
Side effects[b]					
AEs (supplementary information)	21	14 (66.7)	14	12 (85.7)	–
SAEs	21	1 (4.8)	14	6 (42.9)	0.11 [0.01; 0.83]; 0.007
Discontinuation due to AEs	21	0 (0.0)	14	1 (7.1)	Not calculated
Infections and infestations (AEs, SOCs)	21	8 (38.1)	14	12 (85.7)	0.50 [0.29; 0.86]; 0.006

a. RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [8]). Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.
b. Only AEs occurring up to 4 weeks after the last dose of the study medication were considered for patients who continued the study in Part B or C, and AEs up to 8 weeks after the last dose of the study medication for patients who ended participation in the study after Part A.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Due to the outcome-specific high risk of bias, at most hints, e.g. of an added benefit, are possible.

All-cause mortality

No deaths occurred in the relevant subpopulation of the PLUTO study. This resulted in no hint of an added benefit of belimumab + individual concomitant medication in comparison with the ACT; an added benefit is therefore not proven.

Serious adverse events as well as infections and infestations (AEs, System Organ Class [SOC])

A statistically significant difference in favour of belimumab + individual concomitant medication in comparison with placebo + individual concomitant medication was shown for each of the outcomes “serious adverse events (SAEs)” and “infections and infestations”. As a result, there was a hint of lesser harm of belimumab + individual concomitant medication in comparison with the ACT.

Discontinuation due to adverse events

Only one patient had an event of the outcome “discontinuation due to AEs”. This resulted in no hint of greater or lesser harm from belimumab + individual concomitant medication in comparison with the ACT; greater or lesser harm is therefore not proven.

2.3 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [9].

The approach for deriving an overall conclusion on the 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.

2.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented (see Table 3 below).

Table 3: Extent of added benefit at outcome level: belimumab + individual concomitant treatment vs. individual concomitant treatment

Outcome category **Outcome**	**Belimumab + individual concomitant treatment vs. individual concomitant treatment** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	0 % vs. 0 % RR: not calculable	Lesser benefit/added benefit not proven
Morbidity		
No usable data		
Health-related quality of life		
No usable data		
Side effects		
SAEs	4.8 % vs. 42.9 % RR: 0.11 [0.01; 0.83] p = 0.007 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"
Discontinuation due to AEs	0 % vs. 7.1 % RR: not calculated	Greater/lesser harm not proven
Infections and infestations (AEs, SOCs)	38.1 % vs. 85.7 % RR: 0.50 [0.29; 0.86] p = 0.006 probability: "hint"	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ lesser harm, extent: "minor"

a. Probability provided if a statistically significant and relevant effect is present.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

2.3.2 Overall conclusion on added benefit

Table 4 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 4: Positive and negative effects from the assessment of belimumab + individual concomitant treatment in comparison with individual concomitant treatment

Positive effects	**Negative effects**
Serious/severe side effects ▪ SAEs: hint of lesser harm – extent: "considerable"	–
Non-serious/non-severe side effects ▪ infections and infestations: hint of lesser harm – extent: “minor”	
No usable results were available for the outcomes in the categories of morbidity and health-related quality of life.	

Overall, usable results were only available for the outcomes in the category of side effects and for the deaths recorded with AEs. Regarding the outcomes in the categories of serious/severe and non-serious/non-severe side effects, a hint of lesser harm of belimumab with the extent "considerable" and "minor" was shown in each case.

Due to the type of analyses, no meaningfully interpretable results were available for the outcomes of the categories of morbidity and health-related quality of life. However, there was a clear effect particularly regarding SAEs, so that it cannot be assumed that the positive effects were completely called into question by possible results in the categories of morbidity or health-related quality of life. Due to the uncertainty resulting from the unusable results in these outcome categories, the added benefit is non-quantifiable.

In summary, there is a hint of a non-quantifiable added benefit for belimumab + individual concomitant treatment for the treatment of children and adolescents aged 5 to < 18 years with active, autoantibody-positive SLE with a high degree of disease activity (e.g., positive test result for anti-dsDNA antibodies and low complement) despite standard therapy.

2.4 Summary

The information resulting from the commenting procedure and the oral hearing has changed the conclusion on the added benefit of belimumab from dossier assessment A19-94. There is a hint of a non-quantifiable added benefit for belimumab as add-on therapy for the treatment of children and adolescents aged 5 to < 18 years with active, autoantibody-positive SLE with a high degree of disease activity (e.g., positive test result for anti-dsDNA antibodies and low complement) despite standard therapy.

The following Table 5 shows the result of the benefit assessment of belimumab under consideration of dossier assessment A19-94 and the present addendum.

Table 5: Belimumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Patients aged 5 to < 18 years with active, autoantibody-positive SLE with a high degree of disease activity (e.g., positive test result for anti-dsDNA antibodies and low complement) despite standard therapy	Individual treatment choosing from hydroxychloroquine, chloroquine, NSAIDs, glucocorticoids, azathioprine, mycophenolate mofetil (in case of severe kidney involvement), taking into account the respective organ involvement, prior therapy and disease activity	Hint of non-quantifiable added benefit
a. Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; dsDNA: double-stranded deoxyribonucleic acid; G-BA: Federal Joint Committee; NSAID: nonsteroidal anti-inflammatory drug; SLE: systemic lupus erythematosus		

The G-BA decides on the added benefit.

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Appendix A – Further results of the ITT-ACT2 population of the PLUTO study

Table 6: Results (mortality, morbidity, side effects, dichotomous) – RCT, direct comparison: belimumab + concomitant medication vs. placebo + concomitant medication

Study Outcome category Outcome	Belimumab + concomitant medication		Placebo + concomitant medication		Belimumab + concomitant medication vs. placebo + concomitant medication
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
PLUTO					
Mortality					
All-cause mortality	21	0 (0.0)	14	0 (0.0)	Not calculable
Morbidity					
SRI responder	21	13 (61.9)	14	7 (50.0)	1.24 [0.66; 2.31]; 0.567
SLEDAI (reduction by ≥ 4 points vs. baseline)[b]	21	14 (66.7)	14	7 (50.0)	1.33 [0.73; 2.44]; 0.449
PGA responder (deterioration < 0.3 points vs. baseline)	21	19 (90.5)	14	10 (71.4)	1.27 [0.88; 1.81]; 0.198
BILAG responder (neither new organ system with A nor ≥ 2 new organ systems with B since baseline)	21	19 (90.5)	14	10 (71.4)	1.27 [0.88; 1.81]; 0.198
Responder for reduction of prednisone dose[c]	20[d]	6 (30.0)	13[e]	1 (7.7)	3.90 [0.53; 28.78]; 0.150
PedsQL, physical functioning					
≥ 50 % improvement since baseline	21	6 (28.6)	14	2 (14.3)	2.00 [0.47; 8.53]; 0.449
≥ 30 % improvement since baseline	21	7 (33.3)	14	4 (28.6)	1.17 [0.42; 3.25]; 0.807
≤ 30 % deterioration since baseline	21	20 (95.2)	14	10 (71.4)	1.33 [0.94; 1.88]; 0.056

a. RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [8]). Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.
b. A decrease in value indicates a decrease in disease activity.
c. Responders for the analysis of prednisone reduction by ≥ 25% are patients who achieved a ≥ 25% reduction in their average daily prednisone equivalence dose between weeks 44 and 52 in comparison with baseline.
d. Number of patients under prednisone treatment at baseline.

AE: adverse event; BILAG: British Isles Lupus Assessment Group; CI: confidence interval; CSZ: convexity, symmetry, z score; n: number of patients with (at least one) event; N: number of analysed patients; PedsQL: Pediatric Quality of Life Inventory; PGA: physician's global assessment; RCT: randomized controlled trial; RR: relative risk; SLE: systemic lupus erythematosus; SRI: SLE Responder Index; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; vs.: versus

Table 7: Results (symptoms, health-related quality of life) – RCT, direct comparison: belimumab + concomitant medication vs. placebo + concomitant medication

Study Outcome category Outcome	Belimumab + concomitant medication			Placebo + concomitant medication			Belimumab + concomitant medication vs. placebo + concomitant medication
	N[a]	Values at baseline mean[b] (SD)	Change at end of study mean[c] (SE)[d]	N[a]	Values at baseline mean[b] (SD)	Change at end of study mean[c] (SE)[d]	Mean difference [95% CI][e]; p-value[f]
PLUTO (ITT-ACT2 population)							
Symptoms							
PedsQL, fatigue, total	21	65.0 (20.2)	21.4 (7.0)	14	57.5 (13.5)	23.1 (7.0)	−1.7 [−13.8; 10.4]; 0.776
General fatigue	21	60.3 (24.1)	26.2 (8.2)	14	55.4 (16.6)	26.8 (8.4)	−0.5 [−14.8; 13.7]; 0.942
Sleep/rest fatigue	21	60.5 (25.2)	29.4 (8.1)	14	48.5 (20.5)	31.0 (8.3)	−1.6 [−16.1; 12.8]; 0.819
Cognitive fatigue	21	74.0 (22.2)	9.2 (6.4)	14	68.8 (15.8)	9.6 (6.4)	−0.4 [−11.1; 10.3]; 0.941
Health-related quality of life							
PedsQL core, total	21	68.8 (17.8)	22.5 (6.1)	14	65.5 (12.2)	20.1 (6.2)	2.4 [−8.2; 13.0]; 0.646
Physical functioning	21	63.2 (24.3)	29.3 (7.4)	14	57.8 (17.7)	22.0 (7.6)	7.3 [−5.6; 20.2]; 0.257
Emotional functioning	21	71.4 (19.2)	23.5 (7.7)	14	63.6 (22.4)	25.0 (8.1)	−1.5 [−15.0; 12.0]; 0.821
Social functioning	21	79.3 (19.6)	8.1 (4.6)	14	86.1 (15.0)	5.8 (4.8)	2.3 [−5.7; 10.3]; 0.561
School functioning	21	64.5 (20.9)	21.0 (6.2)	14	59.3 (12.8)	21.5 (6.2)	−0.6 [−11.1; 10.0]; 0.916

a. Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline may be based on other patient numbers.
b. Higher values represent a better status or better functioning.
c. Positive changes represent an improvement in status or functioning; calculations with LOCF.
d. Mean value and standard error from ANCOVA.
e. Positive differences indicate an advantage for belimumab.
f. Effect, CI and p-value: ANCOVA adjusted for baseline values, age at baseline (5 to 11 vs. 12 to 17 years) and SLEDAI score (≤ 12 vs. ≥ 13) at baseline.

ANCOVA: analysis of covariance; CI: confidence interval; LOCF: last observation carried forward; N: number of analysed patients; PedsQL core: Pediatric Quality of Life Inventory – Generic Core; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; vs.: versus

Table 8: Results (morbidity, time to first event) – RCT, direct comparison: belimumab + concomitant medication vs. placebo + concomitant medication

Study Outcome category Outcome	Belimumab + concomitant medication		Placebo + concomitant medication		Belimumab + concomitant medication vs. placebo + concomitant medication
	N	Median time to event in weeks [95% CI] Patients with event n (%)	N	Median time to event in weeks [95% CI] Patients with event n (%)	HR [95% CI]; p-value
PLUTO					
Morbidity					
SFI, severe flares	21	NA 2 (9.5)	14	NA 6 (42.9)	0.16 [0.03; 0.81]; 0.027[a]
SFI, severe flares, sensitivity analysis 1[b]	21	1 (4.8)[c]	14	3 (21.4)[c]	RR: 0.22 [0.03; 1.93][c]; p = 0.155[d]
SFI, severe flares, sensitivity analysis 2[e]	21	0 (0)[c]	14	2 (14.3)[c]	RR: 0.14 [0.01; 2.65][c]; p = 0.091[d]

a. Cox proportional hazards model, adjusted for age at baseline (5–11 vs. 12–17 years) and SELENA-SLEDAI score at baseline (< 13 vs. ≥ 13).
b. Sensitivity analysis without consideration of the patients who were rated as having a severe flare only based on an adjustment of the treatment.
c. Institute's calculation.
d. Institute's calculation, unconditional exact test (CSZ method according to [8]).
e. Sensitivity analysis 2 concurs with sensitivity analysis 1, but additionally without consideration of those patients in whom an increase of the SELENA-SLEDAI to > 12 was rated as flare (in line with the original planning in the PLUTO study).

CI: confidence interval; CSZ: convexity, symmetry, z score; HR: hazard ratio; n: patients with event; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial; RR: relative risk; SELENA: Safety of Estrogens in Lupus Erythematosus – National Assessment; SFI: SELENA-SLEDAI SLE Flare Index; SLE: Systemic Lupus Erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; vs.: versus