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Benralizumab (asthma) –

Addendum to Commission A18-11[1]

Addendum

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum:

- Sascha Abbas
- Florina Kerekes
- Regine Potthast
- Anke Schulz
- Volker Vervölgyi

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List of abbreviations

Abbreviation	Meaning
ACQ	Asthma Control Questionnaire
ACT	appropriate comparator therapy
AE	adverse event
AQLQ	Asthma Quality of Life Questionnaire
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
ICS	inhaled corticosteroids
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LABA	long-acting beta-2 agonist
LAMA	long-acting muscarinic antagonist
mITT	modified intention-to-treat
OCS	oral corticosteroids
SAE	serious adverse event
SPC	Summary of Product Characteristics
VAS	visual analogue scale

1 Background

On 26 June 2018, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A18-11 (Benralizumab – Benefit assessment according to §35a Social Code Book V [1]).

The dossier assessment on benralizumab concluded that the analyses on the studies ZONDA, CALIMA and SIROCCO presented by the pharmaceutical company (hereinafter referred to as "the company") in the dossier were unsuitable for the assessment of the added benefit of benralizumab because the appropriate comparator therapy (ACT) specified by the G-BA was not implemented in the control arms [1]. With the written comment [2], the company submitted supplementary information on the studies ZONDA, CALIMA and SIROCCO presented in the dossier [3].

The G-BA commissioned IQWIG with the assessment of the studies ZONDA, CALIMA and SIROCCO under consideration of the information provided in the dossier and the analyses submitted by the company within the framework of the commenting procedure.

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 Assessment of the studies ZONDA, CALIMA and SIROCCO

The study design, the interventions planned in the study protocol and the characteristics of the patient populations analysed by the company for the studies ZONDA, CALIMA and SIROCCO were already presented in the dossier assessment [1].

2.1 Study ZONDA

The randomized, double-blind, placebo-controlled, 3-arm ZONDA study investigated the possibility of dose reduction in the maintenance treatment with oral corticosteroids (OCS) in patients with eosinophilic asthma who are already receiving regular OCS treatment in addition to ongoing treatment with high-dose inhaled corticosteroids (ICS) plus long-acting beta-2 agonists (LABAs). The aim of the ZONDA study was to investigate the effect of benralizumab in 2 dosages, one of which was in compliance with the approval, in comparison with placebo on the intended OCS dose reduction. For this purpose, the patients first underwent an optimization phase before randomization to reduce their OCS treatment to the lowest still effective dosage. After randomization and the start of the study treatment, the OCS dose was gradually decreased further. Returning to a higher dose was possible if asthma symptoms deteriorated. Hence, the patients in the ZONDA study received no escalation in the control arm, but a reduction of their asthma treatment instead. With benralizumab, another asthma medication for asthma control was available in the intervention arm, but not in the placebo arm.

For the dossier assessment, the company analysed the total patient population of the placebo arm and of the approval-compliant benralizumab arm.

2.2 Studies CALIMA and SIROCCO

The studies CALIMA and SIROCCO were randomized, double-blind, placebo-controlled 3-arm studies in patients with uncontrolled asthma under ongoing treatment with medium- or high-dose ICS plus LABAs with or without further maintenance treatments. Both studies compared benralizumab in 2 different dosages, one of which was in compliance with the approval, with placebo. In both studies, another asthma medication for asthma control was available in the intervention arms, but not in the placebo arms.

For the dossier assessment, the company analysed the patient population of the placebo arm and of the approval-compliant benralizumab arm, restricted to patients with eosinophilic asthma receiving high-dose ICS plus LABAs and at least OCS or long-acting muscarinic antagonist (LAMA) (tiotropium) or both (modified intention-to-treat [mITT] population). From the company’s point of view, these are patients for whom the relevant treatment options have already been exhausted and for whom only limited treatment adjustments on an individual level are possible.

2.3 Options for treatment escalation

The company argued in its dossier that treatment options have mostly been exhausted for the analysed mITT populations (total population of ZONDA, subpopulations of CALIMA and SIROCCO).

It was not guaranteed for the patient populations analysed by the company that treatment options at study start had been exhausted in the framework of the maintenance treatments. This particularly applied to patients without OCS as maintenance medication at study start in the studies CALIMA and SIROCCO. These patients without OCS (but with tiotropium) at study start had a potential further escalation option with OCS. In relation to the subpopulation presented by the company, this applied to > 30% of the patients in the placebo arm (see Table 1).

Table 1: Maintenance treatment with LAMA and/or OCS at study start in the mITT populations of the studies ZONDA, CALIMA and SIROCCO analysed by the company

OCS	LAMA	Number of patients n (%)					
		ZONDA		CALIMA		SIROCCO	
		Benralizumab N = 73	Placebo N = 75	Benralizumab N = 44	Placebo N = 43	Benralizumab N = 60	Placebo N = 55
Yes	No	52 (71.2)	54 (72.0)	17 (38.6)	19 (44.2)	35 (58.3)	33 (60.0)
No	Yes	0 (0)	0 (0)	20 (45.5)	15 (34.9)	10 (16.7)	18 (32.7)
Yes	Yes	21 (28.8)	21 (28.0)	7 (15.9)	9 (20.9)	15 (25.0)	4 (7.3)

LAMA: long-acting muscarinic antagonist; mITT: modified intention to treat; n: number of patients with respective maintenance treatment at study start; OCS: oral corticosteroid

The company argued in its comment that, due to their medical histories, additional OCS maintenance treatment was not indicated in the subpopulation of patients without OCS at study start who had no further adjustment in the course of the studies (OCS was initiated in the course of the study in 3 [9.1%] of the patients in the placebo arm of the mITT population of the studies SIROCCO and CALIMA without OCS at study start). According to the company, these patients had numerous potentially contraindicating comorbidities. It presented proportions of the patients with a history of the selected conditions in the subpopulation of the studies CALIMA and SIROCCO without OCS at study start (see Appendix A, Table 5) [2].

The conditions presented by the company were not contraindications. The Summary of Product Characteristics (SPC) only named hypersensitivity to the active substance as contraindication [4,5]. According to the SPC warnings, there is a strict indication for some of the conditions presented by the company (osteoporosis, psychiatric disorders, glaucoma) [4,5]. For diabetes and hypertension, which were also presented by the company, a strict indication applies only to patients whose condition is hard to control [4,5]. Hence, no contraindications to OCS administration can be inferred from the information provided on the medical history. According

to guidelines, OCS should only be used for patients with poor symptom control and/or exacerbations despite treatment according to step 4 of the asthma graded scheme, with good adherence and inhaler technique, and after exclusion of other contributory factors that compromise asthma control. In addition, patients should be informed about typical side effects, and they should be monitored particularly for possible glucocorticoid-induced osteoporosis [6,7]. It is unclear to what extent individual balancing against OCS treatment was conducted in the patients without OCS maintenance treatment in the studies CALIMA and SIROCCO, and hence no further escalation would have been possible for these patients.

In the placebo arms, 72.0% (ZONDA), 44.2% (CALIMA) and 60.0% (SIROCCO) of the patients analysed by the company received no LAMA (but OCS) at study start (see Table 1). According to guidelines, OCS should only be recommended if no asthma control is achieved despite the combined use of different treatment options in step 4 and 5 [7]. For the studies CALIMA and SIROCCO, there was no information on the number of patients who had received a treatment attempt with LAMA (tiotropium) before study inclusion. Information was only provided for the ZONDA study, where 1 patient (1.3%) in the comparator arm, and 2 patients (2.7%) in the intervention arm had stopped treatment with tiotropium bromide before or at randomization. Since tiotropium was not approved at study start, it can be assumed that the proportion with a treatment attempt before study start was low. Hence, it is unclear how many patients without tiotropium at study start would have benefitted from tiotropium already before OCS medication, and who therefore could have received individual treatment with tiotropium according to guidelines.

Omalizumab as an additional ACT option was not available as escalation in the framework of the studies ZONDA, CALIMA and SIROCCO.

In the course of the procedure, the ACT with the already existing escalation options (tiotropium, possibly omalizumab, possibly OCS) was supplemented with possibly mepolizumab in patients who could otherwise not be escalated [8]. Mepolizumab – which was not yet approved at study start – was not available for escalation in the studies ZONDA, CALIMA and SIROCCO. It can be assumed that mepolizumab with the therapeutic indication of severe refractory eosinophilic asthma [9] would have been an option for escalation in a large proportion of the analysed populations.

2.4 Individual treatment adjustments

The company argued in its dossier that individual adjustments in the framework of the study were possible and were also performed in its dossier [3].

According to the information provided in the protocols of the 3 studies included, however, maintenance treatments (including ICS plus LABAs, tiotropium and OCS) were only allowed if they had already been taken before study start and were continued without changes during the studies. An exception were OCS in the ZONDA study, where all patients were taking OCS at study start and where OCS reduction was a primary outcome. The study documents contained

the information that a change was possible if this was deemed medically reasonable by the investigator only for ICS plus LABAs. An adjustment in the course of the study was not allowed for the maintenance treatments tiotropium (all 3 studies) and OCS (CALIMA and SIROCCO) named in the ACT.

Hence, the study protocols did not provide for individual treatment adjustments in the framework of the ACT. Even though, contrary to the protocol specifications, individual patients had adjustments in the course of treatment, these cannot be interpreted as possibility of individual treatment adjustments of all included patients. Instead, it must therefore be assumed that, without the described restriction in the study protocols, further individual adjustments of the maintenance treatments due to poor asthma control would have taken place during the studies.

2.5 Conclusion

As already shown in the dossier assessment of benralizumab, the analyses presented by the company (total population of ZONDA and subpopulations of CALIMA and SIROCCO) were unsuitable for the derivation of an added benefit of benralizumab in comparison with the ACT. On the one hand, it was not guaranteed in the populations analysed by the company that particularly patients without OCS as maintenance treatment at study start had exhausted their treatment options. On the other, individual treatment escalation in the framework of the ACT was not possible in the studies according to the study protocols.

2.6 Results of the populations analysed by the company

In compliance with the commission, the results of the study ZONDA and of the studies CALIMA and SIROCCO are presented in the following sections.

2.6.1 Study ZONDA

The results of the total study population of the ZONDA study (approval-compliant administration of benralizumab; eosinophils ≥ 150/µL, high-dose ICS plus LABAs, in addition at least OCS as maintenance medication at study start) are presented in Table 2.

Table 2: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: benralizumab vs. placebo, ZONDA

Outcome category Outcome	Benralizumab		Placebo		Benralizumab vs. placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Mortality					
All-cause mortality[a]	73	2 (2.7)	75	0 (0)	5.14 [0.25; 105.17]; 0.288[b]
Morbidity					
OCS reduction to ≤ 5 mg/day[c]	73	43 (58.9)	75	25 (33.3)	1.77 [1.22; 2.57]; 0.003[b, d]
OCS reduction to 0 mg/day[c, e]	73	22 (30.1)	75	8 (10.7)	2.83 [1.34; 5.94]; 0.006[b, d]
Asthma exacerbations[f]	73	17 (23.3)	75	39 (52.0)	0.45 [0.28; 0.72]; < 0.001[b, d]
		Mean annual rate [95% CI][g]:			Rate ratio [95% CI]; p-value[g]:
	73	0.54 [0.33; 0.87]	75	1.80 [1.32; 2.46]	0.30 [0.17; 0.53]; < 0.001
Well-controlled asthma (ACQ-6 ≤ 0.75)[h, i, j]	73	24 (32.9)	75	9 (12.0)	2.74 [1.37; 5.49]; 0.004[b]
Well-controlled asthma (ACQ-5 ≤ 0.75)[h, j]	73	22 (30.1)	75	8 (10.7)	2.83 [1.34; 5.94]; 0.006[b]
Health-related quality of life					
AQLQ(S)+12 – improvement by at least 0.5 points[h]	73	44 (60.3)	75	39 (52.0)	1.16 [0.87; 1.54]; 0.312[b, d]
Side effects					
AEs, SAEs	No usable data[k]				
Discontinuation due to AEs	73	3 (4.1)	75	2 (2.7)	1.54 [0.27; 8.96]; 0.630[b]

(continued)

Table 2: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: benralizumab vs. placebo, ZONDA (continued)

a: According to the study documents referred to as AEs leading to death.
b: RR, CI and p-values based on a binary logistic regression analysis.
c: At the end of treatment (week 28), with maintained asthma control according to criteria defined per study protocol.
d: The relative risks presented by the company in the additional analyses and Module 4 were unadjusted. The statistical analysis plan had specified adjustments for the original analyses (logistic regression or Cochran-Mantel-Haenszel test, probably on the odds ratio). A different approach regarding adjustment for different effect measures is not comprehensible.
e: A reduction to 0 mg/day was not possible for patients who used an OCS dose of > 12.5 /day at study start (31 patients in the benralizumab arm and 33 in the placebo arm).
f: Asthma exacerbations were defined as deterioration of asthma leading to OCS pulse therapy, emergency department visit requiring OCS treatment, or hospitalization due to asthma. Of these patients, 1 (1.4%) patient in the benralizumab arm and 9 (12.0%) patients in the placebo arm had asthma exacerbations that only led to emergency department visit or hospitalization.
g: Rates, rate ratios, CI and p-value determined with negative binomial model with treatment group, region, and number of exacerbations in the previous 12 months as covariates, with the logarithm of the follow-up period as offset variable. The mean annual rates and the rate ratio on the outcome "asthma exacerbations" show small inexplicable discrepancies between study report and Module 4, despite the same information on model and adjustment factors.
h: At the end of treatment (week 28); patients with missing or incalculable questionnaire scores at the end of treatment were rated as non-responders: 10.1% for the ACQ and 8.8% of the patients for the AQLQ; differences between the treatment arms < 5%.
i: In addition to the questions on symptoms of the ACQ-5, the ACQ-6 contains a question on the use of SABAs as emergency medication.
j: In the ACQ-6, 10 patients in the benralizumab arm (13.7%) fulfilled the criterion for well-controlled asthma already at study start (0% in the placebo arm). The effect on the interpretation of the result is unclear. For the ACQ-5, the numbers for patients with well-controlled asthma at study start are unknown.
k: No usable data as the AE and SAE rates include asthma symptoms. One year after study start, an amendment to the protocol restricted the documentation of asthma symptoms as AEs as follows: Asthma symptoms or signs, such as wheezing, cough, chest tightness, dyspnoea, breathlessness and productive cough, were rated as AEs if the symptom/sign was serious or new (not in line with the previous history of asthma) or if the patient discontinued the study because of it.

ACQ-6 (ACQ-5): Asthma Control Questionnaire-6 (or 5); AE: adverse event; AQLQ(S)+12: Asthma Quality of Life Questionnaire (S) for 12 years and older, modified and validated version of the AQLQ; CI: confidence interval; n: number of patients with (at least 1) event; N: number of analysed patients; OCS: oral corticosteroid; RCT: randomized controlled trial; RR: relative risk; SABA: short-acting beta-2 agonist; SAE: serious adverse event; vs.: versus

Mortality

There was no statistically significant difference between the treatment groups for the outcome "all-cause mortality".

Morbidity

Statistically significant differences in favour of benralizumab versus placebo were shown both for the operationalizations on OCS reduction to ≤ 5 mg/day or 0 mg/day and for the outcomes "asthma exacerbations" and "asthma control" (Asthma Control Questionnaire [ACQ]-6, ACQ-5) at the end of study.

When interpreting these results, it should be taken into account that reduction of the OCS dosage was mandated by the study design. Hence, patients in the placebo arm (without further escalation options) can be expected to have poorer symptom control than patients in the intervention arm with additional administration of benralizumab. In particular, it should be taken into account that before randomization OCS treatment was reduced to the lowest still effective dosage with maintained asthma control. The outcomes on morbidity can therefore not be rated as an advantage of benralizumab.

Health-related quality of life

No statistically significant difference between the treatment groups was shown for the outcome "Asthma Quality of Life Questionnaire (S) for 12 years and older (AQLQ(S)+12)".

Side effects

No usable data were available for the outcomes "adverse events (AEs)" and "serious adverse events (SAEs)" because asthma symptoms were also documented as AEs. This applied to a relevant proportion of patients with AEs or SAEs. Consideration of the Preferred Term "asthma" alone showed the corresponding AE in 3.6% of the patients in the benralizumab arm and 29.0% in the placebo arm (percentages refer to all patients with AEs), and the corresponding SAE in 14.3% of the patients in the benralizumab arm and 28.6% in the placebo arm (percentages refer to all patients with SAEs).

The result for the outcome "discontinuation due to AEs" was not assumed to be influenced to a relevant degree by events based on asthma symptoms. No statistically significant difference between the treatment groups was shown here.

2.6.2 Studies CALIMA and SIROCCO

The results of the meta-analyses of the studies CALIMA and SIROCCO for the mITT population (approval-compliant administration of benralizumab; eosinophils ≥ 300/µL; high-dose ICS plus LABAs, additional OCS and/or tiotropium as maintenance medication at study start) are presented in Table 3 and Table 4.

Table 3: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: benralizumab vs. placebo, studies CALIMA and SIROCCO, mITT population analysed by the company[a]

Outcome category Outcome Study	Benralizumab N	Benralizumab Patients with event n (%)	Placebo N	Placebo Patients with event n (%)	Benralizumab vs. placebo RR [95% CI]; p-value
Mortality					
All-cause mortality[b]					
CALIMA	43	0 (0.0)	43	0 (0.0)	NC
SIROCCO	59	0 (0.0)	55	0 (0.0)	NC
Total					NC
Morbidity					
Asthma exacerbations[c]					
CALIMA	44	16 (36.4)	43	33 (76.7)	0.47 [0.31; 0.72]; < 0.001[d, e]
SIROCCO	60	19 (31.7)	55	35 (63.6)	0.50 [0.33; 0.76]; 0.001[d, e]
Total					0.49 (0.36; 0.65); < 0.001[f]
		Mean annual rate [95% CI][g]:			Rate ratio [95% CI]; p-value[g]:
CALIMA	44	0.84 [0.53; 1.32]	43	1.74 [1.19; 2.55]	0.48 [0.27; 0.87]; 0.015
SIROCCO	60	0.59 [0.38; 0.91]	55	2.10 [1.49; 2.97]	0.28 [0.16; 0.50]; < 0.001
Total					0.34 [0.23; 0.52]; < 0.001[h]
Well-controlled asthma (ACQ-6 ≤ 0.75)[i, j]					
CALIMA	44	14 (31.8)	43	6 (14.0)	2.28 [0.97; 5.38]; 0.060[d]
SIROCCO	60	16 (26.7)	55	11 (20.0)	1.33 [0.68; 2.62]; 0.403[d]
Total					1.66 [0.98; 2.82]; 0.059[f]
Well-controlled asthma (ACQ-5 ≤ 0.75)[i]					
CALIMA	44	14 (31.8)	43	6 (14.0)	2.28 [0.97; 5.38]; 0.060[d]
SIROCCO	60	14 (23.3)	55	11 (20.0)	1.17 [0.58; 2.35]; 0.666[d]
Total					1.55 [0.91; 2.65]; 0.108[f]
Health-related quality of life					
AQLQ(S)+12 – improvement by at least 0.5 points[i]					
CALIMA	44	29 (65.9)	43	24 (55.8)	1.18 [0.84; 1.66]; 0.338[d, e]
SIROCCO	60	35 (58.3)	55	28 (50.9)	1.15 [0.82; 1.60]; 0.428[d, e]
Total					1.16 [0.91; 1.47]; 0.227[f]
Side effects					
AEs, SAEs, discontinuation due to AEs					
CALIMA				No usable data[k]	
SIROCCO				No usable data[k]	

(continued)

Table 3: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: benralizumab vs. placebo, studies CALIMA and SIROCCO, mITT population analysed by the company[a] (continued)

a: Adult patients with severe, uncontrolled, eosinophilic asthma (high-dose ICS + LABAs, eosinophils ≥ 300/µL) who are already receiving at least OCS or LAMAs or both as additional further maintenance treatments at study start.
b: According to the study documents referred to as AEs leading to death.
c: Asthma exacerbations were defined as deterioration of asthma leading to OCS pulse therapy, emergency department visit requiring OCS treatment, or hospitalization due to asthma. Of these patients, 4 (9.1%) patient in the benralizumab arm and 5 (11.6%) patients in the placebo arm of the CALIMA study had asthma exacerbations that were defined only by emergency department visit or hospitalization; the respective numbers in the SIROCCO study were 5 (8.3%) in the benralizumab arm and 7 (12.7%) in the placebo arm.
d: RR, CI and p-values based on a binary logistic regression analysis.
e: The relative risks presented by the company in the additional analyses and Module 4 were unadjusted. The statistical analysis plan had specified adjustments for the original analyses (logistic regression or Cochran-Mantel-Haenszel test, probably on the odds ratio). A different approach regarding adjustment for different effect measures is not comprehensible.
f: Calculation with IPD meta-analysis (binary logistic regression) with modelling of the adjustment variables as fixed effects.
g: Rates, rate ratios, CI and p-value determined with negative binomial model with treatment group, region, number of exacerbations in the previous 12 months and baseline OCS as covariates, with the logarithm of the follow-up period as offset variable.
h: Calculation with IPD meta-analysis (negative binomial model) with modelling of the adjustment variables as fixed effects.
i: At the end of treatment (CALIMA: week 56, SIROCCO: week 48); patients with missing or incalculable questionnaire scores at the end of treatment were rated as non-responders. Information only available for patients with high-dose ICS and eosinophils ≥ 300/µL (N = 487 in the CALIMA study and N = 534 in the SIROCCO study): 21.6% of the patients in the ACQ and 21.8% in the AQLQ(S)+12 in the CALIMA study, 29.4% of the patients in the ACQ and AQLQ(S)+12 in the SIROCCO study; differences between the treatment arms < 5%.
j: In addition to the questions on symptoms of the ACQ-5, the ACQ-6 contains a question on the use of SABAs as emergency medication.
k: No usable data as the asthma symptoms were documented as AEs. Amendment 1 to the protocol restricted the documentation of asthma symptoms as AEs as follows: Asthma symptoms or signs, such as wheezing, cough, chest tightness, dyspnoea, breathlessness and productive cough, were rated as AEs if the symptom/sign was serious or new (not in line with the previous history of asthma) or if the patient discontinued the study because of it.

ACQ-6 (ACQ-5): Asthma Control Questionnaire-6 (or 5); AE: adverse event; AQLQ(S)+12: Asthma Quality of Life Questionnaire (S) for 12 years and older, modified and validated version of the AQLQ; CI: confidence interval; ICS: inhaled corticosteroid; IPD: individual patient data; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; mITT: modified intention to treat; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculated; OCS: oral corticosteroid; RCT: randomized controlled trial; RR: relative risk; SABA: short-acting beta-2 agonist; SAE: serious adverse event; vs.: versus

Table 4: Results (morbidity, continuous) – RCT, direct comparison: benralizumab vs. placebo, studies CALIMA and SIROCCO, mITT population analysed by the company[a]

Outcome category Outcome Study	Benralizumab N[b]	Benralizumab Values at study start mean (SD)	Benralizumab Change at end of study mean (SD)	Placebo N[b]	Placebo Values at study start mean (SD)	Placebo Change at end of study mean (SD)	Benralizumab vs. placebo MD [95% CI]; p-value[c]
Morbidity							
Health status (EQ-5D VAS)							
CALIMA	36	58.29 (13.21)	14.42 (18.58)	36	53.74 (16.01)	7.61 (17.20)	7.05 [−0.28; 14.37]; 0.060
SIROCCO	48	55.13 (19.20)	12.76 (23.16)	39	59.00 (16.72)	9.34 (20.48)	0.99 [−6.70; 8.68]; 0.801
Total							3.57 [−1.76; 8.89]; 0.189[d]

a: Adult patients with severe, uncontrolled, eosinophilic asthma (high-dose ICS + LABAs, eosinophils ≥ 300/µL) who are already receiving at least OCS or LAMAs or both as additional further maintenance treatments at study start.
b: Number of patients considered in the analysis for the calculation of the effect estimation; the values at study start are based on other patient numbers.
c: MMRM analysis.
d: Calculation with IPD meta-analysis (MMRM) with modelling of the adjustment variables as fixed effects.
CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroid; IPD: individual patient data; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; mITT: modified intention to treat; MMRM: mixed effects model repeated measures; N: number of analysed patients; OCS: oral corticosteroid; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus

Mortality

There were no deaths in the respective mITT population in the CALIMA study or in the SIROCCO study.

Morbidity

A statistically significant difference in favour of benralizumab versus placebo was shown for the outcome “asthma exacerbations”, defined as deterioration of asthma leading to OCS pulse therapy, emergency department visit requiring OCS treatment, or hospitalization due to asthma.

No statistically significant difference between the treatment groups was shown for the outcome “symptoms/asthma control” measured with the ACQ-6 or ACQ-5.

There was no statistically significant difference between the treatment groups for health status (European Quality of Life-5 Dimensions [EQ-5D] visual analogue scale [VAS]).

Health-related quality of life

There was no statistically significant difference between the treatment groups for the outcome "AQLQ(S)+12".

Side effects

No usable data were available for the outcomes "AEs", "SAEs" and "discontinuation due to AEs" because asthma symptoms were also documented as AEs. Since there were no results at the level of individual events for the mITT population, the proportion of patients with AEs due to asthma symptoms was unclear.

3 References

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Appendix A – Further information on the studies CALIMA and SIROCCO

Table 5: Medical history (selection by the company in the comment [2]) – RCT, direct comparison: benralizumab vs. placebo, studies CALIMA and SIROCCO, mITT population without OCS at study start analysed by the company[a]

Characteristics Study	Patients with event n (%)	
	Benralizumab	**Placebo**
Study CALIMA	**N = 20**	**N = 15**
Study SIROCCO	**N = 10**	**N = 18**
Cataract		
CALIMA	0 (0)	1 (6.7)
SIROCCO	1 (10.0)	1 (5.6)
Glaucoma		
CALIMA	1 (5.0)	0 (0)
SIROCCO	0 (0)	1 (5.6)
Diabetes mellitus		
CALIMA	1 (5.0)	1 (6.7)
SIROCCO	0 (0)	0 (0)
Hypertension		
CALIMA	9 (45.0)	3 (20.0)
SIROCCO	1 (10.0)	6 (33.3)
Dyslipidaemia		
CALIMA	4 (20.0)	2 (13.3)
SIROCCO	0 (0)	3 (16.7)
Osteoporosis		
CALIMA	1 (5.0)	3 (20.0)
SIROCCO	1 (10.0)	2 (11.1)
Osteopenia		
CALIMA	0 (0)	0 (0)
SIROCCO	0 (0)	2 (11.1)
Psychiatric disorders		
CALIMA	2 (10.0)	7 (46.7)
SIROCCO	1 (10.0)	6 (33.3)

a: Adult patients with severe, uncontrolled, eosinophilic asthma (high-dose ICS + LABAs, eosinophils ≥ 300/µL) who are already receiving at least LAMAs, but no OCS, as additional further maintenance treatments at study start.

ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; mITT: modified intention to treat; number of patients in the category; N: number of randomized patients as described in footnote a; OCS: oral corticosteroid; RCT: randomized controlled trial; vs.: versus