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List of abbreviations

Abbreviation	Meaning
ACQ	Asthma Control Questionnaire
ACT	appropriate comparator therapy
FEV1	forced expiratory volume in 1 second
IgE	immunoglobulin E
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GINA	Global Initiative for Asthma
ICS	inhaled corticosteroids
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LABA	long-acting bronchodilator
OCS	oral corticosteroids
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 6 June 2016, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A16-03 (Mepolizumab – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

The dossier assessment on mepolizumab concluded that the studies on mepolizumab presented by the pharmaceutical company (hereinafter referred to as "the company") were unsuitable for the assessment of the added benefit because the appropriate comparator therapy (ACT) specified by the G-BA was not implemented in the control arms [1]. With its written comments [2], the company in particular submitted supplementary information on the concomitant treatment in the MENSA study it had presented in the dossier [3].

To be able to make a decision on the added benefit of mepolizumab, the G-BA commissioned IQWiG with further assessments of the studies MENSA and SIRIUS under consideration of the analyses presented by the company in the commenting procedure and the information provided in the dossier.

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

2 Assessment

2.1 Assessment of the MENSA study

The study design of the MENSA study and the interventions mandated according to the study protocol were already presented in the dossier assessment [1].

Patient population in the MENSA study

Patients with uncontrolled severe asthma were enrolled in the MENSA study. On the one hand, the inclusion criteria required persistent airway obstruction (forced expiratory volume in 1 second [FEV1] < 80% predicted [pre-bronchodilator]) and 2 or more exacerbations per year before the start of the study under treatment with high-dose inhaled corticosteroids (ICS) and additional control medication. On the other, the study population showed the following characteristics at the start of the study:

- mean FEV1 about 60% predicted
- mean score of the symptom component of the Asthma Control Questionnaire (ACQ-5) about 2.3 (an ACQ score of > 1.5 is considered to indicate inadequate symptom control [4])
- mean number of episodes of nocturnal awakening requiring rescue medication use per day 0.8 and 0.7 in both treatment groups
- mean number of inhalations of rescue medication per day 1.9 and 1.8 in both treatment groups
- mean number of asthma exacerbations in the year prior to screening 3.8 and 3.5 in both treatment groups, (2 or more exacerbations in 100% of the patients, 3 or more in about 60% of the patients, 4 or more in about 30% of the patients)

This population had inadequate asthma control [4,5]. The treatment initiated before the start of the study was therefore inadequate to ensure the treatment goal, which was asthma control. In this situation, guidelines recommend treatment escalation to achieve symptom control and prevent exacerbations [4,5].

Asthma treatment in the MENSA study

In one study arm of the MENSA study, treatment escalation with mepolizumab was conducted in addition to continuation of the ongoing asthma treatment in the included population with inadequate asthma control. In the comparator arm, in contrast, the study protocol mandated no defined (individual) treatment escalation for all patients; the patients in this arm received placebo in addition to their ongoing treatment [6].

The G-BA specified individual treatment escalation as ACT for the assessment of mepolizumab with reference to the graded scheme by the Global Initiative for Asthma (GINA). The G-BA described the options of treatment escalation as follows:

- individual treatment escalation
  - of moderate-to-high-dose ICS and of long-acting bronchodilators (LABAs), if applicable with oral corticosteroids (short-term) in their lowest effective dose
  - or with tiotropium
  - or, if applicable, in immunoglobulin E (IgE)-mediated pathogenesis of the asthma, omalizumab in addition to high-dose ICS and LABAs and, if applicable, to oral corticosteroid treatment

In particular, the G-BA noted that placebo or unchanged continuation of an inadequate treatment of the severe asthma did not concur with the ACT if the option of treatment escalation still existed.

Since regular treatment escalation in the comparator group in the beginning of the MENSA study was not mandated according to the study protocol, it was relevant for the suitability of the study whether options of treatment escalation were still available for the patient population included and whether these (although not clearly mandated in the study protocol) were used to a sufficient degree (see also explanations in the dossier assessment [1]).

ICS/LABAs

According to the inclusion criteria, patients were to receive ≥ 880 µg daily fluticasone propionate, and thus a high ICS dose, at study inclusion. The study documents or the dossier contained no information on the actual dosage in the study population at the start of the study or on changes in ICS/LABA dosage during the course of the study. An assessment of the additional treatment options for ICS/LABAs can be found in the dossier assessment.

Further control medication

Table 1 shows the use of tiotropium, theophylline, and oral corticosteroids (OCS) in addition to ICS and ICS/LABAs at the start of the study. It was clear from the data that these treatment options, which are options for a treatment escalation according to the GINA graded scheme or (with the exception of theophylline) according to the ACT specified by the G-BA, were not exhausted at the start of the MENSA study.

Table 1: Characteristics of the treatment (in addition to ICS[/LABAs] before the start of the study – RCT, MENSA – mepolizumab vs. placebo, relevant subpopulation

Study Group	N[a]	Patients with tiotropium or theophylline treatment (before the run-in phase)		OCS use at the start of the study (prednisone/prednisolone)	
		Tiotropium n (%)	Theophylline n (%)	n (%)	Mean dose [mg/day] Mean (SD)
MENSA					
Mepolizumab 100 mg	184	31 (17)	31 (17)	50 (27)	12.5 (11.1)
Placebo	176	24 (14)	28 (16)	42 (24)	15.2 (15.1)

a: Number of patients in the relevant subpopulation (ITT-ACT).

ACT: appropriate comparator therapy; ITT: intention to treat; n: number of patients with event; N: number of analysed patients; OCS: oral corticosteroids; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

With the comments on the dossier assessment, the company presented new analyses, from which it could be inferred that, in the relevant subpopulation of the MENSA study, 1 patient (< 1%) in the mepolizumab group and 6 patients (3%) in the placebo group started treatment with tiotropium during the treatment phase of the study. Hence no relevant treatment expansion with tiotropium was conducted in the study.

Table 2 describes the use of non-inhaled corticosteroids in the course of the MENSA study.

Table 2: Use of non-inhaled corticosteroids in the course of the study – RCT, MENSA – mepolizumab vs. placebo, relevant subpopulation

	Mepolizumab 100 mg N = 184 n (%)	**Placebo N = 176 n (%)**
CS[a] use in the course of the study		
Patients with CS[a] use before the run-in phase of the study	58 (32)	49 (28)
Patients with CS[a] use during the treatment phase of the study	89 (48)	112 (64)
Patients with CS[a] use initiated during the treatment phase of the study	77 (42)	103 (59)
Periods of OCS use depending on OCS use at the start of the study		
Patients without OCS use at the start of the study	134 (73)	133 (76)
Patients with OCS use during the treatment phase	36 (27)[b]	65 (49)[b]
Periods with OCS use	117	319
Periods with OCS use for exacerbation	93 (79)	292 (92)
Periods with OCS use without exacerbation	24 (21)	27 (8)
Patients with OCS use at the start of the study	50 (27)	43 (24)
Patients with increased OCS use during the treatment phase	25 (50)[c]	30 (70)[c]
Periods with increased OCS use	151	179
Periods with OCS use for exacerbation	132 (87)	143 (80)
Periods with OCS use without exacerbation	19 (13)	36 (20)
Exacerbations with OCS use		
Patients with clinically significant exacerbations (by definition with OCS use[d])	62 (34)	99 (56)

a: Systemic, oral, parenteral, or intraarticular corticosteroids.
b: % referring to patients without OCS at the start of the study; with reference to all patients in the relevant subpopulation: mepolizumab: 20%, placebo: 37%.
c: % referring to patients with OCS at the start of the study; with reference to all patients in the relevant subpopulation: mepolizumab: 14%, placebo: 17%.
d: Clinically significant exacerbation was defined as asthma deterioration (decrease in morning peak flow and/or increase in the use of rescue medication, and/or increase in the frequency of nocturnal awakening due to asthma symptoms requiring rescue medication use and/or increase in asthma symptoms), which required treatment with systemic corticosteroids (intravenously or orally for at least 3 days or a single intramuscular dose; in patients with OCS as control medication, at least twice the dosage had to be given for at least 3 days) and/or hospitalization and/or treatment at an emergency department [6].
CS: corticosteroids; n: number of patients with event; N: number of analysed patients; OCS: oral corticosteroids; RCT: randomized controlled trial; vs.: versus

The data on the use of corticosteroids were not interpretable regarding the question of how many patients received treatment escalation with OCS as control medication in the course of the study. The proportion of patients with OCS who received corticosteroids only in the framework of treatment of an exacerbation remains unclear for all data. For example, it was described for the placebo group that 103 patients (59%) initiated corticosteroid treatment

during the treatment phase of the MENSA study. Regarding OCS use, the company added in the comment that a total of 95 patients (54%) either initiated OCS in the study (65 patients without OCS at the start of the study) or used an increased dose of OCS (30 patients with OCS at the start of the study). At the same time, exacerbations occurred in 99 patients (56%) (who were treated with OCS). It remains unclear whether the patients had received treatment escalation with OCS and exacerbations occurred despite of this, or whether the corticosteroids were only used to treat exacerbations. The analysis of periods with OCS use suggested that the corticosteroids were primarily used for the treatment of exacerbations and not for regular treatment escalation. For instance, only 27 of 319 episodes (8%) in the placebo group were not linked to an exacerbation.

The mean duration of OCS treatment linked to exacerbations was 10 days in the placebo group and 11 days in the mepolizumab group [6]. This short duration of treatment also suggests that the OCS were not used as additional control medication (see also description of the OCS use as control medication in the SIRIUS study).

The relevance of the question whether the patients had received sufficient treatment escalation with OCS was also shown in the results of a subgroup analysis that investigated the effects of mepolizumab on exacerbations in patients with and without OCS at the start of the study. This subgroup analysis showed proof of an effect modification by OCS as control medication. In the subgroup of patients without OCS at the start of the study, there was a statistically significant advantage in exacerbations for mepolizumab in comparison with placebo. In the subgroup of patients with OCS at the start of the study (and continuation of this treatment according to the protocol), in contrast, there was no statistically significant difference between the treatment groups (Appendix A, Table 9).

The interpretation of the data on OCS use and on exacerbations was also made more difficult by the definition of an exacerbation. It cannot be excluded for the definition of an asthma exacerbation used in the study that the start of OCS treatment as additional control medication was documented as exacerbation without the presence of relevant deterioration of symptoms because decrease in morning peak flow and the initiation of OCS treatment were sufficient for the definition of an exacerbation.

Overall it cannot be inferred from the data that regular treatment escalation with OCS was conducted in the MENSA study.

As a consequence, it also remains unclear whether or to what extent the difference in the proportion of patients with exacerbations between mepolizumab and the comparator arm of the study was due to an effect of mepolizumab or to missing treatment escalation with inadequate asthma treatment in the placebo group. Overall, the study results cannot be interpreted regarding the question of an added benefit of mepolizumab in comparison with treatment escalation.

Further data on the characteristics of the study population and the study results of the MENSA study are presented in Appendix A.

2.2 Assessment of the SIRIUS study

The study design of the SIRIUS study and the interventions mandated according to the study protocol were already presented in the dossier assessment [1]. Table 3 shows the asthma medication that was used in addition to ICS/LABAs before the start of the SIRIUS study.

Table 3: Characteristics of the treatment (in addition to ICS/LABAs) before the start of the study – RCT, SIRIUS – mepolizumab vs. placebo, relevant subpopulation

Study Group	N[a]	Patients with tiotropium or theophylline treatment (before the run-in phase)		OCS use at the start of the study (prednisone/prednisolone)	
		Tiotropium n (%)	Theophylline n (%)	n (%)	Mean dose [mg/day] Mean (SD)
SIRIUS					
Mepolizumab 100 mg	67	13 (19)	9 (13)	67 (100)	12.4 (7.3)
Placebo	65	12 (18)	9 (14)	65 (100)	13.2 (6.3)

a: Number of patients in the relevant subpopulation (ITT-ACT).
ACT: appropriate comparator therapy; ITT: intention to treat; n: number of patients with event; n: number of patients with event; N: number of analysed patients; OCS: oral corticosteroids; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Patient population in the SIRIUS study

The SIRIUS study included patients with severe asthma who had received OCS maintenance treatment regularly in addition to high-dose ICS and another control medication in the 6 months before study inclusion (visit 1) and who had received a stable OCS dose (5–35 mg prednisone (equivalent)/day in the last 4 weeks before study inclusion. Treatment with the additional control medication must have been administered for at least 3 months or there must have been documentation of non-response with an additional control medication within 3 successive months during the 12 months prior to visit 1.

In a so-called optimization phase in the beginning of the study, the dose of the OCS maintenance treatment was titrated to the lowest dose that maintained a stable level of asthma symptoms. The OCS dose was lowered until deterioration of the asthma symptoms (defined as an increase of the ACQ-5 score by 0.5 points compared with visit 1) or exacerbation occurred. Following such deterioration of asthma control, the patients were to be administered the last OCS dosage they had received before the deterioration. The last OCS dose before deterioration of the ACQ-5 score or exacerbation was defined the lowest effective dose.

Then the patients were randomized. A stable lowest effective OCS dose of 5–35 mg prednisone (equivalent)/day for 2 weeks was an inclusion criterion for the randomized phase

of the SIRIUS study was. In addition, there had to be persistent airway obstruction (FEV1 < 80% predicted [pre-bronchodilator]).

At the time point of randomization, the study population showed the following characteristics:

- mean FEV1 about 60% predicted
- mean score of the of the ACQ-5 symptom component about 2.0 (an ACQ score of > 1.5 is considered to indicate inadequate symptom control [4])
- mean number of episodes of nocturnal awakening requiring rescue medication use per day 0.7 and 0.5 in both treatment groups
- mean number of inhalations of rescue medication per day 2.9 and 3.4 in both treatment groups
- mean number of asthma exacerbations in the year prior to screening 3.3 and 2.8 in both treatment groups (2 or more exacerbations in 66% of the patients, 3 or more in 49% of the patients, 4 or more in 34% of the patients)

Individual parameters such as the ACQ or the frequency of exacerbations showed marginally better values than in the patient population in the MENSA study. Despite OCS treatment, there was no complete asthma control in the patient population.

Asthma treatment in the SIRIUS study

After the so-called OCS optimization phase of the SIRIUS study, in which the OCS dose was lowered to a dose that just maintained a status of no deterioration of the ACQ score, the patients were randomized to additional treatment with mepolizumab or placebo. Further asthma medication was only allowed if this had been taken regularly for at least 3 months before randomization. The use of omalizumab was not allowed in the study. At the time point of the study, tiotropium had not been approved and was therefore not available.

After 4 weeks under this treatment, the OCS dose in both studies was further down-titrated following a specified schedule. The dose of the OCS maintenance treatment was reduced every 4 weeks as long as the parameters of asthma control did not worsen more than defined in the study protocol (no dose reduction e.g. if the ACQ changed by 0.5 points or more or exacerbation occurred [7]). Returning to the next higher dose of OCS was possible if asthma symptoms deteriorated or exacerbation occurred. Since asthma symptoms were used for controlling the OCS dose reduction, outcomes on symptoms (and exacerbation) cannot be used to evaluate treatment effects.

The study investigated the possibility of dose reduction in OCS maintenance treatment. One further asthma medication for symptom control was available in the mepolizumab group, but not in the placebo group. It therefore remains unclear whether a guideline-conforming escalation of asthma treatment, e.g. with tiotropium or omalizumab, in the placebo group would have allowed further reduction of the OCS maintenance treatment.

The SIRIUS study can therefore not be interpreted regarding the added benefit of mepolizumab in comparison with treatment escalation with the ACT.

Further data on the characteristics of the study population and the study results of the SIRIUS study are presented in Appendix A.

3 References

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Appendix A – Further information on the studies MENSA and SIRIUS

Table 4: Characteristics of the study populations – RCT, mepolizumab vs. placebo, relevant subpopulation

Study Group	N[a]	Age [years]	Sex [F/M]	FEV1 % predicted	ACQ-5 at baseline	Duration of asthma [years]	Blood eosinophil count at baseline		Region [EU/rest of the world]	Treatment discontin-uation	Study discontin-uation
							< 300 cells /mcL	≥ 300 cells/ mcL			
		Mean (SD)	%	Mean (SD)	Mean (SD)	Mean (SD)	n (%)	n (%)	%	n (%)	n (%)
MENSA											
Mepolizumab 100 mg	184	52 (13)	60/40	58.5 (16.9)	2.26 (1.3)	21 (13)	86 (47)	96 (53)	49/51	ND	9 (4.6)[b, c]
Placebo	176	51 (12)	56/44	61.1 (17.5)	2.31 (1.2)	20 (15)	75 (43)	100 (57)	47/53	ND	12 (6.3)[b, c]
SIRIUS											
Mepolizumab 100 mg	67	51 (13)	64/36	59.1 (16.9)	2.14 (1.3)	18 (12)	33 (49)	34 (51)	73/27	ND	3 (4.3)[c, d]
Placebo	65	50 (10)	45/55	58.4 (18.1)	1.99 (1.2)	20 (14)	37 (57)	28 (43)	74/26	ND	4 (6.1)[c, d]

a: Number of patients in the relevant subpopulation (ITT-ACT). Values that are based on other patient numbers are marked in the corresponding column if the deviation is relevant.
b: Data for the ITT population: mepolizumab N = 194, placebo N = 191.
c: Percentages: Institute's calculation.
d: Data for the ITT population: mepolizumab N = 69, placebo N = 66.
ACQ-5: Asthma Control Questionnaire; ACT: appropriate comparator therapy; F: female; FEV1: forced expiratory volume in 1 second; ITT: intention to treat; M: male; n: number of patients with event; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Table 5: Characteristics of the study populations (number of exacerbations in the year prior to screening) – RCT, mepolizumab vs. placebo, relevant subpopulation

Study Group	N[a]	Exacerbations in the year prior to screening n (%)						
		0	1	2	3	4	> 4	Mean (SD)
MENSA								
Mepolizumab 100 mg	184	0 (0)	0 (0)	70 (38)	45 (24)	28 (15)	41 (22)	3.8 (2.8)
Placebo	176	0 (0)	0 (0)	82 (47)	45 (26)	18 (10)	31 (18)	3.5 (2.7)
SIRIUS								
Mepolizumab 100 mg	67	12 (18)	11 (16)	9 (13)	9 (13)	13 (19)	13 (19)	3.3 (3.4)
Placebo	65	10 (15)	11 (17)	14 (22)	11 (17)	11 (17)	8 (12)	2.8 (2.7)

a: Number of patients in the relevant subpopulation (ITT-ACT).

ACT: appropriate comparator therapy; ITT: intention to treat; n: number of patients with event; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Table 6: Characteristics of the treatment (in addition to ICS[/LABAs]) before the start of the study – RCT, mepolizumab vs. placebo, relevant subpopulation

Study Group	N[a]	Patients with tiotropium or theophylline treatment (before the run-in phase)[b]		OCS use at baseline (prednisone/prednisolone)[b]	
		Tiotropium n (%)	Theophylline n (%)	n (%)	Mean dose [mg/day] Mean (SD)
MENSA					
Mepolizumab 100 mg	184	31 (17)	31 (17)	50 (27)	12.5 (11.1)
Placebo	176	24 (14)	28 (16)	42 (24)	15.2 (15.1)
SIRIUS					
Mepolizumab 100 mg	67	13 (19)	9 (13)	67 (100)	12.4 (7.3)
Placebo	65	12 (18)	9 (14)	65 (100)	13.2 (6.3)

a: Number of patients in the relevant subpopulation (ITT-ACT).

b: The basic therapy for asthma control existing already before the start of the study was continued during the study.

ACT: appropriate comparator therapy; ICS: inhaled corticosteroids; ITT: intention to treat; LABA: long-acting bronchodilator; n: number of patients with event; N: number of analysed patients; OCS: oral corticosteroids; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Table 7: Results (dichotomous outcomes) – RCT, MENSA – mepolizumab vs. placebo, relevant subpopulation, MENSA study (32 weeks)

Outcome category Outcome Study	Mepolizumab N	Mepolizumab Patients with event n (%)	Placebo N	Placebo Patients with event n (%)	Mepolizumab vs. placebo RR [95% CI]; p-value
Mortality					
All-cause mortality	184	0 (0)	176	1 (1)	0.32 [0.01; 7.78][a]; 0.367[b]
Morbidity					
Clinically significant exacerbations[c]	184	62 (34) Annual exacerbation rate: 0.84	176	99 (56) Annual exacerbation rate: 1.76	0.60 [0.47; 0.76][a]; < 0.001[b] Rate Ratio: 0.48 [0.35; 0.65]; < 0.001[d]
Health-related quality of life					
SGRQ responder[e]	184	129 (70)	176	93 (53)	1.33 [1.12; 1.57]; < 0.001
Side effects					
AEs (supplementary information)				No usable data[f]	
SAEs				No usable data[f]	
Discontinuation due to AEs	184	1 (1)	176	4 (2)	0.24 [0.03; 2.12]; 0.161

a: Institute's calculation, asymptotic.
b: Institute's calculation, unconditional exact test (CSZ method according to [8]).
c: Clinically significant exacerbation was defined as asthma deterioration (decrease in morning peak flow and/or increase in the use of rescue medication, and/or increase in the frequency of nocturnal awakening due to asthma symptoms requiring rescue medication use and/or increase in asthma symptoms), which required treatment with systemic corticosteroids (intravenously or orally for at least 3 days or a single intramuscular dose; in patients with OCS as control medication, at least twice the dosage had to be given for at least 3 days) and/or hospitalization and/or treatment at an emergency department [6].
d: GLM (negative-binomial) with the covariables: treatment group, OCS use at baseline (OCS vs. no OCS), region, exacerbations in the year prior to participation in the study (as ordinal variable), FEV1 % predicted at baseline, and the logarithm of the treatment time as offset variable.
e: Patients with a reduction in SGRQ score by ≥ 4 points (a reduction in score indicates improvement) at the end of the study in comparison with the start of the study were defined as responders.
f: Not usable because a deterioration of asthma symptoms was documented as AE.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; FEV1: forced expiratory volume in 1 second; n: number of patients with (at least one) event; N: number of analysed patients; OCS: oral corticosteroids; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SGRQ: St. George's Respiratory Questionnaire; vs.: versus

Table 8: Results (continuous outcomes) – RCT, MENSA – mepolizumab vs. placebo, relevant subpopulation

Outcome category Outcome Study	Mepolizumab			Placebo			Mepolizumab vs. placebo
	N[a]	Baseline values mean (SD)	Values at end of study mean[b] (SE)	N[a]	Baseline values mean (SD)	Values at end of study mean[b] (SE)	MD[b] [95% CI]; p-value
Morbidity							
Episodes of nocturnal awakening with use of rescue medication[c]	183	0.8 (1.07)	0.3 (0.04)	176	0.7 (1.10)	0.4 (0.05)	−0.1 [−0.2; 0.0]; 0.062
Asthma Symptom Score[d]	183	1.6 (1.24)	1.0 (0.07)	176	1.6 (1.25)	1.3 (0.08)	−0.3 [−0.5; 0.0]; 0.019 Hedges' g: −0.25 [−0.46; −0.04][e]

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: MMRM analysis with the covariables: baseline, region, OCS use at baseline (OCS vs. no OCS), exacerbations in the year prior to participation in the study (as ordinal variable), FEV1 % predicted at baseline, medication and visit, the interaction of visit and baseline, and the interaction of visit and treatment group for the study period week 29–32.
c: Mean number of nocturnal awakening due to asthma symptoms requiring rescue medication per study day – measured at baseline (during the last 7 days before administration of the first study medication) and for the study period week 29–32.
d: The Asthma Symptom Score uses a scale of 0–5 to measure the frequency and/or severity of asthma symptoms within the last 24 hours (recorded by the patient in an electronic diary). The higher the score, the greater the impairment.
e: Institute's calculation based on the mean difference and CI of the MMRM.
CI: confidence interval; FEV1: forced expiratory volume in 1 second; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; OCS: oral corticosteroids; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; vs.: versus

Table 9: Subgroups by OCS treatment at the start of the study – RCT, MENSA – mepolizumab vs. placebo, relevant subpopulation

Study Outcome Characteristic Subgroup	Mepolizumab N	Mepolizumab Annual exacerbation rate	Placebo N	Placebo Annual exacerbation rate	Mepolizumab vs. placebo Rate ratio [95% CI]	Mepolizumab vs. placebo p-value
MENSA						
Clinically significant exacerbations						
OCS at the start of the study						
No	134	0.56	133	1.69	0.33 [0.22; 0.50][a]	< 0.001
Yes	50	1.72	43	2.10	0.82 [0.51; 1.31][a]	0.404
					Interaction:	0.004[b]

a: GLM (negative-binomial) with the covariables: treatment group, OCS use at baseline (OCS vs. no OCS), exacerbations in the year prior to participation in the study (as ordinal variable), region, FEV1 % predicted at the start of the study, and the logarithm of the treatment time as offset variable.
b: Institute's calculation, p-value based on Q test.
CI: confidence interval; FEV1: forced expiratory volume in 1 second; N: number of randomized patients; OCS: oral corticosteroids; RCT: randomized controlled trial; vs.: versus

Table 10: Results (dichotomous outcomes) – RCT, SIRIUS – mepolizumab vs. placebo, relevant subpopulation

Outcome category Outcome	Mepolizumab		Placebo		Mepolizumab vs. placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Mortality					
All-cause mortality	67	0 (0)	65	1 (2)	0.32 [0.01; 7.80][a]; 0.366[b]
Morbidity					
Clinically significant exacerbations[c]	67	28 (42) Annual exacerbation rate: 1.41	65	45 (69) Annual exacerbation rate: 2.14	0.60 [0.44; 0.84][a]; 0.002[b] Rate Ratio: 0.66 [0.45; 0.96]; 0.030[d]
OCS responder					
OCS- reduction to ≤ 5 mg/day[e]	67	37 (55)	65	21 (32)	1.71 [1.13; 2.58]; 0.008
OCS- reduction to 0 mg/day[e]	67	10 (15)	65	5 (8)	1.94 [0.70; 5.37]; 0.191
Health-related quality of life					
SGRQ responder[f]	67	38 (57)	65	27 (42)	1.37 [0.96; 1.95]; 0.081
Side effects					
AEs (supplementary information)	No evaluable data[g]				
SAEs	No evaluable data[g]				
Discontinuation due to AEs	67	2 (3)	65	2 (3)	0.97 [0.14; 6.68]; 0.975

a: Institute's calculation, asymptotic.
b: Institute's calculation, unconditional exact test (CSZ method according to [8]).
c: Clinically significant exacerbation was defined as asthma deterioration (decrease in morning peak flow and/or increase in the use of rescue medication, and/or increase in the frequency of nocturnal awakening due to asthma symptoms requiring rescue medication use and/or increase in asthma symptoms), which required treatment with systemic corticosteroids (oral or parenteral, at least twice the dose of the OCS maintenance treatment for at least 3 days and no more than 7 days [extension of the exacerbation treatment possible if exacerbation persisted]) and/or hospitalization and/or treatment at an emergency department [7].
d: GLM (negative binomial) with the covariables: treatment group, OCS use at the start of the study (< 5 years, ≥ 5 years), region, OCS dose at the start of the study, and logarithm of the treatment time as offset variable.
e: In week 20–24.
f: Patients with a reduction in SGRQ score by ≥ 4 points (a reduction in score indicates improvement) at the end of the study in comparison with the start of the study were defined as responders.
g: Not usable because a deterioration of asthma symptoms was documented as AE.

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; ND: no data; OCS: oral corticosteroids; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SGRQ: St. George's Respiratory Questionnaire; vs.: versus

Table 11: Results (continuous outcomes) – RCT, SIRIUS – mepolizumab vs. placebo, relevant subpopulation

Outcome category Outcome	Mepolizumab			Placebo			Mepolizumab vs. placebo
	N[a]	Baseline values mean (SD)	Values at end of study mean[b] (SE)	N[a]	Baseline values mean (SD)	Values at end of study mean[b] (SE)	Mean difference[b] [95% CI]; p-value
Morbidity							
Episodes of nocturnal awakening with use of rescue medication[c]	67	0.7 (0.99)	0.3 (0.08)	65	0.5 (0.73)	0.3 (0.08)	0.0 [−0.2; 0.3]; 0.737
Asthma Symptom Score[d]	67	1.9 (1.40)	1.5 (0.12)	65	1.9 (1.35)	1.8 (0.12)	−0.3 [−0.6; 0.1]; 0.119

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: MMRM analysis with the covariables: start of the study, region, OCS use at the start of the study (< 5 years, ≥ 5 years), OCS dose at the start of the study, medication and visit, the interaction of visit and start of the study, and the interaction of visit and treatment group for the study period week 21–24.
c: Mean number of nocturnal awakening due to asthma symptoms requiring rescue medication per study day – measured at baseline (during the last 7 days before administration of the first study medication) and for the study period week 21–24.
d: The Asthma Symptom Score uses a scale of 0–5 to measure the frequency and/or severity of asthma symptoms within the last 24 hours (recorded by the patient in an electronic diary). The higher the score, the greater the impairment.

CI: confidence interval; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; OCS: oral corticosteroids; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; vs.: versus