Report Synopsis of Study MEMORY

EudraCT-Nr.: 2015-001868-19

Vorlage-Nr.: 2465/01

1) **Name of Sponsor/Company:** University Medical Center of the Johannes Gutenberg-University Mainz represented by the executive board of the University represented by the scientific member of the executive board Univ.-Prof. Dr. med. U. Förstermann delegated to the Director of III. Medical Clinic Univ.-Prof. Dr. med. Matthias Theobald Langenbeckstrasse 1 D-55131 Mainz, Germany	4) **Individual Study Table Referring to Part of the Dossier:** na[1] Volume: na Page: na	*(For National Authority Use only)*
2) **Name of Finished Product:** Nucala 100 mg – Lyophilized product for reconstitution Placebo		
3) **Name of Active Substance:** Mepolizumab (SB-240563)		

5) **Title of Study[2]:**

A randomized, double-blind, placebo-controlled, mono-center study to evaluate the effects of mepolizumab on airway physiology in patients with eosinophilic asthma: the MEMORY study

German title:

Eine randomisierte, doppel-blinde, Placebo-kontrollierte monozentrische Studie zur Bewertung der Effekte von Mepolizumab auf die Atemwegsphysiologie bei Patienten mit eosinophilem Asthma: MEMORY-Studie

Protocol version 1.2 dated 17.09.2015:

Amendment 1 resulting in protocol version V2.0 dated 16.12.2015

- Inclusion of Re-Screening (Trial schedule)
- Adaption of inclusion criterion 4 (Addition of wording “or documented in the previous 24 months”)
- Adaption of exclusion criterion 2 due to Re-Screening (addition of wording: “Patients who experience an infection or exacerbation between screening and randomization can be re-screened four weeks after recovery of the infection or exacerbation with keeping it´s original screening number. The data of the rescreening visit should be documented in the eCRF”)
- Adaption of exclusion criterion 3 (addition of wording “except eosinophil level” and “abnormalities based on known underlying diseases are not excluded”
- Adaption of paragraph Period of observation (chapter 7.3: addition of wording: “or in case of drop outs/premature study end of the patient up to 4-weeks after last intake of study medication”)

6) **Principal Investigator(s):** Priv.-Doz. Dr. Stephanie Korn

7) **Study centre(s):**

PD Dr. Stephanie Korn, III. Medical Clinic, Pulmonary Department, University Medical Center Mainz, Langenbeckstr. 1, D-55131 Mainz, Germany

[1] This information is only required in connection with filing of a dossier for marketing authorization.

[2] The latest protocol version must be clearly stated, this means including all amendments – the amendments are to be declared and identified.

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8) **Publication (reference):**

9) **Studied period (years)**[3]**:**

Date of first enrolment: 30.11.2015

Date of last completed: 22.05.2017

On 14.10.2016 the sponsor notified the temporary halt of the trial.

On 30.05.2017 the sponsor notified the early termination of the trial.

10) **Phase of development:** IIIb

11) **Objectives:**

The primary objective of the trial was to evaluate the effects of mepolizumab (ME) compared with placebo on parameters of airway physiology including bodyplethysmography (forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), residual volume, total lung capacity, airway resistance, and inspiratory capacity), and CO diffusion capacity.

Secondary objectives were:

- To evaluate the effects of mepolizumab compared with placebo on exercise tolerance in a subgroup of patients.
- To evaluate time to clinical response and time to change of baseline parameters of clinical response (sense of smell and taste, lung volumes, FEV1 reversibility, CO diffusion capacity, exhaled NO (eNO), blood eosinophils, eosinophilic cationic protein (ECP), blood periostin).
- To evaluate the effects of mepolizumab compared with placebo (PL) on clinical parameters of asthma control, including ACQ, AQLQ, SGRQ, BDI/TDI and fatigue.
- To evaluate baseline asthma parameters as potential predictors of clinical response (age at onset and duration of asthma, prior asthma medication, presence of nasal polyps, sense of smell and taste, allergic sensitization (skin prick test, total and specific IgE against aeroallergens and Staph. aureus enterotoxin), reversibility of airflow obstruction, exhaled NO (eNO), blood eosinophils, eosinophilic cationic protein (ECP), blood periostin, ANA, ANCA).

12) **Methodology:**

Prospective, mono-center, randomized, double-blind, placebo-controlled trial

Randomization in a 2:1 ratio (mepolizumab:placebo)

The duration of the double-blind treatment period will be 48 weeks with visits occurring every 2 weeks for the first two months, followed by visits every 4 weeks. Patients will receive 100 mg mepolizumab or identical placebo SC every 4 weeks, in total 13 double-blind doses.

Patients will remain on their current stable maintenance treatment throughout the run-in, double-blind treatment and follow-up periods, but are allowed to reduce their dose of systemic corticosteroids based on the investigators discretion.

All patients, including withdrawals, will be asked to return for a follow-up visit approximately 4 weeks after their last dose of double blind treatment.

13) **Number of patients (planned and analyzed):**

Planned: n=90 patients, in detail 60 patients in the mepolizumab group and 30 patients in the placebo group

This trial was prematurely terminated due to recruiting problems. Because of the approval of mepolizumab in the EU and possibly regular treatment of asthma patients with mepolizumab in Germany outside of clinical trials, patients would not participate in a placebo-controlled trial. Patients with a usual high burden of severe asthma declined to participate in the study when realizing that they might be randomized to the placebo arm while the active product was already in the market.

Screened: n=37, Reasons for screening failure: 2x withdrawal of informed consent; 5x FEV1>80% and 1x no exacerbation in the 12 months prior visit 1.

Enrolled: n=29, n=19 in the mepolizumab group and n= 10 in the placebo group;

Analyzed: n=29 (ITT population)

14) **Diagnosis and main criteria for inclusion:**

[3] Here also study suspensions and premature terminations of a trial/premature conclusion of a trial should be listed, including the reasons for that.

Severe eosinophilic asthma

Main inclusion criteria:

Patients meeting all of the following criteria will be considered for enrollment in the trial:

1. Patients must be able to give written informed consent prior to participation in the study, which will include the ability to comply with the requirements and restrictions listed in the consent form.
2. Male or female patients at least 18 years
3. Physician-diagnosis of asthma and evidence of asthma as documented by either reversibility of airflow obstruction (FEV1 ≥ 12% or 200 ml) demonstrated at visit 1 or visit 2 or documented in the previous 24 months.
4. ICS dose must be ≥ 1000 µg/day BDP or equivalent daily with or without maintenance oral corticosteroids.
5. Treatment in the past 12 months with an additional controller medication for at least 3 successive months, e.g., long-acting beta-2-agonist (LABA), leukotriene receptor antagonist (LTRA), or theophylline.
6. Persistent airflow obstruction as indicated by a pre-bronchodilator FEV1 < 80% predicted recorded at Visit 1 or < 90% for patients on oral corticosteroids.
7. An elevated peripheral blood eosinophil level of ≥ 300/µL that is related to asthma or ≥ 150/µL in patients treated with oral corticosteroids as maintenance therapy demonstrated at visit 1 or in the previous 12 months
8. Confirmed history of two or more exacerbations requiring treatment with systemic corticosteroids (intramuscular, intravenous, or oral), in the 12 months prior to visit 1, despite the use of high-dose inhaled corticosteroids. For patients receiving maintenance corticosteroids, the corticosteroid treatment for the exacerbations must have been a two-fold increase or greater in the dose.

Main exclusion criteria:

Patients presenting at least one of the following criteria will not be enrolled in the trial:

1. Current smokers or former smokers with a smoking history of ≥ 10 pack years (number of pack years = (number of cigarettes per day / 20) x number of years smoked). Patients who have not smoked for ≥ 6 months before visit 1 and have < 10 pack years can be included into the study.
2. Presence of a clinically important lung condition other than asthma. This includes current infection, bronchiectasis, pulmonary fibrosis, bronchopulmonary aspergillosis, or diagnoses of emphysema or chronic bronchitis (chronic obstructive pulmonary disease other than asthma) or a history of lung cancer.
3. Patients who have received omalizumab [Xolair] within 130 days of Visit 1.
4. Patients who have received any biological to treat inflammatory disease within 5 half-lives of visit 1

15) **Test product, dose and mode of administration, batch number:**

Mepolizumab (100 mg SC every 4 weeks for 52 weeks/13 injections)

Mepolizumab Batch No: 142387338 (4505-1).

Lyophilisat of mepolizumab was reconstituted with water for injection (Aqua Mini Plasco B.Brauns 10 ml: Batch No: 16034017 and 16104012).

Placebo: NaCl 0,9% Mini Plasco Fresenius 10 ml (Batch No: 20HMF025, 20IIF020, 20IMH003, 20KAH029, 20KBH002, 20IFF020 and 20HMF025)

16) **Duration of treatment:**

Every 4 weeks for 52 weeks, in total 13 injections

17) **Reference therapy, dose and mode of administration, batch number:**

Placebo (SC every 4 weeks for 52 weeks/13 injections)

18) **Criteria for evaluation[4]:**

The following description of endpoints is taken from the statistical analysis plan (changes to the protocol were made- see section "statistical methods"):

Efficacy:

The primary endpoint was the mean change from baseline in pre- bronchodilator forced expiratory volume FEV_1 after 1 second at visit 10 (week 24). FEV_1 was evaluated only if the bronchodilator had been washed out (6 hours for short-acting

[4] This section should also contain information about the chosen risk management approach, as outlined by ICH E3, section 9.6 (only if the study was approved after June 14th, 2017).

bronchodilators and 12 hours for long-acting bronchodilators).

Secondary Efficacy Endpoints:

Change from baseline in parameters of airway physiology/ Correlation with response

Change from baseline over the 48-week treatment period at visit 4, 7, 10, 13, 16 and at time of response* in absolute values of pre- and post-bronchodilator forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), residual volume (RV), expiratory reserve volume (ERV), intra-thoracic gas volume (IGTV), total lung capacity (TLC), airway resistance (Rtot), inspiratory capacity (IC), and CO diffusion capacity (DLCO)

Change from baseline in parameters of sub-maximal constant-load cycle ergometry

Change from baseline (visit 2) at visit 4, 7, 10, 13 and 16 in exercise endurance time and exertional dyspnea and fatigue (Borg CR10 Scale®)

Change from baseline in other parameters

Change from baseline in

- number of days off school/work within the last 12 months at week 52
- number of patients with chronic sinusitis and loss of smell and taste over the 48-week treatment period
- sense of smell and taste, FEV1 reversibility, exhaled NO (eNO) and blood eosinophils at time of clinical response*

Evaluation of time to clinical response/ premature discontinuation

Time to clinical response*/ time to premature discontinuation is defined as the time from initiation of treatment until response*/premature discontinuation. The time to clinical response*/ time to premature discontinuation will be censored for patients without the respective event at the date of the last available visit.

Analysis of exacerbations

- Clinically significant exacerbations requiring oral or systemic corticosteroids, hospitalization, and/or emergency department (ED) visits.
- Exacerbations requiring hospitalization (including admittance to an intensive care unit (ICU)) or ED visits
- Time to first clinically significant exacerbation requiring oral or systemic corticosteroids, hospitalization, and/or emergency department (ED) visits
- Time to first exacerbation requiring hospitalization or emergency department (ED) visit

*Response is defined as

- Improvement in FEV1 of ≥ 20 % from baseline (visit 2; only if the bronchodilator has been washed out) or
- Improvement in asthma control from baseline indicated by an increase in ACQ of ≥ 0.5 points or
- Reduction of oral corticosteroids of ≥ 50 % from baseline with no exacerbation in the following 8 weeks or
- Reduction of exacerbations of ≥ 50 % from baseline for evaluation of number of responders at the end of the trial. The average number of exacerbations per month at baseline will be evaluated for the prior 12 months and will be compared to the average number of exacerbations in the 12 months treatment phase. In case patients drop-out at an earlier stage, the average number of exacerbations per month will be calculated from treatment start till the last available visit, unless drop-out occurred due to an adverse event or unless patients stayed within the study for less than 6 months.

Quality of life

- Mean change from baseline in clinical parameters of asthma control, including ACQ-5, Mini-AQLQ, SQRG, BDI/TDI and fatigue at every study visit
- GETE rating by physician and patient at time of response and over the 52-week treatment period at pre-specified timepoints (1, 3, 6, 9 and 12 months)

Safety:

Routine safety assessments were incorporated throughout and/or at the end of treatment period including AE and SAE reporting, withdrawals, pregnancy, hematological and clinical chemistry parameters, ECG and vital signs (pulse rate and systolic and diastolic blood pressure).

In this trial, the period of observation for collection of adverse events extended from first intake of study medication up to the end of the 4-week follow-up period.

19) **Statistical methods:**

There was an interim analysis planned in Q2 2016 which was not performed (in agreement with ethics commission and PEI) due to the small sample size concerning the number of patients as well as the number of finished trial visits.

The final biometric analyses were pre-specified in a statistical analysis plan which was finalized and authorized before database lock.

Primary analysis population was the intention-to-treat (ITT) population. Within ITT population analyses patients were assigned to the treatment to which they were randomized.

In the primary analysis the mean change in pre-bronchodilator forced expiratory volume FEV_1 after 1 second at visit 10 (week 24) was analyzed by analysis of covariance (ANCOVA) with treatment as fixed effect and the baseline value as covariate. Additionally, the pre-bronchodilator FEV_1 was analyzed by a mixed model repeated measurement (MMRM) which compensates at least partly for missing values. Additional terms for visit and the interaction term of visit and treatment were included in the model.

For secondary analyses, continuous parameters (e.g. the lung function parameters) were evaluated by analyses of covariance (ANCOVAs) for each time point of measurement with treatment as fixed effect and the baseline value as covariate. Specific analyses were repeated within MMRM models analogous to the primary analysis. In analyses of laboratory parameters, vital signs and questionnaires exploratory p-values of t-test or chi-square test were calculated whenever applicable.

Pearson's correlation coefficients were calculated in order to analyze the relationship between the response and the change from baseline of each lung function parameter at visit 10.

Time to event data were compared between groups by log-rank test and displayed by Kaplan-Meier plots including the median time to event and the corresponding 95% confidence intervals if available. For the analysis of numbers of clinically significant exacerbations and numbers of exacerbations requiring hospitalization every subject was assigned to a score (x+a)/(y+b), where x was the number of events, y the time within treatment (in weeks), and a and b arbitrary constants to avoid bindings at zero. The constants a and b were set to a=1 and b=2. Both groups were compared by the Wilcoxon rank sum test.

Safety variables were analyzed by descriptive methods, i.e. by absolute and relative frequency counts.

Due to the exploratory nature of the study all analyses i.e. statistical tests were considered as exploratory.

Deviations from the study protocol:

The ITT definition from the protocol was modified. The original definition "all randomized patients with at least one dose of trial treatment and with at least one available post-baseline assessment of the primary variable" was modified to "all randomized patients" as the former definition from the protocol would have been too restrictive. The primary variable was the change to baseline in FEV_1 at week 24, so only patients with measurements in week 24 would have been included into the ITT population (no LOCF was performed). When re-defining the ITT to "all randomized patients with at least one dose of trial treatment and with at least one available post-baseline assessment of the FEV1" this new ITT is identical to "all randomized" patients.

Analyses in the per protocol population (PP) were skipped as the PP was identical to the ITT population.

Exploratory endpoints were not assessed due to the reduced number of patients after early termination of the study. Also no subgroup analyses were performed.

Instead of time to change of baseline parameters the change of baseline parameters at time of response were evaluated.

The number of patients with nasal polyps was not analyzed as planned as all of the patients either received oral corticosteroids (which are known to reduce the size of nasal polyps) in the course of the study or had their polyps removed.

Due to the small sample size there were no ECP and blood periostin measurements performed.

20) **Summary – Conclusions[5]:**

The study was prematurely terminated due to failure to recruit a sufficient number of subjects in the planned study period. It was planned to include 90 subjects in this trial.

On 14.10.2016 the sponsor notified the temporary halt of the trial because the recruitment has clearly decreased in the MEMORY study due to approval of mepolizumab (the investigational medicinal product of the MEMORY study), which was granted in February 2016, patients are unfortunately not able to recruit into the MEMORY study, since patients all want to receive the medication regularly.

18 Patients still received study medication at time of the halt. After the last patient completed the trial the sponsor notified the early termination of the trial on 30.05.2017.

Due to the small sample size the power of the applied statistical tests is rather low, limiting the conclusions on the primary and secondary outcomes considerably. Therefore the following statistical analyses are of purely exploratory nature.

[5] Results should also summarize important deviations from the predefined quality tolerance limits and remedial actions taken (only if the study was approved after June 14th, 2017).

Efficacy results:

Disposition

A total of 29 patients were enrolled into the study before the trial was stopped prematurely. All patients were contained in each study population, therefore analyses of the per protocol population were skipped. 15 patients completed the study according to the protocol (ME: 13 patients (68.4%); PL: 2 patients (20.0%)).

The visit compliance in the ME group was much better than in the PL group. 63.2% of the ME group, but only 20.0% of the PL group participated in every study visit. In total, almost half of the patients discontinued the study prematurely (14 patients; 48.3%), 6 in the ME group (31.6 %) and 8 (80.0%) in the PL group. Premature discontinuation in the ME group was mainly due to feeling no benefit or due to exacerbations (2 patients each (10.5%)). In the PL group, 5 patients (50.0%) discontinued due to the absence of a benefit. After week 8 there was a constant decline in patient numbers in both groups, but especially in the PL group. Only 20% of the patients in the PL group were present in week 48 (ME group: 13 patients (68.4%)). This limits the conclusions on the longer term outcomes considerably.

Time to premature discontinuation

Patients from the PL group discontinued the study significantly earlier than patients from the ME group (p=0.0162; see figure 1 below). Median time to discontinuation in the PL group was 224.5 (56.0/ 308.0) days. In the ME group the median time could not be determined as more than 50% completed the study.

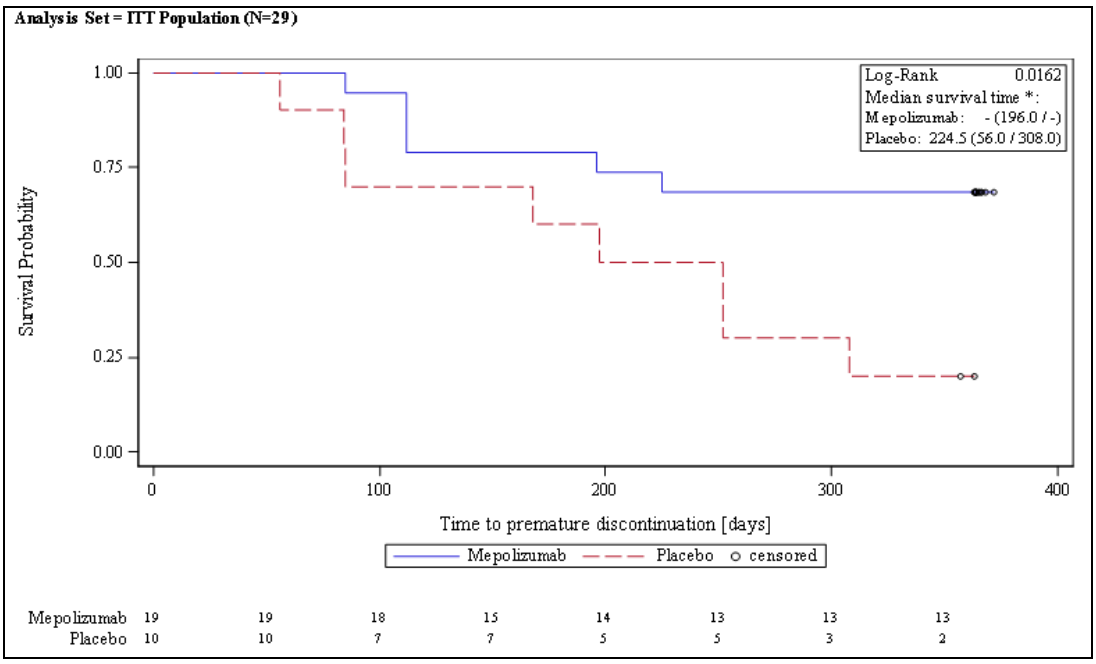


Figure 1: Time to premature discontinuation

Demographics and baseline characteristics

Mean age was 52.9 (±11.5) years in the ME group and 57.1 (±12.0) years in the PL group. 42.1% in the ME group and 50% in the PL group were female. All patients were Caucasians. No statistically significant differences were observed in any of the demographic parameters.

Mean duration of the asthma disease was higher in the ME group (23.7 ±18.1 years) than in the PL group (16.9 ±11.8 years) but on a non-significant level (p= 0.2351).

Furthermore, no significant differences between the groups were detected in type of smoker, pack years and time since quitting smoking.

Regarding the number of exacerbations of asthma no statistically striking differences were observed between the two treatment groups. The mean number of exacerbations during the last 12 months prior to visit 1 was 5.3 (±3.4) in the ME group and 5.2 (±2.2) in the PL group.

Concerning the days of illness due to asthma there was a clear difference between the ME and the PL group (table 1 below). Patients in the ME group had 16.6 (±20.3) days of illness whereas the PL group had 28.7 (±20.8) days and therefore an almost 2-fold higher amount of missing days at work. Nevertheless, differences are statistically not significant (p= 0.2466). It should be noted that about 40 % of the patients in both groups are pensioners or incapacitated for work.

Table 1: Days of Illness Due to Asthma

Analysis Set = ITT Population (N=29)

Variable	Mepolizumab (N=19)	Placebo (N=10)	Total (N=29)
Is the patient pensioner or incapacitated for work?			
Yes	8 (42.11%)	4 (40.00%)	12 (41.38%)
No	11 (57.89%)	6 (60.00%)	17 (58.62%)
P (Chi2-Test)		0.9129	
Number of sick days during the last 12 months prior visit 1			
N	11	6	17
Mean (SD)	16.64 (20.34)	28.67 (20.76)	20.88 (20.70)
Min	0.0	0.0	0.0
Q1	1.00	12.00	3.00
Median	8.00	30.50	12.00
Q3	37.00	49.00	40.00
Max	60.0	50.0	60.0
Wilcoxon-Mann-Whitney test (p-value)		0.2466	
Missing	8	4	12

Incremental cycle ergometry

Only 12 patients participated in incremental cycle ergometry, 9 in the ME group and 3 in the PL group. Eligible patients for ergometry test according to the protocol were patients with a FEV1>50% at screening (n=19). Some eligible patients declined the participation in the test or could not participate due to AEs or concomitant diseases. Significant differences between the two groups were observed in systolic blood pressure at all measured time points, meaning prior the ergometer test (ME: 130.1 (±12.0) mmHg; PL: 156.0 (±7.9) mmHg; p= 0.0067), at termination of the ergometer test (ME:143.7 (±21.6) mmHg; PL: 176.7 (±6.4) mmHg; p= 0.0023) and 5 minutes after the ergometer test (ME:125.3 (±11.7) mmHg; PL: 150.0 (±8.0) mmHg; p=0.0088). However, these differences were not observed when measuring blood pressure later during the constant load ergometry. There were no significant differences observed in other parameters of the ergometer test, neither in diastolic blood pressure or pulse measurements nor in the number of ECG findings.

Prior and concomitant diseases and therapies

All patients of the ME group and 9 patients (90.0%) of the PL group had any prior or concomitant diseases or concomitant therapies (301 diseases and therapies in total, ME: 180; PL: 121). Most frequently diseases and therapies in the following system organ classes were registered:

- 63 (20.9%) surgical and medical procedures (ME: 38 (21.1%); PL: 25 (20.7%)),
- 28 (9.3%) musculoskeletal and connective tissue disorders (ME: 14 (7.8%); PL 14 (11.6%)),
- 24 (8.0%) metabolism and nutrition disorders (ME: 19 (10.6%); PL: 5 (4.1%)),
- 23 (7.6%) infections and manifestations (ME: 17 (9.4%); PL: 6 (5.0%)), and
- 22 (7.3%) respiratory, thoracic and mediastinal disorders (ME: 14 (7.8%); PL: 8 (6.6%)).

The prior and concomitant drugs for obstructed airway diseases are presented in table 2. Anticholinergics (ME 12 patients (63.2%); PL: 8 patients (80%)), inhaled glucocorticoids (ME: 18 patients (94.7%); PL: 10 patients (100%)) and selective beta-2-adrenoreceptor agonists (ME: 18 patients (94.7%); PL: 10 patients (100%)) were the most frequently used drugs.

Table 2: Prior and Concomitant Drugs For Obstructive Airway Diseases Coded with ATC (WHO)

Analysis Set = ITT Population (N=29)

Variable	Mepolizumab (N=19)	Placebo (N=10)	Total (N=29)
Drugs For Obstructive Airway Diseases			
Adrenergics and other drugs for obstructive airway diseases	1 (5.26%)	0 (0.00%)	1 (3.45%)
Adrenergics in combination with anticholinergics	1 (5.26%)	0 (0.00%)	1 (3.45%)
Antiallergic agents, excl. corticosteroids	1 (5.26%)	1 (10.00%)	2 (6.90%)
Anticholinergics	12 (63.16%)	8 (80.00%)	20 (68.97%)
Glucocorticoids (inhaled)	18 (94.74%)	10 (100.00%)	28 (96.55%)
Leukotriene receptor antagonists	5 (26.32%)	5 (50.00%)	10 (34.48%)
Selective beta-2-adrenoreceptor agonists	18 (94.74%)	10 (100.00%)	28 (96.55%)
Xanthines	4 (21.05%)	3 (30.00%)	7 (24.14%)

Extent of exposure to study treatment/ compliance

Patients in the ME group remained within the study for a longer duration than patients from the PL group (see table 3 below). Compliance was high in both groups with 98.8 (±3.6) % in the ME group and 100.0 (±0.0) % in the PL group.

Table 3: Extent of Exposure to Study Treatment/ Compliance

Analysis Set = ITT Population (N=29)

Variable	Mepolizumab (N=19)	Placebo (N=10)	Total (N=29)
Duration of therapy [days]			
N	19	10	29
Mean (SD)	294.21 (111.42)	215.00 (109.14)	266.90 (115.23)
Min	85.0	84.0	84.0
Q1	196.00	85.00	168.00
Median	364.00	224.50	357.00
Q3	365.00	308.00	364.00
Max	372.0	363.0	372.0
P (t-Test)		0.0810	
Missing	0	0	0
Compliance [%]			
N	19	10	29
Mean (SD)	98.84 (3.61)	100.00 (0.00)	99.24 (2.95)
Min	86.0	100.0	86.0
Q1	100.00	100.00	100.00
Median	100.00	100.00	100.00
Q3	100.00	100.00	100.00
Max	100.0	100.0	100.0
P (t-Test)		0.1790	
Missing	0	0	0

SD: Standard Deviation, T-Test: Satterthwaite

Primary analysis

The primary endpoint of this study was the mean change from baseline in pre-bronchodilator forced expiratory volume FEV_1 after 1 second measured at visit 10 (week 24).

Table 4 below shows a non-significant result (p= 0.7688) for the treatment effect. The difference between the treatment groups is -0.08 (-0.68 / 0.51) liters, with a slightly higher reduction of the FEV_1 in the PL group. As well as in the following analyses the low number of participants especially in the placebo group should be kept in mind. In this case only 5 patients in the control group had measurements of the FEV_1 in week 24.

Table 4: Primary Variable - ANCOVA: Mean Change of FEV_1* from Baseline to Week 24

Analysis Set = ITT Population (N=29)

Effect	LS-Mean (Lower 95% CI / Upper 95% CI)	p-value
Mepolizumab	0.22 (-0.09 / 0.52)	
Placebo	0.30 (-0.20 / 0.80)	
Difference between treatments	-0.08 (-0.68 / 0.51)	
Treatment		0.7688
Baseline value of FEV1 (week 0)		0.0964

CI: Confidence limit
Number of analyzed patients: 18
*FEV_1: Pre-bronchodilator forced expiratory volume after 1 second.
*FEV_1 was evaluated only if the bronchodilator has been washed out.

The result of the primary analysis was confirmed by the MMRM analysis (table 5 below). No significant result was observed. The estimate for the difference in treatment effect was 0.0136 (-0.3967 / 0.4238; p=0.9463) liters.

Table 5: Primary Variable - MMRM-Model: Mean Change of FEV_1* from Baseline to Week 24

Analysis Set = ITT Population (N=29)

	Values
Effect / F-Test (Type 3)	
Treatment	0.7363
Baseline value	0.2088
Week	0.6289
Treatment * Week	0.2713
Baseline value * Week	0.4918
Differences of Least Square Means	
Effect	Treatment
Estimate	0.0136
Lower/Upper Confidence Limit	-0.3967 / 0.4238
p-value (t distribution)	0.9463

*FEV_1: Pre-bronchodilator forced expiratory volume after 1 second.
*FEV_1 was evaluated only if the bronchodilator has been washed out.

FEV_1 prior salbutamol from baseline at other time points

Tables 6-10 below show FEV_1 assessments at week 4, 12, 36, 48 and at time of response. In none of these assessments a statistically relevant difference was detected. Placebo measurements always provide the higher FEV_1 value except in week 4. This unexpected effect could be explained by the constitution of the remaining patients in the placebo group and again the low sample

size (see also the discussion of this aspect in the conclusions section).

Table 6: ANCOVA: Mean Change of FEV_1* prior Salbutamol [liters] from Baseline to Week 4

Analysis Set = ITT Population (N=29)

Effect	LS-Mean (Lower 95% CI / Upper 95% CI)	p-value
Mepolizumab	0.09 (-0.20 / 0.39)	
Placebo	0.09 (-0.28 / 0.46)	
Difference between treatments	0.00 (-0.47 / 0.48)	
Treatment		0.9842
Baseline Value (Week 0)		0.0440

CI: Confidence limit
Number of analyzed patients: 26
*FEV_1 was evaluated only if the bronchodilator has been washed out.

Table 7: ANCOVA: Mean Change of FEV_1* prior Salbutamol [liters] from Baseline to Week 12

Analysis Set = ITT Population (N=29)

Effect	LS-Mean (Lower 95% CI / Upper 95% CI)	p-value
Mepolizumab	0.12 (-0.19 / 0.44)	
Placebo	0.45 (-0.08 / 0.99)	
Difference between treatments	-0.33 (-0.97 / 0.30)	
Treatment		0.2878
Baseline Value (Week 0)		0.1495

CI: Confidence limit
Number of analyzed patients: 23
*FEV_1 was evaluated only if the bronchodilator has been washed out.

Table 8: ANCOVA: Mean Change of FEV1* prior Salbutamol [liters] from Baseline to Week 36

Analysis Set = ITT Population (N=29)

Effect	LS-Mean (Lower 95% CI / Upper 95% CI)	p-value
Mepolizumab	0.26 (-0.11 / 0.62)	
Placebo	0.73 (-0.05 / 1.51)	
Difference between treatments	-0.48 (-1.37 / 0.42)	
Treatment		0.2677
Baseline Value (Week 0)		0.4816

CI: Confidence limit
Number of analyzed patients: 15
*FEV_1 was evaluated only if the bronchodilator has been washed out.

Table 9: ANCOVA: Mean Change of FEV_1* prior Salbutamol [liters] from Baseline to Week 48

Analysis Set = ITT Population (N=29)

Effect	LS-Mean (Lower 95% CI / Upper 95% CI)	p-value

Mepolizumab	0.31 (-0.07 / 0.68)	
Placebo	0.86 (-0.13 / 1.84)	
Difference between treatments	-0.55 (-1.62 / 0.52)	
Treatment		0.2828
Baseline Value (Week 0)		0.3329

CI: Confidence limit
Number of analyzed patients: 14
*FEV_1 was evaluated only if the bronchodilator has been washed out.

Table 10: ANCOVA: Mean Change of FEV1* prior Salbutamol [liters] from Baseline to Time of Response
Analysis Set = ITT Population (N=29)

Effect	LS-Mean (Lower 95% CI / Upper 95% CI)	p-value
Mepolizumab	0.24 (-0.09 / 0.57)	
Placebo	0.23 (-0.20 / 0.66)	
Difference between treatments	0.01 (-0.54 / 0.56)	
Treatment		0.9746
Baseline Value (Week 0)		0.3109

CI: Confidence limit
Number of analyzed patients: 24
*FEV_1 was evaluated only if the bronchodilator has been washed out.

Regarding the absolute values of FEV_1 (table 11 below), mean values at baseline were 1.8 (±0.8) liters in the ME group and1.6 (±0.6) liters in the PL group. At week 24 the change to baseline was 0.2 (±0.5) liters in the ME group and 0.4 (±0.5) liters in the PL group.

Table 11: FEV1*: Actual Absolute Value

Analysis Set = ITT Population (N=29)

Variable/ Visit		Mepolizumab (N=19)	Placebo (N=10)	Total (N=29)
FEV_1 after 1 sec. (absolute actual value) [liters]				
Baseline (week 0)	N	18	10	28
	Mean (SD)	1.83 (0.79)	1.59 (0.57)	1.75 (0.72)
	Min	0.8	0.9	0.8
	Q1	1.21	1.13	1.17
	Median	1.81	1.56	1.70
	Q3	2.22	2.11	2.17
	Max	3.3	2.6	3.3
	P (t-Test)		0.3683	
	Missing	1	0	1
Week 24	N	14	5	19
	Mean (SD)	1.94 (0.79)	1.76 (0.59)	1.89 (0.73)
	Min	0.7	1.1	0.7
	Q1	1.21	1.22	1.21
	Median	1.95	1.88	1.88

	Q3	2.70	2.12	2.48
	Max	3.3	2.5	3.3
	P (t-Test)		0.6125	
	Missing	5	5	10
Changes week 24 compared to baseline (week 0)	N	13	5	18
	Mean (SD)	0.18 (0.54)	0.40 (0.52)	0.24 (0.53)
	Min	-0.5	-0.1	-0.5
	Q1	-0.24	0.09	-0.21
	Median	0.08	0.11	0.10
	Q3	0.32	0.96	0.51
	Max	1.3	1.0	1.3
	P (t-Test)		0.4435	
	Missing	6	5	11
Follow-up	N	16	7	23
	Mean (SD)	1.94 (0.83)	1.79 (0.36)	1.90 (0.71)
	Min	0.7	1.3	0.7
	Q1	1.35	1.41	1.41
	Median	1.77	1.82	1.82
	Q3	2.39	2.14	2.15
	Max	3.4	2.2	3.4
	P (t-Test)		0.5488	
	Missing	3	3	6
Changes follow-up compared to baseline (week 0)	N	15	7	22
	Mean (SD)	0.11 (0.54)	0.22 (0.55)	0.14 (0.53)
	Min	-0.6	-0.5	-0.6
	Q1	-0.34	-0.15	-0.15
	Median	0.03	0.04	0.04
	Q3	0.28	0.90	0.28
	Max	1.7	1.0	1.7
	P (t-Test)		0.6646	
	Missing	4	3	7

*FEV_1: Pre-bronchodilator forced expiratory volume after 1 second.
*FEV_1 was evaluated only if the bronchodilator has been washed out.
SD: Standard Deviation, T-Test: Satterthwaite

Secondary endpoints

Response/ Time to clinical response

Figure 2 shows the time to clinical response in both treatment groups. 27 patients had a response; one patient of each group had no response, respectively. The median time to response was 29.0 (15.0/ 43.0) days in the ME group and 25 (12.0/ 56.0) days in the PL group. No significant difference between the treatment groups was observed (p= 0.5263).

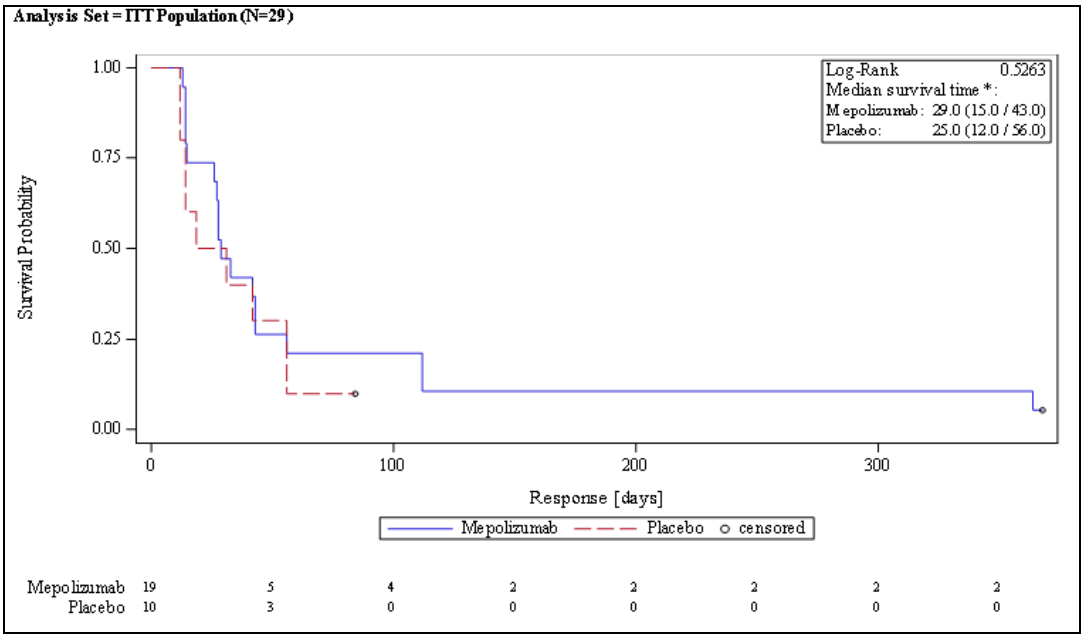


Figure 2: Time to clinical response

Change from baseline in FEV_1 after salbutamol, FVC, RV, TLC, RAW, IC, DLCO, ITGV and ERV

FEV_1 was also assessed by ANCOVA after the administration of the salbutamol dose at the same time points as the primary variable. Significant results were detected in assessments at week 12, 36 and 48, but in all cases the placebo group displayed a bigger improvement in FEV_1. The greatest difference between the treatments was detected in week 36 (-0.93 (-1.51 / -0.35) litres, p=0.0044).

The following pre-bronchodilator lung function parameters were assessed at the same time points as the primary endpoint: FVC, RV, TLC, RAW, IC, DLCO, ITGV and ERV. Some of these parameters showed a significant result in ANCOVA analysis, but always with the higher improvement in the placebo group:

- FVC in week 36 (ME: 0.11 (-0.21 / 0.43) liters; PL: 0.92 (0.24 / 1.60) liters; p= 0.0380),
- R_{tot} in week 36 (ME: 0.06 (-0.07 / 0.20) kPa*s/l; PL: -0.43 (-0.75 / -0.11) kPa*s/l; p= 0.0126),
- IC in week 24 (ME: 0.16 (-0.10 / 0.42) liters; PL: 0.73 (0.28 / 1.19) liters; p= 0.0349),
- IC in week 36 (ME: 0.27 (-0.01 / 0.56) liters; PL: 1.20 (0.59 / 1.81) liters; p=0.0112),
- IC in week 48 (ME: 0.23 (-0.08 / 0.55) liters; PL: 1.35 (0.50 / 2.20) liters; p= 0.0221),
- RV in week 36 (ME: -0.21 (-0.57 / 0.14) liters; PL: -1.16 (-1.91 / -0.41) liters; p=0.0297)
- DLCO in week 36 (ME: 0.07 (-0.47 / 0.60) mmol/min/kPa; PL: 1.45 (0.37 / 2.53) mmol/min/kPa; p=0.0283)

Most significant results were obtained in week 36. At that point only 3 patients of the PL group and 13 of the ME group were still participating in the study visits. Very often measurements in week 48 were close to the significance level of 5 % when week 36 was already significant.

In none of the MMRM analyses a significant effect was detected.

Correlation of response to changes in lung function parameters

In order to analyze which of the lung function parameters is suited in the best way to predict response, Pearson' s correlation coefficients were calculated for all lung function parameters. Table 12 below presents the coefficients at week 24.

Table 12: Pearson's Correlation: Response vs. Change from Baseline in Lung Function Parameters at Week 24

Analysis Set = ITT Population (N=29)

Visite	Statistics	Value
FEV_1 prior salbutamol	Number of Observations (n)	18
	Pearson's Correlation Coefficient	0.14550

	p Value	0.5646
FEV_1 after salbutamol	Number of Observations (n)	18
	Pearson's Correlation Coefficient	0.19271
	p Value	0.4436
FVC	Number of Observations (n)	20
	Pearson's Correlation Coefficient	0.34660
	p Value	0.1344
R tot	Number of Observations (n)	20
	Pearson's Correlation Coefficient	-0.16872
	p Value	0.4770
ERV	Number of Observations (n)	20
	Pearson's Correlation Coefficient	0.50006
	p Value	0.0247
IC	Number of Observations (n)	20
	Pearson's Correlation Coefficient	0.06560
	p Value	0.7835
ITGV	Number of Observations (n)	20
	Pearson's Correlation Coefficient	-0.02637
	p Value	0.9121
RV	Number of Observations (n)	20
	Pearson's Correlation Coefficient	-0.21355
	p Value	0.3660
TLC	Number of Observations (n)	20
	Pearson's Correlation Coefficient	-0.04121
	p Value	0.8630
DLCO (mmol/min/kPa)	Number of Observations (n)	19
	Pearson's Correlation Coefficient	-0.00151
	p Value	0.9951
DLCO (% of nominal value)	Number of Observations (n)	19
	Pearson's Correlation Coefficient	0.01104
	p Value	0.9642

*FEV1 was evaluated only if the bronchodilator has been washed out.

The strongest correlation was found for the ERV with r= 0.50 (p= 0.0247), followed by FVC with r=0.35 (p=0.1344), meaning that a change in these parameters predict the response in the best way compared to the other lung function parameters. Interestingly, the FEV_1 prior salbutamol only had a correlation of r=0.15 (p= 0.5646). The smallest correlation coefficient was observed for DLCO

with r= -0.0015 (p= 0.9951).

Reversibility of airflow obstruction

FEV_1 reversibility was assessed at each visit. At baseline, mean vales were almost identical (see table 13 below). After start of treatment, a strong, but nevertheless not significant reduction in reversibility in the ME group could be observed while in the PL group an increase in reversibility was detected. The smallest p-value was obtained in week 12 (p=0.0906); the highest reduction in reversibility in week 48 (ME: -10.5 (±29.1)%; PL: -8.9 (±30.2)%; p= 0.9548) though it should be noted that there were only 2 patients remaining in the PL group.

Table 13: Reversibility Testing

Analysis Set = ITT Population (N=29)

Variable/ Visit		Mepolizumab (N=19)	Placebo (N=10)	Total (N=29)
Reversibility				
Baseline (week 0)	N	19	10	29
	Mean (SD)	17.97 (22.77)	17.43 (18.03)	17.79 (20.93)
	Min	0.0	3.1	0.0
	Q1	5.00	6.98	5.95
	Median	12.75	9.94	10.10
	Q3	20.00	22.75	20.00
	Max	94.8	54.9	94.8
	P (t-Test)		0.9449	
	Missing	0	0	0
Changes week 12 compared to baseline (week 0)	N	18	7	25
	Mean (SD)	-8.53 (23.30)	3.23 (9.93)	-5.24 (20.93)
	Min	-86.2	-13.7	-86.2
	Q1	-14.96	-2.56	-12.80
	Median	-2.48	3.26	0.33
	Q3	2.98	8.94	5.88
	Max	19.3	18.4	19.3
	P (t-Test)		0.0906	
	Missing	1	3	4
Changes week 24 compared to baseline (week 0)	N	15	5	20
	Mean (SD)	-7.42 (29.79)	1.27 (16.93)	-5.25 (27.00)
	Min	-96.2	-15.5	-96.2
	Q1	-14.12	-8.15	-12.65
	Median	2.41	-1.46	0.47
	Q3	8.83	2.45	8.38
	Max	27.2	29.0	29.0
	P (t-Test)		0.4356	
	Missing	4	5	9
Changes week 36 compared to baseline (week 0)	N	13	3	16

	Mean (SD)	-9.42 (29.52)	3.77 (18.38)	-6.95 (27.75)
	Min	-96.0	-14.2	-96.0
	Q1	-10.31	-14.16	-12.16
	Median	0.26	2.89	1.58
	Q3	5.48	22.57	5.52
	Max	19.7	22.6	22.6
	P (t-Test)		0.3719	
	Missing	6	7	13
Changes week 48 compared to baseline (week 0)	N	13	2	15
	Mean (SD)	-10.47 (29.08)	-8.92 (30.21)	-10.26 (28.11)
	Min	-92.0	-30.3	-92.0
	Q1	-11.41	-30.28	-15.72
	Median	-3.29	-8.92	-3.29
	Q3	6.68	12.44	7.26
	Max	18.5	12.4	18.5
	P (t-Test)		0.9548	
	Missing	6	8	14
Changes at time of response compared to baseline (week 0)	N	18	9	27
	Mean (SD)	-9.71 (24.56)	-5.92 (15.34)	-8.45 (21.68)
	Min	-97.2	-34.1	-97.2
	Q1	-14.10	-12.70	-14.10
	Median	-4.90	-5.74	-5.74
	Q3	1.20	3.93	3.93
	Max	19.7	20.5	20.5
	P (t-Test)		0.6275	
	Missing	1	1	2

SD: Standard Deviation, T-Test: Satterthwaite

Exhalative nitrogen oxide (eNo)

ENo was measured at all visits. No significant difference was detected between the two groups, though a clear decline was observed in the ME group, but not always in the PL group.

At time of response, ANCOVA analyses showed a difference of -15.2 (-33.2 / 2.8) ppb between the treatments with a reduction in the ME group and an increase in the PL group (p= 0.0937; see table 14 below).

Table 14: ANCOVA: Mean Change of exhaled Nitrogen Oxide (eNO) from Baseline to Time of Response

Analysis Set = ITT Population (N=29)

Effect	LS-Mean (Lower 95% CI / Upper 95% CI)	p-value
Mepolizumab	-5.14 (-15.41 / 5.13)	
Placebo	10.05 (-4.54 / 24.65)	

Difference between treatments	-15.19 (-33.15 / 2.77)	
Treatment		0.0937
Baseline value (week 0)		0.0899

CI: Confidence limit
Number of analyzed patients: 27

Change from baseline in parameters of sub-maximal constant-load cycle ergometry

Exercise endurance time

Exercise endurance times improved in the ME group compared to baseline after start of treatment. The adjusted mean difference in mean change in exercise endurance time from baseline between the two groups in week 24 was 519.4 (-1821.01 / 2859.84 seconds; table 15 below). The treatment effect was statistically not significant (p= 0.2170). There was also an initial improvement in the PL group in week 4, but after week 4 endurance times declined.

Again, only few patients participated in the ergometer test especially in the control group, therefore results have to be regarded with caution. After week 24 no ANCOVA analysis was possible as no patient from the control group had participated in the ergometer test.

Table 15: ANCOVA: Mean Change in Exercise Endurance From Baseline to Week 24 [Seconds]
Analysis Set = ITT Population (N=29)

Effect	LS-Mean (Lower 95% CI / Upper 95% CI)	p-value
Mepolizumab	334.35 (-781.83 / 1450.53)	
Placebo	-185.06 (-2181.22 / 1811.10)	
Difference between treatments	519.41 (-1821.01 / 2859.84)	
Treatment		0.2170
Baseline Value (Week 0)		0.4617

CI: Confidence limit
Number of analyzed patients: 4

Exertional dyspnea (BORG CR10 Scale)

When assessing the BORG scale before the ergometer test, scores in the ME group declined compared to baseline in all weeks in which a measurement was possible. In the PL group no clear tendency could be observed. At termination of the ergometer test and 5 min after the ergometer test the same trend as before start of the test was detected. After week 24 no ANCOVA analysis was possible due to the lack of patients participating in the test. No statistically significant differences were observed.

Fatigue(BORG CR10 Scale)

Prior to the ergometer test adjusted mean values show an increase in both treatment groups, (ME 0.28 (-1.10 / 1.67); PL 1.40 (-1.05 / 3.85)). The assessment at week 12 displayed a statistically significant difference between the groups (table 16 below) with a decrease in the ME group and an increase in the PL group. This trend was also observed in weeks 12 and 24, though no significant p-values were obtained.

Table 16: ANCOVA: Mean Change From Baseline to Week 12 - Borg scale prior to the ergometer test: Fatigue
Analysis Set = ITT Population (N=29)

Effect	LS-Mean (Lower 95% CI / Upper 95% CI)	p-value
Mepolizumab	-0.83 (-1.29 / -0.36)	
Placebo	1.96 (0.66 / 3.26)	
Difference between treatments	-2.78 (-4.22 / -1.35)	
Treatment		0.0058
Baseline value (week 0)		0.0014

Cl: Confidence limit
Number of analyzed patients: 7

In the ME group there was a constant decline over the weeks on the BORG Fatigue scale at termination of the ergometer test. In the PL group, adjusted mean values first decreased in week 4, then increased and finally decreased again in week 24. No significant results were detected.

Measurements 5 min after the ergometer test showed a decline in the ME group and an increase in the PL group after 4 weeks. These trends grew stronger in week 12, whereas both groups showed a decrease in week 24 . No significant differences were observed.

Number of days off school/ work within the last 12 months from baseline to week 52

The number of sick days (not documented for pensioners, patients incapacitated for work or homemaker; ME group n=7, PL group n=4) declined in the ME group whereas at the same time a clear increase in the PL group took place (see table 17 below). However, a closer look on the data show, that though 6 patients in the placebo group had data on the number of sick days before visit1, only one patient from the PL group had data at week 52 and could be included into the analysis. Therefore, the analysis of the change to baseline in this group was not possible in a proper way (table 18 below). In the ME group the number of sick days reduced from 16.6 (±20.3) to 12.1 (±14.9).

Table 17: ANCOVA: Mean Change of Number of Sick Days Within the Last 12 Months From Baseline to Week 52 (*)

Analysis Set = ITT Population (N=29)

Effect	LS-Mean (Lower 95% Cl / Upper 95% Cl)	p-value
Mepolizumab	-0.67 (-7.73 / 6.40)	
Placebo	11.66 (-7.43 / 30.74)	
Difference between treatments	-12.32 (-32.80 / 8.16)	
Treatment		0.1826
Number of sick days during the last 12 months prior visit 1		0.0456

Cl: Confidence limit
Number of analyzed patients: 8
(*) The analysis does not include patients who were retired or incapacitated for work.

Table 18: Days of Illness Due to Asthma Within Last 12 Months (*) (ITT Population)

Analysis Set = ITT Population (N=29)

Variable	Mepolizumab (N=19)	Placebo (N=10)	Total (N=29)
Number of sick days during the last 12 months prior visit 1			
N	11	6	17
Mean (SD)	16.64 (20.34)	28.67 (20.76)	20.88 (20.70)
Min	0.0	0.0	0.0
Q1	1.00	12.00	3.00
Median	8.00	30.50	12.00
Q3	37.00	49.00	40.00
Max	60.0	50.0	60.0
P (t-Test)		0.2764	
Missing	8	4	12
Number of days off school/work within the last 12 months at week 52			

N	7	1	8
Mean (SD)	12.14 (14.88)	16.00 (-)	12.63 (13.85)
Min	0.0	16.0	0.0
Q1	0.00	16.00	0.50
Median	6.00	16.00	11.00
Q3	20.00	16.00	19.00
Max	40.0	16.0	40.0
P (t-Test)		--	
Missing	12	9	

(*) The analysis does not include patients who were retired or incapacitated for work.
SD: Standard Deviation, T-Test: Satterthwaite

Comorbidities- Chronic sinusitis, Smell disorder, Taste disorder, Nasal polyps

Both improvement as well as decline were observed more frequently in the ME group than in the PL group for chronic sinusitis, smell disorder and taste disorders, but no significant test results were obtained at any of the time points assessed. The analysis of nasal polyps was omitted as all patients with nasal polyp received oral corticosteroids (known to reduce the size of nasal polyps) in the course of the study or had their polyps removed.

Blood eosinophils

Analyses of the blood eosinophils showed a clear reduction in the ME group after treatment initiation. Table 19 shows the concentrations at week 2, 4, 12, 24, 36, 48 and at follow-up. After baseline eosinophil levels dropped from 400.9 (±386.0)/ µl to 153.1 (±121.8)/ µl in week 2 in the ME group whereas levels first increase in the PL group (428.7 (±345.5)/ µl vs. 486.3 (±474.7) / µl). After week 2, eosinophil levels reduced further and then remained constant in the ME group and slightly reduced until the end in the placebo group. At time of response the adjusted mean difference between the treatment groups was a significant with -186.14 (-345.31 / -26.98) eosinophils/ µl (p= 0.0238; see table 20 below)

Table 19: Hematology

Analysis Set = Safety Population (N=29)

Variable/ Visit		**Mepolizumab (N=19)**	**Placebo (N=10)**	**Total (N=29)**
Eosinophils [/µl]				
Baseline (week 0)	N	19	10	29
	Mean (SD)	400.9 (386.0)	428.7 (345.5)	410.5 (366.5)
	Min	24	50	24
	Q1	160.0	137.0	152.0
	Median	297.0	349.5	299.0
	Q3	496.0	613.0	515.0
	Max	1628	1050	1628
	P (t-Test)		0.8455	
	Missing	0	0	0
Week 2	N	18	10	28
	Mean (SD)	153.1 (121.8)	486.3 (474.7)	272.1 (333.0)
	Min	10	20	10
	Q1	55.0	277.0	72.0
	Median	150.0	339.0	169.0
	Q3	186.0	377.0	339.0
	Max	424	1498	1498
	P (t-Test)		0.0551	

	Missing	1	0	1
Week 4	N	18	10	28
	Mean (SD)	132.7 (118.7)	472.2 (263.3)	253.9 (243.8)
	Min	9	180	9
	Q1	68.0	272.0	77.0
	Median	112.5	382.0	186.5
	Q3	193.0	783.0	358.0
	Max	492	924	924
	P (t-Test)		0.0026	
	Missing	1	0	1
Week 12	N	18	7	25
	Mean (SD)	160.3 (148.2)	477.9 (252.3)	249.2 (229.4)
	Min	11	155	11
	Q1	71.0	244.0	98.0
	Median	107.5	518.0	140.0
	Q3	152.0	744.0	380.0
	Max	493	828	828
	P (t-Test)		0.0148	
	Missing	1	3	4
Week 24	N	15	5	20
	Mean (SD)	158.3 (142.7)	466.0 (211.9)	235.3 (207.7)
	Min	41	235	41
	Q1	57.0	345.0	79.5
	Median	91.0	460.0	120.0
	Q3	305.0	491.0	359.5
	Max	486	799	799
	P (t-Test)		0.0273	
	Missing	4	5	9
Week 36	N	13	3	16
	Mean (SD)	116.1 (127.6)	436.0 (499.5)	176.1 (250.8)
	Min	9	28	9
	Q1	47.0	28.0	41.0
	Median	79.0	287.0	87.0
	Q3	102.0	993.0	190.0
	Max	494	993	993
	P (t-Test)		0.3827	
	Missing	6	7	13
Week 48	N	13	2	15
	Mean (SD)	119.8 (119.9)	406.0 (103.2)	158.0 (152.4)
	Min	26	333	26

	Q1	49.0	333.0	49.0
	Median	74.0	406.0	74.0
	Q3	138.0	479.0	333.0
	Max	390	479	479
	P (t-Test)		0.1100	
	Missing	6	8	14
Follow-up	N	19	10	29
	Mean (SD)	118.6 (128.5)	384.5 (288.0)	210.3 (232.0)
	Min	11	17	11
	Q1	51.0	175.0	60.0
	Median	76.0	349.5	95.0
	Q3	136.0	651.0	297.0
	Max	560	836	836
	P (t-Test)		0.0181	
	Missing	0	0	0

SD: Standard Deviation, T-Test: Satterthwaite

Table 20: ANCOVA: Mean Change of Blood Eosinophils from Baseline to Time of Response

Analysis Set = ITT Population (N=29)

Effect	**LS-Mean (Lower 95% CI / Upper 95% CI)**	**p-value**
Mepolizumab	-242.23 (-334.13 / -150.34)	
Placebo	-56.09 (-186.05 / 73.87)	
Difference between treatments	-186.14 (-345.31 / -26.98)	
Treatment		0.0238
Baseline value (week 0)		<.0001

CI: Confidence limit
Number of analyzed patients: 27

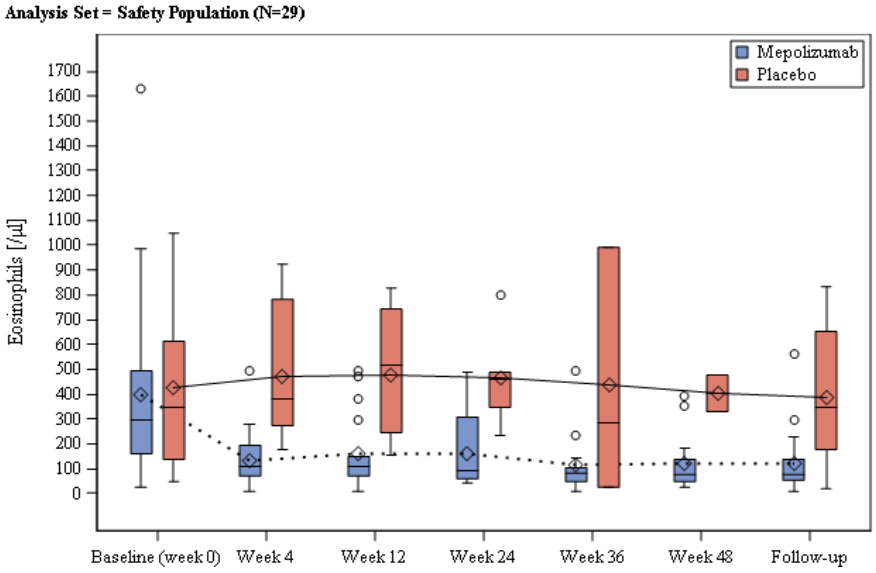


Figure 3: Blood Eosinophils

Analysis of Exacerbations

Clinically significant exacerbations

Clinically significant exacerbations were regarded as exacerbations requiring oral or systemic corticosteroids, hospitalization, and/ or emergency department visits. In the course of the study patients of the PL group suffered from slightly more exacerbations than the patients from the ME group (ME: 0.8 (±1.4); PL: 1.2 (±0.8); see table 21 below). In the original, unadjusted analysis, no significant difference was detected (p= 0.1097). In a second analysis a score was applied to the data. With this score bindings at zero were avoided and the time within study was included into the calculation. Results after application of the score showed a significant difference between the two treatment groups (p=0.0297) with less exacerbations in the ME group.

Regarding the time to first clinically significant exacerbation (figure 4 below), a significant difference between the treatments was observed as well. Median time was 364.0 (85.0/ 368.0) days in the ME group vs. 79.5 (22.0/ 173.0) in the PL group (p=0.0153).

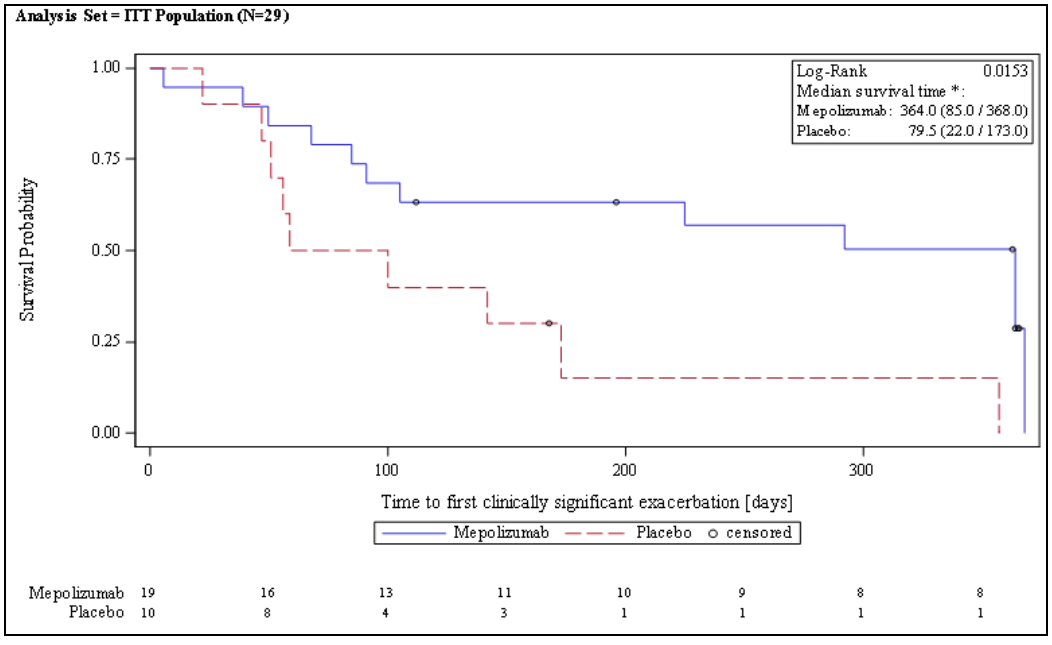


Figure 4: Time to first clinically significant exacerbation

Clinically significant exacerbations requiring hospitalization, ICU or ER

The same effect was observed for clinically significant exacerbations requiring hospitalization. On average 0.2 (±0.5) exacerbations were observed in the ME group and 0.3 (±0.7) in the PL group (p= 0.1097; see table 21 below). Using the score described above, a significant effect was observed (p=0.0298).

Regarding the corresponding time-to-event data, no statistically significant differences were observed (figure 5 below). As there were only few patients with any event, median times could not be calculated.

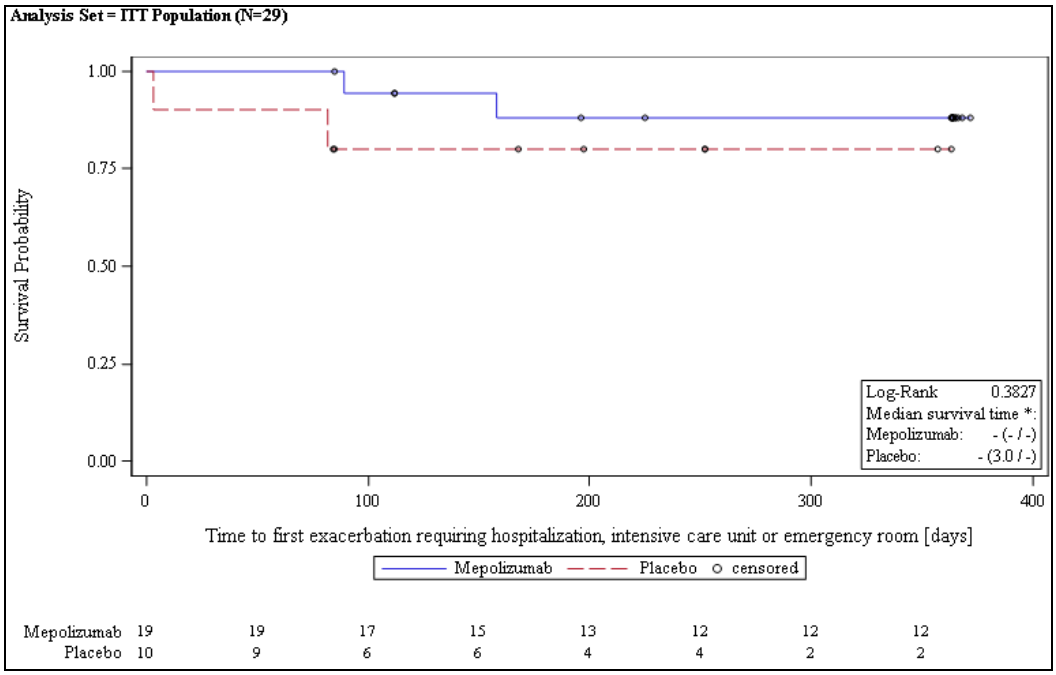


Figure 5: Time to first clinically significant exacerbation requiring hospitalization

Table 21: Analysis of exacerbations
Analysis Set = ITT Population (N=29)

Variable	Mepolizumab (N=19)	Placebo (N=10)	Total (N=29)
Number of clinically significant exacerbations			
N	19	10	29
Mean (SD)	0.84 (1.38)	1.20 (0.79)	0.97 (1.21)
Min	0.0	0.0	0.0
Q1	0.00	1.00	0.00
Median	0.00	1.00	1.00
Q3	1.00	2.00	2.00
Max	4.0	2.0	4.0
Wilcoxon-Mann-Whitney test (p-value)		0.1097	
Missing	0	0	0

Score(*) regarding clinically significant exacerbations			
N	19	10	29
Mean (SD)	0.05 (0.04)	0.08 (0.04)	0.06 (0.04)
Min	0.0	0.0	0.0
Q1	0.02	0.06	0.02
Median	0.03	0.07	0.06
Q3	0.07	0.14	0.08
Max	0.2	0.1	0.2
Wilcoxon-Mann-Whitney test (p-value)		0.0297	
Missing	0	0	0
Number of asthma exacerbations requiring hospitalization			
N	19	10	29
Mean (SD)	0.16 (0.50)	0.30 (0.67)	0.21 (0.56)
Min	0.0	0.0	0.0
Q1	0.00	0.00	0.00
Median	0.00	0.00	0.00
Q3	0.00	0.00	0.00
Max	2.0	2.0	2.0
Wilcoxon-Mann-Whitney test (p-value)		0.5152	
Missing	0	0	0
Score(*) regarding exacerbations requiring hospitalisation			
N	19	10	29
Mean (SD)	0.04 (0.04)	0.05 (0.04)	0.04 (0.04)
Min	0.0	0.0	0.0
Q1	0.02	0.03	0.02
Median	0.02	0.04	0.03
Q3	0.04	0.07	0.06
Max	0.2	0.1	0.2
Wilcoxon-Mann-Whitney test (p-value)		0.0298	
Missing	0	0	0

(*) Score: (x+a)/(y+b), where x is the number of events, y is the time within therapy (in weeks), a and b are arbitrary constants to avoid bindings at zero. The constants a and b are set to a=1 and b=2.

Quality of Life: Questionnaires

Asthma control questionnaire (ACQ-5)

The Questionnaire has 5 questions with 7 answer options (0-6; 0= no impairment, 6= maximum impairment). The overall ACQ-5-Score is the mean value of the 5 questions and hence lies between 0 (totally controlled) and 6 (severely uncontrolled). A score below 1.0 is considered to have an adequately controlled asthma. If one or more questions could not be answered, the overall score

could not be calculated.

Mean ACQ values at baseline were similar in both groups (ME: 2.9 (±1.5); PL: 2.8 (±1.1)). Scores reduced slightly over time, with a significant higher reduction in the PL group than in the ME group in week 48 (ME: -0.7 (±1.1); PL: -1.4 (±0.0); p= 0.0445). However, only 2 patients were left in the PL group, whereas 13 patients in the ME group had evaluable ACQ-5 data.

Asthma Quality of Life Questionnaire (Mini AQLQ)

The instrument has 15 questions in the domains *Symptoms* (5 items), *Activities* (4 items), *Emotions* (3 items) and Environment (3 items) with 7 answer options, respectively. For each of the 4 domains the average score was calculated.

Mean Mini-AQLQ score at baseline was 4.0 (±1.5) and 3.6 (±1.1) in the ME and the PL group, respectively. There was an increase in both groups until week 48, with a higher increase in the PL group (difference to baseline ME: 0.8 (±0.9); PL: 2.2 (±0.6). Analyses of the domains did not show any significant differences except for the *Emotions* domain in week 24 (change to baseline in the ME group: 0.7 (±1.5); PL group: 1.8 (±0.7); p=0.0343) and week 40 (ME: 1.0 (±1.2); PL: 2.4 (±0.6); p=0.0264).

Baseline Dyspnea Index (BDI)

The questionnaire has 3 domains (*Functional impairment*, *Magnitude of task*, *Magnitude of effort*) and 24 items. Categories are rated in five grades from 0 (very severe) to 4 (no impairment). There are three additional options in each category, which do not contribute to the scoring, allow circumstances, in which dyspnea cannot be rated. Total Score is the sum of all three domains and ranges from 0 to 12. If one category cannot be rated, the Total score cannot be calculated.

Most abundant at baseline was the degree of severity 3 in both groups (ME: 8 patients; 42.1%; PL: 4 patients (40.0%)). No significant differences were detected.

Transition Dyspnea Index (TDI)

Measures changes in the dyspnea severity from the baseline as established by the BDI. Consists of three domains (*Change in functional impairment*, *Change in Magnitude of Task*, *Change in Magnitude of Effort*) with 24 items. Rated by seven grades ranging from -3 (major deterioration) to +3 (major improvement). The Total Score is the sum of all 3 domains and ranges from -9 to +9. In case of missing items the score cannot be calculated.

The following significant differences between the groups were observed:

- Changed functional impairment week 8: More often improvement in the ME group was detected, and more often deterioration in the PL group (p= 0.0107).
- Change of resilience week 6 and 8: Improvement was observed more often in the ME group (p= 0.0094 (week 6) and p= 0.0208 (week 8)).
- Change of amount of effort week 6 and 12: Improvement was observed more often in the ME group (p= 0.0422 (week 6) and p= 0.0305 (week 12))
- TDI total score week 20: A higher increase in the TDI is detected in the ME group (4.7 (±3.2)) compared to a slight increase in the PL group (0.6 (±2.9)).

Fatigue Visual Scale

The Score is the number circled. Score ranges from 0-10, with the higher score indicating more fatigue.

At baseline the degree of fatigue was mainly rated as moderate by the patients in both groups. No significant differences were observed over time when analysing the categorical data. Evaluating the fatigue on a numerical scale, mean values at baseline were 4.4 (±2.4) and 4.0 (±1.4) in the ME and in the PL group, respectively. Significant differences were observed in week 12 (change to baseline ME: 0.0 (±1.8); PL: -2.1 (±1.6); p= 0.0124) with the placebo group having a more favourable outcome.

Global Evaluation of Treatment Effectiveness (GETE)

The GETE evaluates how much improvement in asthma control the patient has experienced compared to baseline on a five-point categorical scale, ranging from “Excellent” to “Worsening” (no assessment at screening and baseline). The score is evaluated by the physician as well as by the patient.

In both ratings no significant differences between the groups were detected. Often, a significant improvement of control or a discernible, but limited control was stated in both groups.

St. Georg Respiratory Questionnaire (SGRQ)

At the beginning of the study the SGRQ-C was used instead of the SGRQ, so the first patients in the study did not have results for the SGRQ at baseline and at early visits. In the course of the study the SGRQ-C was replaced by the SGRQ, so patients who were included into the study at a later point in time only had SGRQ results. In order to obtain baseline and early visit values for the first study participants, the SGRQ-C answers were be transformed to a SGRQ score as described in the SGRQ-C manual.

The SGRQ consists of 17 questions. Scores were calculated for the three components Symptoms, Activity, and Impacts as well as a total score. Each questionnaire response has a unique empirically derived 'weight' (for further information see SGRQ manual version 2.3, June 2009). The lowest possible weight is zero and the highest is 100.

Baseline values for the total score were 55.8 (±15.7) and 54.5 (±15.4) for the ME and the PL group, respectively. Regarding the change to baseline, no significant differences were detected with exception of the Activity domain, in which a significant difference

was obtained in week 48 (change to baseline ME: -8.7 (±10.9); PL: -33.5 (±6.3); p= 0.0383).

Summary concerning efficacy and quality of life:

Due to the premature stop of the study, only a fraction of the intended sample size was achieved. The premature stop was due to recruiting problems. Patients with a usual high burden of severe asthma declined to participate in a study when realising that they might be randomised to the placebo arm while the active product was already in the market.

A huge number of patients discontinued the study at early visits especially in the placebo group, in which also a significantly shorter time to premature discontinuation was observed. This led to small sample sizes reducing the power of the applied statistical tests. Moreover, it has to be assumed that mainly patients of the placebo group with tolerable asthma symptoms stayed within the study, possibly leading to a bias when it comes to comparison of the two treatment groups. Therefore the reliability of the results of this study is limited; analyses only have exploratory character.

It was not possible to a show a significant effect of mepolizumab on the pre-bronchodilator FEV_1. Analyses of lung function parameters and response indicate a better correlation of lung function parameters like ERV and FVC with the response than pre-bronchodilator FEV_1. No statistically striking differences were observed in the number of responders as well as in time to clinical response. Especially the ergometer test was of limited information because only a fraction of the 29 patients participated (restricted by FEV_1 value). Questionnaires on quality of life did not reveal significant differences between the treatment groups in the course of the study.

However, some of the secondary endpoints showed a favourable outcome for mepolizumab: The number of days off school/ work was reduced in the year of study treatment, though a statistical comparison to the placebo group was not possible due to the lack of data. After treatment initiation, blood eosinophils were significantly lower in the mepolizumab group than in the placebo group. Levels remained constantly low in the mepolizumab group in the course of the study. The number of exacerbations was significantly lower in the mepolizumab group when taking into consideration that the duration of study varied among the patients. The time to the first clinically significant exacerbation was significantly shorter in the placebo group than in the mepolizumab group.

In summary, results suggest that mepolizumab had a beneficial effect on different parameters in patients with eosinophilic asthma as demonstrated in earlier trials.

Safety results:

Definitions of adverse events (AE), serious adverse events (SAE), adverse reactions and suspected serious adverse reactions (SUSAR) are given in the trial protocol (see appendix). All AEs reported by the subject or detected by the investigator were documented on the appropriate pages of the case report form (CRF). The intensity of the adverse event and the causal relation to studied drug and/or procedures were assessed by the investigator under blinded conditions. The sponsor of the clinical trial ensured that all legal reporting requirements were met. All AEs were coded with the Medical Dictionary for Regulatory Activities (MedDRA).

Table 22: Overview of reported AEs:

	Mepolizumab (ME)		Placebo (PL)		Total	
	Number of patients (N=19)	Number of AEs (nAEs=164)	Number of patients (N=10)	Number of AEs (nAEs=72)	Number of patients (N=29)	Number of AEs (nAEs=236)
Any AEs	19 (100 %)	164 (100 %)	10 (100 %)	72 (100 %)	29 (100 %)	236 (100 %)
Any fatal AEs	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
Any serious AEs (SAEs)	5 (26.3 %)	9 (5.5 %)	2 (20.0 %)	2 (2.8 %)	7 (24.1 %)	11 (4.7 %)
Any related AEs	6 (31.6 %)	8 (4.9 %)	5 (50.0 %)	13 (18.1 %)	11 (37.9 %)	21 (8.9 %)
Any related SAEs	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
Any AEs leading to premature study discontinuation	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
Any AEs leading to actions regarding the studied drug	1 (5.3 %)	1 (0.6 %)	0 (0 %)	0 (0 %)	1 (3.5 %)	1 (0.4 %)

Adverse events:

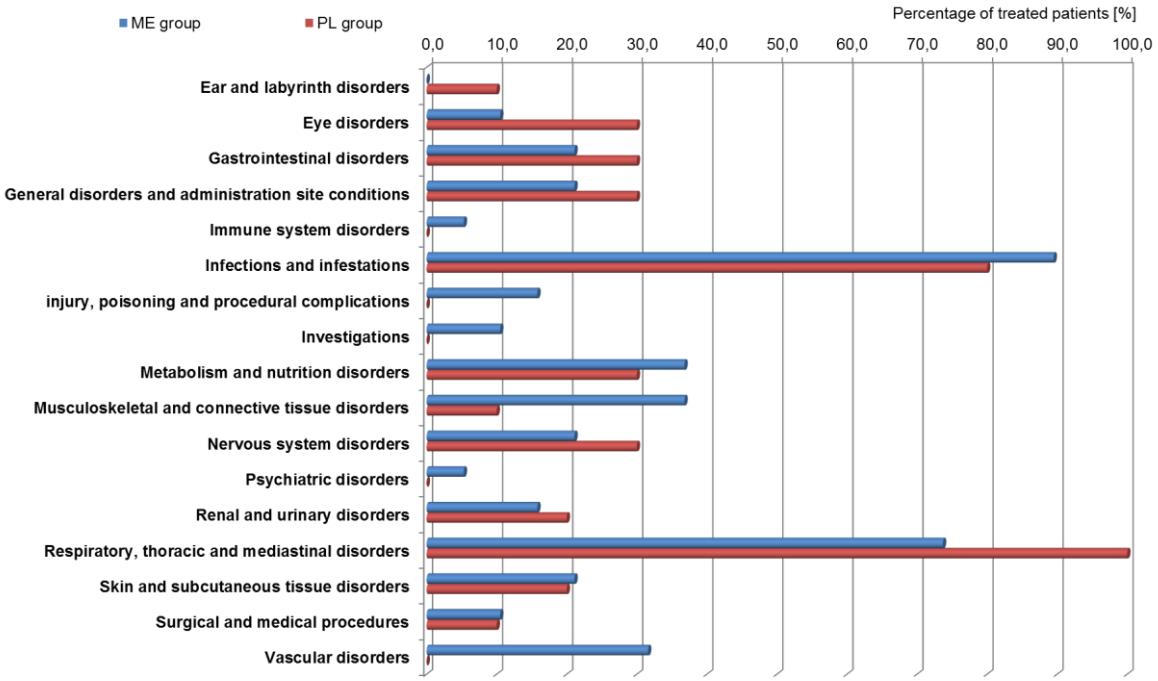
All patients reported at least one AE. A total of 236 AEs were reported, thereof, 164 (69.5 %) in the ME group, 72 (30.5 %) in the PL group.

The following AEs occurred in more than 3 (10.3 %) patients (MedDRA preferred terms):

- asthma (exacerbation) in 14 (73.7 %) patients of the ME vs. 10 (100 %) patients of the PL group
- nasopharyngitis in 12 (63.2 %) patients of the ME vs. 5 (50.0 %) patients of the PL group
- bronchitis in 8 (42.1 %) patients of the ME vs. 4 (40.0 %) patients of the PL group

- chronic sinusitis in 8 (42.1 %) patients of the ME vs. 0 (0 %) patient of the PL group
- hypokalaemia in 6 (31.6 %) patients of the ME vs. 1 (10.0 %) patient of the PL group
- fatigue in 2 (10.5 %) patients of the ME vs. 2 (20.0 %) patients of the PL group
- headache in 3 (15.8 %) patients of the ME vs. 3 (30.0 %) patients of the PL group
- hypertension in 4 (21.1 %) patients of the ME vs. 0 (0 %) patient of the PL group

The following figure gives an overview of the frequency of reported AEs in both treatment groups in the specific System Organ Classes (SOC; only SOCs with at least one AE displayed).



Most of the patients experienced presumable due to underlying disease one or more AEs in the SOCs “Infections and Infestations” and “Respiratory, thoracic and mediastinal disorders”. The slightly higher frequency of reported AEs in the SOC “respiratory, thoracic and mediastinal disorders” in the PL group documents a higher efficacy of add-on mepolizumab than placebo in controlling asthmatic symptoms. In contrast to 73.7% patients in the ME group, all patients in the PL group experienced at least one asthma exacerbation. Other reported AEs in the SOC “respiratory, thoracic and mediastinal disorders” are: sputum increased (1 patient in the ME group and 2 patients in the PL-group), dysphonia (1 patient in the PL-group), expistaxis (1 patient in the ME-group), nasal polyps (1 patient in the PL-group) and productive cough (1 patient experiencing 2 events in the PL-group). In the SOC “vascular disorders” adverse events were only reported in the ME group. In detail the following adverse events falling in SOC “vascular disorders” were reported: (worsening of) hypertension (4 patients), hypertensive crisis (2 patients), hot flush and haematoma on left upper arm (one patient each). In the SOC “musculoskeletal and connective tissue disorders” slightly more adverse events were reported in the ME group than in the PL group. Events occurring under ME and falling in the SOC “musculoskeletal and connective tissue disorders” are: arthralgia (3 patients), pain in extremity (3 patients), intervertebral disc protrusion, musculoskeletal pain and stiffness and periarthritis (1 patient each). In addition to this, only minor differences between both treatment groups concerning the frequency of AEs are noticeable.

Adverse events leading to discontinuation of the studied drug

Only one AE led to discontinuation of the studied drug. This AE (hypokalaemia) was graded as not serious and with a moderate severity. It occurred in a patient under ME treatment and was judged as not related to the intake of the studied drug.

Adverse events considered as related to the studied drug

In 21 (8.9 %) of all AEs a positive causal relation was assessed between the occurrence of the AE and the administration of the studied drug. 8 of these adverse reactions occurred in the ME group in 6 (31.6 %) patients and 13 in 5 (50 %) patients in the PL group. In detail the following adverse reactions occurred in the ME group: chronic sinusitis (2 events), nasopharyngitis, epistaxis, sputum increased, fatigue, haematuria and nephrolithiasis. No adverse reaction was graded as serious or severe.

Severity of adverse events

6 AEs in 4 (13.8%) patients, thereof 3 in the ME group and 1 in the PL group, were graded as severe. The vast majority of AEs were graded as mild (29 (17.7 %) in the ME group and 9 (12.5 %) in the PL group) or moderate (130 (79.3 %) in the ME group and

62 (86.1 %) in the PL group). In detail the following severe adverse events occurred in the ME group: asthma (exacerbation) (2 events in 1 patient), pneumonia, bronchitis bacterial and suicidal ideation in 1 patient each.

Seriousness of adverse events

In summary, 11 (4.7 %) AEs were judged as serious. These 11 SAE terms were reported in 9 SAE reports and occurred in 7 (24.1 %) patients. 9 serious adverse events occurred in 5 (26.3%) patients in the ME group and 2 events occurred in 2 (20%) patients in the PL group. 3 (15.8%) patients in the ME group and 2 (20%) patients in the PL group experienced asthma (exacerbations) resulting in a hospitalization. In the appendix a Line Listing of all occurred SAEs is attached. In the ME group the following SAEs were reported:

- patient 01/001: nasal polypectomy; outcome: recovering
- patient 01/007: pneumonia; outcome: recovered
- patient 01/014: asthma (exacerbation); outcome: recovered
- patient 01/014: asthma (exacerbation); outcome: recovered
- patient 01/017: bronchitis bacterial and suicidal ideation; outcome: recovering
- patient 01/017: asthma (exacerbation); outcome: recovered
- patient 01/025: asthma (exacerbation) and drug hypersensitivity; outcome: recovered

In the PL group the following SAEs were reported:

- 01/010 asthma (exacerbation); outcome: recovering
- 01/026 asthma (exacerbation); outcome: recovered

No SAE had a fatal outcome. No SAE led to study discontinuation or actions regarding the trial drug.

Laboratory parameters / Vital signs

For the corresponding box plots see figures 1.1- 2.10 in the appendix.

Hematology

No statistically significant differences in laboratory values were observed with the exception of the monocytes numbers at week 16 (ME: 6.7 (±2.3); PL: 4.9 (±1.4); p= 0.0358)) and blood eosinophils (see secondary endpoints).

Clinical Chemistry

Single parameter measurements displayed statistically significant differences between the two groups: AST (GOT) week 48 (ME: 25.6 (±5.7) U/l; PL: 20.5 (±0.7) U/l; p= 0.0087) and ALT (GPT) week 2 (ME: 19.9 (±6.3) U/l; PL: 27.1 (±8.3); p= 0.0308). For sodium group differences were significant in week 2, 20, 24 and 44. Nevertheless, values stayed relatively constant to the measurement in week 2 (ME: 141.3 (±2.1) mmol/l; PL: 139.8 (±1.5) mmol/l; p= 0.0425). Creatinine measurements from week 12 - week 24 were statistically significant, but mean values show that the significance is rather caused by the comparably high standard deviation. Mean values stay constant around 0.8 and 0.9 mg/dl.

Vital signs

There were no statistically striking differences in the vital signs measurements except for pulse week 6 (ME: 81.2 (±15.3); PL: 70.6 (±8.9); p= 0.0310) and week 40 (ME: 75.1 (±9.3); PL: 63.0 (±6.0); p=0.0417), as well as body temperature at the follow up visit (ME: 35.8 (0.57); PL: 35.4 (±0.37); p= 0.0389).

ECG Measurements

ECG measurements over the time were rated as “normal” or “clinically not relevant” with one exception: In the ME group in week 6 one patient (5.6%) had a clinically relevant ECG. In each visit a certain percentage of patients has an abnormal, clinically not relevant ECG in each group, with a significant difference in week 12 (ME: 3 (16.7%); PL: 4 (57.1 %); p= 0.0430).

Allergy types

There were no statistically significant findings between the two groups concerning different types of allergies.

Urinalysis

No statistically significant differences were observed between the two treatment groups.

ECP and blood periostin measurements

Due to the small sample size there were no ECP and blood periostin measurements performed.

Summary concerning safety:

In summary, it can be stated that all patients in the MEMORY trial experienced AEs but only very few AEs were graded as related or severe. Most of the reported AEs (e.g. asthma exacerbation, infections) and most of the reported SAEs occurred on the basis of the already preexisting asthma. Both, the slightly but markedly higher frequency of patients experiencing AEs in the SOC “respiratory, thoracic and mediastinal disorders” and the higher frequency of patients experiencing asthma exacerbation resulting

in a hospitalization in the PL group document the higher efficacy of add-on mepolizumab in controlling asthmatic symptoms. Most of the AEs were graded as mild or moderate and no drug related serious adverse event occurred. No patient died during trial participation. We conclude that the investigated mepolizumab therapy was well tolerated in patients with eosinophilic asthma.

Conclusion:

Due to the premature stop of the study the sample size was significantly lower than planned. At the same a high number of patients especially from the placebo group discontinued the study at early visits. It has to be assumed that in this group mainly patients with tolerable asthma symptoms stayed within the study, possibly leading to a bias when it comes to comparison of the two treatment groups. These circumstances limit the conclusions on the outcomes of this study considerably. The present analyses were therefore conducted only in an exploratory manner.

There was no statistical significant difference in the primary endpoint (mean change from baseline in pre-bronchodilator forced expiratory volume FEV_1 after 1 second measured at visit 10 (week 24)). In addition, there was no statistically striking differences in the number of responders as well as in time to clinical response.

However, some of the secondary endpoints gave hints on a favourable outcome for mepolizumab: The number of days off school/ work was reduced in the year of study treatment, though a statistical comparison to the placebo group was not possible due to the lack of data. After treatment initiation, blood eosinophils were significantly lower in the mepolizumab group than in the placebo group. Levels remained constantly low in the mepolizumab group in the course of the study. The number of exacerbations was significantly lower in the mepolizumab group when taking into consideration that the duration of study varied among the patients. The time to the first clinically significant exacerbation was significantly shorter in the placebo group than in the mepolizumab group.

In summary, the results confirm the beneficial effects and favourable safety profile of mepolizumab that had been described in clinical trials earlier.

I hereby confirm, that the data in the results report were collected properly and are correct.

21) **Date of the report:**

Print Name: PD Dr. Stephanie Korn

Signature: