

Benralizumab rapidly improves asthma control in Austrian real-life severe eosinophilic asthmatics

To the Editor,

In severe eosinophilic asthmatics (SEA), benralizumab, a monoclonal antibody directed against the alpha chain of the IL-5-receptor, has shown efficacy in phase 3 randomized controlled trials (RCTs) (SCIROCCO and CALIMA).^{1,2} However, severe asthmatics enrolled in RCTs poorly reflect real-life patients.³ Both SIROCCO and CALIMA required positive reversibility testing according to GINA guidelines ($+12\%$ and $+200$ mL FEV₁) as an inclusion criterion and excluded patients with a smoking history of more than 10 pack-years.^{1,2} So far, only one benralizumab real-life study has been published demonstrating clinically significant asthma control test (ACT) improvements in 13 severe asthmatics 4 weeks after treatment initiation.⁴

In this real-life, single-centre, single-arm, non-interventional, retrospective study, we aimed to investigate the effectiveness of benralizumab in Austrian SEA patients. We analysed data from patients treated at our severe asthma clinic (Hospital Hietzing, Vienna, Austria) between 1 May 2018 and 31 July 2019. Data collection was conducted at baseline, 24 hours after treatment initiation, 1 week after initiation and at every benralizumab injection for up to 48 weeks. All patients who received benralizumab according to local prescribing criteria were enrolled. Exclusion criteria were previous or current enrolment in a clinical trial with benralizumab. The study was approved by the local ethics committee.

Asthma control was documented using ACT and the asthma control questionnaire 6-item scale (ACQ6). Furthermore, pre-bronchodilator FEV₁, fraction of exhaled nitric oxide (FeNO, ppb), OCS dose (mg of prednisolone equivalent) and adverse events (AE) were documented. The primary outcome was to find out whether a clinically significant improvement of patient-reported asthma control can be observed after the first benralizumab dose. For that purpose, ACQ6 (minimal clinically important difference [MCID] 0.5)⁵ after 1 week and ACT (MCID 3)⁶ after 4 weeks were compared with baseline.

The key secondary (type I error protected) outcomes were ACQ6 at 4 weeks, ACQ6 and ACT at 32 weeks and FEV₁ (MCID 230 mL)⁷ at 24 hours, 1, 4 and 32 weeks. All the other measures until 48 weeks compared with baseline were considered exploratory secondary outcomes.

Two post hoc subgroup analyses compared asthma control and FEV₁ until week four in patients grouped based on their smoking history and reversibility testing according to GINA guidelines, if available.⁸ Safety of benralizumab was evaluated based on AEs.

Results are presented as mean $\pm$ standard deviation (SD) or median and interquartile ranges (IQR). Comparisons between baseline and subsequent visits were made using a paired 2-tailed

TABLE 1 Patients' characteristics at baseline

Patients with SEA who received at least one treatment with benralizumab (N = 56)	
Age (y), ($\pm$ SD)	60 ($\pm$ 5.3)
Age at diagnosis (y), (IQR)	47 (33-54)
Former smokers, all, N (%)	25 (45%)
Pack-years	24 ($\pm$ 16)
Former smokers, ≥ 10 pack-years, N (%)	22 (39%)
Female patients, N (%)	23 (41%)
Body mass index (kg/m ²), ($\pm$ SD)	27.5 ($\pm$ 4.5)
CRSwNP, N (%)	23 (41%)
Annual exacerbation rate, median (IQR)	3.5 (2-5)
Patients on maintenance OCS, N (%)	12 (21%)
OCS dose in patients on maintenance OCS, mg in prednisolone equivalent, median (IQR)	5.6 (5.0-22.5)
Any mAB treatment before, N (%)	11 (20%)
Omalizumab before, N (%)	4 (7%)
Reslizumab before, N (%)	8 (14%)
Mepolizumab before, N (%)	1 (2%)
FEV ₁ (L) pre BD, ($\pm$ SD)	2.07 ($\pm$ 0.82)
FEV ₁ (% predicted), ($\pm$ SD)	63 ($\pm$ 21)
ACT, ($\pm$ SD)	15.1 ($\pm$ 5.3)
Patients with an ACT ≤ 19 , N (%)	46 (82%)
ACQ6, ($\pm$ SD)	2.35 ($\pm$ 1.12)
PBEC (cells/ μ L), (IQR)	420 (220-638)
FeNO (ppb), (IQR)	48 (28-86)

Abbreviations: ACQ6, asthma control questionnaire 6-item scale; ACT, asthma control test; BD, bronchodilator; CRSwNP, chronic rhinosinusitis with nasal polyps; FeNO, fraction of exhaled nitric oxide; FEV₁, forced expiratory volume in one second; IQR, interquartile range; mAB, monoclonal antibody; OCS, oral corticosteroids; PBEC, peripheral blood eosinophil count; SD, standard deviation; SEA, severe eosinophilic asthma.

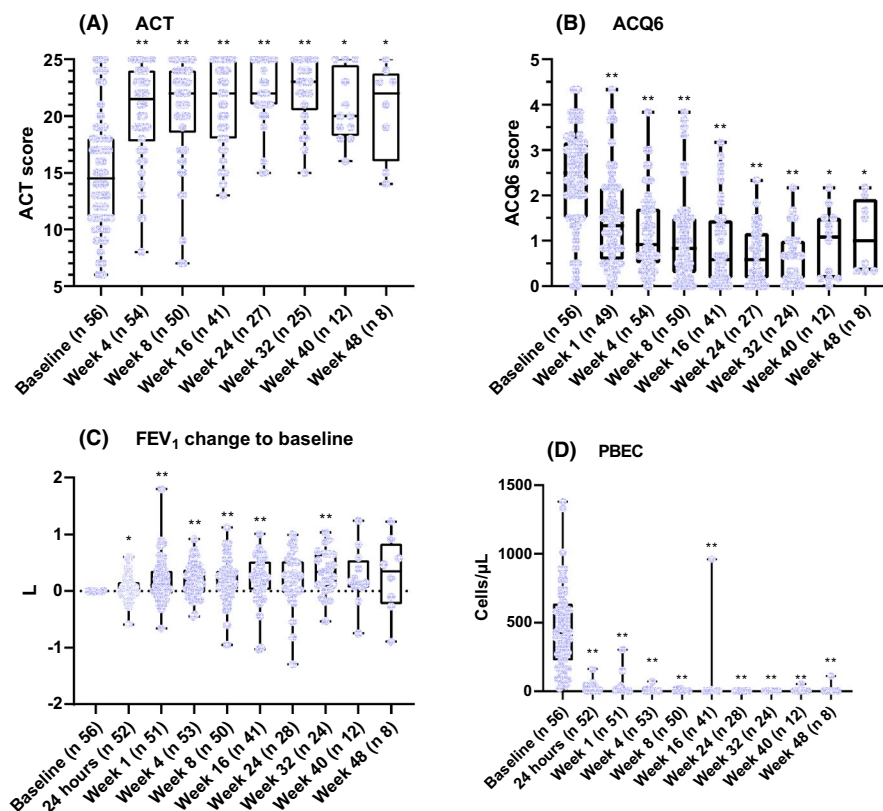


FIGURE 1 Box and whiskers plots of ACT (A), ACQ6 (B), changes in FEV₁ (L) from baseline (C) and PBEC (D) at baseline and subsequent visits. Boxes show median and interquartile range, whiskers maximum and minimum. ACT assesses asthma control during the past 4 wk. ACQ6 assesses asthma control during the past week. ACQ6, asthma control questionnaire 6-item scale; ACT, asthma control test; FEV₁, forced expiratory volume in one second; PBEC, peripheral blood eosinophilic count. * $P < .05$, ** $P < .001$

t test or Wilcoxon signed-rank test, depending on the normality of the data. To account for multiplicity, the required P -value to reach statistical significance was defined as $<.025$ in the co-primary and $<.007$ in the key secondary outcomes (Bonferroni correction). All statistical analyses were performed using SPSS Version 25.0 (IBM Corporation).

Fifty-six patients were included. Demographic and clinical characteristics of the study population are summarized in Table 1. In 25 patients (45%), data were available up to week 32. Only one patient discontinued benralizumab, all other patients still received benralizumab by the end of the study period. Five patients (9%) received benralizumab more frequently (Q4W-Q6W) than the Q8W dosing schedule (see supplement).

The median ACT score improved by 7.0 points from 14.5 (11.0–18.0) at baseline to 21.5 (18.0–24.0) at 4 weeks ($P < .001$, $n = 54$) and the median ACQ6 score improved by 1.17 points from 2.50 (1.50–3.17) at baseline to 1.33 (0.67–2.17) at week one ($P < .001$, $n = 49$). Improvement of patient-reported outcomes remained statistically and clinically significant (see Figure 1A,B).

The median FEV₁ increases from 1.91 L (1.25–2.50) at baseline to 2.04 L (1.31–2.50) at 24 hours ($P = .03$, $n = 52$) and from 2.22 L (1.52–2.59) at baseline to 2.42 L (2.12–3.01) at week 32 ($P < .001$, $n = 25$) were statistically, but not clinically significant (+130 and +200 mL). Both the median FEV₁ increases from 1.91 L (1.25–2.55) at baseline to 2.21 L (1.36–2.73) at week one ($P < .001$, $n = 53$) and the median FEV₁ increases from 2.01 L (1.25–2.51) at baseline to 2.24 L (1.41–2.68) at week four ($P = .001$, $n = 53$) were clinically significant (+300 and +230 mL) (see Figure 1C).

There was an immediate depletion of the PBEC (see Figure 1D). Although FeNO was statistically significantly reduced compared with baseline at weeks 8, 16, 32 and 40, no apparent trend in FeNO measurement was observed (see Figure S2). Twenty-two patients (39%) would not have been eligible for RCTs based on their smoking history (former smokers ≥ 10 pack-years).^{1,2} The treatment response in these patients was equivalent to patients eligible for RCT inclusion based on their smoking history (see Table S2). Reversibility testing was available in 30 patients (57%). Only in half of those patients ($n = 15$) reversibility was classified as positive.⁸ The treatment response was equivalent for patients with positive and negative reversibility testing (see Table S3). No severe AEs occurred. No AE resulted in treatment discontinuation.

To our knowledge, this is the largest and longest benralizumab real-life study to date. This study shows that the efficacy observed in large RCTs translates to real-life effectiveness in SEA patients. ACT and ACQ6 showed an immediate improvement, as demonstrated in the co-primary endpoints. Lung function also improved, although not as rapidly and consistently as asthma control. Two patient groups which were excluded from both SIROCCO and CALIMA, as well as from most other severe asthma RCTs, are former smokers with a smoking history of more than 10 pack-years, as well as patients with negative reversibility testing according to GINA criteria.^{1,2,8} Both groups were prevalent in our study and improved equally well compared with patients who would have been eligible for inclusion in these studies based on smoking status and reversibility. This is the first study to demonstrate effectiveness of benralizumab in these patients. A limitation of this study is that due to the study design,

only few patients received benralizumab for more than 32 weeks ($n = 12$ at 40 weeks and $n = 8$ at 48 weeks). Furthermore, only few patients received OCS at baseline ($n = 12$). Therefore, a statistical assessment of the OCS sparing effect was not deemed appropriate.

Based on these results, we can demonstrate that benralizumab is effective, safe and well tolerated in Austrian SEA patients in a real-life setting. Improvements in asthma control and lung function are immediate in most patients.

ACKNOWLEDGEMENTS

We thank Dr Andrea Schrott for statistical support.

CONFLICT OF INTERESTS

Dr Renner, Dr Marth, Mrs Patocka and Prof. Idzko have nothing to disclose. Prof. Pohl reports personal fees from Astra Zeneca, Boehringer Ingelheim, Chiesi, GSK, GILEAD, MedImmune, Menarini, Novartis, Sciotech and Teva, outside the submitted work.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Online supporting information to: Benralizumab rapidly improves asthma control in Austrian real-life severe eosinophilic asthmatics.

Online supporting information – methods:

After 48 weeks most of our patients received the treatment through general pulmonology practices or general practitioners and only visited our clinic for three-monthly reevaluation visits. After 48 weeks patients were still monitored for severe adverse events and exacerbations, but clinical outcomes were not anymore collected for study purposes. Asthma control was documented using ACT (measuring asthma control in the previous month) and ACQ6 (measuring asthma control in the previous week) at baseline, one week (only ACQ6), four weeks, eight weeks and 16 weeks after treatment initiation and every eight weeks after that until week 48. FEV₁, FeNO, PBEC and peripheral basophil count (both in cells/ μ L) were documented at every visit. OCS dose (mg of prednisolone equivalent) was documented at every visit except 24 hours after treatment initiation. Pre-bronchodilator FEV₁ was measured using the Jaeger Masterscreen PFT (Carl Reiner, Vienna, Austria). Fraction of exhaled nitric oxide (FeNO, ppb) was measured with a NIOX VERO® (Aerocrine, Solna, Sweden). AEs and exacerbations were documented at every visit. Severe AEs were defined as serious hypersensitivity including anaphylaxis, malignancies, serious infectious, and AEs leading to benralizumab discontinuation.

Parametric and non-parametric tests were chosen based on the normality of the data. Data were tested for normality using the Shapiro-Wilk test. Differences in mean/median from baseline were calculated using listwise exclusion to ensure comparability. Between-group comparisons in the subgroup analysis (comparing the treatment effect between patients eligible for RCT inclusion based on smoking status and reversibility testing, and patients not eligible) were performed using two-factor mixed model ANOVA. Pearson correlation analyses were used to measure linear dependence and results were expressed as Pearson coefficient r . Furthermore, for ACT, ACQ6 and FEV₁, generalized linear mixed models (GLMMs) were performed to assess changes over time and support the co-primary and key-secondary outcomes. For all exploratory secondary endpoints P values of $<.05$ were considered significant. Safety data were described descriptively. All analyses were performed on the full analysis set.

Online supporting information – results:

Median follow-up (including follow-up times after week 48) was 235 days (IQR 116-369). One patient who had previously received reslizumab, and who had been switched to benralizumab because of the route of application, was switched back to reslizumab after week 24 on his own wish. ACT had been stable from baseline (24 points) until week 16 (25 points) and deteriorated at week 24 (21 points). Similar developments were also seen for ACQ6 and FEV1 and FeNO. PBEC did not change after an initial decrease to 0 cells/ μ L 24 hours after baseline. No other patients discontinued benralizumab treatment in the study period. Five patients (9%) received benralizumab more frequently (4-6 weekly) than the Q8W dosing schedule because the lengthening of the dosing interval resulted in a subjective worsening of asthma control. For the purpose of statistical analysis some of the visits (weeks 16, 24, 32, 40 and 48 after baseline) were adjusted to the closest visit ($\pm$ two weeks at week 32 after baseline) in four of these patients to fit the visits of the study design. Three out of those five patients received maintenance OCS at baseline.

Data on specific IgE testing was available in 54 patients (96%). Sensitization to allergens was found in 30 of these patients (55%). Unfortunately, no data on clinically relevant allergies was available for this analysis. Only four patients had previously met the prescription criteria for omalizumab treatment. Twenty-five percent of patients had a sensitization to *Aspergillus fumigatus*, 16% to cat dander, 14% to grass pollen and house dust mite, 10% to birch pollen and 5% to dog dander and *Artemisia* pollen.

The median ACT score improved by 6 points from 17 (11-19) at baseline to 23 (21-25) at week 32 ($p < .001$, N 25). The median ACQ6 score improved by 1.58 points from 2.50 (1.50-3.17) at baseline to .92 (.50-1.67) at week 4 ($p < .001$, N 54) and by 1.57 points from 2.24 (1.25-2.83) to .67 (.17-1.00) at week 32 ($p < .001$, N 24). (see Figure 1AB). After one week ACQ6 was clinically significantly improved in 71% of all patients. At week four, ACT was clinically significantly improved in 65% of all patients. Thus, around two-thirds of patients showed a clinically significant improvement in asthma control immediately after treatment initiation. The improvements to baseline for both ACT and ACQ6 score were also statistically and clinically significant in all other, exploratory, outcomes (weeks 8, 16, 24, 40 and 48). From week 32 to week 48 a small and neither clinically nor statistically significant deterioration in patient-reported asthma control outcomes can be seen (see Figure 1).

The FEV₁ improvements to baseline were statistically but not clinically significant for weeks 8, 16, and 24 (exploratory secondary outcome). The FEV₁ improvements to baseline at weeks 40 and 48 were clinically significant (+243 and +270 mL) but not statistically significant, possibly due to the low sample size at these visits (N 12 and 8) (exploratory secondary outcome) (see Figure 1). FEV₁ improvements in % predicted compared to baseline were statistically significant for all timepoints except week 48. These improvements were highly statistically significant ($p<.001$) in most timepoints (see Figure e3A).

Out of the 12 patients who received OCS at baseline, three were able to stop OCS within the study period. One patient was able to stop OCS at week 4 (baseline dose 1.6 mg), one patient at week 32 (baseline dose 5 mg) and one patient at week 40 (baseline dose 25 mg). Due to the small number of patients who received OCS at baseline, OCS dose did not undergo formal statistical analysis, and no assessment of a steroid sparing effect in our patients can be made. Four patients without maintenance OCS at baseline received a single short-term (max. one week) OCS treatment for an exacerbation between baseline and week 48.

FeNO did not correlate with asthma control at baseline ($r=-.05$, $p=.78$ for ACT and $r=.13$, $p=.35$ for ACQ6) or week 4 ($r=.16$, $p=.27$ for ACT and $r=-.26$, $p=.07$ for ACQ6). At week 32 ACQ6 showed a weak but statistically significant positive correlation with FeNO ($r=.45$, $p=.03$) but not ACT ($r=-.33$, $p=.11$).

In the GLMMs immediate and long-lasting improvements similar to the co-primary and key-secondary endpoints (comparing baseline to individual time-points) were observed. The general time effect for ACT was highly significant ($F=14.852$; $p<.001$). There was a highly significant effect of each timepoint when using baseline as a reference category for ACT ($p<.001$ for all timepoints). Similarly, the general time effect for ACQ6 was highly significant ($F=14.352$; $p<.001$). There was a highly significant effect of each timepoint when using baseline as a reference category for ACQ6 ($p<.001$ for all timepoints). The general time effect for FEV₁ (L) was significant ($F=2.490$; $p=.013$). Except for 24 hours post baseline ($p=.052$), there was a significant effect of each timepoint when using baseline as a reference category for FEV₁ (L) (week 1, $p=.002$; week 4, $p=.002$; week 8, $p=.007$; week 16, $p=.006$; week 24, $p=.007$; week 32, $p<.001$; week 40, $p=.003$; week 48, $p=.033$).

One patient had a PBEC of 960 cells/ μ L at week 16. This did not coincide with a worsening of asthma control or lung function. Also, the peripheral blood basophil count decreased immediately (24 hours) after treatment initiation. This decrease, while not a complete depletion as seen in the PBEC, was highly statistically significant ($p < .001$) for most timepoints (see Figure e3B). Forty-three upper-respiratory tract infections were documented. Three patients reported fatigue. No other AEs occurred more than once. No injection-site reactions were observed.

In 23 patients (41%), CRSwNP was documented at baseline. In 22 of these patients, information about CRSwNP symptoms during benralizumab treatment was available. Thirteen patients reported an improvement, 8 reported no change, and one patient reported a worsening of CRSwNP symptoms during benralizumab treatment. Three patients underwent functional endoscopic sinus surgery during benralizumab treatment.

Online supporting information – eFigures and eTables

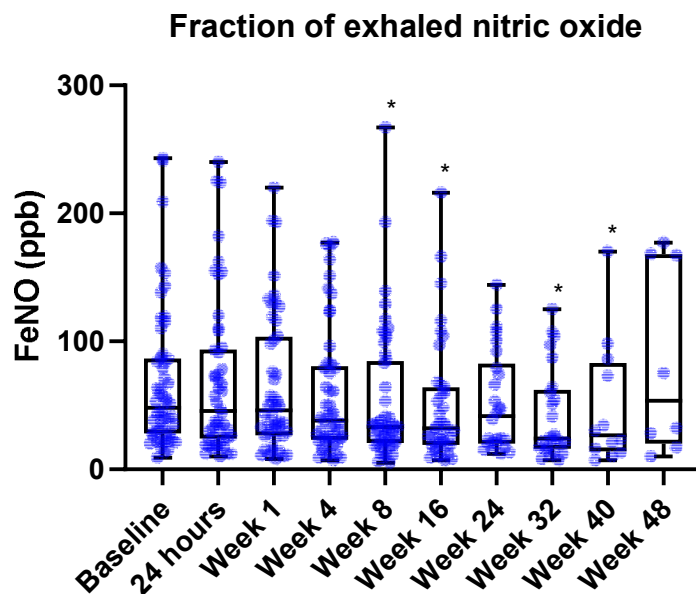


Figure S2. Box and whiskers plot of FeNO at baseline and subsequent visits. Boxes show median and interquartile range, whiskers maximum and minimum. FeNO, fraction of exhaled nitric oxide. * $p < .05$.

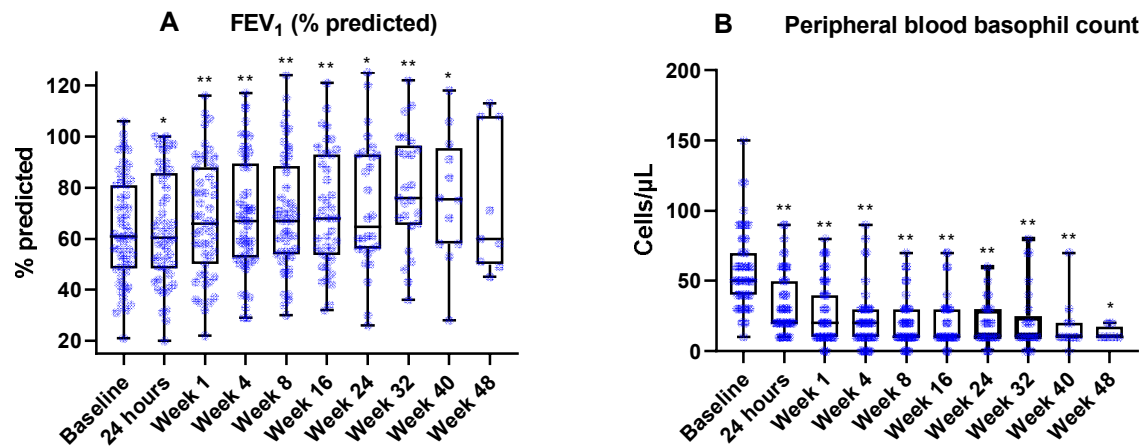


Figure S3. Box and whiskers plots of FEV₁ (% predicted) (A) and peripheral blood basophil count (B) at baseline and subsequent visits. Boxes show median and interquartile range, whiskers maximum and minimum. FEV₁, forced expiratory volume in one second. * $p < .05$, ** $p < .001$.

		N	Baseline Mean/Median	SD/IQR	Timepoint Mean/Median	SD/IQR	Difference	P
ACT Week 4								
	E	33	17	12-20	21	18-23	+4	<.001_b
	NE	21	12	9-17	23	19-27	+11	<.001_b
							P<.001^a	
ACQ6 Week 1								
	E	28	2.15	1.42-2.92	1.17	.67-1.67	-0.89	<.001_b
	NE	21	2.81	±1.00	1.76	±1.17	-1.05	<.001_b
							P=.40^a	
ACQ6 Week 4								
	E	33	2.30	1.33-3.00	.67	.5-1.67	-1.63	<.001_b
	NE	21	2.73	±.98	1.29	±.91	-1.44	<.001_b
							P=.08^a	
FEV1 24 h								
	E	32	1.91	1.29-2.45	2.02	1.38-2.40	+110 mL	.08 ^b
	NE	20	1.95	±.88	2.00	±.92	+50 mL	.20 ^b
							P=.52^a	
FEV1 Week 1								
	E	30	2.03	±.83	2.24	±.95	+210 mL	.02^b
	NE	21	2.01	±.90	2.16	±.95	+150 mL	.01^b
							P=.57^a	
FEV1 Week 4								
	E	33	2.05	±.82	2.27	±.90	+220 mL	<.001
	NE	20	2.00	±.91	2.15	±.92	+150 mL	.01
							P=.35^a	

Table S2: Subgroup analysis of patients eligible (E) and not eligible (NE) for inclusion into benralizumab phase 3 randomized controlled trials based on smoking history (former smokers ≥10 pack-years). Bold results highlight statistical and clinical significance. a: *p*-values depict the statistical significance of between-group comparisons (E vs. NE) of treatment response; b: *p*-values depict the statistical significance of within-group treatment effect (baseline vs. timepoint); SD: Standard deviation; IQR: Interquartile range; ACT: Asthma control test; ACQ6: Asthma control questionnaire 6-item scale; FEV1: Forced expiratory volume in one second

		N	Baseline Mean/Medi an	SD/IQR	Timepoint Mean/Med ian	SD/IQR	Differenc e	P
ACT Week 4								
	PR	15	13	10-17	22	18-23.5	+9	.001^b
	NR	14	13.7	±3.5	19.7	±3.2	+6	<.001^b
							<i>P</i> =.86 ^a	
ACQ6 Week 1								
	PR	15	2.36	±1.29	1.52	±1.21	-.84	.001^b
	NR	12	2.99	±.63	1.75	±.99	-1.24	.003^b
							<i>P</i> =.29 ^a	
ACQ6 Week 4								
	PR	15	2.50	1.50-3.17	.67	.33-1.50	-1.83	.001^b
	NR	14	3.01	±.58	1.43	±.79	-1.58	<.001
							<i>P</i> =.29 ^a	
FEV1 24 h								
	PR	13	2.11	1.87-2.48	2.24	2.02-2.46	+130 mL	.084 ^b
	NR	15	1.82	±.76	1.88	±.86	+60 mL	.34 ^b
							<i>P</i> =.38 ^a	
FEV1 Week 1								
	PR	15	2.21	±.57	2.47	±.67	+260 mL	.09 ^b
	NR	12	1.77	±.75	2.01	±.90	+240 mL	.047^b
							<i>P</i> =.97 ^a	
FEV1 Week 4								
	PR	15	2.21	1.91-2.47	2.33	2.24-2.54	+120 mL	.01^b
	NR	14	1.70	1.10-2.60	1.95	1.25-3.04	+250 mL	.01^b
							<i>P</i> =.95 ^a	

Table S3: Subgroup analysis of patients with positive (PR) and negative (NR) reversibility testing according to GINA criteria. Bold results highlight statistical and clinical significance. a: *p*-values depict the statistical significance of between-group comparisons (PR vs. NR) of treatment response; b: *p*-values depict the statistical significance of within-group treatment effect (baseline vs. timepoint); SD: Standard deviation; IQR: Interquartile range; ACT: Asthma control test;

125 ACQ6: Asthma control questionnaire 6-item scale; FEV1: Forced expiratory volume in one
126 second