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Real-world mepolizumab in the prospective severe asthma REALITI-A study – initial analysis

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Mepolizumab has demonstrated efficacy in patients with severe eosinophilic asthma in the controlled environment of clinical trials. These initial data from the prospective REALITI-A study show that similar results are obtained in a real-world setting.
Abstract [249/250 words]

**Background:** Efficacy of mepolizumab, an anti-interleukin-5 monoclonal antibody, was demonstrated in randomised, controlled trials; data on its real-world impact in routine clinical practice are starting to emerge. We assessed the effectiveness and safety of mepolizumab prescribed for patients in the real world.

**Methods:** REALITI-A is a global, prospective, observational cohort study, collecting data from routine healthcare visits from patients with asthma. Patients newly prescribed mepolizumab for severe asthma with 12 months’ relevant medical history pre-mepolizumab (collected retrospectively) were enrolled. An initial analysis of data from early initiators who had completed 1-year follow-up (as of 28 February 2019) was conducted. The primary objective was to compare the rate of clinically significant exacerbations (CSEs; requiring oral corticosteroids [OCS] and/or hospitalisation/emergency department [ED] visit) before and after mepolizumab; exacerbations requiring hospitalisation/ED visit and change in maintenance OCS use were secondary objectives. Treatment-related adverse events (AEs) were reported.

**Results:** Overall, 368 mepolizumab-treated patients were included. Rates of CSEs were reduced by 69% from 4.63/person/year pre-treatment to 1.43/person/year during follow-up ($P<0.001$), as were those requiring hospitalisation and/or ED visits (from 1.14/person/year to 0.27/person/year; 77% reduction). In 159 patients with maintenance OCS dose data available during the pre-treatment period, median daily dose decreased from 10.0 mg/day (pre-treatment) to 5.0 mg/day by Week 21–24 of follow-up, sustained until Week 53–56. No new safety signals were reported.
Conclusion: These data demonstrate that the effectiveness of mepolizumab is consistent with clinical trial results under real-world settings, with significant reductions in exacerbations and daily maintenance OCS dose.

Key words [≤10; not selected from a list – free text]: blood eosinophil; exacerbation; mepolizumab; oral corticosteroid; real world; severe asthma
Introduction

Of the estimated 300 million people worldwide with asthma, 5%–10% are expected to experience severe disease, placing a significant burden on patients and healthcare systems [1-6]. Many patients with severe asthma receiving maximal inhaled controller medication continue to experience exacerbations [1]. Severe eosinophilic asthma is one of several phenotypes of severe asthma, and is associated with persistent eosinophilic inflammation, reduced lung function, poor asthma control, and recurrent exacerbations, with/without systemic corticosteroid (SCS) use [1, 7-11].

Mepolizumab is an anti-interleukin-5 monoclonal antibody that selectively inhibits eosinophilic inflammation [12]. In clinical trials, add-on mepolizumab therapy, to standard of care, reduced exacerbations, decreased oral corticosteroid (OCS) dependence, and improved lung function, asthma control and health-related quality of life versus matched placebo in patients with severe eosinophilic asthma with a history of exacerbations [13-16]. It is approved as an add-on treatment for patients with severe eosinophilic asthma [17, 18].

Clinical trial eligibility criteria often result in a more homogenous patient population regarding demographics and disease characteristics than patients treated in routine clinical practice [8, 19]. Although clinical trials have high internal validity, they do not replicate real-world conditions[20]. Indeed, a manifesto by the Respiratory Effectiveness Group stated it is necessary to obtain data on outcomes from patients treated in the real world for external validity, to complement clinical trials and guide treatment-related decisions [21]. The 24-month REALITI-A study evaluates mepolizumab use in clinical practice. Here, we report an initial analysis of data from patients who had completed 12-month follow-up by 28 February 2019, following mepolizumab initiation. They represent some of the first to be prescribed mepolizumab in real-world clinical practice.

Methods

Subjects

Eligible patients were aged ≥18 years with a current clinical diagnosis of asthma, a physician decision to initiate mepolizumab treatment and relevant medical records for ≥12 months pre-enrolment and who had provided informed consent for study participation. Prior use of other biologic medications was permitted; those who had received mepolizumab in the year pre-enrolment were excluded.
Patients who had participated in an interventional clinical trial within the year pre-enrolment were also excluded. Patients were recruited from 51 centres in 7 countries (Table 1).

Study design

REALITI-A (GSK ID: 204710) is a global, prospective, single-arm, observational cohort study enrolling patients diagnosed with asthma and newly prescribed mepolizumab treatment (physician decision) (Figure 1; Supplementary Information). The index date was the first mepolizumab administration. Enrolment could occur before or after the index date; if occurring before the index date, there was a variable-length run-in period (driven by local prescribing and dispensing practices) between the enrolment and index dates, where the same therapy was continued. There was no run-in period when the enrolment and index dates were the same day or when enrolment occurred after the index date (maximum 7 days permitted from index to enrolment).

The pre-mepolizumab treatment period ended on the index date and started: (1) 365 days pre-enrolment date if the index date was before the enrolment date; (2) 365 days (+1 day) if the index date and enrolment date were the same; or (3) 365 days (+run-in period +1 day) if the enrolment date was pre-index date. Data were collected retrospectively at enrolment (and, if relevant, prospectively during the run-in period) from medical records and patient recall for the previous year.

The 12-month follow-up period after initiating mepolizumab was from the index date (+1 day) to the first of: death, withdrawal of consent, or end of follow-up. The present analysis was conducted in the first cohort of participants in the study who, at 28-February-2019, had completed 12 months’ follow-up after starting mepolizumab. Data were collected prospectively at asthma healthcare visits (routine or unscheduled) during the 12-month post-index period; no visits were scheduled specifically for this observational study. The study population subset included in this analysis were enrolled from December 2016 to February 2018; full study population enrolment completed on 31-October-2019.

Outcomes

The primary objective was to compare the clinically significant asthma exacerbation rate in the pre-mepolizumab treatment period versus the 12-month follow-up period. Clinically significant exacerbations (CSEs) were defined as a deterioration in asthma requiring SCS (any dose; oral steroids [e.g. prednisone] for ≥3 days or a single systemic administration of corticosteroids [intravenous/intramuscular dose]) and/or hospitalisation and/or emergency department (ED) visit.
For patients already receiving maintenance SCS, at least double the existing maintenance dose for ≥3 days was required. Exacerbations treated with courses of corticosteroids separated by <7 days were classed as the same exacerbation (based on data entry by physicians).

Secondary objectives compared the following outcomes in the same periods: asthma exacerbation rates requiring hospitalisation and/or ED visit, or hospitalisation only, and proportion of patients without CSEs, and those achieving >0%–<50% and ≥50%–100% reductions in CSE rates. Additionally, for patients who reported at enrolment they were receiving maintenance OCS (Supplementary Information), the change and percent reduction in median daily maintenance OCS dose from pre-treatment to 12 months after initiating mepolizumab were assessed. The proportion of patients receiving maintenance OCS pre-mepolizumab treatment who discontinued maintenance OCS with mepolizumab was also reported. Change from baseline in blood eosinophil count (BEC) was also assessed. Safety objectives included reported mepolizumab-related adverse events (AEs) and serious AEs (SAEs). The relationship of AEs to mepolizumab was determined by the investigator without further adjudication.

Analysis

With the assumption that 25% of patients would withdraw during the full study period (Supplementary Information), a 12-month mepolizumab treatment period with 200 patients was expected to have 90% power to detect a 35% reduction in CSEs at the two-sided 5% level. The treated population, used for all effectiveness and safety evaluations, included all enrolled patients who received ≥1 mepolizumab dose. Subgroup analyses were performed by BEC (<150, ≥150–<300, ≥300 cells/µL) at index or the most recent count available pre-index. Additional post hoc subgroup analyses for CSEs were performed by maintenance OCS use and dose in the pre-treatment period (yes vs no; <10 vs ≥10 mg/day), age at enrolment (<65 years vs ≥65 years of age) and prior omalizumab use during lifetime (yes vs no), and for BEC by maintenance OCS use and dose in the pre-treatment period.

A treatment-policy estimand approach for treatment discontinuation was used in this study, which provided an estimate of the expected effect of mepolizumab using all data collected during the 12-month follow-up period, regardless of whether patients discontinued mepolizumab. This analysis corresponds to an intent-to-treat analysis in a clinical trial.

The exacerbation rate in the pre-treatment and 12-month follow-up periods was analysed using negative binominal regression with time period (pre-treatment and 12-month follow-up) as a
covariate. The mean estimate variance was corrected for within-patient correlation by use of generalised estimating equations (GEEs). The proportion of patients without CSEs was analysed using logistic regression, and pre-treatment versus post-treatment initiation period data were compared via GEEs with time period as a covariate. Proportions of patients with ≥50% reduction in CSE rates are also reported. The mean OCS dose was calculated for each patient over each 28-day period during pre-treatment and the 12-month follow-up. For the mean calculation, a 0 mg dose was assumed if no data were recorded for a specific day (Supplementary Information); if a recorded dose could not be interpreted, the mean was based on the number of days with interpretable data. Summary statistics (including median) of the OCS maintenance dose were based on the mean value calculated as described above. Patient-specific percentage change from baseline in maintenance OCS daily dose was calculated at each post-treatment time point. Applying distribution-free method [22] to this variable, the median percent reduction (with 95% confidence interval [CI]) from baseline was estimated at 12 months post-treatment initiation (i.e. Week 53–56). The ratio to baseline for BEC was assessed using mixed model repeated measures. Only data on mepolizumab-related AEs or other GSK products were collected during the study.

This study was conducted in accordance with the Declaration of Helsinki. Local ethical approval was obtained per study site.

Results

Patients

Overall, 368 patients received ≥1 mepolizumab dose in the treated population. The UK enrolled the most patients (n=136) in this analysis (Table 1). The mean body mass index at enrolment was 28.7 kg/m², 39% (n=143/364) of patients were current/former smokers, and 48% (n=174/365) were receiving maintenance OCS pre-mepolizumab treatment (Table 1). Of those with baseline BEC data available, 51/357 (14%) had baseline BECs of <150 cells/µL, 45/357 (13%) had counts ≥150–<300 cells/µL, and 261/357 (73%) had counts ≥300 cells/µL. When stratified by baseline BEC, 32/51 (63%), 32/45 (71%), and 108/258 (42%) patients in the <150, ≥150–<300, and ≥300 cells/µL subgroups, respectively, reported using maintenance OCS in the pre-treatment period. Additionally, 38% (n=140/368) of patients had a clinical history of nasal polyps.

At data cut-off, patients had received a mean (standard deviation [SD]) of 11.4 (3.11) mepolizumab treatments, with a mean (SD) treatment duration of 340.4 (87.24) days. Overall, 70/368 (19%)
patients discontinued mepolizumab during the 12-month follow-up; the most common reason was participant decision (27/368; 7%), while 13/368 (4%) patients reported lack of efficacy (Supplementary Table 1).

**Exacerbations**

The CSE rate fell from 4.63/person/year in the pre-mepolizumab treatment period to 1.43/person/year in the 12-month follow-up, equating to a significant 69% reduction (rate ratio 0.31, 95% CI 0.27,0.35; P<0.001) (Figure 2). Exacerbation rate reductions were similar across baseline BEC subgroups (Figure 2).

The exacerbation rate requiring hospitalisation and/or ED visits was also significantly reduced by 77% from 1.14/person/year pre-treatment to 0.27/person/year during follow-up (rate ratio 0.23, 95% CI 0.18,0.30; P<0.001); reductions were observed across all baseline BEC subgroups (Figure 2). Additionally, there was a significant reduction (P<0.001) in the exacerbation rate requiring hospitalisation in the overall population following treatment, with a similar trend observed across all baseline BEC subgroups.

Overall, 67% (n=247/366) of patients achieved a ≥50% reduction in CSEs from pre-treatment to 12 months after mepolizumab initiation; this rose to 73% (247/340) when those without a prior history of exacerbations pre-treatment were excluded (Table 2). Furthermore, a significantly higher proportion of patients had no CSEs during follow-up (48%) versus pre-treatment (7%; odds ratio 12.13, 95% CI 8.03,18.33; P<0.001) (Figure 3). Across baseline BEC subgroups, the proportion of patients without CSEs during follow-up rose to 38%–49% versus 7%–9% during pre-treatment (Figure 3). CSEs assessed by maintenance OCS use and dose in the pre-treatment period, age at enrolment and prior omalizumab use are shown in the Supplementary Information; Supplementary Figure 1.

**Maintenance OCS**

Data on maintenance OCS dose during pre-treatment were available for 159 patients (Supplementary Information). The median daily maintenance OCS dose fell from 10.0 (quartile [Q] 1: 5.0; Q3: 15.0) mg/day during pre-treatment to 5.0 (Q1: 0.9; Q3: 10.0) mg/day by Week 21–24, and remained at the same level until Week 53–56 (median: 5.0; Q1: 0.0; Q3: 7.5 mg/day). The corresponding median percent reduction was 52% (95% CI 50.0,75.0) (i.e. Week 53–56) (Figure 4). Of the 125 patients on maintenance OCS at Week 53–56 with data available, 82 remained on OCS at
Week 53–56, with 34% (n=43/125) of patients discontinuing OCS while on mepolizumab (Figure 5) (data are from the while-on-treatment estimand for treatment discontinuation).

In the <150, ≥150–<300 and ≥300 cells/µL baseline BEC subgroups, the median daily maintenance OCS dose during pre-treatment was reduced from 12.8, 11.3 and 9.8 mg/day, respectively, to 6.5, 5.0 and 2.5 mg/day by Week 53–56; reductions were seen as early as Week 9–12, Week 13–16, and Week 5–8, respectively (Figure 4). At Week 53–56, median percent reductions from baseline in median daily maintenance OCS dose in the <150, ≥150–<300, and ≥300 cells/µL baseline BEC subgroups were 51% (95% CI 22,74), 23% (0,69) and 74% (50,100), respectively.

**BEC**

Following mepolizumab treatment initiation, BEC was reduced from least squares geometric mean 370 (95% CI 320, 410) cells/µL at baseline to 60 (50, 80) cells/µL at months 9–12 (median [Q1, Q3] BEC values were 442 [270, 800] cells/µL at baseline and 90 [40, 100] cells/µL at months 9–12). This corresponds to a reduction of 83% to 60 cells/µL (least squares mean ratio to baseline [95% CI] at months 9–12: 0.17 [0.13, 0.21]). The reduction in BEC was observed by months 0–3, and was maintained throughout the 12-month follow-up. **Supplementary Table 2** presents BEC by maintenance OCS use and dose in the pre-treatment period.

**Safety**

Overall, 53/368 (14%) patients experienced an investigator-determined treatment-related AE during follow-up (Table 3). The most common AEs (occurring in ≥2% of patients) were disorders classified as affecting the nervous system (predominantly headache), general and administration site, musculoskeletal and connective tissue, skin and subcutaneous tissue, and gastrointestinal tract. Treatment-related SAEs were experienced by 2/368 (<1%) patients during follow-up (Table 3). Treatment-related SAEs of hypersensitivity and pharyngeal swelling were experienced by 1 patient each. During follow-up, 9/368 (2%) patients experienced a treatment-related AE, leading to permanent treatment discontinuation (Table 3). No treatment-related deaths occurred.

**Discussion**

The REALITI-A study is a prospective, global, observational, self-controlled cohort study being conducted to collect real-world data from patients with asthma who were newly prescribed mepolizumab treatment. These initial results showed real-world mepolizumab initiation led to significant reductions in the annual asthma exacerbation rate and clinically meaningful reductions in
daily maintenance OCS dose versus pre-mepolizumab treatment. Furthermore, there were no new safety concerns with mepolizumab when compared with results from previous randomised controlled trials (RCTs). These initial data confirm mepolizumab effectiveness in a real-world setting.

We found the rates of CSEs and exacerbations requiring hospitalisation and/or ED visits were significantly reduced with mepolizumab treatment initiation versus before initiation. Reductions in CSEs were observed regardless of older age, maintenance OCS at enrolment or prior use of omalizumab. The treatment-policy estimand included data from patients who discontinued mepolizumab, providing a conservative effectiveness estimate. Our results support those from the clinical trials MENDA (NCT01691521) and MUSCA (NCT02281318), where patients receiving mepolizumab (subcutaneous dose) experienced respective 53% and 58% reductions in the rate of CSEs versus placebo, despite the placebo effect observed in both studies [14, 15]. Additionally, our data are also consistent with findings from several smaller, observational studies of real-world mepolizumab treatment for severe asthma [23-27].

Daily maintenance OCS use was also assessed. We observed a clinically meaningful reduction in the median daily maintenance OCS dose during follow-up in patients who were on maintenance OCS pre-mepolizumab treatment. Reductions were also meaningful when assessed by baseline BECs, although the smaller sample sizes resulted in larger variability. Approximately one-third of patients discontinued maintenance OCS by Week 53–56. Similar to our results, a 50% reduction in the median OCS dose in patients receiving mepolizumab versus placebo was demonstrated in the SIRIUS trial (NCT01691508), and have also been reported in smaller real-world observational studies [13, 23-27]. These reductions are particularly important in patients with severe asthma given the risk of AEs associated with chronic SCS use, irrespective of dose level, and the additional healthcare costs related to corticosteroid-induced AEs in patients with severe asthma [28, 29]. Thus, this large international, prospective REALITI-A study, together with the findings from these smaller observational studies, provides evidence that the clinical benefits observed with mepolizumab in clinical trials translate to the real-world setting and indicates that mepolizumab may help reduce the severe asthma healthcare burden.

In contrast with RCTs with selected, homogeneous populations, this real-world study included a heterogeneous population, with a broader spectrum of comorbidities and concomitant medications versus those typically permitted in RCTs. Additionally, unlike RCTs, this real-world population was subject to payer reimbursement criteria, which differed among countries. Data from REALITI-A complement those from RCTs; however, more importantly, they highlight mepolizumab
effectiveness in the context of real-world clinical practice. The REALITI-A patient population had particularly severe asthma, as approximately half of the patients received maintenance OCS pre-mepolizumab treatment, and patients had an average of 1.2 exacerbations requiring hospitalisation and/or ED visits in the 12 months pre-study enrolment. It is perhaps not surprising these early treatment initiators in this analysis had such severe disease as new treatments are often channelled to those in the most severe spectrum of the disease [30]. Furthermore, nearly 50% of patients in this initial analysis were from the UK, where treatment-eligibility criteria are particularly more stringent than enrolment criteria applied in clinical trials, and the eligibility criteria in many other REALITI-A countries. However, despite the REALITI-A population in this analysis being more severe than those patients with severe eosinophilic asthma in the RCTs [13-16] with no previous smoking history or lung function status restrictions, clinical outcomes are at least as good as those in the clinical trial setting. Thus, the REALITI-A study provides conformational validity of the more formal trials, and as such, identifies that the therapeutic benefit of mepolizumab is translated in the real-world environment.

The relationship between higher BECs and mepolizumab responses in patients with severe asthma has been identified in previous studies [13-16], with increasing evidence supporting mepolizumab use in patients with baseline BECs ≥150 cells/µL [31-33]. This population is defined by serious morbidity, which increases with higher eosinophil counts (which act as a predictor of mepolizumab response for exacerbation reduction) [15, 34-38]. In our study, similar reductions in the CSE rate and the median daily maintenance OCS use between pre-treatment and follow-up were seen across all baseline blood eosinophil groups, including the <150 cells/µL group. Although mepolizumab is licensed for the treatment of severe eosinophilic asthma and usually requires evidence of elevated blood eosinophils [18], the treated severe asthma population in this real-world setting included 51 (14%) patients with baseline BECs <150 cells/µL on entry. However, most of these patients had confirmatory evidence of severe eosinophilic asthma, since they had BECs ≥300 cells/µL during the previous year (and run-in period if relevant) (67%; 34/51) and/or were requiring maintenance OCS at enrolment (63%; 32/51).

Limitations of real-world studies include the capturing of data from standard clinical care recording; therefore, there may be missing information. To mitigate this, one study entry criterion was that patients needed 12 months’ relevant medical records available before enrolment; this was done so information on exacerbation history could be obtained as accurately as possible. Nevertheless, it is possible some historic exacerbations were overlooked, owing to inadequate recording or self-
medication, which would lead to an underestimation of the impact of mepolizumab. Additionally, as REALITI-A is a real-world study, therapy could be discontinued or changed by the patient or physician. Patient behaviour may be harder to control in real-world studies, and discontinuation rates in real-world studies have been shown to be higher than those observed in RCTs, with patient decision and lack of efficacy accounting for most treatment withdrawals [39]. In this 1-year study, 19% of patients discontinued treatment, which is similar to the rate observed in other real-world studies [39]. Some of these individuals may not have had a positive response to mepolizumab and discontinued from the study. It is feasible that some patients had severe eosinophilic asthma alongside other diseases, and any continued symptoms in these patients may have been due to non-asthma disease and incorrectly interpreted as a lack of response to mepolizumab. However, only 4% discontinued mepolizumab because of lack of efficacy, so this is unlikely to be a significant confounding factor. Patients may also have withdrawn owing to failure to meet payer reimbursement criteria, an option that was not listed on the electronic case report form.

Furthermore, the treatment-policy estimand approach for treatment discontinuation used, whereby all who received ≥1 mepolizumab dose were included, attempts to limit any bias owing to study drop-outs. As this is an ongoing study and an interim analysis on a subcohort of patients, changes to the datasets may occur; however, all efforts were made to finalise the data to the best standard. Finally, REALITI-A is not a placebo-controlled study; therefore, outcomes may represent a combination of treatment effect and other behavioural changes. While this is inherent in all real-world open-label studies, this analysis of early initiators in the real world shows that the effects of mepolizumab are consistent with those demonstrated in the severe asthma clinical trials, and identifies the clinical benefits of mepolizumab are translated in the severe asthma population in the real world.

In conclusion, data from this initial analysis of mepolizumab treatment initiation in patients with asthma treated in routine clinical practice demonstrated mepolizumab was associated with significant reductions in asthma exacerbations and clinically significant reductions in maintenance OCS use. Additionally, mepolizumab was well tolerated with a safety profile that appeared to be similar to previous clinical studies conducted in patients with severe eosinophilic asthma [14-16]. These data also show the mepolizumab efficacy found in clinical trials translates to the real world, and provide valuable insights into treatment outcomes in patients treated in this setting.
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Data sharing

This study was conducted in accordance with the Declaration of Helsinki. Local ethical approval was obtained for each study site. All patients provided informed consent. Upon completion of the primary analysis, anonymised individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.
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Tables and figure legends

Table 1. Demographics and clinical characteristics during the pre-mepolizumab treatment period (baseline)

|                          | Total population N=368 |
|--------------------------|------------------------|
| Age at enrolment, years, N=367 |                        |
| Mean (SD), Median (Q1, Q3) | 53.1 (13.72), 54.0 (44.0, 63.0) |
| Female, n (%), N=367       | 226 (62)               |
| Race, N=368               |                        |
| White/Caucasian           | 337 (92)               |
| Asian, Native Hawaiian or other Pacific Islander | 17 (5)      |
| Black/African American    | 5 (1)                  |
| Other/multiple            | 9 (2)                  |
| Country, n (%), N=368     |                        |
| UK                       | 136 (37)               |
| Italy                    | 87 (24)                |
| Germany                  | 44 (12)                |
| Canada                   | 40 (11)                |
| Belgium                  | 29 (8)                 |
| Spain                    | 24 (7)                 |
| USA                      | 8 (2)                  |
| BMI at enrolment, kg/m^2, N=368 |                    |
| Mean (SD), Median (Q1, Q3) | 28.7 (7.26), 27.5 (23.7, 32.4) |
| Smoking history at enrolment, n (%), N=364 | |
| Never smoked             | 221 (61)               |
| Current smoker           | 10 (3)                 |
| Former smoker            | 133 (37)               |
| Asthma duration at enrolment, years, N=360 | |
| Mean (SD), Median (Q1, Q3) | 20.03 (15.13), 17.41 (7.00, 30.66) |
| Previous use of omalizumab, n (%), N=365 | |
| Never                    | 108 (30)               |
| Past                     | 83 (23)                |
| Current                  | 174 (48)               |
| Daily maintenance OCS dose, mg/day,‡ N=159 | |
| Mean (SD)                | 14.4 (19.48)           |
| Median (Q1, Q3)          | 10.0 (5.0, 15.0)       |
| Rate of exacerbations, person/year, N=366 | \(\text{Clinically significant exacerbations}\) |
| Mean (SD)                | 4.63 (4.09)           |
| **Median (Q1, Q3)** | **3.0 (2.0, 6.0)** |
|----------------------|-------------------|
| **Exacerbations requiring hospitalisation and/or ED visits** | **Mean (SD)** |
| | **1.14 (2.26)** |
| | **Median (Q1, Q3)** |
| | **0 (0.0, 1.0)** |
| **Exacerbations requiring hospitalisation** | **Mean (SD)** |
| | **0.60 (1.33)** |
| | **Median (Q1, Q3)** |
| | **0 (0.0, 1.0)** |
| **Blood eosinophil count,§ cells/µL, N=357** | **Geo mean (SD logs)** |
| | **370 (1.248)** |
| | **Median (Q1, Q3)** |
| | **442 (270, 800)** |
| | **<150, n (%)** |
| | **51 (14)** |
| | **150–<300, n (%)** |
| | **45 (13)** |
| | **≥300, n (%)** |
| | **261 (73)** |
| **Lung function,§** | **Pre-bronchodilator FEV₁ (L), N=201** |
| | **Mean (SD)** |
| | **1.94 (0.791)** |
| | **Median (Q1, Q3)** |
| | **1.84 (1.39, 2.42)** |
| | **Pre-bronchodilator FVC (L), N=201** |
| | **Mean (SD)** |
| | **2.93 (1.017)** |
| | **Median (Q1, Q3)** |
| | **2.82 (2.28, 3.57)** |
| | **Pre-bronchodilator FEV₁/FVC, N=201** |
| | **Mean (SD)** |
| | **0.66 (0.122)** |
| | **Median (Q1, Q3)** |
| | **0.66 (0.58, 0.73)** |
| | **Pre-bronchodilator % predicted FEV₁ (%), N=200** |
| | **Mean (SD)** |
| | **64.41 (20.339)** |
| | **Median (Q1, Q3)** |
| | **65.65 (47.60, 80.33)** |
| | **Reversibility (%), N=39** |
| | **Mean (SD)** |
| | **6.97 (8.326)** |
| | **Median (Q1, Q3)** |
| | **4.93 (0.90, 13.48)** |
| | **Post-bronchodilator FEV₁ (L), N=70** |
| | **Mean (SD)** |
| | **2.06 (0.941)** |
| | **Median (Q1, Q3)** |
| | **2.08 (1.34, 2.72)** |
| | **Post-bronchodilator FVC (L), N=70** |
| | **Mean (SD)** |
| | **3.07 (1.202)** |
| | **Median (Q1, Q3)** |
| | **3.04 (2.10, 3.88)** |
| | **Post-bronchodilator FEV₁/FVC, N=70** |
| | **Mean (SD)** |
| | **0.66 (0.131)** |
| | **Median (Q1, Q3)** |
| | **0.67 (0.58, 0.75)** |
| | **Post-bronchodilator % predicted FEV₁ (%), N=70** |
| | **Mean (SD)** |
| | **67.22 (23.188)** |
| | **Median (Q1, Q3)** |
| | **69.10 (48.09, 85.25)** |
| **ACQ-5 score,§ N=350** | **Mean (SD)** |
| | **3.0 (1.35)** |
| | **Median (Q1, Q3)** |
| | **3.2 (2.2, 4.0)** |
| **Medical history reported during 12 months prior to the enrolment date, N=368** | **Any** |
| | **Recognised to be associated with asthma** |
| | **Any asthma related** |
| | **Hay fever** |
| | **343 (93)** |
| | **292 (79)** |
| | **193 (52)** |
Chronic sinusitis 145 (39)
Nasal polyps 140 (38)
Any drug hypersensitivity 127 (35)
Nasal polypectomy 96 (26)
Atopic dermatitis 47 (13)
Anaphylaxis 24 (7)

| Conditions of interest (reported in ≥5% of patients)       |   |
|-----------------------------------------------------------|---|
| Any condition of interest                                 | 285 (77) |
| Gastroesophageal reflux disease                           | 137 (37) |
| Depression                                                | 73 (20)  |
| Osteoporosis                                              | 66 (18)  |
| Anxiety                                                   | 59 (16)  |
| Hyperlipidemia                                            | 58 (16)  |
| Food allergy                                              | 47 (13)  |
| Fractures                                                 | 40 (11)  |
| Diabetes                                                  | 36 (10)  |
| Cataract                                                  | 34 (9)   |
| Pneumonia§                                                | 34 (9)   |
| COPD                                                      | 33 (9)   |
| Oropharyngeal candidiasis†                                 | 33 (9)   |

*During the enrolment period, 13/71 (18%) patients had received omalizumab treatment outside of a clinical trial, and the remaining 58/71 (82%) patients received omalizumab treatment more than 12 months prior to enrolment that may have been within or outside of a clinical trial (data were collected for 12 months prior to enrolment only); in those patients who received omalizumab in the prior 12 months, typically, the end of omalizumab treatment was approximately 1–2 months prior to starting mepolizumab. †Reported by the patient. ‡During the period including the index date and the 27 days prior to index, or any other 27-day period in the last 6 months if no records existed 27 days immediately prior to index. §Latest record prior to index. ¶Pneumonia cases were limited to the prior 12 months. Percentages may not add up to 100% owing to rounding.

ACQ-5, Asthma Control Questionnaire; BMI, body mass index; COPD, chronic obstructive pulmonary disorder; ED, emergency department; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; OCS, oral corticosteroid; Q, quartile; SD, standard deviation.
Table 2. Patients achieving a reduction* in the rate of CSEs during the 12-month follow-up period

|                                | Total population (N=368)† | Population with ≥1 exacerbation in the pre-mepolizumab treatment period (N=340)‡ |
|--------------------------------|----------------------------|---------------------------------------------------------------------------------|
| ≥50–100% reduction, n (%)     | 247 (67)                   | 247 (73)                                                                         |
| >0–<50% reduction, n (%)      | 52 (14)                    | 52 (15)                                                                          |
| No change/increase, n (%)     | 66 (18)                    | 40 (12)                                                                          |
| Missing§                      | 1 (<1)                     | 1 (<1)                                                                           |

*Based on 365 days prior to enrolment plus any exacerbations starting during run-in. †Denominator based on patients with data for historical exacerbations only (n=366). ‡Denominator based on patients with ≥1 historical exacerbations only (n=340); patients with 0 historical exacerbations were excluded (n=26).
§One patient did not have data during the follow-up period and is therefore not included in any of the categories.

CSE, clinically significant exacerbation.
Table 3. Treatment-related AEs and SAEs

| Category                                                | Total population (N=368) |
|---------------------------------------------------------|--------------------------|
| AEs, number of patients (%)                             | 53 (14)                  |
| AEs occurring most frequently (>2% of patients), number of events (%) |                       |
| Nervous system disorders                                | 26 (7)                   |
| General disorders and administration site conditions    | 12 (3)                   |
| Musculoskeletal and connective tissue disorders         | 9 (2)                    |
| Skin and subcutaneous tissue disorders                  | 9 (2)                    |
| Gastrointestinal disorders                              | 6 (2)                    |
| AEs leading to treatment discontinuation*, number of patients (%) | 9 (2)            |
| AEs leading to study withdrawal, number of patients (%)  | 7 (2)                    |
| SAEs, number of events (%)                              | 2 (<1)                   |
| Hypersensitivity                                        | 1 (<1)                   |
| Pharyngeal swelling                                     | 1 (<1)                   |
| Fatal SAEs, number of events (%)                        | 0 (0)                    |

*The AEs leading to treatment discontinuation included headache (n=2 [<1%]), dizziness (n=1 [<1%]), paraesthesia (n=1 [<1%]), dyspepsia (n=1 [<1%]), nausea (n=1 [<1%]), palpitations (n=1 [<1%]), tachycardia (n=1 [<1%]), vertigo (n=1 [<1%]), non-cardiac chest pain (n=1 [<1%]), hypersensitivity (n=1 [<1%]), arthralgia (n=1 [<1%]), pharyngeal swelling (n=1 [<1%]) and pruritus (n=1 [<1%]); 2 AEs were not coded. AE, adverse event; SAE, serious adverse event.
**Figure legends**

**Figure 1.** Study design

*If enrolment occurred before the index date, there was a variable-length run-in period where patients continued with the same therapy. There was no run-in period when the enrolment and index dates were the same day or when the index date occurred before enrolment. †There will be a 12-month interim analysis of the full study population (primary and secondary objectives) and a 24-month analysis of the full study population (secondary objectives). ‡Data cut-off February 28, 2019.

**Figure 2.** Asthma exacerbation rates in the pre-mepolizumab-treatment period* and 12-month follow-up period

*365 days prior to enrolment plus any exacerbations starting during run-in.

BEC, blood eosinophil count; CI, confidence interval; CSE, clinically significant exacerbation; ED, emergency department.

**Figure 3.** Proportion of patients with no CSEs in the pre-mepolizumab treatment period* and 12-month follow-up period

*365 days prior to enrolment plus any exacerbations starting during run-in.

BEC, blood eosinophil count; CSE, clinically significant exacerbation.

**Figure 4.** Maintenance OCS use after initiation with mepolizumab treatment for (a) the overall population, and according to the following baseline blood eosinophil groups (b) <150 cells/µL, (c) ≥150–300 cells/µL, and (d) ≥300 cells/µL*

*The median percentage change was calculated using the distribution-free method (Hahn G, Meeker W. Statistical Intervals: A Guide for Practitioners. New York: Wiley; 1991) with patient-specific percentage change from baseline as a variable.

BL, baseline; OCS, oral corticosteroid.
Figure 5. Proportion of patients on maintenance OCS at enrolment who continued with maintenance OCS after treatment initiation with mepolizumab

Data are from the while-on-treatment estimand for treatment discontinuation (i.e. data considered up to treatment discontinuation).

BL, baseline; OCS, oral corticosteroid
Enrolment

Mepolizumab initiation (index date)

12 months pre-enrolment

Post-mepolizumab treatment initiation

Run-in

12 months

24 months

Pre-mepolizumab treatment period

Follow-up period:

12 months

24 months

Data collected retrospectively at enrolment

Data collected prospectively at routine healthcare visits

Initial analysis of data from patients who had completed 12 months of follow-up (early treatment initiators) (N=368)
### Exacerbations requiring hospitalisation and/or ED visits

|              | Rate ratio (95% CI) | P-value |
|--------------|---------------------|---------|
| Total population | 1.14 (0.27, 0.30) | $P<0.001$ |
| Baseline BEC <150 cells/µL | 1.76 (0.46, 0.41) | $P<0.001$ |
| Baseline BEC ≥150–<300 cells/µL | 1.32 (0.36, 0.48) | $P<0.001$ |
| Baseline BEC ≥300 cells/µL | 1.02 (0.22, 0.30) | $P<0.001$ |

### Exacerbations requiring hospitalisation

|              | Rate ratio (95% CI) | P-value |
|--------------|---------------------|---------|
| Total population | 0.60 (0.28, 0.38) | $P<0.001$ |
| Baseline BEC <150 cells/µL | 1.26 (0.34, 0.55) | $P<0.001$ |
| Baseline BEC ≥150–<300 cells/µL | 0.87 (0.30, 0.58) | $P<0.001$ |
| Baseline BEC ≥300 cells/µL | 0.45 (0.25, 0.38) | $P<0.001$ |

**Note:**
- Pre-mepolizumab treatment period
- 12-month follow-up period
Proportion of patients with no clinically significant exacerbations (%)

- **Pre-mepolizumab treatment period**
- **12-month follow-up period**

1. **Total population (n=366)**
   - Pre-mepolizumab: 48%
   - 12-month follow-up: 7%

2. **Baseline BEC <150 cells/µL (n=51)**
   - Pre-mepolizumab: 43%
   - 12-month follow-up: 8%

3. **Baseline BEC ≥150–<300 cells/µL (n=45)**
   - Pre-mepolizumab: 38%
   - 12-month follow-up: 9%

4. **Baseline BEC ≥300 cells/µL (n=259)**
   - Pre-mepolizumab: 49%
   - 12-month follow-up: 7%
Supplementary material

Real-world mepolizumab in the prospective severe asthma REALITI - A study – initial analysis

Harrison T, et al.

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Contents

Supplementary Information

Study design (page 2)

Maintenance OCS dose (page 2)

Analysis: withdrawal rate (page 2)

Clinically significant exacerbations according to maintenance OCS use and dose, age and prior omalizumab use (page 3)

BEC at baseline and during follow-up according to maintenance OCS use and dose at baseline (page 3)

Supplementary Table 1. Reasons for discontinuation from the study (page 4)

Supplementary Figure 1. Clinically significant asthma exacerbation rates in the pre-mepolizumab-treatment period and 12-month follow-up period according to maintenance OCS use and dose, age at enrolment and prior omalizumab use (page 5)

Supplementary Table 2. Baseline BEC and 12-month follow-up period according to maintenance OCS use and dose in the in the pre-mepolizumab-treatment period (page 6)
Supplementary Information

Study design
The assignment of a patient to a particular therapeutic strategy was not decided in advance by the study protocol but was determined by the usual practice of medicine. The decision to prescribe a particular drug was also clearly dissociated from the decision to include the patient in the study. No visits were scheduled specifically for this observational study, and data were collected at usual asthma healthcare visits (routine or unscheduled). All data captured for the 12 months pre-enrolment and during the study period were entered into an electronic case report form (eCRF) as part of the routine healthcare visit. To avoid enrolment bias, sites were expected to enrol all eligible patients who presented at their site and to maintain screening logs of all patients meeting eligibility criteria, along with reasons for non-enrolment of otherwise eligible patients.

Maintenance OCS dose
Maintenance OCS use in the pre-treatment period was defined as the mean daily maintenance OCS dose (expressed as prednisone equivalent dose, mg/day) in the period including the index date and the 27 days pre-index, or any other 27-day period within a maximum of 6 months pre-index if no records existed 27 days immediately pre-index.

The approach to impute the daily maintenance OCS dose as 0 mg in this study if there were gaps in the dates recorded on the eCRF was based on the fact that the eCRF requested all instances of OCS dose use between the visits to be recorded. Data collection is based on patient recall, and querying data gaps can therefore be impossible and/or unreliable since a patient may have withdrawn from the study or a patient may not be able to recall information owing to the length of elapsed time.

Analysis: withdrawal rate
The sample size calculation was based on data from the mepolizumab COSMOS extension study (MEA115661/NCT01842607)[40], where 159 participants who received placebo in the MENSA study (MEA115588/NCT01691521)[15] switched to mepolizumab in the COSMOS study and completed both studies. A total of 25% of participants were assumed to withdraw over the course of the study, 20% in the first and 5% in the second year. Following these assumptions, a study with 12 months of mepolizumab treatment designed to detect a 35% decrease with 90% power at the two-sided 5% level would require approximately 200 participants (with an assumed dispersion parameter of 0.8).
Clinically significant exacerbations according to maintenance OCS use and dose, age and prior omalizumab use

When assessed by maintenance OCS at enrolment (‘never’, ‘current or past’), the reduction in clinically significant exacerbations with mepolizumab treatment, compared with the pre-mepolizumab treatment period, was similar (69% reduction in both subgroups) (Supplementary Figure 1). However, it should be noted that exacerbations were higher in the pre-mepolizumab treatment period in the ‘current or past’ subgroup compared with the ‘never’ subgroup. Those on low-dose (<10 mg/day) OCS at enrolment experienced a 65% reduction in exacerbations and those on high-dose (≥10 mg/day) OCS a 59% reduction (Supplementary Figure 1). Older age did not impact the effectiveness of mepolizumab in the real world, since reductions in the clinically significant exacerbation rate were similar in patients aged <65 and ≥65 years of age (68%–72% reductions) (Supplementary Figure 1). The reductions in exacerbations with mepolizumab were 60% and 71% in those with and without prior use of omalizumab therapy, respectively (Supplementary Figure 1).

BEC at baseline and during follow-up according to maintenance OCS use and dose

Patients receiving OCS at baseline had lower baseline BEC than those not receiving OCS. Patients receiving high-dose OCS at baseline had lower baseline BEC compared with those on low-dose OCS at baseline. Compared with baseline, mepolizumab treatment reduced BECs by 86%, 75% and 77% at months 9–12 in those not receiving OCS, and in those receiving low-dose (<10 mg/day) and high-dose (≥10 mg/day) OCS, respectively (Supplementary Table 2). These reductions occurred by months 0–3 and were maintained throughout the 12-month follow-up.
**Supplementary Table 1. Reasons for discontinuation from the study**

| Reason for discontinuation       | Patients, n (%) |
|----------------------------------|-----------------|
|                                  | N=368           |
| Total                            | 70 (19)         |
| Participant decision             | 27 (7)          |
| Investigator discretion          | 14 (4)          |
| Reported lack of efficacy        | 13 (4)          |
| AEs                              | 8 (2)           |
| Other reasons                    | 7 (2)           |
| Missing                          | 1 (<1)          |

AE, adverse event.
**Supplementary Figure 1.** Clinically significant asthma exacerbation rates in the pre-mepolizumab-treatment period* and 12-month follow-up period according to maintenance OCS use and dose, age at enrolment and prior omalizumab use

| Maintenance OCS (pre-mepolizumab treatment) | Exacerbation rate/person/year | Rate ratio (95% CI) (follow-up vs pre-treatment) |
|---------------------------------------------|-------------------------------|-----------------------------------------------|
| Never                                       | 4.26                          | 0.31 (0.24, 0.39)                              |
|                                             | 1.50                          | (n=108)                                       |
| Current or past                             | 4.76                          | 0.31 (0.27, 0.36)                              |
|                                             | 1.49                          | (n=256)                                       |
| <10 mg/day                                  | 4.95                          | 0.35 (0.28, 0.44)                              |
|                                             | 1.76                          | (n=72)                                        |
| ≥10 mg/day                                  | 4.73                          | 0.41 (0.32, 0.53)                              |
|                                             | 1.95                          | (n=87)                                        |

| Age group (at enrolment)                    | Rate ratio (95% CI) (follow-up vs pre-treatment) |
|---------------------------------------------|--------------------------------------------------|
| ≥65 years of age                            | 0.28 (0.21, 0.36)                                |
|                                             | 3.92                                            | (n=78)                                        |
| <65 years of age                            | 0.32 (0.27, 0.36)                                |
|                                             | 4.82                                            | (n=287)                                       |

| Prior treatment with omalizumab             | Rate ratio (95% CI) (follow-up vs pre-treatment) |
|---------------------------------------------|--------------------------------------------------|
| No                                          | 0.29 (0.25, 0.33)                                |
|                                             | 4.64                                            | (n=293)                                       |
| Yes                                         | 0.40 (0.30, 0.53)                                |
|                                             | 4.70                                            | (n=71)                                        |

*365 days prior to enrolment plus any exacerbations starting during run-in. †During the period including the index date and the 27 days prior to index, or any other 27-day period in the last 6 months if no records existed 27 days immediately prior to index.

CI, confidence interval; OCS, oral corticosteroid.
**Supplementary Table 2.** Baseline BEC and 12-month follow-up period according to maintenance OCS use and dose in the pre-mepolizumab-treatment period* and 12-month follow-up period

| Maintenance OCS status at baseline | BEC, cells/µL |       |       |
|-----------------------------------|---------------|-------|-------|
|                                   | Baseline      | Follow-up period (at month 9–12) |
| Not receiving (n=108)             |               |       |       |
| Geo mean (±SD log)                | 412 (1.092)   | –     |       |
| Median (Q1, Q3)                   | 500 (315, 800)| –     |       |
| LS geo mean at month 9–12 (95% CI)| 410 (330, 510)| 60 (40, 90) |     |
| LS mean ratio to baseline at month 9–12 (95% CI) | – | 0.14 (0.08, 0.22) |       |
| Receiving* (n=257)                |               |       |       |
| Geo mean (±SD log)                | 352 (1.308)   | –     |       |
| Median (Q1, Q3)                   | 410 (240, 800)| –     |       |
| LS geo mean at month 9–12 (95% CI)| 350 (300, 410)| 60 (50, 80) |     |
| LS mean ratio to baseline at month 9–12 (95% CI) | – | 0.18 (0.14, 0.24) |       |
| Receiving <10 mg/day (n=72)       |               |       |       |
| Geo mean (±SD log)                | 352 (1.118)   | –     |       |
| Median (Q1, Q3)                   | 384 (245, 740)| –     |       |
| LS geo mean at month 9–12 (95% CI)| 350 (270, 450)| 90 (60, 130) |     |
| LS mean ratio to baseline at month 9–12 (95% CI) | – | 0.25 (0.16, 0.38) |       |
| Receiving ≥10 mg/day (n=87)       |               |       |       |
| Geo mean (±SD log)                | 234 (1.460)   | –     |       |
| Median (Q1, Q3)                   | 300 (190, 600)| –     |       |
| LS geo mean at month 9–12 (95% CI)| 230 (180, 310)| 60 (30, 90) |     |
| LS mean ratio to baseline at month 9–12 (95% CI) | – | 0.23 (0.13, 0.41) |       |

*Also includes patients with past use of maintenance OCS (>26 weeks of a year).

BEC, blood eosinophil count; CI, confidence interval; Geo, geometric; LS, least squares; OCS, oral corticosteroids; SD, standard deviation; Q, quartile.