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Early View

Original article

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Mepolizumab in a population with severe eosinophilic asthma and corticosteroid dependence: results from a French early access programme

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Summary: Mepolizumab is associated with improvements in several clinically meaningful outcomes and demonstrates a favourable safety profile in a population with severe eosinophilic asthma, outside of the controlled environment of a clinical trial.

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Abstract

Background: Mepolizumab was available in France as part of an early access programme for patients with severe eosinophilic asthma (nominative Temporary Use Authorization [nATU]) before its commercialisation. This study aimed to characterise patients who received mepolizumab in the nATU.

Methods: This retrospective, observational study analysed data from the hospital medical records of patients up to 24 months after treatment initiation. Study objectives were to describe patient baseline characteristics, the evolution of disease severity and treatment modifications during follow-up; safety was also investigated.

Findings: Overall, 146 patients who received ≥1 dose of mepolizumab were included. At inclusion, patients had a mean age of 58.2 years with a mean severe asthma duration of 13.4 years, and 37.0% had respiratory allergies. Patients experienced on average 5.8 exacerbations/patient/year at baseline, 0.6 and 0.5 of which required hospitalisation and emergency department visits, respectively. These values improved to 0.6, 0.1 and 0.1 exacerbations/patient/year, respectively, at 24 months of follow-up. Most patients (92.8%) were using oral corticosteroids at baseline, compared with 34.7% by 24 months of follow-up. Moreover, mean blood eosinophil counts improved from 722 cells/µL at baseline to 92 cells/µL at 24 months of follow-up; lung function and asthma control followed a similar trend.

Interpretation: Results confirm findings from clinical trials, demonstrating that mepolizumab is associated with important improvements in several clinically meaningful outcomes and has a favourable safety profile in a population with severe eosinophilic asthma, outside of the controlled environment of a clinical trial.

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Keywords: Severe eosinophilic asthma; real-world data; medical records; mepolizumab; exacerbations; safety

Introduction

Asthma is a common respiratory disease affecting approximately 360 million people worldwide and an estimated 3.5–10.3% of the population in France [1, 2]. A small proportion of patients with asthma suffer from severe asthma [3], which consists of several clinically distinct phenotypes and endotypes [4-7]. The severe eosinophilic phenotype is characterised by persistent eosinophilic inflammation, reduced lung function and asthma control, and recurrent exacerbations despite the use of high-dose inhaled corticosteroids (ICS), other controllers and chronic or repeated use of systemic corticosteroids [4, 8].

Mepolizumab, an anti-interleukin-5 monoclonal antibody, selectively inhibits eosinophilic inflammation [9] and is approved as an add-on treatment for patients with severe eosinophilic asthma [10-12]. Randomised controlled trials (RCTs) have shown that compared with placebo, mepolizumab reduces the rate of exacerbations, decreases oral corticosteroid (OCS) dependence, and improves lung function, asthma control and health-related quality of life [13-16]. Although data from RCTs can confer critical insights into the clinical efficacy and safety of a therapy, these studies are often designed to meet one specific primary objective such as assessing changes in OCS dose or exacerbation rate. Moreover, RCTs can include a limited patient population, which is not reflective of the general asthma population, due to narrow eligibility criteria [17]. It is therefore also important to obtain data on the effects of a treatment outside the constraints of a formal clinical trial.

Mepolizumab was approved for use in patients with severe eosinophilic asthma in the European Union in December 2015 [10]. Patients in France were given access to mepolizumab before it became commercially available in February 2018, as part of an early access programme (nominative Temporary Use Authorization [nATU]), and were later reimbursed by Sécurité Sociale [18]. The nATU was restricted to patients deemed unable to wait for commercialisation due to disease severity. A protocol was established between the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) and the manufacturer (GSK), which mandated the patient monitoring procedure, collection of data relating to efficacy and safety and actual conditions of use. To understand the typical patient pathway and describe the characteristics of patients who received early mepolizumab treatment in a real-world setting, data collected during the nATU, plus data retrospectively collected from patient medical records, were analysed. The aim was to characterise patients

included in the nATU and describe disease severity evolution and treatment modifications up to 24 months after treatment initiation.

Methods

Study design and treatment

This retrospective, observational study (GSK ID: 207943; HO-17-18317) included data from hospital medical records of patients with severe eosinophilic asthma who started mepolizumab treatment (100 mg subcutaneously [SC] 4-weekly) in France as part of the nATU. Medical data mandated by the nATU protocol were collected from 9 June, 2015 to 2 March, 2016 (during the nATU) and from 2 March, 2016 to February 2018 (post-nATU), which allowed for a retrospective follow-up period of up to 24 months following treatment initiation. Data recorded during and after the nATU but not mandated by the nATU protocol were also included. This study was declared to the Expert Committee for Research, Studies and Evaluations in Health on 21 December, 2017, and the declaration of compliance with reference methodology MR003 was made to the National Commission for Data Protection and Liberties on 8 January, 2018.

Participating medical centres

Participating medical centres had ≥3 patients in the nATU and agreed to their participation. The majority of pulmonology departments involved in this study were based at University hospitals (further details in Supplementary Section 1).

Patients

Patients enrolled in the nATU received ≥1 injection of mepolizumab at a participating centre, evidenced by physician-completed treatment access forms. All delays of 4 weeks ± 1 week between two consecutive mepolizumab injections were to be reported. To justify the request for mepolizumab and help inform subsequent validation by the ANSM and GSK, physicians were required to certify that: the patient had severe eosinophilic asthma (without features of eosinophilic granulomatosis with polyangiitis); no other suitable treatment options were currently available; inclusion in a RCT wasn't possible; the patient's clinical health status required an urgent change of treatment to avoid severe exacerbations and/or severe steroid side effects. Treatment access forms included information on blood eosinophil counts, exacerbation rates, symptom control and OCS dose. No strict eligibility

criteria were described to allow the request validation by GSK and patients had to be willing to disclose their personal medical records.

Endpoints and assessments

The primary objective was to describe the profile of patients included in the nATU, using additional data to those collected within the nATU. Baseline characteristics were assessed over the 12 months preceding mepolizumab initiation, and included: asthma duration; smoking history; geographic localisation; comorbidities; employment status; asthma-induced disability; socio-economic status; complementary health insurance status; number of asthma-related exacerbations, including those requiring hospitalisation or an emergency department (ED) visit; atopic status; blood immunoglobulin-E (IgE), eosinophil and neutrophil levels; OCS dose; previous treatment adherence (estimated by investigators); forced expiratory volume in 1 second (FEV_1); FEV_1/forced vital capacity (FVC) ratio. Asthma exacerbations were defined as disease worsening requiring an ED visit, hospitalisation, and/or use of OCS for ≥48 hours or an increase of ≥50% in daily OCS dose . Atopic status was determined by ≥1 positive skin prick test or allergen-specific IgE blood test (IgE level >0.1 UI).

Secondary objectives were to describe the evolution of disease control and treatment modifications during the follow-up period (≤24 months after mepolizumab initiation). To assess these, we examined: the number of exacerbations and how they were managed (e.g. whether OCS, an ED visit and/or hospitalisation were required); FEV_1; FEV_1/FVC ratio; mepolizumab withdrawal date and reason (if applicable). Asthma exacerbation rates and OCS use/dose were also analysed by blood eosinophil count at inclusion (<300, 300-<500, 500-<700 and ≥700 cells/µL) and an analysis to evaluate the different levels of patients' responses to mepolizumab over the first 12 months of treatment (based on a ≥50% reduction in exacerbation rate and a ≥50% reduction in OCS dose) was also performed (Supplementary Sections 2 and 3). Safety endpoints included: incidence of adverse events (AEs); serious AEs (SAEs); AEs of interest.

Statistical analyses

Mean asthma exacerbation rates were reported as exacerbations/patient/year; the evolution of exacerbation rates was analysed using a Poisson regression model. A trend analysis was performed on the FEV_1, FVC, FEV_1/FVC ratio data, Asthma Control Test (ACT)

scores and blood eosinophil counts across the inclusion and follow-up periods using a mixed linear model with repeated measurements. A Kaplan–Meier method was used to estimate the duration of treatment with mepolizumab. Statistical analysis was conducted using SAS software (version 9.4 SAS institute Inc., Cary, NC, USA).

Results

Patient population

Of the 160 patients included in the nATU, 146 (91.9%) from 20 participating centres receiving ≥1 injection of mepolizumab were included in this study; 13 (8.1%) patients did not receive mepolizumab and were excluded (Supplementary Figure 1). One patient received mepolizumab to treat severe chronic obstructive pulmonary disease, while awaiting a lung transplantation, and was considered ineligible by the Scientific Committee and excluded from all analyses except the safety analyses. Overall, 61 patients (41.8%) had 103 injections with a delay >4 weeks. The reasons for these delays were only documented for 19 injections and included departure for holidays, death of a relative, health problem unrelated to mepolizumab and patient forgot.

Baseline demographics and clinical characteristics are outlined in Table 1. Of the 62 patients with confirmed allergies, 54 (87.1%) were sensitised to aeroallergens (pollen, dander, mould, cockroaches), 12 (19.4%) had food allergies and 5 (8.1%) had skin allergies. Almost all patients (93.8%) had ≥1 comorbidity; the most common were ear, nose and throat pathologies (56.2%), cardiovascular diseases (35.0%) and gastroesophageal reflux disease (38.7%) (Table 1). In addition, 38.7% of patients had nasal polyps, 17.5% had allergic rhinits and 16.1% had aspirin-exacerbated respiratory disease. Furthermore, most patients (92.8%) were receiving OCS at inclusion (mean daily dose 20.6 ± 16.5 mg prednisolone equivalent), and 65.9% had previously received omalizumab (Table 1).

In the 12 months preceding mepolizumab initiation, the mean rate of exacerbations was 5.8 events/patient/year, 0.6 and 0.5 of which required hospitalisation and emergency department visits (Table 2). The mean blood eosinophil count at baseline was 722 cells/µl and a large proportion (n=115; 86.5%) of patients reported their asthma as having a significant impact on their daily activities.

Follow-up data

Patients attended on average 8.4 follow-up visits after treatment initiation; the mean follow-up duration was 24.2 months owing to some patients infrequently returning to hospital and having a final visit date that exceeded 24 months. Consecutive injections of mepolizumab were administered on average 4.2 weeks apart. A total of 48 patients discontinued mepolizumab during follow-up with the majority reporting a lack of efficacy or lack of efficacy associated with an AE (n=29) (Supplementary Table 1). Three months after their first injection, 91% of patients were still receiving mepolizumab; this reduced to 81% by 6 months and subsequently to 69% and 66% at Months 12 and 24.

Mean exacerbation rates for total exacerbations and for those requiring hospitalisation and ED visits were lower on-treatment than at baseline (Table 2); this trend was observed regardless of blood eosinophil counts at inclusion (Supplementary Table 2). Compared with baseline, fewer patients used maintenance OCS during follow-up (92.8% at baseline vs 41.1% and 34.7% at 12 and 24 months) and those still using OCS required lower doses (Figure 1); similar trends were seen when data were stratified by blood eosinophil counts at inclusion (Supplementary Figure 3 and Supplementary Table 3). Mean percent-predicted pre-bronchodilator FEV_1 improved versus baseline at all follow-up time points; mean FEV_1 steadily increased to approximately 70% of the predicted value during the first 10 months of treatment and then stabilised (Figure 2A). Mean FEV_1/FVC ratios also increased during the first 10 months of treatment and then stabilised. After 3 months of mepolizumab the mean ACT score was 17.4 points; this surpassed the minimal clinically important difference (MCID) of ≥3 points from baseline (10.2 points) and the response was sustained throughout the study period (Figure 2B and 2C). Mean (standard deviation) baseline blood eosinophil counts (cells/μL) decreased from 722 (± 500.0) to 101 (± 83.9) at 3 months, 75 (± 63.7) at 12 months, and 92 (± 72.3) at 24 months (Figure 3).

Safety

During the study, 276 pharmacovigilance events were reported by 100 patients. Of these, 103 corresponded to drug misuse (all reporting an incorrect dosing interval); 173 were identified as AEs possibly related to mepolizumab according to patients' medical records. A total of 99 patients reported 159 non-serious AEs; 41 patients discontinued mepolizumab as a result of these events (29 reported "drug considered ineffective"). The most commonly

reported AEs which were possibly drug-related (n ≥5% of events) included: drug considered ineffective (n=31); headache (n=14); asthenia (n=12); and asthma (n=10) (Table 3). AEs of interest included five events in the System Organ Class (SOC) category "Infections and infestations", five events in "Vascular disorders", two events related to "allergic and non-allergic reactions" and one event in "local injection site reactions" (Table 4). A total of eight patients reported 14 SAEs that were possibly drug-related; the most common was asthma (n=3 events). In this study, no patients experienced severe systemic reactions, severe cardiac AEs or neoplasms. One death was reported (resulting from an asthma exacerbation) and deemed unrelated to mepolizumab by the physician.

Discussion

Early access programmes (e.g. the nATU) allow patients who do not meet the strict eligibility criteria for RCTs, but might still benefit from mepolizumab treatment, to gain access to the drug before its commercialisation. Moreover, data collected from these programmes can provide insights on the wider use of mepolizumab in a patient population that closely resembles real life [19]. Here, we investigated the effectiveness and safety of mepolizumab using data from patients with severe eosinophilic asthma enrolled in the nATU. We found that mepolizumab was associated with several clinical benefits, including clinically meaningful reductions in exacerbations and daily OCS doses, consistent with results from two RCTs that assessed these outcomes separately [14].

We identified several indicators of severe disease among patients in the nATU, which included high annual exacerbation rates, with most patients requiring maintenance OCS and experiencing a considerable disease burden. The degree of disease severity among these patients was generally greater than that of those enrolled in RCTs. For instance, patients enrolled in the Phase III MENSA and MUSCA studies had a mean rate of 2.7–3.8 exacerbations/year before screening (vs 5.8 in this study) [13, 15]. Additionally, the proportion of patients in this study requiring maintenance OCS at inclusion was higher (92.8%) than in the MENSA and MUSCA studies (23–27%) [13, 15]. These findings are not unexpected, since patients in the nATU had a justified need to receive mepolizumab before it became commercially available. There also appears to be an over-representation of late-onset, eosinophilic asthma with nasal polyposis in the nATU population compared with the MUSCA trial (38.7% of patients in the nATU vs 17–21% in MUSCA) [15]. Nonetheless, disease severity in this study was similar to that of a real-world study of patients receiving

omalizumab [20] and other early access programmes, including the omalizumab and dupilumab ATUs in France [21, 22].

The prevention of exacerbations remains an important therapeutic target for patients with asthma [23]. In this study, we observed an 86.2% reduction from baseline in exacerbation rate after both 12 and 24 months of follow-up. In MENSA and MUSCA, exacerbation rates were reduced by 53% and 58% following 32 and 24 weeks with mepolizumab (100 mg SC) versus placebo [14, 15]. Other studies based on real-world data have also associated mepolizumab with a reduction in exacerbations [24-27]; in one recent example (N=25), 82.6% of patients experienced fewer exacerbations and 47.8% experienced no exacerbations on-treatment [24]. When we analysed data by blood eosinophil count at inclusion, reductions in exacerbation rate and OCS use/dose were seen across all subgroups (although the sample sizes were small). Interestingly, the rates of exacerbations requiring hospitalisation were low considering the severity of disease among the study population. This may be owing to the majority of patients being recruited in University hospitals specialising in severe asthma, where patients typically have action plans to facilitate disease management.

We found that approximately 33.0% and 62.5% of patients receiving mepolizumab experienced ≥50% reductions in daily OCS dose at 6 and 12 months (Supplementary Section 2). Montero-Perez *et al* also reported that approximately 60% of patients experienced a reduction in OCS dose after 12 months of treatment (although this was not limited to reductions ≥50%) [24]. It should be noted that in the SIRIUS RCT, ≥50% reductions in daily OCS dose from baseline were observed among 54% of patients following 6 months of mepolizumab treatment [14]. Although this is a greater proportion of patients than in our study, OCS doses are typically lowered more gradually in a real-world setting than in the down-titration protocols followed in RCTs. It is therefore likely that OCS tapering was conducted more slowly in our study than in SIRIUS, as supported by peak improvements in FEV_1 and ACT score after 6 months of mepolizumab in the nATU. Moreover, we observed a relapse in OCS use/dose at 24 months of follow-up. However, this may be explained by differences in the number of patients between timepoints (18 months; n=91 and 24 months; n=75).

With regards to safety, we found that over the 24-month study period, headache and asthma were the most-commonly reported AEs and the occurrence of allergic, non-allergic,

and injection-site reactions was low. These results are in agreement with those from RCTs [14, 15], and indicate that mepolizumab is well-tolerated in a setting that more closely resembles real life. During the nATU 48 patients discontinued mepolizumab, 11 of whom reported a lack of drug efficacy associated with AEs. The high discontinuation rate observed (32.9%) may be explained by mepolizumab being a new product at the time of the study with no market approval, and thus no available stopping rules or guidelines. As such, physicians could stop treatment after a few months if no benefit was seen.

The main limitation of this study was the retrospective nature of the data collection and analysis. It should be noted that ACT score data were missing for approximately 40–60% of patients, although we did observe changes from baseline in ACT scores that exceeded the MCID in those patients with data available. The patients who discontinued mepolizumab in this study (owing to AEs or lack of efficacy) were not included in the safety and efficacy results; since these measures depend on both the number of patients participating in the analysis and the duration of treatment, the data reported should be interpreted with caution. In addition, baseline ICS doses were not recorded in the medical data used for this study; these therefore could not be included in our assessments of baseline characteristics and evolution of disease among the nATU patient population. Results may also be subject to confounding factors such as more stringent compliance, resulting from the regular contact with healthcare professionals that is required for biologic administration, or from patients having previously received another biologic therapy (e.g. omalizumab). Finally, patients in this study had particularly severe disease, based on the nATU criteria for early access to treatment, and were treated at University hospitals with expertise in managing severe asthma. As a result, our data may not be reflective of the overall severe asthma population, particularly those who receive care outside of this environment.

Nonetheless, these data from patients with severe eosinophilic asthma who received mepolizumab in the French early access programme confirm the effectiveness of mepolizumab in reducing exacerbation rates and OCS dependency as well as improving lung function in a setting which closely resembles real-life use. In addition, safety findings were consistent with those observed in clinical trials. Although additional studies are needed to fully assess the safety and effectiveness of mepolizumab in real-world, long-term, clinical practice, this analysis provides useful information for physicians who are considering treatment options for their patients with severe eosinophilic asthma.

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Conflicts of interests

CT declares: consultancy services, speaking at conferences, and participation in clinical research projects with GSK, AstraZeneca, Novartis, Roche, Sanofi, Chiesi and TEVA. PC has acted as a consultant for Boehringer Ingelheim, Johnson & Johnson, GSK, Merck Sharp & Dohme, AstraZeneca, Novartis, Teva, Chiesi, and Sanofi, has served on advisory boards for Almirall, Boehringer Ingelheim, Johnson & Johnson, GSK, AstraZeneca, Novartis, Teva, Chiesi, and Sanofi, reports lecture fees from Boehringer Ingelheim, Centocor, GSK, AstraZeneca, Novartis, Teva, Chiesi, Boston Scientific, and ALK-Abelló, and has received industry-sponsored grants from Roche, Boston Scientific, Boehringer Ingelheim, Centocor, GSK, AstraZeneca, ALK-Abelló, Novartis, Teva, and Chiesi. GD declares: consultancy for Novartis Pharma, AstraZeneca, GSK, Boehringer Ingelheim, Mundi Pharma, Vivisol, TEVA and ALK; participation at medical meetings for GSK, AstraZeneca, Novartis Pharma, Chiesi, MSD, Takeda, AGIR à dom, Orkyn, TEVA, Mundi Pharma, ALK, and Stallergène; participation in clinical research projects for GSK, ALK, Novartis Pharma, Boehringer Ingelheim, Vitalair, AB

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References

1. Soriano JB, Abajobir AA, Abate KH, Abera SF, Agrawal A, Ahmed MB, Aichour AN, Aichour I, Aichour MTE, Alam K. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet Respiratory Medicine* 2017: 5(9): 691-706.
2. European Academy of Allergy and Clinical Immunology. Global Atlas of Asthma. 2013 [cited 2019 September]; Available from: http://www.eaaci.org/GlobalAtlas/Global_Atlas_of_Asthma.pdf
3. Hekking P-PW, Wener RR, Amelink M, Zwinderman AH, Bouvy ML, Bel EH. The prevalence of severe refractory asthma. *Journal of Allergy and Clinical Immunology* 2015: 135(4): 896-902.
4. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, Adcock IM, Bateman ED, Bel EH, Bleecker ER. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *European respiratory journal* 2014: 43(2): 343-373.
5. Pavord ID, Beasley R, Agusti A, Anderson GP, Bel E, Brusselle G, Cullinan P, Custovic A, Ducharme FM, Fahy JV. After asthma: redefining airways diseases. *The Lancet* 2018: 391(10118): 350-400.
6. Kuruvilla ME, Lee FE-H, Lee GB. Understanding asthma phenotypes, endotypes, and mechanisms of disease. *Clinical reviews in allergy & immunology* 2019: 56(2): 219-233.
7. Holguin F, Cardet JC, Chung KF, Diver S, Ferreira DS, Fitzpatrick A, Gaga M, Kellermeyer L, Khurana S, Knight S. Management of Severe Asthma: a European Respiratory Society/American Thoracic Society Guideline. *European respiratory journal* 2019: 1900588.
8. Buhl R, Humbert M, Bjermer L, Chanez P, Heaney LG, Pavord I, Quirce S, Virchow JC, Holgate S. Severe eosinophilic asthma: a roadmap to consensus. *Eur Respiratory Soc* 2017: 1;49(5): pii: 1700634.
9. Menzella F, Lusuardi M, Galeone C, Taddei S, Zucchi L. Profile of anti-IL-5 mAb mepolizumab in the treatment of severe refractory asthma and hypereosinophilic diseases. *Journal of asthma and allergy* 2015: 8: 105.
10. European Medicines Agency. Assessment Report - Nucala. July 2018 [cited 2019 July]; Available from: https://www.ema.europa.eu/en/documents/variation-report/nucala-h-c-3860-ii-0013-g-epar-assessment-report-variation_en.pdf
11. GlaxoSmithKline. Mepolizumab (NUCALA) US prescribing information. September 2019 [cited 2019 July]; Available from: https://gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Nucala/pdf/NUCALA-PI-PIL.PDF
12. Global Initiative for Asthma. Global strategy for asthma management and prevention. June 2019 [cited 2019 July]; Available from: https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf
13. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, Humbert M, Katz LE, Keene ON, Yancey SW, Chanez P, Investigators M. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014: 371(13): 1198-1207.
14. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, Ortega HG, Pavord ID, Investigators S. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med* 2014: 371(13): 1189-1197.
15. Chupp GL, Bradford ES, Albers FC, Bratton DJ, Wang-Jairaj J, Nelsen LM, Trevor JL, Magnan A, Ten Brinke A. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised,

double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. *Lancet Respir Med* 2017: 5(5): 390-400.
16. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, Ortega H, Chanez P. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *The Lancet* 2012: 380(9842): 651-659.
17. Pahus L, Alagha K, Sofalvi T, Vachier I, Bourdin A, Molinari N, Chanez P. External validity of randomized controlled trials in severe asthma. *American journal of respiratory and critical care medicine* 2015: 192(2): 259-261.
18. Launet Q, Brouard A, Doreau C. Drugs under temporary use authorisation: 50 years of French drug development. *Revue d'histoire de la pharmacie* 2004: 52(341): 47-54.
19. Patil S. Early access programs: Benefits, challenges, and key considerations for successful implementation. *Perspectives in clinical research* 2016: 7(1): 4–8.
20. Humbert M, Taillé C, Mala L, Le Gros V, Just J, Molimard M. Omalizumab effectiveness in patients with severe allergic asthma according to blood eosinophil count: the STELLAIR study. *European Respiratory Journal* 2018: 51(5): 1702523.
21. Molimard M, de Blay F, Didier A, Le Gros V. Effectiveness of omalizumab (Xolair) in the first patients treated in real-life practice in France. *Respiratory medicine* 2008: 102(1): 71-76.
22. Caminati M, Cegolon L, Vianello A, Chieco Bianchi F, Festi G, Marchi MR, Micheletto C, Mazza F, Tognella S, Senna G. Mepolizumab for severe eosinophilic asthma: a real-world snapshot on clinical markers and timing of response. *Expert review of respiratory medicine* 2019: 13(12): 1205-1212.
23. Bourdin A, Bjermer L, Brightling C, Brusselle GG, Chanez P, Chung KF, Custovic A, Diamant Z, Diver S, Djukanovic R. ERS/EAACI statement on severe exacerbations in asthma in adults: facts, priorities and key research questions. *European respiratory journal* 2019: 54(3): 1900900.
24. Montero-Pérez O, Contreras-Rey MB, Sánchez-Gómez E. Effectiveness and safety of mepolizumab in severe refractory eosinophilic asthma: results in clinical practice. *Drugs in context* 2019: 8.
25. Strauss RA, Jawhari N. Mepolizumab in the treatment of severe eosinophilic asthma: Results from a physician in the field. *Annals of Allergy, Asthma & Immunology* 2018: 121(1): 121-123.
26. Bagnasco D, Caminati M, Menzella F, Milanese M, Rolla G, Lombardi C, Bucca C, Heffler E, Paoletti G, Testino E. One year of mepolizumab. Efficacy and safety in real-life in Italy. *Pulmonary pharmacology & therapeutics* 2019: 58: 101836.
27. Pertzov B, Unterman A, Shtraichman O, Shitenberg D, Rosengarten D, Kramer MR. Efficacy and safety of mepolizumab in a real-world cohort of patients with severe eosinophilic asthma. *Journal of Asthma* 2019: 1-6.

Table 1. Baseline demographics and clinical characteristics

	Total N=146
Age, years	58.2 (13.6)
Sex, n (%)	
Female	66 (45.2)
BMI, kg/m^2	N=137
	27.2 (5.1)
Patients with BMI ≥30, n (%)	32 (21.9)
Duration of severe asthma, years	N=128
	13.4 (12.1)
Respiratory allergies, n (%)	54 (37.0)
Disability due to asthma*, n (%)	N=127
	29 (22.8)
Smoking, n (%)	N=145
Current	11 (7.6)
Never smoked	77 (53.1)
Blood eosinophil count, cells/µL	N=130
	721.7 (500.0)
Blood IgE total level, kIU/L	N=78
	563.4 (773.0)
Blood neutrophil count, Giga/L	N=120
	6.4 (3.5)
ACT score	N=62
	10.2 (4.5)
FEV_1, mL	N=142
	1883.0 (823.2)
FEV_1, % predicted value	N=142
	62.0 (19.4)
FEV_1/FVC ratio	N=58
	58.8 (12.5)
Comorbidities, n (%)	
Any comorbidity	137 (93.8)
AERD	22 (16.1)
Allergic rhinitis	24 (17.5)
Cardiovascular disease	48 (35.0)
Depression/anxiety	29 (21.2)
Diabetes	26 (19.0)
Dyslipidemia	17 (12.4)
GERD	53 (38.7)
Nasal polyps	53 (38.7)
Osteoporosis	51 (37.2)
Other comorbidities	46 (33.6)
Sleep apnoea syndrome	31 (22.6)

Smoking/smoking-related comorbidities	8 (5.8)
Prior omalizumab treatment, n (%)	91 (65.9)
Current treatment, n (%)	
OCS	128 (92.8)
Methylprednisolone	2 (1.6)
Prednisolone	11 (8.9)
Prednisone	111 (89.5)
Other anti-asthmatic treatment	136 (93.2)

All values are mean (standard deviation) unless otherwise stated; data were available for all patients unless otherwise stated. Blood eosinophil count was the highest value in the previous 12 months.

*Declarative item.
ACT, Asthma Control Test; AERD, aspirin exacerbated respiratory disease; BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; IgE, immunoglobulin E; OCS, oral corticosteroid.

Table 2. Summary of exacerbations during the baseline and follow-up periods

	Baseline (N=134)	**12 months (N=96)**	**24 months (N=75)**
Patients with no exacerbations, n (%)	-	48 (50.0)	34 (45.3)
Exacerbations, mean (SD) events/patient/year	5.8 (4.4)	0.8 (1.1)	0.8 (0.9)
Exacerbations requiring hospitalisation, mean (SD) events/patient/year	0.6 (1.5)	0.1 (0.4)	0.1 (0.4)
Exacerbations requiring an ED visit, mean (SD) events/patient/year	0.5 (0.9)	0.1 (0.3)	0.1 (0.3)

At baseline, 12 patients had missing data. At months 12 and 24 of follow-up, 42 and 31 patients had discontinued treatment, and 8 and 40 had no follow-up, respectively.

ED, emergency department; SD, standard deviation.

Table 3. AEs and SAEs considered possibly related to study drug, according to patient medical records

Event SOC/PT	**Number of events (%)**	**Number of patients**
Total	**173**	**100**
AEs possibly related to mepolizumab	**159**	**99**
General disorders and administration site conditions	62 (39.0)	46
Nervous system disorders	24 (15.1)	20
Respiratory, thoracic and mediastinal disorders	21 (13.2)	13
Gastrointestinal disorders	14 (8.8)	10
Musculoskeletal and connective tissue disorders	10 (6.3)	7
Skin and subcutaneous tissue disorders	9 (5.7)	9
Vascular disorders	5 (3.1)	4
Infections and infestations	3 (1.9)	2
Injury, poisoning and procedural complications*	2 (1.3)	2
Renal and urinary disorders	2 (1.3)	2
Cardiac disorders	1 (0.6)	1
Ear and labyrinth disorders	1 (0.6)	1
Eye disorders	1 (0.6)	1
Immune system disorders	1 (0.6)	1
Investigations	1 (0.6)	1
Pregnancy, puerperium and perinatal conditions	1 (0.6)	1
Reproductive system and breast disorders	1 (0.6)	1
SAEs possibly related to mepolizumab	**14**	**8**
Respiratory, thoracic and mediastinal disorders	4 (28.6)	2
Musculoskeletal and connective tissue disorders	3 (21.4)	1
General disorders and administration site conditions	2 (14.3)	2
Nervous system disorders	2 (14.3)	2
Infections and infestations	2 (14.3)	2
Hepatobiliary disorders	1 (7.1)	1
Most common drug-related AEs and SAEs possibly related to		

mepolizumab (n≥5%)		
Drug ineffective	31 (17.9[†])	30
Headache	14 (8.1[†])	14
Asthma[‡]	13 (7.5[†])	3
Asthenia	12 (6.9[†])	12

*Excluding 103 events of inappropriate schedule of product administration for 61 patients; [†]% of total drug-related AEs and SAEs (N=173); [‡]included exercise induced asthma, asthmatic crisis, and aggravated condition. AE, adverse event; PT, preferred term; SAE, serious adverse event; SOC, System Organ Class.

Table 4. Adverse events of interest (N=15)

Event SOC/PT	n (%)
AEs related to allergic and non-allergic reactions	2 (13.3)
Generalised rash	1 (6.7)
Rash	1 (6.7)
Local injection-site reactions	1 (6.7)
Injection-site erythema	1 (6.7)
Infections*	5 (33.3)
Herpes virus infection	1 (6.7)
Oral herpes	1 (6.7)
Pharyngitis	1 (6.7)
Pneumonia†	1 (6.7)
Purulent sputum†	1 (6.7)
Malignancies‡	–
Vascular disorders	5 (33.3)
Hot flush	3 (20.0)
Capillary fragility	1 (6.7)
Hypertension	1 (6.7)
Cardiac disorders	
Palpitations	1 (6.7)

*based on the Infections and infestations SOC; †Events deemed serious by the treating investigator; ‡based on the Neoplasms SOC; – not reported.

PT, preferred term; SOC, System Organ Class.

Figure 1. (A) Change in mean OCS dose and **(B)** proportion of patients not receiving maintenance OCS during follow-up period

*mg prednisolone equivalent. At baseline, 8 patients had missing data. At months 12 and 24 of follow-up, 42 and 31 patients had discontinued treatment, and 8 and 40 had no follow-up, respectively.
OCS, oral corticosteroid; SD, standard deviation.

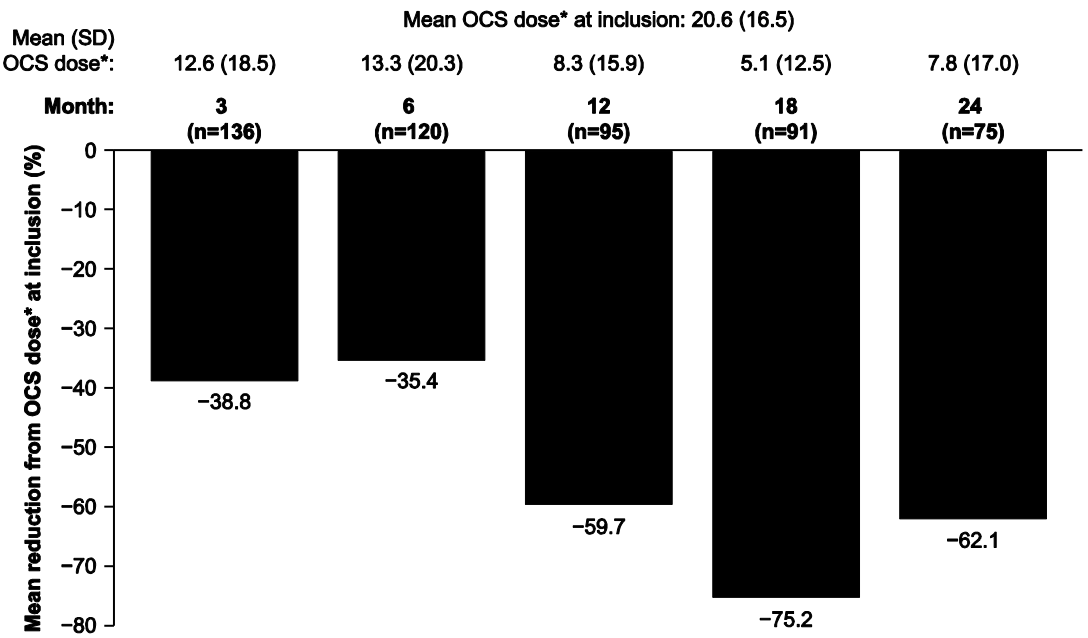
Figure 2. (A) Evolution of percent-predicted pre-bronchodilator FEV_1, **(B)** FEV_1/FVC ratio, and **(C)** ACT score during the follow-up period

Continuous lines represent evolution of each score; dotted lines indicate the confidence interval.
ACT, Asthma Control Test; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

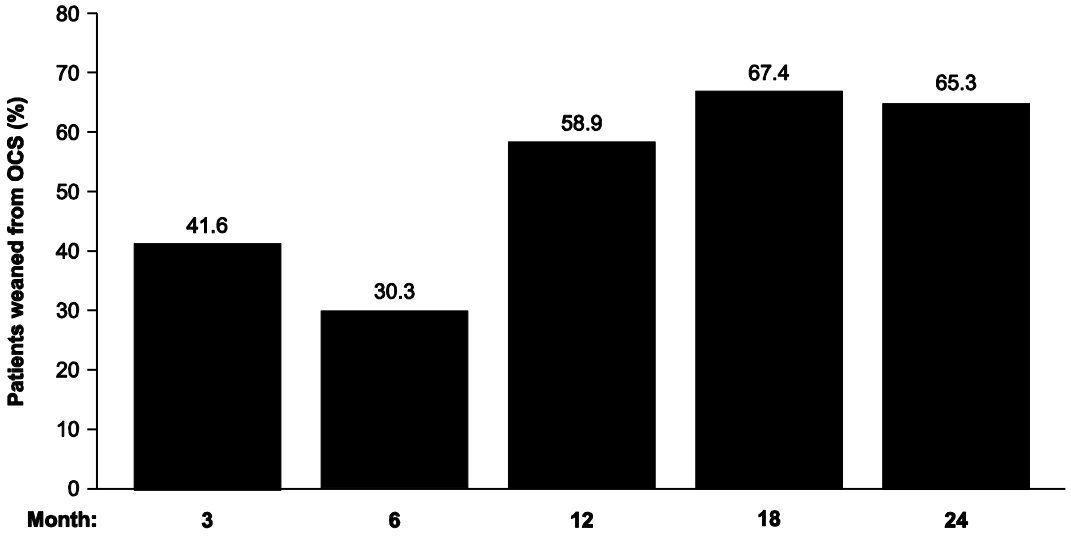
Figure 3. Evolution of eosinophil counts during the follow-up period

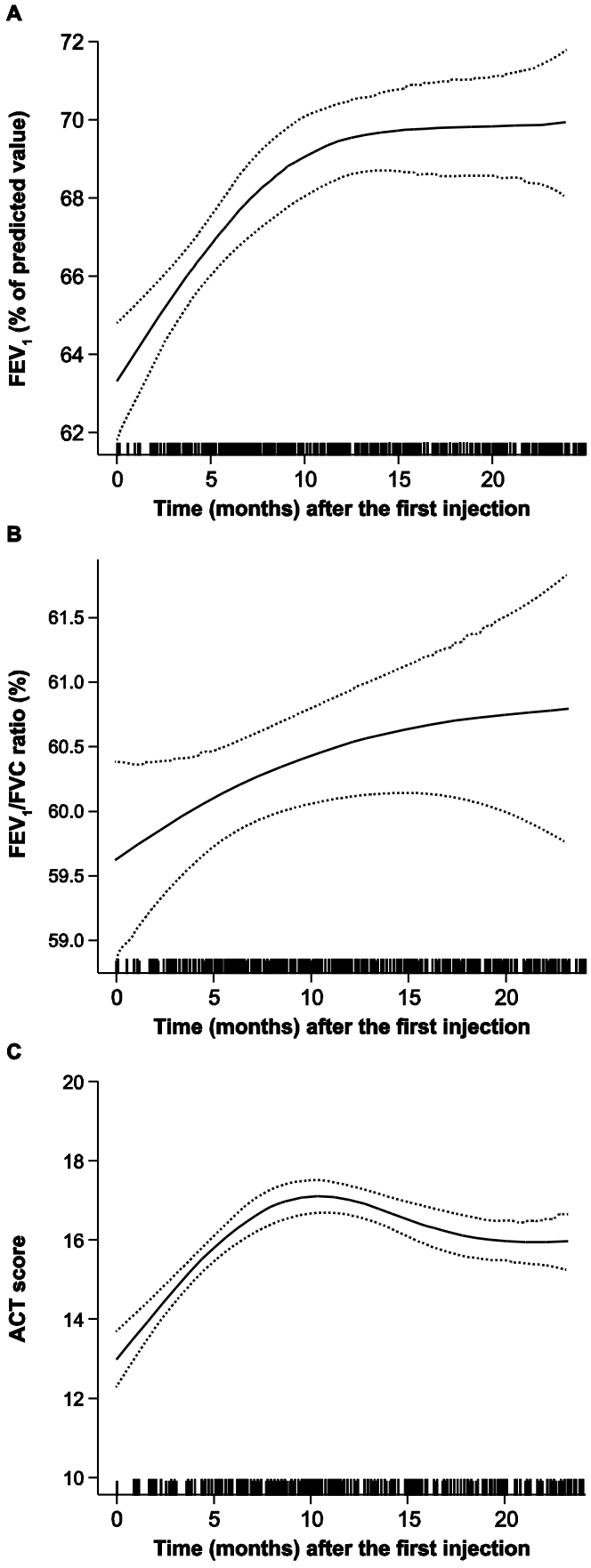
Continuous lines represent evolution of each score; dotted lines indicate the confidence interval.

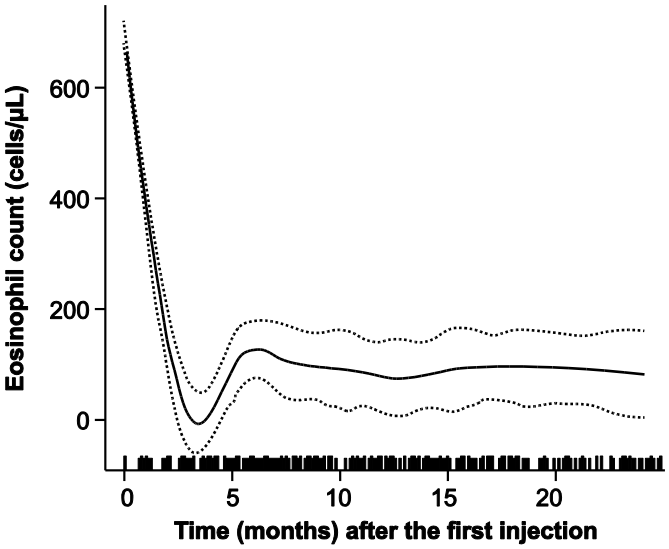
A


Mean OCS dose* at inclusion: 20.6 (16.5)
Mean (SD) OCS dose*:
12.6 (18.5)
13.3 (20.3)
8.3 (15.9)
5.1 (12.5)
7.8 (17.0)
Month:
3 (n=136)
6 (n=120)
12 (n=95)
18 (n=91)
24 (n=75)
Mean reduction from OCS dose* at inclusion (%)
0
−10
−20
−30
−40
−50
−60
−70
−80
−38.8
−35.4
−59.7
−75.2
−62.1

B


Patients weaned from OCS (%)
80
70
60
50
40
30
20
10
0
41.6
30.3
58.9
67.4
65.3
Month:
3
6
12
18
24


A
72
70
68
66
64
62
FEV1 (% of predicted value)
0
5
10
15
20
Time (months) after the first injection
B
61.5
61.0
60.5
60.0
59.5
59.0
FEV1/FVC ratio (%)
0
5
10
15
20
Time (months) after the first injection
C
20
18
16
14
12
10
ACT score
0
5
10
15
20
Time (months) after the first injection


Eosinophil count (cells/µL)
600
400
200
0
0
5
10
15
20
Time (months) after the first injection

Supplementary materials

Mepolizumab in a population with severe eosinophilic asthma and corticosteroid dependence: results from a French early access programme

Taillé *et al.*

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Contents

Supplementary Table 3. Mean OCS dose during the baseline and follow-up periods stratified by blood eosinophil count at inclusion

Supplementary Section 1. Further information on participating medical centres

University hospitals were part of the Clinical Research Initiative in Severe Asthma Network and the Clinical Research Initiative in Severe Asthma: a Lever for Innovation & Science, and were officially recognised by the Institut national de la santé et de la recherche médicale (French Clinical Research Infrastructure Network). At all centres, treatment access and follow-up medical records were filed by a clinical research assistant.

Supplementary Section 2. Analysis to evaluate the different levels of patients' responses to mepolizumab treatment

Methods

An analysis was conducted to evaluate the different levels of patients' responses to mepolizumab over the first 12 months of treatment. Two criteria, a ≥50% reduction in exacerbation rate and a ≥50% reduction in oral corticosteroid (OCS) dose, were evaluated by paired analysis (Chi-squared test). The level of treatment response was categorised into four groups: i) ≥50% reduction in exacerbation rate and an OCS dose reduction; ii) ≥50% reduction in exacerbation rate and ≥50% OCS dose reduction; iii) ≥50% reduction in exacerbation rate and no requirement for maintenance OCS; iv) no exacerbations and no maintenance OCS requirement.

Results

In the 6 months following mepolizumab initiation, 31.8% of patients had ≥50% reductions in exacerbation rate and ≥50% reductions in OCS daily dose; in the 12 months following treatment initiation this proportion increased to 57.1% of patients. The proportions of patients who had no exacerbations and no requirement for maintenance OCS at 6 months and at 12 months following treatment initiation were 20.6% and 41.7%, respectively. (Supplementary Figure 2)

Supplementary Section 3. Analysis to evaluate the efficacy outcomes (exacerbation rate and OCS dose) according to blood eosinophil count at inclusion

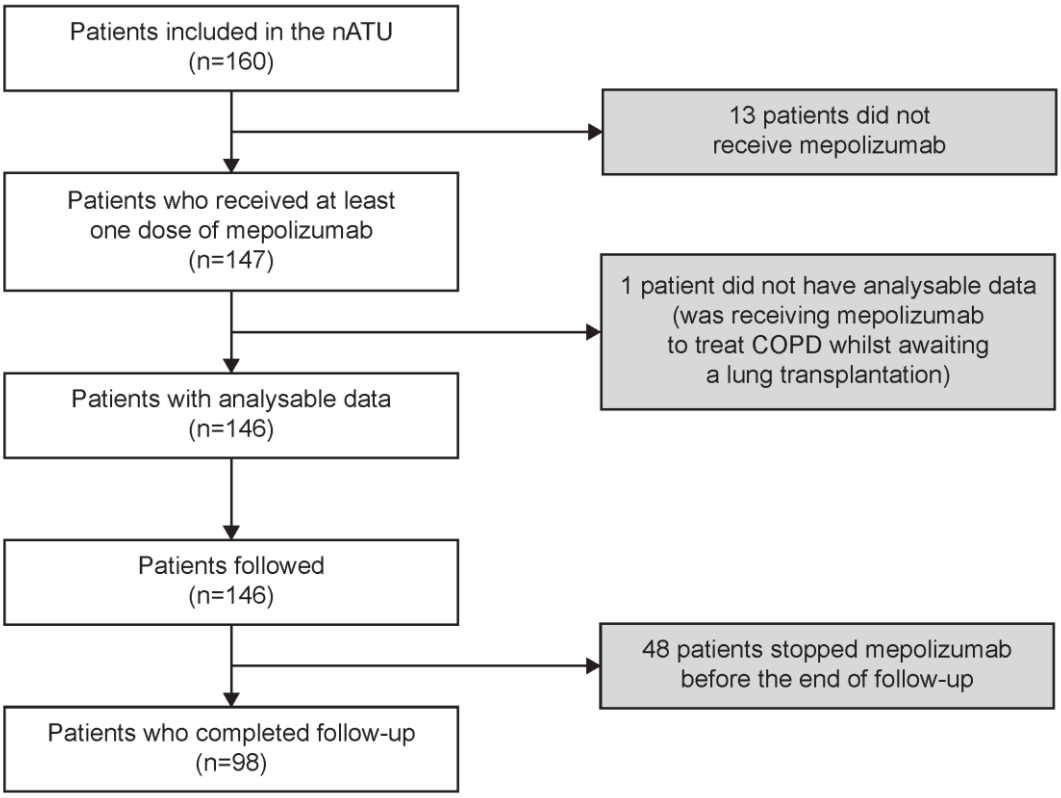
Methods

An analysis was conducted to evaluate the mean rate of asthma-related exacerbations, including those requiring hosptialisation or an emergency department (ED) visit, and mean OCS dose over the 24 months after treatment initiation, stratified by blood eosinophil count at inclusion. Four blood eosinophil count thresholds were used for this analysis; <300, 300–<500, 500–<700 and ≥700 cells/µL.

Results

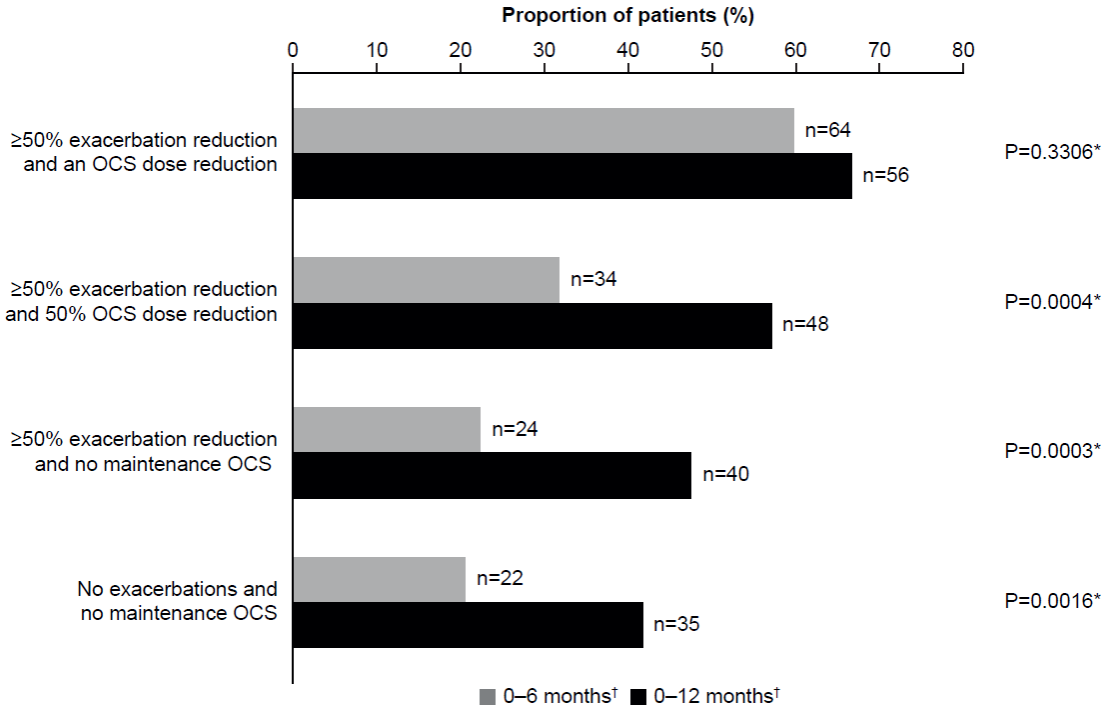
In the 12 and 24 months following mepolizumab treatment initiation, reductions in exacerbation rate were seen irrespective of blood eosinophil counts and the proportion of patients with no exacerbations was highest in the ≥700 cells/µL subgroup (Supplementary Table 2). Reductions in the mean OCS dose from baseline to follow-up were also seen regardless of blood eosinophil count at inclusion, although the reduction was smallest in the 300–<500 cells/µL subgroup (Supplementary Figure 3 and Supplementary Table 3).

Supplementary Figure 1. Summary of patient inclusion and follow-up



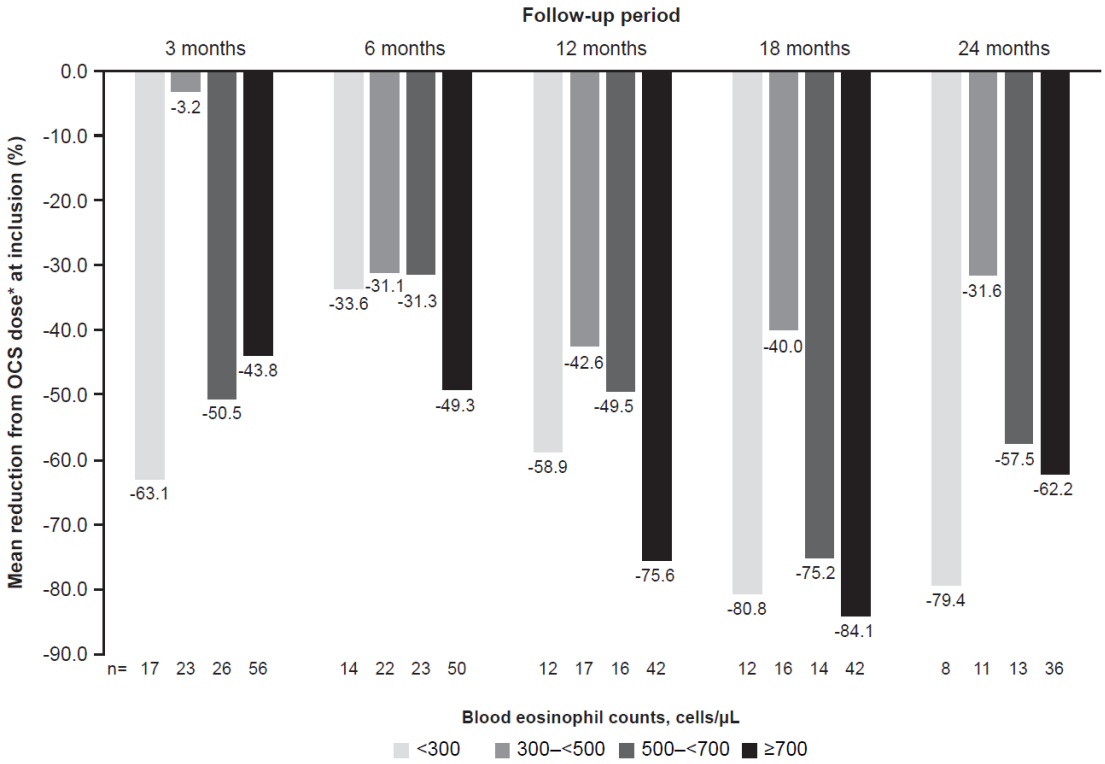
COPD, chronic obstructive pulmonary disease.

Supplementary Figure 2. Analysis to evaluate the different levels of patients' responses to mepolizumab treatment



*P values determined using the Chi-squared test; †Missing data: n=16 at 0–6 months; n=12 at 0–12 months.
OCS, oral corticosteroid.

Supplementary Figure 3. Change in mean OCS dose from baseline to follow-up stratified by blood eosinophil count at inclusion



*mg prednisolone equivalent.
N, number of patients; OCS, oral corticosteroid; SD, standard deviation.

Supplementary Table 1. Reasons for discontinuation of mepolizumab across the study

	Total N=146
Discontinuation of mepolizumab, n (%)	
No	98 (67.1)
Yes	48 (32.9)
Reasons for stopping, n (%)	
Lack of efficacy*	18 (37.5)
AEs[†]	12 (25)
Lack of efficacy associated with an AE	11 (22.9)
Patient choice	5 (10.4)
Pregnancy	1 (2.1)
Patient death (death not related to mepolizumab)	1 (2.1)

*Clinical decision based on physician's judgement; [†]the most commonly reported AEs (excluding a lack of efficacy) that led to treatment discontinuation were: asthma, asthenia and headaches.
AE, adverse event.

Supplementary Table 2. Summary of exacerbations during the baseline and follow-up periods stratified by blood eosinophil count at inclusion

Blood eosinophil count	<300 cells/µL			300–500 cells/µL			500–700 cells/µL			≥700 cells/µL		
Patients with blood eosinophil counts available	**Baseline (n=18)**	**12 months (n=12)**	**24 months (n=8)**	**Baseline (n=23)**	**12 months (n=17)**	**24 months (n=11)**	**Baseline (n=28)**	**12 months (n=16)**	**24 months (n=13)**	**Baseline (n=61)**	**12 months (n=42)**	**24 months (n=36)**
Patients with no exacerbations, n (%)	- (-)	9 (75.0)	4 (50.0)	- (-)	5 (29.4)	4 (36.4)	- (-)	7 (43.8)	2 (15.4)	- (-)	23 (54.8)	20 (55.6)
Exacerbations, mean (SD) events/patient/year	7.1 (5.6)	0.4 (0.8)	0.9 (1.1)	6.9 (5.1)	1.2 (1.2)	0.7 (0.6)	5.3 (3.8)	0.8 (1.0)	1.5 (1.1)	5.8 (3.9)	0.8 (1.2)	0.6 (0.7)
Exacerbations requiring hospitalisation, mean (SD) events/patient/year	0.5 (0.6)	0.3 (0.6)	0.0 (-)	1.5 (3.0)	0.1 (0.2)	0.1 (0.3)	0.5 (0.8)	0.1 (0.3)	0.4 (1.0)	0.5 (1.0)	0.0 (0.2)	0.0 (-)
Exacerbations requiring an ED visit, mean (SD) events/patient/year	0.3 (0.4)	0.3 (0.6)	0.0 (-)	0.7 (1.1)	0.1 (0.2)	0.0 (-)	0.4 (0.8)	0.1 (0.3)	0.3 (0.6)	0.5 (1.1)	0.0 (0.2)	0.0 (-)

ED, emergency department; n, number of patients; SD, standard deviation.

Supplementary Table 3. Mean OCS dose during the baseline and follow-up periods stratified by blood eosinophil count at inclusion

	Baseline N=130	**3 months N=112**	**6 months N=109**	**12 months N=87**	**18 months N=84**	**24 months N=68**
Blood eosinophil count <300 cells/µL at inclusion, n	18	17	14	12	12	8
n (% of response)	18 (100.0)	17 (100.0)	14 (100.0)	12 (100)	11 (91.7)	8 (100.0)
Mean (SD)	21.4 (18.7)	7.9 (9.7)	14.2 (20.8)	8.8 (12.5)	4.1 (7.4)	4.4 (7.3)
Blood eosinophil count 300–500 cells/µL at inclusion, n	23	23	22	17	16	11
n (% of response)	22 (95.7)	23 (100.0)	22 (100.0)	17 (100.0)	16 (100.0)	11 (100.0)
Mean (SD)	19.0 (12.4)	18.4 (22.0)	13.1 (13.7)	10.9 (27.2)	11.4 (26.1)	13.0 (16.5)
Blood eosinophil count 500–700 cells/µL at inclusion, n	28	26	23	16	14	13
n (% of response)	26 (92.9)	25 (96.2)	21 (91.3)	16 (100.0)	14 (100.0)	13 (100.0)
Mean (SD)	21.4 (16.3)	10.6 (14.8)	14.7 (14.5)	10.8 (17.0)	5.3 (7.1)	9.1 (11.8)
Blood eosinophil count ≥700 cells/µL at inclusion, n	61	56	50	42	42	36
n (% of response)	60 (98.4)	56 (100.0)	50 (100)	41 (97.6)	42 (100.0)	36 (100.0)
Mean (SD)	20.1 (16.2)	11.3 (18.8)	10.2 (23.1)	4.9 (8.4)	3.2 (5.8)	7.6 (21.2)

N, number of patients; OCS, oral corticosteroids; SD, standard deviation.