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Usability of mepolizumab single-use prefilled syringe for patient self-administration

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ABSTRACT

Objective: A liquid mepolizumab formulation in a single-use prefilled syringe (PFS) is under development. We evaluated the usability of mepolizumab self-injected via PFS by patients with severe eosinophilic asthma (SEA), or their caregivers, in clinic and at home.

Methods: This open-label, single-arm, Phase IIIa study included patients with SEA, aged ≥ 12 years, and receiving mepolizumab (100 mg subcutaneously) every 4 weeks for ≥ 12 weeks prior to screening. Patients with SEA not receiving mepolizumab at screening who met additional criteria were also included. Patients/caregivers self-administered mepolizumab (100 mg subcutaneously) via PFS every 4 weeks for 12 weeks. The first (Week 0) and third (Week 8) dose were observed in clinic; the second dose (Week 4) was unobserved at home. Primary and secondary endpoints were the proportion of patients who successfully self-administered their third and second doses, respectively. Injection success was determined by investigator/site staff. Patient experience, mepolizumab trough concentrations, blood eosinophil counts, and safety were also assessed.

Results: Of the 56 patients/caregivers who self-administered ≥ 1 dose of mepolizumab, 55 completed the study. All patients were reported to have successfully self-administered their third mepolizumab dose in clinic ($N=55$, 100%); this was further evidenced by trough concentrations/blood eosinophil counts. Most patients/caregivers found the PFS easy and convenient to use with 75% ($n=42$) expressing little/no anxiety about using the device at home. Incidence of on-treatment drug-related adverse events was low (4%); none were fatal.

Conclusions: Patients/caregivers successfully self-administered mepolizumab via the PFS both in clinic and at home, with no new safety concerns identified.

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Introduction

Mepolizumab is an anti-interleukin-5 monoclonal antibody approved as an add-on maintenance treatment for patients (≥ 12 years of age) with severe eosinophilic asthma, and for adult patients with eosinophilic granulomatosis with polyangiitis (EGPA) (1). Treatment with mepolizumab has been shown to reduce blood eosinophil counts as well as to reduce exacerbations, improve lung function and health-related quality of life in patients with severe eosinophilic asthma, and in patients with EGPA was associated with more accrued time in remission and a lower frequency of relapse (2–6). In addition to standard of care treatment, mepolizumab is well tolerated

with a safety profile similar to placebo (3–6), and has a favorable long-term safety profile (7). Furthermore, the efficacy and safety of both intravenous and subcutaneous (SC) administration of mepolizumab have been demonstrated in a number of clinical studies across a range of eosinophilic diseases (2–10).

Currently, the approved formulation of mepolizumab is a sterile, single-use, preservative-free, lyophilized drug product for SC administration once every 4 weeks by healthcare professionals, which must be reconstituted with sterile water for injection using an aseptic technique (1). As part of the lifecycle of mepolizumab, a liquid drug product is being developed as a ready-to-use prefilled syringe assembled into either a

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safety syringe (PFS) or autoinjector (AI), which patients (or their caregivers) may self-administer SC, at home, potentially increasing patient convenience and facilitating compliance.

Self-administered medications (via an AI or PFS) offer several advantages as they allow flexibility in scheduling, portability, and potentially minimize healthcare costs by reducing clinic visits (11,12). A single-use PFS also ensures that the exact dosage of drug is administered while minimizing the risk of contamination (13).

The objective of this Phase III study was to evaluate the usability of a single-dose PFS for the self-administration of mepolizumab (100 mg SC) both in clinic and at home in patients with severe eosinophilic asthma.

Methods

Study design

This was an open-label, single-arm, repeat-dose, multicenter Phase III study of mepolizumab as a liquid drug product administered via a PFS in patients with severe eosinophilic asthma (Study 205667; NCT03021304). The study was conducted across 15 sites in five countries (four sites in the USA, three in the Netherlands, three in the Russian Federation, three in Sweden, and two in Canada) from 1 February 2017 to 8 August 2017. The study consisted of a pre-screening visit (Visit 0) that occurred up to 14 days prior to the start of screening, including the day of screening, a screening visit (Visit 1) that initiated a screening period of 1 to 4 weeks, and a 12-week treatment period (Visits 2, 3, and 4/Weeks 0, 4, and 8), where Visit 2/Week 0 was the start of the treatment period. Permissible visit intervals were 4 weeks $\pm$ 1 week to give investigators/patients some flexibility for making appointments. The treatment period concluded with the End of Study assessments at Visit 5/Week 12, 4 weeks after the last dose of mepolizumab was given at Week 8. This study was approved by the appropriate regulatory and ethics committees, and conducted in accordance with the Declaration of Helsinki 2008 and Good Clinical Practice guidelines. Written informed consent was obtained from each patient prior to study participation.

Patients

Patients ≥ 12 years of age with a diagnosis of asthma (14) for ≥ 2 years were enrolled into this study. Two groups of patients were included: (i) patients who

were currently receiving mepolizumab (100 mg SC) every 4 weeks for ≥ 12 weeks prior to screening, and (ii) patients not receiving mepolizumab treatment at screening, who were required to meet the following additional criteria: a blood eosinophil count ≥ 150 cells/ μ L at screening or ≥ 300 cells/ μ L in the previous year, receiving regular treatment with a high-dose inhaled corticosteroid in the previous 12 months, receiving an additional controller medication (or a documented failure of an additional controller medication for ≥ 3 successive months) in the previous 12 months, and ≥ 1 asthma exacerbations requiring systemic corticosteroids (SCS) in the previous 12 months. Both groups of patients were to have normal liver function before commencing study treatment. Exclusion criteria included pre-specified concurrent medical conditions such as respiratory disease, current eosinophilic disease other than severe eosinophilic asthma, known and pre-existing parasitic infection within 6 months of screening, current cancer or history of cancer (in remission for < 12 months prior to screening), use of prohibited concomitant medications, history of alcohol/substance abuse or hypersensitivity to any component of the study medication.

Treatments

Mepolizumab (100 mg SC) as a liquid drug product in a PFS was self-administered by the patient (or their caregiver) every 4 weeks over a treatment period of 12 weeks. If the patient chose to have their caregiver perform the injection all doses were to be injected by the same caregiver. "Self-administration" is used throughout to describe injections administered by the patient or their caregiver.

Training was provided at Week 0 prior to self-administration of the first dose of mepolizumab, consisting of an introduction to the product instructions for use (IFU), a step-by-step guide including text and pictures provided by the device manufacturer to ensure the device is used safely and effectively by patients. The second dose of mepolizumab was self-administered by the patients/caregivers at home (24 h after the visit at Week 4) and patients/caregivers had the IFU for support as well as the option to request further guidance via telephone or an unscheduled clinic visit. The final dose of mepolizumab was self-administered by the patients/caregivers within the clinic (at Week 8) under the observation of investigator/site staff without any further training though they had the IFU for support.

Endpoints and assessments

The primary endpoint of the study was the proportion of patients who were able to successfully self-administer their observed third dose in the clinic at Week 8, as determined by the investigator/site staff. The secondary endpoint was the proportion of patients who were able to successfully self-administer their unobserved second dose (at home) at Week 4. Injection success was determined by the investigator/site staff based on the Observer or At Home Checklists (which consisted of a list of injection steps derived from the IFU), and by visual inspection of the PFS. The Observer Checklist was completed by the investigator site/staff during the observed, in-clinic self-administrations (first and third dose), whereas the At Home Checklist was completed by the patient (or their caregiver) immediately following the unobserved, self-administration at home (second dose). For the second dose, injection success was determined at the next scheduled visit (Week 8). Other endpoints included; proportion of patients able to successfully self-administer at Weeks 0, 4, and 8, investigator evaluation of user/device errors, and patient/caregiver assessment of device usability and functionality via questionnaire.

Blood samples for assessment of mepolizumab plasma concentrations were collected at Week 0 (pre-dose), and at Week 4, Week 8 (pre-dose), and at the End of Study Visit/Week 12 (trough concentration [C_{trough}]). Plasma samples were analyzed using a validated enzyme-linked immunosorbent assay (assay range: 50 ng/ml to 5,000 ng/ml). Blood eosinophil counts, for determination of ratio to baseline at each time point, were measured at screening, Week 0 (pre-dose), Week 4, Week 8 (pre-dose), and at the End of Study Visit/Week 12 as part of standard hematological assessment.

The incidence of asthma exacerbation, defined as worsening of asthma requiring the use of SCS for ≥ 3 consecutive days and/or hospitalization and/or an emergency department visit, was recorded. Safety endpoints included the incidence of adverse events (AEs) and serious AEs (SAEs), including systemic reactions and injection-site reactions, level of self-reported pain recorded on an eDiary immediately, 1 h and 24 h after the injection, and incidence of immunogenicity.

Sample size and statistical analysis

No formal sample size calculations were performed. Approximately 75 patients were to be screened based on the assumption of a 30% screen failure rate. To provide at least 50 patients with complete study data,

55 patients (attempting ≥ 1 self-administration of mepolizumab) were to be enrolled based on an estimated 10% dropout rate.

Two populations were defined for analysis as follows: (i) All Patients (AP) Enrolled population comprising all patients for whom a record existed in the database – this population was used to summarize reasons for screen failures; (ii) All Patients Treated (APT) population comprising patients/caregivers who attempted at least one self-administration of mepolizumab liquid drug product in a PFS – this population was used to assess all endpoints relating to PFS use, asthma exacerbations, immunogenicity, safety, PK, and PD.

The number and percentage of patients able to successfully self-administer a dose of mepolizumab at Week 0, 4, and/or 8 using the PFS with the 95% confidence intervals (CI) were reported. The denominator for the percentage was the number of patients/caregivers attempting an injection at the respective time point, and CIs were generated using the Exact (Clopper Pearson) method for binomial proportions. No hypothesis testing was planned or performed. Mepolizumab plasma concentrations were summarized descriptively by previous mepolizumab use. Blood eosinophil counts were log transformed, and absolute values were summarized descriptively by previous mepolizumab use. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient population

Of the 58 patients who were screened (AP population), two (3%) patients did not meet the inclusion/exclusion criteria (Figure 1), and the APT population included 56 (97%) patients. All 56 patients/caregivers who commenced the treatment period attempted to self-administer at least one dose of study treatment, and 55 (98%) patients completed the study (Figure 1). One patient who was not receiving treatment with mepolizumab at screening discontinued study treatment at Week 4 after the second dose due to lack of efficacy. The caregiver of this patient reported being extremely anxious about self-administering mepolizumab using the PFS at home, and the patient also went on to experience a SAE of asthma exacerbation that led to withdrawal from the study. Almost three-quarters of patients ($n = 40$, 71%) had no prior experience with self-injecting medication. Of the 16 (29%) patients that did have prior experience, 9 (56%) had

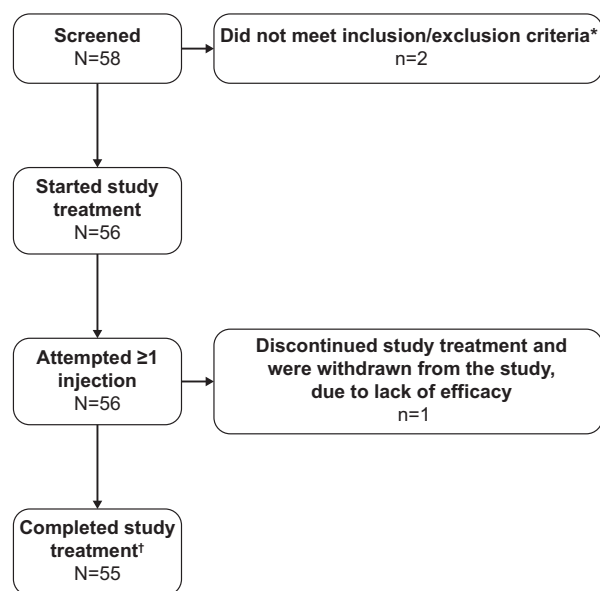


Figure 1. Summary of patient disposition (AP population).

*Including protocol-defined baseline criteria. Screen failure includes any patient who completed at least one screening procedure, but the patient/caregiver did not attempt to self-administer a dose of mepolizumab in a PFS. †Study completion includes any patient who adhered to the study treatment and assessment schedule and completed all assessments at the End of Study Visit. AP, All Patients Enrolled; PFS, pre-filled syringe.

previously used a PFS, 4 (25%) had used an AI, and 4 (25%) had used a vial and syringe.

Patient demographics and baseline characteristics are shown in Table 1. Two adolescents (12 to 17 years; 4%) and seven (13%) patients ≥ 65 years of age were included in this study (Table 1). The mean asthma duration was 22.3 years with 30 (54%) patients having a duration of ≥ 20 years. In addition, a smaller proportion of patients were receiving mepolizumab treatment at screening compared with those who were not (23 patients [41%] vs. 33 patients [59%]) (Table 1). One patient was recorded as currently receiving mepolizumab at screening, despite having only received one prior dose of mepolizumab 100 mg SC; no other inclusion/exclusion criteria deviations were reported.

Primary and secondary endpoints

At Week 8, all patients ($N=55$, 100% [95% CI 94%, 100%]) were reported by the investigator/site staff to have successfully self-administered their third dose of mepolizumab using the PFS in clinic. Similar results were seen at Week 4 when mepolizumab was self-administered at home ($N=56$, 100% [95% CI 94%, 100%]) (Table 2).

Other injection success endpoints

Of the 56 patients in the APT population, 88% ($n=49$) performed the first injection themselves rather than have their caregiver give the injection. This proportion remained consistent at the subsequent doses (87% [$n=48$] at Week 4 and 92% [$n=48$] at Week 8). For patients/caregivers who attempted all three injections, self-administration of mepolizumab was reported as successful in all patients (100%; $n=55$). The proportion of patients self-injecting mepolizumab into either their abdomen or thigh was similar, and this proportion remained consistent across the treatment period (Week 0: 50% [$n=28$] and 39% [$n=22$] respectively, Week 4: 47% [$n=26$] and 42% [$n=23$], Week 8: 48% [$n=25$] and 46% [$n=24$]).

User/device errors

There were no critical user errors or PFS failures that affected injection success. For all injections, the majority of patients/caregivers ($\geq 95\%$) completed each injection step “easily” without repeated reference to the IFU. Results from the Observer and At Home Checklists showed that some patients/caregivers reported having “some difficulty” in completing some injection steps (Table 2). None of these patients/caregivers continued to have difficulty with the same steps during subsequent self-administrations.

Device usability and functionality

Almost all patients (98% [$n=55$]) expressed they were satisfied or very satisfied with using the PFS at home and would recommend this device to other patients with asthma. Some patients/caregivers (25%) expressed that they felt moderately, very or extremely anxious self-administering the PFS at home (Table 3). However, at study completion, 55 (98%) patients expressed that they were moderately, very, or extremely confident in their ability to use the PFS correctly at home. Exit interviews performed in a subset of patients ($n=7$) confirmed that the feelings of anxiety about self-injecting diminished with each injection as they became more familiar with the device. Of the patients who were receiving mepolizumab at screening ($n=23$), 96% ($n=22$) preferred to self-administer their treatment at home, while one (4%) patient preferred having the injection administered by a healthcare professional within the clinic.

Table 1. Demographics and baseline characteristics (APT population).

	Mepolizumab PFS (N = 56)
Females, n (%)	33 (59)
Age (years) ^a	
Mean (SD)	50.8 (12.98)
Range	15, 74
Age group (years), n (%)	
12–17	2 (4)
18–64	47 (84)
≥65–84	7 (13)
BMI (kg/m ²), mean (SD)	31.1 (8.47)
Ethnicity, n (%)	
White	47 (84)
Black/African-American	8 (14)
Asian	1 (2)
Disease duration (years)	
Mean (SD)	22.3 (14.67)
Range	2, 57
Patients not currently receiving mepolizumab, n (%)	33 (59)
Screening blood eosinophil count, median (range), n = 32	325 (100–1420)
Patients currently receiving mepolizumab, n (%)	23 (41)

^aAge is imputed when full date of birth is not provided. Birth day and month is imputed with 30 June.

APT: All Patients Treated; BMI: body mass index; PFS: prefilled syringe; SD: standard deviation.

Table 2. Summary of injection success including observer and at home checklists (APT population).

Dose interval	Mepolizumab PFS (N = 56), number of patients, n (%)
Week 0, first dose (injection observed, in clinic)	
Attempted injections	56 (100)
Successful injections ^{a, b}	56 (100)
Observer Checklist completed	56
Steps completed with some difficulty or repeated references to IFU	
Plunger fully depressed [†]	3 (5)
Expiration date checked	2 (4)
Liquid checked	2 (4)
Skin pinched around the injection site and needle inserted at an angle	2 (4)
Needle guard activated ^c	2 (4)
Plunger depressed slowly ^c	1 (2)
Week 4, second dose (injection unobserved at home)	
Attempted injections	56 (100)
Successful injections ^{a, b}	56 (100)
At Home Checklist completed	55
Steps completed with some difficulty or repeated references to IFU	
Skin pinched around the injection site and needle inserted at an angle	2 (4)
Plunger fully depressed ^c	2 (4)
Check liquid clear	1 (2)
Plunger depressed slowly ^c	1 (2)
Needle guard activated ^c	1 (2)
Week 8, third dose (injection observed in clinic)	
Attempted injections	55 (98)
Successful injections ^{a, b}	55 (100)
Observer Checklist completed	52
Steps completed with some difficulty or repeated references to IFU	
Expiration date checked	1 (2)
Skin pinched around the injection site and needle inserted at an angle	1 (2)
Needle guard activated ^c	1 (2)

^aDenominator was the number of patients/caregivers attempting an injection at that visit.

^b95% CIs were 94, 100.

^ccritical injection step.

APT: All Patients Treated; CI: confidence interval; IFU: instructions for use; PFS: prefilled syringe.

PK

In patients receiving mepolizumab at screening, mean mepolizumab plasma C_{trough} remained similar during the study treatment period and was overall consistent with the baseline value. In patients not receiving mepolizumab at screening, mean C_{trough} increased following each self-administration and at the End of Study Visit/Week 12 the mean C_{trough} was similar to

that observed in patients already receiving mepolizumab at screening (Figure 2). Mean C_{trough} were found to be similar across the three injection sites (abdomen, thigh, and arm).

PD

As expected, at study initiation, the geometric mean baseline blood eosinophil count was lower (54 cells/ μ L

Table 3. Patient/caregiver perception of PFS usability (APT population).

Mepolizumab PFS (N=56), Number of patients, n (%)	
Ease to self-administer using safety syringe at home	
How easy was it to give yourself an injection using the safety syringe at home? ^a	
Not at all	2 (4)
Moderately	8 (14)
Very	26 (46)
Extremely	20 (36)
Confidence at study completion in ability to use safety syringe at home	
At the end of the study, how confident were you about your ability to use the safety syringe in the correct way on your own when you were not at the doctor's office? ^a	
Not at all	1 (2) ^b
Moderately	4 (7)
Very	25 (45)
Extremely	26 (46)
Anxiety felt about self-administering mepolizumab using the safety syringe at home	
How anxious did you feel about administering mepolizumab using the safety syringe at home?	
Not at all	31 (55)
A little	11 (20)
Moderately anxious	7 (13)
Very anxious	6 (11)
Extremely anxious	1 (2) ^b
Preferred injection site	
Which injection site did you prefer?	
Upper thigh	30 (54)
Abdomen	26 (46)

^aThere were no patients in the "A little confident" category.

^bthis patient was withdrawn from the study due to lack of efficacy.

APT: All Patients Treated; PFS: prefilled syringe.

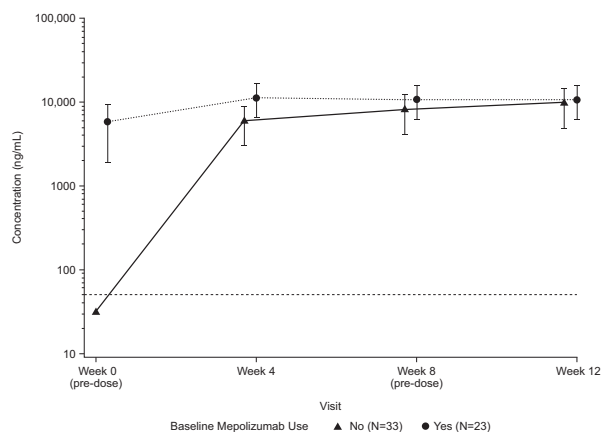


Figure 2. Mean plasma mepolizumab concentration-time plots (C_{trough}) by baseline mepolizumab use (APT population). Data are presented as mean $\pm$ SD. Lower limit of quantification was 50 ng/mL. APT: All Patients Treated; SD: standard deviation.

[95% CI 38, 75]) in patients who were receiving mepolizumab at screening compared with those not receiving mepolizumab at screening (193 cells/ μ L [95% CI 125, 299]). However, geometric mean blood eosinophil counts from Week 4 onwards were similar between the two groups during the study treatment period (Figure 3). By Week 12, geometric mean blood eosinophil counts were reduced to 34 cells/ μ L in patients not receiving mepolizumab at screening and 48 cells/ μ L in patients receiving mepolizumab at

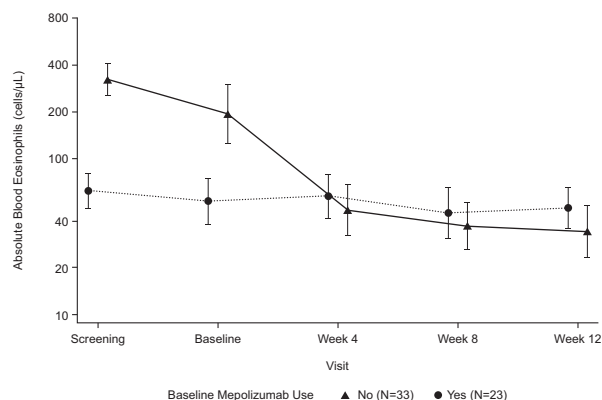


Figure 3. Absolute blood eosinophils by baseline mepolizumab use (APT population). Data are presented as geometric mean $\pm$ 95% CI. APT: All Patients Treated; CI: confidence interval.

screening. The geometric mean blood eosinophil counts and ratio at each visit to baseline were found to be similar across the three injection sites (abdomen, thigh, and arm).

Asthma exacerbations

Seven (13%) patients experienced ≥ 1 asthma exacerbation and were subsequently treated with SCS/oral corticosteroids; five of these patients were receiving treatment with mepolizumab at screening.

Table 4. Adverse events (APT population).

	Mepolizumab PFS (N = 56), Number of patients, n (%)
Any on-treatment AE	17 (30)
Drug-related ^a	2 (4)
Led to withdrawal from the study	1 (2)
Common on-treatment AEs occurring in ≥3%	
Viral upper respiratory tract infection	4 (7)
Asthma exacerbation	2 (4)
Any on-treatment SAE	3 (5)
Non-fatal	3 (5)
Any AE of special interest	1 (2)
General disorders and administration site conditions	
Any event	1 (2)
Local injection-site reaction	1 (2)

^aAs judged by the investigator.

AE: adverse event; APT: All Patients Treated; PFS: prefilled syringe; SAE: serious adverse event.

Safety

The overall incidence of on-treatment AEs was 30%, and 2 (4%) patients reported AEs that were considered drug-related by the investigator (Table 4), which included local injection-site reactions and psoriasis. None of these drug-related AEs resulted in withdrawal from the study. The most common on-treatment AEs were viral upper respiratory tract infection (7% [$n = 4$]) and asthma exacerbation (4% [$n = 2$]). Three patients reported on-treatment SAEs, none of which were fatal. One patient with an SAE of asthma exacerbation was withdrawn from the study; this was the only AE leading to study treatment discontinuation.

The proportion of patients reporting any pain (visual analog scale [VAS] score 0 [no pain] to 100 [worst possible pain]) immediately following injection was 64% ($n = 36$) at Week 0, 54% ($n = 22$) at Week 4, and 51% ($n = 24$) at Week 8. Pain intensity was low with a median VAS score of 1.0–2.5. At 1 h and 24 h following each of the injections, the proportion of patients experiencing pain decreased, as did the relative degree of pain reported (Table 5). The most commonly reported description of pain immediately after each dose was sharp/stinging (31% at Week 0, 41% at Week 4, and 38% at Week 8). At 1 h and 24 h after each injection the most commonly reported description of pain was “other” (ranging from 45% to 87% and 45% to 69%, respectively), which included any pain that was not described as sharp/stinging, dull/aching, or burning.

In this study, immunogenicity was assessed at baseline and at End of Study. The number of patients with detectable anti-drug antibodies post-baseline was low (two patients; 4%), and no patients developed neutralizing antibodies over the 12-week treatment period.

Discussion

This is the first study to evaluate the usability and safety of a liquid formulation of mepolizumab

delivered by a single-use PFS to patients with severe eosinophilic asthma. All patients/caregivers were reported to have successfully self-administered their second and third doses of mepolizumab at Week 4 and Week 8, demonstrating the usability of the PFS device to administer mepolizumab both in clinic and at home without supervision. For the PFS, it was also demonstrated in this study, that a single training session and the IFU were sufficient for patients/caregivers to acquire the skills to successfully self-administer mepolizumab using the device. Results of an associated study, assessing the self-administration of mepolizumab liquid drug product using a single-use AI conducted in 159 patients have shown comparable results, where almost all patients/caregivers were able to successfully self-administer mepolizumab at home or in clinic (15).

Overall, no user errors impacting injection success were reported by the investigator/site staff based on injection observations or after inspection of the PFS devices following the self-administration of mepolizumab. Most patients/caregivers found the device easy to use, and by the end of the treatment period, expressed confidence in their ability to self-administer mepolizumab using the PFS device at home. A few patients/caregivers ($n = 7$) reported feeling very or extremely anxious about self-administering mepolizumab with a PFS at home. Exit interviews, performed in a subset of patients ($n = 7$), suggest that the feelings of anxiety about self-injecting diminished with each injection as patients/caregivers became more familiar with the device. Nonetheless, for patients concerned/anxious about self-administration with a PFS, a device such as an AI, which simplifies the process and shrouds the needle from view, could be an alternative. Most patients expressed that they were satisfied or very satisfied with using the PFS device at home and all except one patient expressed a preference for being able to self-inject at home. This study suggested that for most patients, the option to

Table 5. Injection pain summary (APT population).

Dose interval	Mepolizumab PFS (N = 56) Number of patients, n (%)		
	Time following self-administration		
	Immediately	1 h	24 h
Week 0, first dose, <i>n</i>	56	51	53
Patients experiencing any pain (VAS score >0)	36 (64)	15 (29)	16 (30)
Pain greater than expected	4 (11)	1 (7)	0
Pain acceptable ^a	36 (100)	15 (100)	16 (100)
VAS score, <i>n</i>			
Mean (SD)	9.1 (13.93)	2.2 (5.95)	1.8 (4.93)
Median	2.5	0.0	0.0
Range	0, 57	0, 27	0, 25
Week 4, second dose, <i>n</i>	41	42	46
Patients experiencing any pain (VAS score >0)	22 (54)	16 (38)	11 (24)
Pain greater than expected	1 (5)	3 (19)	1 (9)
Pain acceptable ^a	22 (100)	16 (100)	10 (91)
VAS score, <i>n</i>			
Mean (SD)	5.4 (9.96)	3.5 (11.90)	2.1 (8.91)
Median	2.0	0.0	0.0
Range	0, 45	0, 70	0, 58
Week 8, third dose, <i>n</i>	47	47	46
Patients experiencing any pain (VAS score >0)	24 (51)	11 (23)	11 (24)
Pain greater than expected	6 (25)	2 (18)	2 (18)
Pain acceptable ^a	24 (100)	11 (100)	11 (100)
VAS score			
Mean (SD)	4.6 (11.57)	1.1 (2.81)	0.9 (2.26)
Median	1.0	0.0	0.0
Range	0, 72	0, 13	0, 10

^aAll patients were asked if the pain was acceptable, despite the degree of pain experienced and the relative pain to expectation.

VAS score: 0 (no pain) to 100 (worst possible pain).

APT: All Patients Treated; PFS: prefilled syringe; SD: standard deviation; VAS: visual analog scale.

self-administer their medication is a viable treatment option and offers an alternative for patients who may prefer self-administration at home as opposed to administration in clinic. Furthermore, the self-administration of mepolizumab at home may help to reduce healthcare resources use and improve convenience to the patients by reducing the need to attend the clinic.

The PK and PD profiles broadly corroborate the successful self-administration of mepolizumab liquid formulation by the PFS. One patient was reported by the investigator/site staff to have successfully self-administered the study treatment based on the inspection of the returned PFS and enquiring from the patient about injection success; however, based on a review of their PK and PD profiles, it is possible that this patient did not perform the injection step completely.

At study initiation, geometric mean absolute blood eosinophil counts were 193 cells/ μ L in patients not receiving mepolizumab at screening, and 54 cells/ μ L in patients receiving mepolizumab at screening, and by the End of Study Visit the absolute blood eosinophil counts were reduced to 34 cells/ μ L and 48 cells/ μ L, respectively. These reductions in absolute blood eosinophil counts were not affected by the choice of injection site, and were consistent with those observed in a previous randomized placebo-controlled

mepolizumab trial, where reductions to approximately 50 cells/ μ L were reported (4).

The incidence of pain associated with injection was low, reported as being acceptable, and decreased following each injection. This trend for a decrease in pain scores with increasing experience with injections has been previously reported in another trial using a PFS containing a different monoclonal antibody product, adalimumab (11) and this effect may be due to the patients change in expectations of pain, and the patient becoming more tolerant to the pain with repeated self-injections.

Overall, a low incidence of on-treatment AEs was reported, and most AEs were considered by the investigator as unrelated to the study treatment. Three patients experienced non-fatal on-treatment SAEs, two of these resolved with continued study treatment, and one led to withdrawal from the study. As expected in this population, the most common AEs (reported in $\geq 3\%$ of patients) were asthma exacerbation and viral upper respiratory tract infection. The safety profile including immunogenicity reported here is similar to that observed in previous trials of patients with severe eosinophilic asthma using the approved reconstituted lyophilized drug product (given as a 100 mg SC injection once every 4 weeks) (3–7) and was also broadly consistent with the associated AI study, where 35%

(56/159) and 2.5% (4/159) of patients reported on-treatment AEs or SAEs, respectively, and 5 patients experienced drug-related AEs (15).

In this study, the number of patients ($N=56$) was small and the treatment period was relatively short (12 weeks), hence the ability to detect new safety concerns was limited. Of note, any changes to the manufacturing process for the liquid drug product compared with the lyophilized drug product were minimized. Furthermore, the liquid drug product was assessed against the lyophilized drug product prior to clinical evaluation, using comprehensive biochemical/biophysical comparability evaluations, with comparability between the two products being demonstrated. Therefore, the likelihood of clinically significant differences in the systemic exposure, efficacy, safety, and/or immunogenicity of the liquid drug product in the PFS as compared with the reconstituted lyophilized drug product is considered to be low. The broadly consistent safety profile between this study and the separate study with the AI device (15), and with the lyophilized drug product (3–7) suggest that the liquid drug product is similar to the currently marketed lyophilized drug product.

Another limitation of this study was that the study population contained a small proportion of adolescent (4%) and older patients (≥ 65 years, 13%). Further information on the usability of the PFS device in these populations would be beneficial; given that these populations may be more likely to experience difficulties in using the device. For the PFS device, human factor studies have shown that the device can be successfully used across a variety of age groups, education levels, and physical and visual capabilities (including hand impairments) (16). This study may also be subject to selection bias as only the patients who were willing to self-administer mepolizumab at home participated in the study, and this selection bias could mean that these data may not fully extrapolate to the entire mepolizumab population.

In conclusion, the results from this open-label, single-arm, repeat-dose, multicenter study demonstrate that all patients/caregivers were able to successfully administer the liquid formulation of mepolizumab using the single-use PFS both in clinic and at home. The liquid formulation delivered via the PFS was well tolerated in patients with severe eosinophilic asthma over the 12-week treatment period and had a safety profile similar to the currently approved reconstituted lyophilized drug product. Taken together, these results suggest that the self-administration of mepolizumab liquid drug product delivered via a PFS is a viable

alternative to the reconstituted lyophilized drug product delivered in the clinic and offers patients the convenience to be able to self-inject at home.

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Declaration of interests

RF, JHB, IP, and EB are all GSK employees and stockholders. EHB received grants from AstraZeneca, GSK, Novartis, Roche and TEVA, and received fees for speaking and consulting from AstraZeneca, Boehringer Ingelheim, GSK, Novartis and Sanofi. DB received grant/research/clinical trial support from GSK, Teva, AstraZeneca, Pearl, Novartis, Genentech, Lupin, Mylan, Boehringer Ingelheim, Menlo and consulted/participated in advisory boards for GSK, Gerson-Lehman, Guidepoint Global. LB has given lectures or participated in advisory boards for Airsonett, ALK-Abello, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Meda, Sanofi and Teva.

Data sharing statement

Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

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