



ORIGINAL ARTICLE

A Phase 1 study of the long-acting anti-IL-5 monoclonal antibody GSK3511294 in patients with asthma

Dave Singh¹  | Rainard Fuhr² | Nicholas P. Bird³  | Sarah Mole⁴ |
Kelly Hardes⁵ | Yau Lun Man⁴ | Anthony Cahn⁴ | Steven W. Yancey⁶ |
Isabelle J. Pouliquen⁷

¹Medicines Evaluation Unit, Manchester University NHS Foundation Trust, University of Manchester, Manchester, UK

²Early Phase, Parexel International, Berlin, Germany

³Biostatistics, GSK, Stevenage, UK

⁴Discovery Medicine, GSK, Stevenage, Hertfordshire, UK

⁵Global Clinical Science and Delivery, GSK, Brentford, Middlesex, UK

⁶Respiratory Therapeutic Area, GSK, Research Triangle Park, NC, USA

⁷Affiliation at time of study: Clinical Pharmacology Modelling & Simulation, GSK, Brentford, Middlesex, UK

Correspondence

Nicholas P. Bird, Biostatistics, GSK, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY.

Email: nick.p.bird@gsk.com.

Funding information

GlaxoSmithKline, Grant/Award Numbers: GSK ID 205722, NCT03287310

Aims: GSK3511294 is a humanized anti-interleukin (IL)-5 monoclonal antibody (mAb) engineered for extended half-life and improved IL-5 affinity versus other anti-IL-5 mAbs. This study examined its safety, tolerability, pharmacokinetics (PK) and effect on blood eosinophil counts.

Methods: This was a double-blind, parallel-group, single-ascending-dose, multicenter, Phase 1 study (205 722;NCT03287310) in patients with asthma and a blood eosinophil count ≥ 200 cells μL^{-1} . Patients were randomized 3:1 within dose cohorts to receive a single subcutaneous dose of GSK3511294 (2, 10, 30, 100 or 300 mg) or placebo and followed for up to 40 weeks to assess safety (primary endpoint), ratio to baseline in blood eosinophil count, plasma PK parameters and frequency/titers of binding antidrug antibodies (all secondary).

Results: Forty-eight patients received the study drug and completed the study. Adverse events (AEs) occurred in 92% of placebo-treated and 81% of GSK3511294-treated patients. There were no AEs leading to study withdrawal or serious AEs; hypersensitivity (one event in one patient) and injection-site reaction (three events in two patients) occurred infrequently. Marked reductions (>48%) in blood eosinophil count were seen from 24 hours post-dose with all GSK3511294 doses but not placebo; suppression was maintained for longer with increasing dose (82% and 83% adjusted reductions vs placebo with 100 and 300 mg, respectively, at week 26). PK were linear and dose proportional over the dose range; terminal half-life was 38-53 days.

Conclusions: GSK3511294 was well tolerated, with linear and dose proportional PK, extended half-life and blood eosinophil count reduction, supporting less frequent dosing versus other anti-IL-5 mAbs.

KEYWORDS

anti-interleukin-5, biologic therapy, eosinophilic asthma, extended pharmacology, safety

The authors confirm that the PI for this paper is Dave Singh and that he had direct clinical responsibility for patients.

Trial registration: ClinicalTrials.gov, NCT03287310.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2021 GlaxoSmithKline. *British Journal of Clinical Pharmacology* published by John Wiley & Sons Ltd on behalf of British Pharmacological Society.

What is already known about this subject

- Several biologic therapies targeting interleukin (IL)-5/IL-5 receptor are approved for use in patients with severe eosinophilic asthma.
- However, these treatments typically require dosing every 4-8 weeks.
- We investigated the safety, tolerability and pharmacology of GSK3511294, a humanized anti-IL-5 monoclonal antibody that has an extended half-life versus other anti-IL-5 biologics.

What this study adds

- Single-dose subcutaneous GSK3511294 (2-300 mg) was well tolerated.
- GSK3511294 half-life was extended and blood eosinophil count reductions from baseline were observed from 24 hours post-GSK3511294 and sustained over 26 weeks.
- These findings provide a foundation for the continued clinical development of GSK3511294 for use in patients with severe eosinophilic asthma.

1 | INTRODUCTION

Eosinophils are involved in the pathogenesis of several inflammatory diseases including asthma, eosinophilic granulomatosis with polyangiitis (EGPA) and hypereosinophilic syndrome (HES), driving inflammatory responses through the production and release of granule proteins and inflammatory mediators.¹⁻⁴ Interleukin (IL)-5 is a key mediator in the growth and differentiation of eosinophils in bone marrow, and in their recruitment and activation within tissues.^{4,5} As circulating eosinophils in the blood have a short half-life (8-18 hours),⁶ monoclonal antibodies (mAbs) targeting IL-5 lead to a rapid reduction in the circulating cell population.⁷ Therefore, eosinophil count reduction through IL-5 inhibition is an established therapeutic strategy for several eosinophil-associated diseases.⁷

Several mAbs targeting IL-5 (mepolizumab, reslizumab) or the IL-5 receptor (benralizumab) are currently approved as add-on maintenance treatments for severe eosinophilic asthma.⁸⁻¹⁰ Mepolizumab is also approved for the treatment of EGPA and HES.⁸ In patients with severe eosinophilic asthma, these mAbs reduce exacerbation frequency and symptom burden, and improve health-related quality of life.¹¹⁻¹⁴ However, these treatments require subcutaneous (SC) dosing every 4-8 weeks as per the approved administration schedule,⁸⁻¹⁰ and this frequent dosing may be associated with medication nonadherence, and consequent healthcare resource utilization and costs.^{15,16}

GSK3511294 is a humanized anti-IL-5 mAb (immunoglobulin G1, kappa) that has been engineered to provide an extended half-life and improved affinity for IL-5 compared with approved anti-IL-5 mAbs. As GSK3511294 binds to the same epitope as mepolizumab, these modifications are not expected to change the clinical efficacy and safety profile but instead confer a longer duration of action. In a cell-based in vitro assay, GSK3511294 demonstrated an approximately 29-fold increase in IL-5 potency versus mepolizumab (GSK data on file). In a single dose pharmacokinetics (PK)/pharmacodynamics (PD) study in cynomolgus monkeys, GSK3511294 showed an approximately 2-fold

reduction in clearance compared with mepolizumab and demonstrated an IL-5 binding affinity approximately 30-fold greater than mepolizumab, as evaluated by total IL-5 profile and duration of blood eosinophil suppression. Return to 50% of the maximal blood eosinophil suppression effect was observed at around day 169 post-dose for GSK3511294 (1 mg/kg) and day 29 for mepolizumab (1 mg/kg) (GSK data on file). This longer duration of action may reduce the frequency of dosing required and improve convenience for patients, potentially leading to greater treatment compliance.¹⁵

The aim of the current single ascending dose, first-time-in-human Phase 1 study was to examine the safety, tolerability, immunogenicity, PK and PD effect on blood eosinophil counts of GSK3511294, administered SC in patients with asthma with a blood eosinophil count ≥ 200 cells μL^{-1} at screening.

2 | METHODS

2.1 | Study design

This was a randomized, double-blind, placebo-controlled, parallel-group, single ascending dose (GSK3511294 2, 10, 30, 100 and 300 mg), multicentre, Phase 1 first-in-human study conducted at two German and three UK clinical research centres in hospital settings (ClinicalTrials.gov identifier NCT03287310, GSK study 205 722). The study comprised a screening period of up to 28 days, a 4-9 day (dependent on country regulator requirement) inpatient monitoring period and a post-dosing follow-up period of up to 40 weeks (dose-dependent based on the predicted blood eosinophil count profile). The trial protocol is available via the GSK Clinical Studies Register at <https://www.gsk-studyregister.com/en/>.

The study was conducted in accordance with International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice, applicable country-specific and patient privacy requirements, and the ethical

principles of the Declaration of Helsinki. All patients provided written informed consent prior to participation in the study.

2.2 | Patients

Eligible patients were male or female (of nonchildbearing potential), 18–65 years of age with body weight ≥ 50 kg, body mass index between 19 and 32 kg m^{-2} , physician-diagnosed asthma for ≥ 12 months, screening pre-bronchodilator forced expiratory volume in 1 second (FEV_1) $\geq 60\%$ of predicted normal value, Asthma Control Test (ACT) score > 19 , asthma controlled on as-needed short-acting β_2 -agonist (SABA) and stable low-to-moderate dose of inhaled corticosteroid (ICS) or stable low-to-moderate dose of ICS/long-acting β_2 -agonist (LABA) combination therapy (ICS was up to a maximum daily dose dependent on ICS medication [Supplementary Table S1] and was required to be stable for ≥ 12 weeks prior to study treatment), a blood eosinophil count of $\geq 200 \text{ cells } \mu\text{L}^{-1}$ at screening and high-sensitivity C-reactive protein (hsCRP) $< 10 \text{ mg L}^{-1}$ at screening (see Supporting Information, Supplementary for further details of inclusion and exclusion criteria).

Patients were excluded from the study if they had experienced an asthma exacerbation requiring systemic corticosteroids (within 12 weeks of screening) or overnight hospitalization (within 6 months of screening), had a history of life-threatening asthma (within 5 years of screening), or significant pulmonary diseases other than asthma or respiratory infection or had opportunistic infection or parasitic infestation (see Supporting Information, Supplementary, for further details).

Patients abstained from taking prescription or nonprescription drugs within 7 days or 5 half-lives (whichever was longer) prior to dosing and until completion of follow-up. Patients were permitted to continue taking SABA, ICS alone or ICS/LABA therapies throughout the study. Prohibited asthma medications are listed in Supporting Information Table S2.

2.3 | Treatments

Each patient received a single SC dose of GSK3511294 (2, 10, 30, 100 or 300 mg) or matched placebo (0.9% w/v sodium chloride SC injection) (Supporting Information Figure S1). In each cohort, patients were randomized 3:1 to receive GSK3511294 or placebo. In each cohort sentinel dosing was used, with one patient from the placebo and one from the GSK3511294 group dosed first; if no safety issues were identified in these sentinel individuals over an observation period of at least 72 hours, the remaining patients in the cohort were dosed. The follow-up period was 32 weeks (cohorts 1 [2 mg or placebo] and 2 [10 mg or placebo]), 36 weeks (cohorts 3 [30 mg or placebo] and 4 [100 mg or placebo]) or 40 weeks (cohort 5 [300 mg or placebo]) after dosing.

The PK of GSK3511294 in humans following SC administration were predicted based on PK data from cynomolgus monkeys and prior knowledge of the PK of mepolizumab. The pharmacology of

GSK3511294 in humans was simulated using a semimechanistic stochastic PK/PD model developed previously based on mepolizumab pharmacology data and adjusted by the fold difference in clearance and binding affinity improvements observed in the GSK3511294 preclinical studies. From this model, the therapeutic dose range for GSK3511294 SC was expected to be between 30 and 100 mg administered every 6 months for severe asthma to achieve blood eosinophil count reductions at steady-state trough concentrations similar to those observed with mepolizumab 100 mg SC every 4 weeks. The starting and maximum doses were selected based on their predicted reduction in blood eosinophil count, expected to be well tolerated based on prior experience with mepolizumab at similar blood eosinophil reductions. The starting dose of 2 mg was expected to correspond to an average maximum reduction in blood eosinophil count of 75% (approximately 2 weeks post-dosing), with a return to approximately 50% of the maximum response at around 150 days post-dose. This dose was expected to be well tolerated, to allow evaluation of blood eosinophil count return towards baseline, and to assess the *in vivo* potency of GSK3511294 in humans. The maximum dose of 300 mg was expected to correspond to an average maximum reduction in blood eosinophil count of 93%, which was anticipated to be well tolerated based on prior experience with a 750 mg IV mepolizumab dose which elicited an average blood eosinophil count reduction of 88% at trough concentration when administered every 4 weeks for at least 12 months and had been well tolerated.¹⁷

2.4 | Randomization and blinding

The randomization sequence was computer-generated centrally using validated internal software. A separate randomization schedule was created for each cohort with two strata to capture randomization for the sentinel patients and the remaining patients in each cohort: patients were randomized 1:1 (sentinel patients), 5:1 for cohorts 1, 2 and 5 and 8:2 for cohorts 3 and 4, to GSK3511294 or placebo, respectively. Investigators, patients and pharmacy monitors were blinded to study treatment, but the study statistician and clinical pharmacologist, in addition to bioanalytical laboratory and pharmacy staff involved in the preparation of SC administration syringes, had access to the randomization code. Additionally, one of the study managers was unblinded so they could discuss any treatment-related issues with unblinded monitors.

2.5 | Study endpoints and assessments

The primary endpoints were the proportion of patients with adverse events (AEs) and serious AEs (SAEs), including AEs of special interest (AESIs) of hypersensitivity, type III hypersensitivity/vasculitis and local injection-site reactions, vital signs, electrocardiograms (ECGs) and clinical laboratory safety data, including haematology and clinical chemistry, hsCRP and complement C3 and C4 until the end of follow-up. Secondary endpoints were ratio to baseline in absolute blood

eosinophil count, plasma PK parameters of GSK3511294, and frequency and titres of binding antidrug antibodies (ADAs) to GSK3511294 (see Supporting Information, Supplementary for full details).

Exploratory endpoints were change from baseline in FEV₁, forced vital capacity (FVC), percent predicted normal FEV₁ and peak expiratory flow, serum total IL-5 levels, levels of circulating immune complexes (CICs), change from baseline in asthma biomarkers (eosinophil derived neurotoxin [EDN], eotaxin, macrophage derived chemokine [MDC], monocyte chemotactic protein 4 [MCP-4/CCL13], thymus and activation-regulated chemokine [TARC/CCL17]), and the relationship between GSK3511294 plasma concentration and blood eosinophil count.

2.6 | Sample size and statistical analysis

Sample sizes were based on feasibility, with a planned sample size of 48 patients to include eight patients in cohorts 1 (2 mg or placebo), 2 (10 mg or placebo) and 5 (300 mg or placebo), and 12 patients in cohorts 3 (30 mg or placebo) and 4 (100 mg or placebo). Cohorts 3 and 4 included larger sample sizes to generate more data at the expected therapeutic dose range. The safety population was used for all safety analyses and included all randomized patients who received a dose of study treatment (based on treatment received). The PK population, used for the PK analysis, included patients in the safety population for whom a PK sample was obtained and analysed. The PD population included patients in the safety population for whom a post-dose PD (eg, blood eosinophil, serum total IL-5) sample was obtained and analysed.

Because this study was a Phase 1 for GSK3511294, there were no formal statistical hypotheses to be tested. The assessment of the safety and tolerability of single SC doses of GSK3511294 did not include any formal comparisons. For the PK and PD data, when appropriate, an estimation approach was adopted and point estimates with corresponding confidence intervals were provided. For the analysis of blood eosinophil count data, posterior means and corresponding 95% credible intervals were constructed for each dose and time point.

Blood eosinophil ratio to baseline (following log-transformation) data were analysed using a mixed model repeated measures model, with fixed categorical effects of treatment, planned time point and treatment-by-planned time point interaction and fixed continuous covariates of log baseline blood eosinophil count and log baseline blood eosinophil count-by-planned time point interaction. A supportive analysis using a Bayesian dose response four-parameter E_{max} model for data at week 26 was also conducted. PK parameters were derived by standard noncompartmental analysis using Phoenix WinNonlin Version 8.1. An initial assessment of dose proportionality was explored for area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time (AUC_{0-∞}) and maximum observed concentration (C_{max}) following single SC doses of GSK3511294 using a power model and an analysis of variance (ANOVA) method. Exploratory population PK and PK/PD analyses

were conducted using SAS software (version 9.4) and nonlinear mixed-effects modelling (NONMEM) software (version 7.3), respectively (see Supporting Information, Supplementary for further details).

2.7 | Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.¹⁸

3 | RESULTS

3.1 | Patient population

The study was conducted from 17 October 2017 to 31 July 2019. Of 178 patients screened, 50 were randomized, of whom 48 received the study drug, completed the study and were included in the safety and PD populations; two patients were randomized but withdrawn prior to dosing at the investigator's discretion (Supporting Information Figure S2). Most patients were men (n = 46/48, 96%) and of white background (n = 43/48, 90%), and age was similar across treatment groups (Table 1). All patients were receiving concomitant asthma medications that had been initiated prior to screening; 38/48 (79%) were receiving salbutamol. Overall, 16/48 (33%) patients had allergy and 12/48 (25%) had hay fever.

3.2 | Primary endpoints

A similar proportion of patients had AEs in the placebo (92%) and GSK3511294 all doses (81%) groups (Table 2). No AEs leading to study withdrawal, SAEs or deaths were reported. The most common (≥20%) AEs reported in the GSK3511294 all-doses group were nasopharyngitis (36%) and headache (25%), while rhinitis (25%) and cough (25%) were most commonly reported in the placebo group (Table 2). Of note, nasopharyngitis (36% vs 17%), headache (25% vs 0%) and injection-site reaction (17% vs 6%) were more frequent (difference >10%) in the GSK3511294 all-doses group versus placebo, while rhinitis and cough were more frequent in the placebo group (25% vs 11% and 25% vs 0%, respectively, for the GSK3511294 all-doses group). All AEs were of mild or moderate intensity, except for one patient in the GSK3511294 100 mg group who reported three AEs of severe intensity, musculoskeletal chest pain, fall and contusion, which were reported 124, 145 and 145 days after dosing, respectively. All three AEs resolved and were considered unrelated to study intervention by the investigator. Drug-related AEs were reported for three patients receiving placebo and three patients receiving GSK3511294 (Table 2). There was no evidence of a dose effect for any AEs.

TABLE 1 Demographics and baseline characteristics (safety population)

Parameter	Placebo (n = 12)	GSK3511294				
		2 mg (n = 6)	10 mg (n = 6)	30 mg (n = 9)	100 mg (n = 9)	300 mg (n = 6)
Age, years, mean (SD)	44.0 (13.4)	43.5 (10.7)	44.7 (13.2)	44.9 (10.2)	42.0 (10.8)	45.2 (11.2)
Male, n (%)	12 (100)	6 (100)	6 (100)	9 (100)	8 (89)	5 (83)
BMI, kg m ⁻² , mean (SD)	26.6 (3.3)	26.6 (2.7)	27.4 (2.7)	24.6 (3.1)	24.7 (2.8)	27.5 (2.0)
Weight, kg, mean (SD)	83.1 (15.5)	82.3 (7.6)	87.9 (6.9)	80.5 (14.0)	76.6 (7.7)	87.3 (8.2)
Race, n (%)						
Asian	1 (8)	0 (0)	0 (0)	1 (11)	0 (0)	0 (0)
Black/African American	0 (0)	1 (17)	0 (0)	1 (11)	0 (0)	0 (0)
White	10 (83)	5 (83)	6 (100)	7 (78)	9 (100)	6 (100)
Multiple	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ethnicity, n (%)						
Not Hispanic or Latino	12 (100)	6 (100)	6 (100)	9 (100)	9 (100)	6 (100)
Family history of premature CAD ^a , n (%)	0 (0)	0 (0)	0 (0)	0 (0)	1 (11)	1 (17)
Underlying conditions, n (%)						
Hypertension	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	10 (83)	5 (83)	4 (67)	7 (78)	6 (67)	4 (67)
Concomitant asthma medications, n (%)	12 (100)	6 (100)	6 (100)	9 (100)	9 (100)	6 (100)
ACT score, mean (SD)	22.8 (1.6)	22.7 (2.0)	20.8 (1.0)	22.0 (1.5)	23.1 (1.1)	23.8 (1.3)
Lung function, mean (SD)						
FEV ₁ % predicted	79.1 (11.1)	81.0 (3.8)	81.2 (11.7)	77.0 (10.3)	89.0 (20.0)	78.8 (12.8)
FEV ₁ , mL	3149 (722)	3210 (345)	3313 (426)	3160 (604)	3533 (750)	3125 (725)
FVC, mL	4801 (642)	4693 (348)	5042 (578)	5000 (1029)	4989 (1089)	4567 (824)
Blood eosinophil count, cells μL ⁻¹ , geometric mean (SD logs)	359 (0.3479)	288 (0.3166)	304 (0.3740)	398 (0.3404)	365 (0.4146)	301 (0.3016)
Total serum IL-5, n (%) with values <LLQ	11 (92)	5 (83)	3 (50)	6 (67)	8 (89)	5 (83)

Abbreviations: ACT, Asthma Control Test; BMI, body mass index; CAD, coronary artery disease; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; IL, interleukin; LLQ, lower limit of quantification; SD, standard deviation.

^aHistory in first-degree relatives only (biological parent, sibling or child).

One event within the hypersensitivity Standardized MedDRA Query (preferred term, rash; verbatim, 'localized rash both bends of arms') occurred in one patient in the GSK3511294 30 mg group 82 days after dosing and injection-site reactions occurred in two patients, one in the placebo group and one in the GSK3511294 300 mg group. The rash event was nonserious, of mild intensity, resolved within 10 days and was considered by the Investigator to be unrelated to study treatment. Further details of the injection-site reactions are provided in the Supporting Information, Supplementary Results. No anaphylaxis events and no events suggestive of type III hypersensitivity/vasculitis were reported.

No treatment effects for haematology or clinical chemistry parameters (including hsCRP) across the GSK3511294 dose groups were observed. No notable changes from baseline in complement C3 or C4 values were observed across GSK3511294 dose groups (Supporting Information Figure S3). Additionally, no treatment effect was observed for ECG parameters or vital signs across the GSK3511294 dose groups.

3.3 | Secondary endpoints

3.3.1 | Blood eosinophil count

Geometric mean absolute blood eosinophil counts (Figure 1A) and adjusted geometric mean ratio to baseline blood eosinophil count (Figure 1B) showed marked reductions (>48%) from the first post-dose assessment (day 2, 24 hours) in all GSK3511294 dose groups but not in the placebo group. Reductions of 54% and 53% were observed at 24 hours in the 100 and 300 mg groups, respectively. There was a dose-related difference in duration of reduction, with suppression of blood eosinophil counts maintained for longer with increasing dose. At week 26 (6 months) there was a clear dose response with adjusted geometric mean ratio to baseline blood eosinophil counts versus placebo of 31% (2 mg), 41% (10 mg), 72% (30 mg), 82% (100 mg) and 83% (300 mg).

TABLE 2 Adverse events occurring in >1 patient in any group during the study (safety population)

Event, n (%)	Placebo (n = 12)	GSK3511294					All doses (n = 36)
		2 mg (n = 6)	10 mg (n = 6)	30 mg (n = 9)	100 mg (n = 9)	300 mg (n = 6)	
Any AE	11 (92)	2 (33)	6 (100)	8 (89)	9 (100)	4 (67)	29 (81)
All AEs							
Any	11 (92)	2 (33)	6 (100)	8 (89)	9 (100)	4 (67)	29 (81)
<i>Infections and infestations</i>	6 (50)	2 (33)	2 (33)	4 (44)	8 (89)	2 (33)	18 (50)
Nasopharyngitis	2 (17)	2 (33)	1 (17)	3 (33)	5 (56)	2 (33)	13 (36)
Rhinitis	3 (25)	0 (0)	1 (17)	1 (11)	2 (22)	0 (0)	4 (11)
Gastroenteritis	0 (0)	0 (0)	0 (0)	0 (0)	2 (22)	0 (0)	2 (6)
<i>Nervous system disorders</i>	1 (8)	1 (17)	2 (33)	3 (33)	3 (33)	2 (33)	11 (31)
Headache	0 (0)	1 (17)	1 (17)	2 (22)	3 (33)	2 (33)	9 (25)
<i>Injury, poisoning and procedural complications</i>	4 (33)	0 (0)	2 (33)	3 (33)	1 (11)	1 (17)	7 (19)
Arthropod sting	0 (0)	0 (0)	0 (0)	2 (22)	0 (0)	0 (0)	2 (6)
Rib fracture	0 (0)	0 (0)	2 (33)	0 (0)	0 (0)	0 (0)	2 (6)
<i>Gastrointestinal disorders</i>	4 (33)	1 (17)	2 (33)	0 (0)	3 (33)	0 (0)	6 (17)
Diarrhea	0 (0)	1 (17)	0 (0)	0 (0)	1 (11)	0 (0)	2 (6)
Dyspepsia	0 (0)	0 (0)	2 (33)	0 (0)	0 (0)	0 (0)	2 (6)
<i>Immune system disorders</i>	2 (17)	1 (17)	3 (50)	2 (22)	1 (11)	1 (17)	8 (22)
Seasonal allergy	2 (17)	1 (17)	2 (33)	2 (22)	1 (11)	1 (17)	7 (19)
Allergy to animal	0 (0)	0 (0)	1 (17)	1 (11)	0 (0)	0 (0)	2 (6)
<i>Respiratory, thoracic and mediastinal disorders</i>	3 (25)	0 (0)	1 (17)	1 (11)	3 (33)	1 (17)	6 (17)
Oropharyngeal pain	1 (8)	0 (0)	1 (17)	0 (0)	2 (22)	1 (17)	4 (11)
Asthma	1 (8)	0 (0)	0 (0)	1 (11)	1 (11)	0 (0)	2 (6)
Cough	3 (25)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
<i>General disorders and administration site conditions</i>	4 (33)	0 (0)	1 (17)	1 (11)	1 (11)	1 (17)	4 (11)
Medical device site reaction	2 (17)	0 (0)	1 (17)	0 (0)	1 (11)	0 (0)	2 (6)
<i>Skin and subcutaneous tissue disorders</i>	0 (0)	0 (0)	0 (0)	3 (33)	2 (22)	0 (0)	5 (14)
Dry skin	0 (0)	0 (0)	0 (0)	2 (22)	0 (0)	0 (0)	2 (6)
<i>Musculoskeletal and connective tissue disorders</i>	1 (8)	0 (0)	0 (0)	0 (0)	2 (22)	1 (17)	3 (8)
Back pain	1 (8)	0 (0)	0 (0)	0 (0)	2 (22)	0 (0)	2 (6)
<i>Investigations</i>	0 (0)	0 (0)	0 (0)	1 (11)	0 (0)	1 (17)	2 (6)
Peak expiratory flow rate decreased	0 (0)	0 (0)	0 (0)	1 (11)	0 (0)	1 (17)	2 (6)
Drug-related AEs							
Any	3 (25)	1 (17)	0 (0)	0 (0)	0 (0)	2 (33)	3 (8)
Injection-site hematoma	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	1 (3)
Injection-site swelling	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	1 (3)
Mouth ulceration	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Seasonal allergy	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	1 (3)
Nasopharyngitis	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)
Cough	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

AE, adverse event.

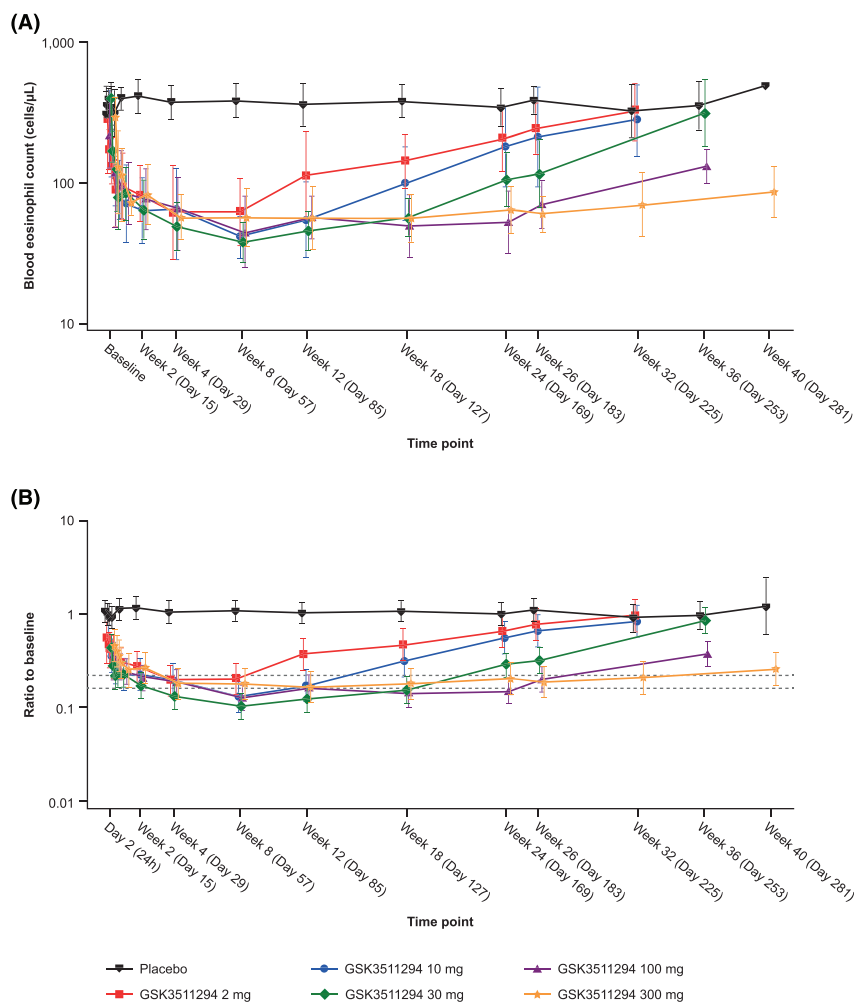


FIGURE 1 Geometric mean (95% CI) absolute blood eosinophil counts (A) and adjusted geometric mean (95% CI) of ratio to baseline blood eosinophil data (B) following a single subcutaneous GSK3511294 dose in patients with mild-to-moderate asthma (PD population). For (B), analysis was performed using an MMRM model on log-transformed data, with fixed categorical effects of treatment, planned time point and treatment-by-planned time point interaction and fixed continuous covariates of log baseline blood eosinophil count and log baseline blood eosinophil count-by-planned time point interaction. A Toeplitz covariance structure was used. The reference line at ratio = 0.22 indicates a 78% reduction from baseline compared with placebo, as observed in the Phase 3b mepolizumab MUSCA trial.¹⁴ The reference line at ratio = 0.16 indicates an 84% reduction from baseline compared with placebo, as observed in the mepolizumab MENSA pivotal Phase 3 trial.¹³ CI, confidence interval; MMRM, mixed model repeated measures; PD, pharmacodynamic

3.3.2 | Plasma PK parameters

Mean GSK3511294 plasma concentration-time profiles are shown in Figure 2. Overall GSK3511294 exposure ($AUC_{0-\infty}$ and C_{max}) increased dose proportionally, except between 2 and 10 mg for undetermined reasons (Table 3, Supporting Information Table S3 and Supporting Information, Supplementary Results). Across all tested GSK3511294 doses, median time of occurrence of C_{max} (t_{max}) ranged from 8 to 14 days and geometric mean terminal phase half-life ($t_{1/2}$) ranged from 38 to 53 days (38 to 44 days excluding the 2 mg starting dose) (see Supporting Information, Supplementary Results) and was not dose-dependent. There was no evidence of target-mediated disposition.

3.3.3 | Exploratory population PK analysis

GSK3511294 plasma concentration-time data were described by a one-compartment PK model with first-order absorption and elimination; bodyweight was included as a covariate on clearance and volume. Population PK parameter estimates of 0.132 L/day for apparent clearance, 7.88 L for apparent volume and 41 days for half-life

were consistent with the results from the noncompartmental analysis (Supporting Information Table S4).

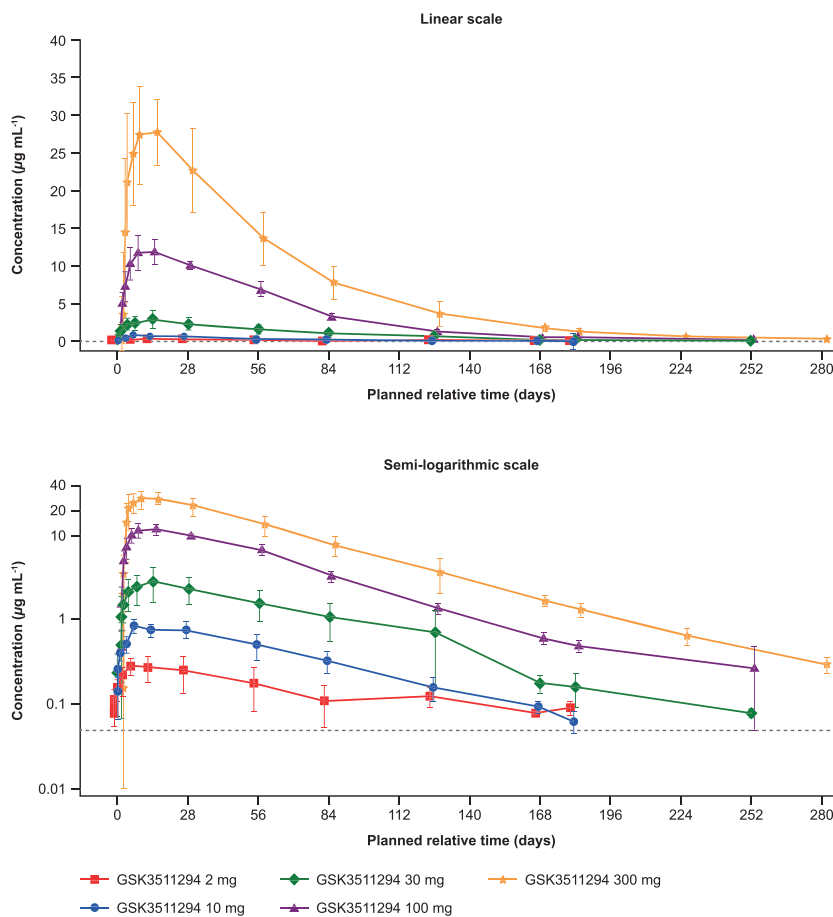
3.3.4 | Exploratory population PK/PD analysis

The relationship between GSK3511294 plasma concentrations and blood eosinophil counts was described by an indirect response two-compartment model, with observed baseline blood eosinophil count included as a covariate on baseline blood eosinophil count and maximum effect. Population PD parameters of $\sim 0.1 \mu\text{g mL}^{-1}$ for the characteristic concentration resulting in 50% of maximum effect (approximately 10-times lower than that previously estimated for mepolizumab¹⁹) and 87% for maximum effect were estimated (Supporting Information Table S5).

3.3.5 | Immunogenicity

At baseline, all patients were negative for ADAs. Post-baseline, 9/36 patients (25%) receiving GSK3511294 and 0/12 patients receiving

FIGURE 2 Mean (SD) plasma concentration-time plot of GSK3511294 following a single subcutaneous dose in patients with mild-to-moderate asthma (PK population). The dashed line represents the lower limit of quantification ($0.05 \mu\text{g mL}^{-1}$). In the event that mean $-$ SD was <0 , this value was set to 0.01 on the semi-logarithmic axis. PK, pharmacokinetic; SD, standard deviation



placebo tested positive for ADAs. Of the nine confirmed ADA-positive patients, five were in the 30 mg dose group, which also had the highest median serum total IL-5 concentrations (data not shown). Titres were generally low (range 80-320, which includes the 1/80 sample dilution during the assay) and within four serial dilutions of being negative. AEs reported by patients who were positive for ADAs were similar to those reported by patients who were negative for ADAs. There were no major differences in the GSK3511294 plasma concentration and blood eosinophil count time profiles between ADA-positive and ADA-negative patients.

3.4 | Exploratory endpoints

Changes from baseline in lung function parameters generally increased with increasing GSK3511294 dose. At week 40 (day 281), patients treated with GSK3511294 300 mg ($n = 6$) demonstrated a greater mean (95% CI) increase from baseline compared with placebo ($n = 2$) in FEV₁ (240 [68, 412] mL vs 105 [not calculable (NC)] mL), FVC (250 [74, 426] mL vs 145 [NC] mL) and percent predicted normal FEV₁ (7.65% [1.76, 13.54] vs 3.85% [NC]). For all study visits, an increase in geometric mean serum total IL-5 from baseline was noted for all GSK3511294 dose groups, without a clear dose response, whereas serum total IL-5 concentrations in the placebo group remained similar to baseline throughout the study

(Supporting Information Figure S4). The geometric mean CIC values for the placebo and GSK3511294 dose groups were within the normal range ($0-5.0 \mu\text{gEq mL}^{-1}$) throughout the study, and any changes from baseline were minimal (CIC ratio to baseline geometric mean across all time points: placebo, 0.761-1.159; GSK3511294 dose groups, 0.855-1.257). Reductions from baseline in EDN were seen following GSK3511294 treatment (week 18 EDN ratio to baseline geometric mean: placebo, 0.95; GSK3511294 dose groups, 0.16-0.53), but no significant changes were noted with the other assessed biomarkers.

4 | DISCUSSION

This Phase 1 study assessed the safety, tolerability, immunogenicity, PK and PD effect on blood eosinophil counts of single ascending SC doses of GSK3511294 up to 300 mg to guide dose selection and dosing interval in the next phase of clinical development. The study design was different to many Phase 1 clinical trials, as we studied patients with mild-to-moderate asthma and a baseline blood eosinophil count similar to the intended population, rather than healthy volunteers. This enabled acquisition of safety and tolerability data in addition to early information on the pharmacological and clinical effect of GSK3511294 in a patient population that was representative of the intended target population. In addition, the

TABLE 3 GSK3511294 plasma PK parameters following single SC administration of different GSK3511294 doses in patients with mild-to-moderate asthma (PK population)

Parameter ^a	GSK3511294				
	2 mg (n = 6)	10 mg (n = 6)	30 mg (n = 9)	100 mg (n = 9)	300 mg (n = 6)
AUC _{0-∞} , day ⁻¹ µg mL ⁻¹	24.8 (14.9, 41.3), 51.6	68.9 (53.9, 88.0), 23.6	208.3 (155.3, 279.4), 39.6	846.7 (800.3, 895.8), 7.3	1873.7 (1439.3, 2439.1), 25.5
AUC _{0-t} , day ⁻¹ µg mL ⁻¹	18.4 (10.3, 32.7), 59.2	62.1 (46.4, 83.2), 28.4	201.4 (148.7, 272.9), 41.1	830.2 (784.2, 879.0), 7.4	1855.6 (1421.1, 2423.0), 25.8
AUC _{0-week 26} , day ⁻¹ µg mL ⁻¹	21.8 (14.2, 33.5), 42.7	64.5 (50.1, 82.9), 24.3	199.9 (148.8, 268.5), 39.9	805.4 (759.1, 854.5), 7.7	1789.5 (1364.6, 2346.5), 26.3
%AUCex, %	24.4 (16.9, 35.1), 35.8	7.8 (3.7, 16.4), 81.6	3.0 (2.0, 4.4), 55.6	1.4 (0.8, 2.5), 88.3	0.9 (0.6, 1.3), 35.1
C _{max} , µg mL ⁻¹	0.34 (0.26, 0.44), 25.3	0.88 (0.72, 1.06), 18.3	2.81 (2.07, 3.81), 41.1	12.25 (10.85, 13.83), 15.9	28.60 (22.48, 36.39), 23.3
t _{max} , days (median [min, max])	11.0 (7.0, 28.0)	8.0 (7.0, 28.9)	13.9 (4.0, 28.0)	14.0 (4.0, 16.0)	13.9 (2.0, 15.0)
t _{last} , days (median [min, max])	84.5 (84.0, 182.0)	176.5 (126.0, 185.0)	182.0 (182.0, 254.8)	252.0 (250.0, 255.0)	280.0 (278.0, 283.0)
CL/F, L day ⁻¹	0.08 (0.05, 0.13), 51.6	0.15 (0.11, 0.19), 23.6	0.14 (0.11, 0.19), 39.6	0.12 (0.11, 0.13), 7.3	0.16 (0.12, 0.21), 25.5
Vz/F, L	6.11 (4.18, 8.95), 37.6	9.19 (6.45, 13.10), 34.7	7.81 (5.80, 10.53), 40.4	6.63 (6.04, 7.27), 12.1	9.34 (6.82, 12.78), 30.6
t _{1/2} , days	52.5 (36.0, 76.7), 37.3	43.9 (37.1, 52.0), 16.2	37.6 (34.6, 40.8), 10.7	38.9 (35.6, 42.6), 11.7	40.4 (37.8, 43.2), 6.3

Abbreviations: %AUCex, percentage of AUC_{0-∞} obtained by extrapolation; %CVb, between-patient coefficient of variation; λz, terminal phase elimination rate constant; AUC_{0-∞}, area under the concentration-time curve from time zero (pre-dose) extrapolated to infinity; AUC_{0-t}, area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a patient across all treatments; AUC_{0-week 26}, area under the concentration-time curve from time zero to week 26; CL/F, apparent clearance following SC dosing; C_{max}, maximum observed concentration; PK, pharmacokinetics; SC, subcutaneous; t_{1/2}, terminal phase half-life; t_{last}, time of last quantifiable concentration; t_{max}, time of occurrence of C_{max}; Vz/F, apparent volume of distribution after SC administration.

^aData show geometric mean (95% CI), %CVb, unless otherwise stated.

study included an extended follow-up period of 32-40 weeks to fully evaluate the pharmacological duration of action and, specifically, the impact on blood eosinophil counts. All single doses of GSK3511294 were well tolerated in this study population of adults with mild-to-moderate asthma. Reductions from baseline in blood eosinophil counts were observed from 24 hours post-GSK3511294 administration and were sustained over 26 weeks in the 100 and 300 mg groups, likely attributable to the improved affinity for IL-5 and extended half-life of this mAb.

The overall incidence of AEs/AESIs was similar between GSK3511294 and placebo treatment groups. The overall incidence of ADAs with GSK3511294 was 25%. Titre values were generally low and did not appear to impact GSK3511294 plasma concentrations, blood eosinophil counts or the incidence of AEs. Overall, these safety data are consistent with results for other anti-IL-5 mAbs.¹²⁻¹⁴ It should be emphasized that ADA assays are specifically developed for a drug, and as such have different parameters (eg, sensitivity, specificity). The ADA assay used in this study to detect anti-GSK3511294 antibodies is different to the ADA assay used for detecting anti-mepolizumab antibodies in the mepolizumab clinical trials. Consequently, the incidences of ADAs against GSK3511294 and mepolizumab cannot be compared.

The current study included patients with a screening blood eosinophil count ≥ 200 cells μL^{-1} to ensure the relevance and translatability of the PD effects on blood eosinophil counts in a severe eosinophilic asthma population. All assessed GSK3511294 doses markedly reduced blood eosinophil counts from baseline by the first post-dose assessment at 24 hours, with the greatest reduction noted at week 8 for most dose groups. While the reduction was dose independent up to week 8, a clear dose response was observed in the return of blood eosinophil counts back towards baseline. Notably, the suppression of blood eosinophil counts was more prolonged in the 100 and 300 mg dose groups, with adjusted reductions in blood eosinophil count compared with placebo of 82% and 83%, respectively, at week 26; these reductions are similar to the approximately 84% reduction observed with mepolizumab versus placebo at week 32 following 4-weekly repeat dosing during the Phase 3 MENSA trial.¹³ Additionally, these reductions were substantially prolonged compared with those seen following 4-weekly mepolizumab administration in a previous clinical pharmacology dose ranging study; in that study blood eosinophil counts began to return towards baseline 8 weeks after the final mepolizumab dose with all doses tested (12.5-250 mg SC).¹⁹

The effect of GSK3511294 on blood eosinophil counts is likely attributable to its increased affinity for IL-5, as well as the longer half-life of the antibody compared with currently available anti-IL-5/IL-5R mAbs.⁸⁻¹⁰ The PK of GSK3511294 was linear and dose-proportional over the 10-300 mg SC dose range, with $t_{1/2}$ ranging between 38 and 53 days across all doses, compared with $t_{1/2}$ of 16-22 days for mepolizumab and 15.5 days for benralizumab.^{8,10} Together, these data support a uniquely long extended dosing interval for GSK3511294 compared with currently available IL-5/IL-5R therapies, which may reduce the need for clinic attendance, potentially improving treatment

compliance.¹⁵ Indeed, ongoing investigations of GSK3511294 in patients with asthma will utilize a 6-month dosing interval.

Increases in serum total IL-5 were seen following administration of all GSK3511294 doses, but not in the placebo group. As the total IL-5 assay detects both bound and free IL-5, these increases reflect binding of GSK3511294 to IL-5 and therefore target engagement. The levels of serum total IL-5 observed in this study were higher than those reported with mepolizumab,¹⁹ further reflecting the increased affinity of GSK3511294 for IL-5. Additionally, the exploratory asthma biomarker results for the study mirror those observed with mepolizumab treatment using the same biomarker panel.^{20,21} Reductions in EDN, an eosinophil granule protein,²² were seen following GSK3511294 treatment, likely due to GSK3511294's eosinophil-modulating actions, but there were no significant changes in the other assessed biomarkers.

The strengths of this study include the relatively long duration of the follow-up period for a Phase 1 study, which allowed collection of robust safety data and characterization of the pharmacology of GSK3511294. In addition, a wide range of doses was included, spanning a 150-fold range of 2-300 mg. The limitations of the study included the small sample size for evaluation of the lung function endpoints. Nonetheless, these results provide a strong foundation for further investigation into the clinical effects of GSK3511294 in patients with asthma with an eosinophilic phenotype.

5 | CONCLUSIONS

GSK3511294 was well tolerated in adult patients with mild-to-moderate asthma, and showed linear and dose proportional PK. The study demonstrated the extended half-life of GSK3511294 and prolonged reduction in blood eosinophil counts after a single dose, with the reduction similar to that observed with mepolizumab at its therapeutic dose, showing the potential for less frequent dosing compared with currently available anti-IL-5/IL-5R antibodies. This Phase 1 study provides the foundation for continued clinical development of GSK3511294 as a treatment for severe asthma with an eosinophilic phenotype.

PATIENT CONSENT

All patients provided written informed consent prior to participation in the study.

ACKNOWLEDGEMENTS

The authors would like to dedicate this manuscript to the memory of Joanna Marks-Konczalik who was involved in the conception, design, data analysis and interpretation of this study. Editorial support (in the form of writing assistance, including preparation of the draft manuscript under the direction and guidance of the authors, collating and incorporating authors' comments for each draft, assembling tables and figures, grammatical editing and referencing) was provided by Roisin McCorkell at Fishawack Indicia Ltd, UK, part of Fishawack Health, and was funded by

GlaxoSmithKline (GSK). This study was funded by GlaxoSmithKline (GSK ID 205722; NCT03287310).

COMPETING INTERESTS

D.S. has received personal fees from Aerogen, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, CSL Behring, Epiendo, Genentech, GlaxoSmithKline, Glenmark, Gossamerbio, Kinaset, Menarini, Novartis, Pulmatrix, Sanofi, Teva, Theravance and Verona. R.F. is an employee of Parexel, the clinical research organization funded by GlaxoSmithKline for study conduct. N.P.B., S.M., K.H., Y.L.M., A.C. and S.W.Y. are employees of GSK and hold stocks/shares. I.J.P. is a former employee of GSK who holds stocks/shares, and is now an employee of AstraZeneca.

CONTRIBUTORS

All authors reviewed and revised the manuscript, approved the final version and made the decision to submit the manuscript for publication. Additionally, S.M., I.J.P. and N.P.B. were involved in the conception and design of the study, D.S. and R.F. were involved in the acquisition of the data, and I.J.P., K.H., Y.L.M., N.P.B., S.W.Y. and A.C. were involved in the data analysis and interpretation.

DATA AVAILABILITY STATEMENT

Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com. The trial protocol is available at <https://www.gsk-studyregister.com/en/>.

ORCID

Dave Singh  <https://orcid.org/0000-0001-8918-7075>

Nicholas P. Bird  <https://orcid.org/0000-0002-5977-2561>

REFERENCES

- Curtis C, Ogbogu P. Hypereosinophilic syndrome. *Clin Rev Allergy Immunol*. 2016;50(2):240-251.
- Furuta S, Iwamoto T, Nakajima H. Update on eosinophilic granulomatosis with polyangiitis. *Allergol Int*. 2019;68(4):430-436.
- Klion AD, Ackerman SJ, Bochner BS. Contributions of eosinophils to human health and disease. *Annu Rev Pathol*. 2020;15(1):179-209.
- McBrien CN, Menzies-Gow A. The biology of eosinophils and their role in asthma. *Front Med (Lausanne)*. 2017;4:93.
- Corren J. Inhibition of interleukin-5 for the treatment of eosinophilic diseases. *Discov Med*. 2012;13(71):305-312.
- Kovalszki A, Weller PF. Eosinophilia. *Prim Care*. 2016;43(4):607-617.
- Legrand F, Klion AD. Biologic therapies targeting eosinophils: current status and future prospects. *J Allergy Clin Immunol Pract*. 2015;3(2):167-174.
- GSK Nucala (mepolizumab) prescribing information. Available from: https://gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Nucala/pdf/NUCALA-PI-PIL-IFU-COMBINED.PDF. Accessed 1 November 2020.
- Teva Cinqair (reslizumab) prescribing information. Available from: <https://www.cinqair.com/globalassets/cinqair/prescribinginformation.pdf>. Accessed 1 November 2020.

- AstraZeneca Fasenna (benralizumab) prescribing information. Available from: <https://www.azpicentral.com/fasenna/fasenna.pdf#page=1>. Accessed 1 November 2020.
- Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med*. 2015;3(5):355-366.
- FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2128-2141.
- Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med*. 2014;371(13):1198-1207.
- Chupp GL, Bradford ES, Albers FC, et al. 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.
- Gelhorn HL, Balantac Z, Ambrose CS, Chung YN, Stone B. Patient and physician preferences for attributes of biologic medications for severe asthma. *Patient Prefer Adherence*. 2019;13:1253-1268.
- Heaney LG, Horne R. Non-adherence in difficult asthma: time to take it seriously. *Thorax*. 2012;67(3):268-270.
- Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet*. 2012;380(9842):651-659.
- Alexander SPH, Christopoulos A, Davenport AP, et al. The Concise Guide to PHARMACOLOGY 2019/20: Catalytic receptors. *Br J Pharmacol*. 2019;176(Suppl 1):S247-S296.
- Pouliquen IJ, Kornmann O, Barton SV, Price JA, Ortega HG. Characterization of the relationship between dose and blood eosinophil response following subcutaneous administration of mepolizumab. *Int J Clin Pharmacol Ther*. 2015;53(12):1015-1027.
- Ortega HG, Yancey SW, Mayer B, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. *Lancet Respir Med*. 2016;4(7):549-556.
- Yancey SW, Keene ON, Albers FC, et al. Biomarkers for severe eosinophilic asthma. *J Allergy Clin Immunol*. 2017;140(6):1509-1518.
- Kim CK. Eosinophil-derived neurotoxin: a novel biomarker for diagnosis and monitoring of asthma. *Korean J Pediatr*. 2013;56(1):8-12.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Singh D, Fuhr R, Bird NP, et al. A Phase 1 study of the long-acting anti-IL-5 monoclonal antibody GSK3511294 in patients with asthma. *Br J Clin Pharmacol*. 2022;88(2):702-712. <https://doi.org/10.1111/bcp.15002>