IL-33 receptor inhibition in subjects with uncontrolled asthma: A randomized, placebo-controlled trial

Courtney Crim, MD,[a] Sally Stone, BSc,[b] Valerie Millar, MSc,[b] Sally Lettis, PhD,[b] Elisabeth H. Bel, MD, PhD,[c] Andrew Menzies-Gow, PhD,[d] Pascal Chanez, MD, PhD,[e] Sally Wenzel, MD,[f] Njira Lugogo, MD MSc,[g] and Eugene R. Bleecker, MD[h] *Research Triangle Park, NC; Amsterdam, The Netherlands; London, United Kingdom; Marseille, France; Pittsburgh, Pa; Ann Arbor, Mich; and Tucson, Ariz*

Background: Most biologics for severe asthma target only type 2 immunity. Inhibition of IL-33 signaling has the potential to target type 2 and non–type 2 pathways.

Objective: This multicenter phase IIA study evaluated the safety and efficacy of GSK3772847, a human mAb directed against the IL-33 receptor (IL-33R) in subjects with moderate-to-severe uncontrolled asthma.

Methods: Adults with uncontrolled asthma despite inhaled corticosteroid/long-acting β_2-agonist therapy received equivalent replacement medication (open-label fluticasone propionate/salmeterol [500/50 μg, twice daily]) for 2 weeks before randomization at week 0. At weeks 0, 4, 8, and 12, participants were administered blinded placebo or 10 mg/kg of intravenous GSK3772847. At week 2, salmeterol was discontinued; thereafter, fluticasone propionate was titrated by approximately 50% on weeks 4, 6, 8, and 10. Asthma control was assessed until week 16. Participants with loss of asthma control discontinued treatment. The primary end point was loss of asthma control; secondary end points were the efficacy, safety, tolerability, pharmacodynamics, and pharmacokinetics of GSK3772847.

Results: At week 16, 56 participants (81%) and 45 (66%) receiving placebo and GSK3772847, respectively, had loss of asthma control (an 18% reduction [95% credible interval = 2%-35%]). Early loss of asthma control prevented full analysis of the secondary efficacy end points after week 4. The most frequent classes of treatment-related adverse events were cardiac disorders (n = 3 [4%] in both groups) and musculoskeletal/connective tissue disorders (with GSK3772847, n = 3 [4%]; with placebo n = 0). Target engagement of IL-33R by GSK3772847 was demonstrated.

Conclusion: Treatment with GSK3772847 may be beneficial for patients with uncontrolled asthma. Further studies are warranted. (J Allergy Clin Immunol Global 2022;1:198-208.)

Key words: *Asthma, IL-33, GSK37772847, mAb, placebo-controlled trial, randomized trial, IL-1 receptor-like 1 protein*

Between 5% and 10% of patients with asthma experience severe asthma.[1,2] Most biologics for management of severe asthma target type 2 (T2)-associated immune pathways. Before the US approval of tezepelumab (an anti–thymic stromal lymphopoietin antibody) in 2021, no biologics targeting non- or low-T2–driven asthma mechanisms were available.[3-5]

The airway epithelium plays a role in asthma pathogenesis.[3,6] Insult to the airway epithelium releases cytokines, including IL-33.[3] Single-nucleotide polymorphisms within the *IL33* region are

From [a]Research and Development, GSK, Research Triangle Park; [b]Biostatistics, GSK, Stockley Park, London; [c]the Department of Respiratory Medicine, Amsterdam University Medical Center, University of Amsterdam; [d]the Department of Respiratory Medicine, Royal Brompton Hospital, London; [e]the Department of Respiratory Diseases, C2VN Inserm University of Aix-Marseille; [f]the Asthma Institute at University of Pittsburgh Medical Center, Pulmonary Allergy and Critical Care Medicine Division and Department of Environmental and Occupational Health, Pittsburgh; [g]Internal Medicine, Division of Pulmonary, Critical Care Medicine, University of Michigan, Ann Arbor; and [h]the Department of Medicine, University of Arizona, Tucson.

Supported by GlaxoSmithKline (grant GSK 207597).

Disclosure of potential conflict of interest: C. Crim and S. Lettis were employees of GlaxoSmithKline (GSK), the study sponsor, during the conduct of the study and hold restricted shares in GSK. S. Stone and V. Millar are employees of and hold restricted shares in GSK. E. H. Bel has received nonfinancial support from GSK during conduct of the study and has also recieved grants from GSK, Teva, and Roche and personal fees from GSK, AstraZeneca, Teva, Sanofi/Regeneron, Sterna, and Chiesi. A. Menzies-Gow has attended advisory boards for AstraZeneca, GSK, Novartis, Sanofi, and Teva; received speaker fees from AstraZeneca, Novartis, Roche, and Teva; participated in research with AstraZeneca, for which his institution has been remunerated; attended international conferences with Teva; and made consultancy agreements with AstraZeneca, Sanofi, and Vectura. P. Chanez has attended advisory boards and provided consultancy for and received lecture fees from ALK-Abelló, Almirall, Boehringer-Ingelheim, GSK, AstraZeneca, Novartis, Teva, and Chiesi, and his institution received a grant from Aix-Marseille University. S. Wenzel has received grants from GSK, Pieris, AstraZeneca, Sanofi Genzyme, Knopp, Teva, and Boehringer Ingelheim and personal fees from GSK, AstraZeneca, and Sanofi-Genzyme. N. Lugogo has attended advisory boards for AstraZeneca, GSK, Genentech, Novartis, Teva, and Sanofi; participated in clinical trials for AstraZeneca, GSK, and Sanofi, for which her institution has been remunerated; and made a consultancy agreement with AstraZeneca. E. R. Bleecker has participated in clinical trials administered through Wake Forest and University of Arizona with AstraZeneca, MedImmune, Boehringer Ingelheim, Genentech, Novartis, Regeneron, and Sanofi Genzyme and has performed paid consultancy with AstraZeneca, MedImmune, Boehringer Ingelheim, Genentech, Novartis, Regeneron, Sanofi, Genzyme, ALK-Abelló, GSK, and Teva.

Received for publication January 19, 2022; revised June 16, 2022; accepted for publication July 3, 2022.

Available online August 17, 2022.

Corresponding author: Courtney Crim, MD, Division of Pulmonary and Critical Care Medicine, University of North Carolina, Chapel Hill, NC. E-mail: crim52c@nc.rr.com.

2772-8293

https://doi.org/10.1016/j.jacig.2022.07.002

Abbreviations used
ACQ: Asthma Control Questionnaire
AE: Adverse event
FENO: Fractional exhaled nitric oxide concentration
FP: Fluticasone propionate
ICS: Inhaled corticosteroid
IL-33R: IL-33 receptor
LABA: Long-acting β_2-agonist
LoAC: Loss of asthma control
PEF: Peak expiratory flow
SAE: Serious adverse event
SAL: Salmeterol
sIL-33R: Soluble IL-33R
T2: Type 2

associated with asthma susceptibility and elevated blood eosinophil counts,[7-9] and single-nucleotide polymorphisms in the promoter region of *IL33* are correlated with IL-33 expression in bronchial epithelial cells from patients with asthma.[10] Furthermore, a rare *IL33* loss-of-function variant was shown to confer protection against asthma development.[11] IL-33 levels are correlated with viral (rhinovirus) infection-induced asthma exacerbations, a leading cause of severe treatment-refractory exacerbations.[12,13]

IL-33 binds to the *IL1RL1* gene product IL-33 receptor (IL-33R), which exists in both membrane-bound (IL-33R) and soluble (sIL-33R) forms.[14] IL-33R stimulation enhances both T_H2 cell- and T_H1 cell–associated immune responses in mast cells, basophils, T_H2 cells, invariant natural killer cells, and natural killer cells.[15-17] In patients with severe asthma, the level of sIL-33R in serum is elevated during exacerbations,[18] and high serum sIL-33R levels (>18 ng/mL) predict future exacerbations.[19] IL-33 may also have a cardioprotective role.[20,21] The association of IL-33 with asthma and its inflammatory effects suggest that inhibition of IL-33 signaling may have potential as add-on therapy targeting both T2 and non-T2 disease mechanisms.

The human IgG2σ mAb GSK3772847 inhibits IL-33 signaling by binding to the extracellular domain of IL-33R. GSK3772847 was well tolerated by participants with mild asthma in a first-time-in-humans study.[22] The current phase IIA proof-of-concept trial (ClinicalTrials.gov identifier NCT03207243) used a downtitration design that gradually withdrew standard asthma control medications (inhaled corticosteroids [ICSs] and long-acting β_2-agonists [LABAs]) to evaluate the ability of GSK3772847 to prevent loss of asthma control (LoAC), as well as to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of GSK3772847 in participants with moderate-to-severe uncontrolled asthma.

METHODS

Study design

The design of this phase IIA, randomized, placebo-controlled, double-blind, stratified, parallel-group study is shown in Fig 1 (for the study protocol, see https://clinicaltrials.gov/ProvidedDocs/43/NCT03207243/Prot_000.pdf). Following run-in, participants were centrally randomized (1:1) to GSK3772847 or placebo. To ensure sufficient participants with presumptive low-T2–driven disease, randomization was stratified by screening blood eosinophil counts (<150 cells/μL vs ≥150 cells/μL), using a GlaxoSmithKline-generated randomization schedule and interactive web response system (RAMOS NG).

The study was conducted according to the Declaration of Helsinki and approved by appropriate national, regional, or investigational center ethics committees or institutional review boards. Each participant provided written informed consent before starting the study.

Treatments

At run-in, participants switched their regular ICS/LABA asthma treatment to study-supplied, open-label background therapy of fluticasone propionate (FP)/salmeterol (SAL), 500/50 μg twice daily (Fig 1). Adherence to background FP/SAL and FP was monitored with the dose counter intrinsic to the DISKUS device.

During the treatment period, participants received GSK3772847, 10 mg/kg, or placebo intravenously every 4 weeks. At week 2 (visit 4), SAL was stopped and the dose of FP was reduced by approximately 50% every 2 weeks until week 10 (visit 8). Participants meeting predefined LoAC criteria discontinued treatment, stopped taking FP/SAL (or FP), resumed an investigator-chosen asthma regimen, and entered a follow-up period (defined as end of treatment). The early-withdrawal assessment was performed 4 weeks after the last dose, with follow-up visits 4, 8, and 12 weeks after the early-withdrawal assessment (defined as end of study).

Study population

Participants were enrolled between September 25, 2017, and May 15, 2019, from 65 centers in Australia, Canada, Mexico, the Russian Federation, Ukraine, and the United States. Participants were at least 18 years of age with a documented diagnosis of moderate-to-severe asthma (based on the Global Initiative for Asthma 2016 report[1]) and met the following criteria: treatment for at least 4 months with a LABA and high-dose ICS (defined as FP, 500 μg, twice daily or the equivalent); bronchodilator reversibility of at least 12% and 200 mL in FEV_1 value at screening, prior documented reversibility, or history of bronchial hyperresponsiveness; an Asthma Control Questionnaire (ACQ)-5 score of at least 1 but less than 4 at screening; and at least 1 asthma exacerbation within the 12 months before screening that required treatment with systemic corticosteroids and/or hospitalization. Additional eligibility and randomization criteria are described in the Online Data Supplement (available at www.jaci-global.org).

End points and assessments

The primary efficacy end point was the proportion of participants with LoAC over weeks 0 to 16. LoAC was defined as 1 or more of the following: an ACQ-5 score increase of 0.5 or more from baseline (measured at the end of run-in), a prebronchodilator decrease in FEV_1 value by more than 7.5% from baseline, the inability to downtitrate ICSs according to the predefined schedule based on the investigator's assessment at any point following randomization, or a clinically significant asthma exacerbation (requiring oral corticosteroids and/or hospitalization).

Secondary end points included the proportion of participants with LoAC over weeks 0 to 6; time to LoAC; number of clinically significant exacerbations; change from baseline in prebronchodilator FEV_1 value, fractional exhaled nitric oxide (FENO) concentration, and blood eosinophil count up to week 4; patient-reported outcomes; summaries of adverse events (AEs), serious AEs (SAEs), and AEs of special interest (identified per the Online Data Supplement); electrocardiogram changes from baseline; and Holter abnormalities. All secondary end points are listed in the Online Data Supplement.

The relationship between screening blood eosinophil count and either LoAC or FEV_1 was an exploratory analysis.

sIL-33R assay

The sIL-33R assays were developed in-house at GlaxoSmithKline by using human recombinant sIL-33R as a reference. The free assay uses GSK3772847 as a capture reagent for sIL-33R, thereby detecting sIL-33R not bound to GSK3772847. The assay measuring total sIL-33R level uses a different capture antibody, binding sIL-33R in a region that does not compete with GSK3772847 and detects all forms of sIL-33R. Serum level of sIL-33R was quantified via

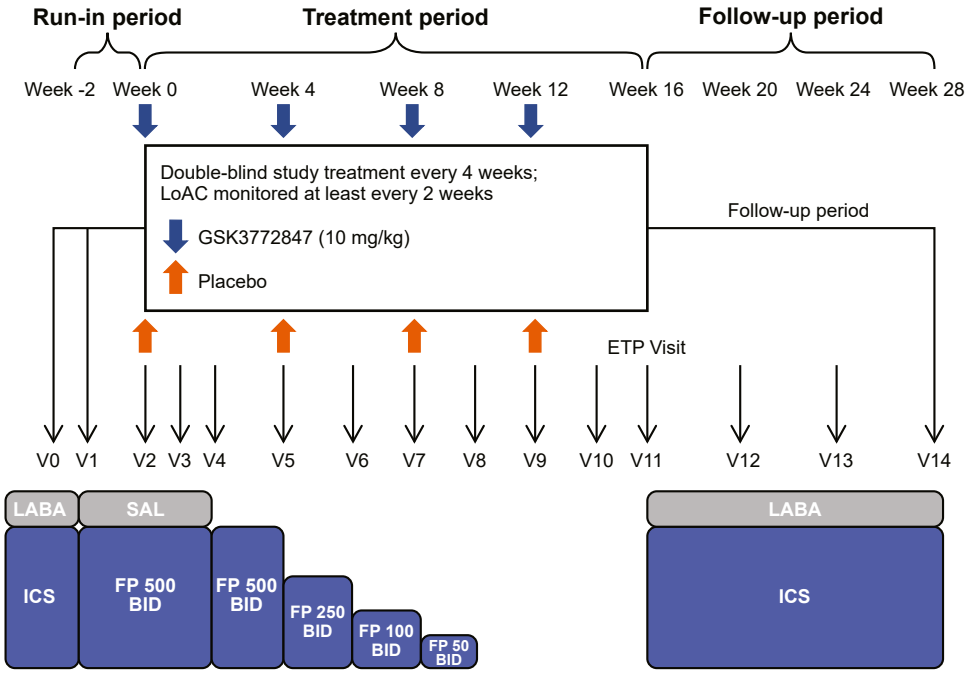

FIG 1. Study design. Note that the run-in period extended from visit 1 to start of the treatment period at visit 2 (2 weeks). *BID*, Twice per day; *ETP*, end of treatment phase; *V*, visit.

electrochemiluminescence immunoassay with lower limits of quantification of 0.025 ng/mL for free sIL-33R and 0.32 ng/mL for total sIL-33R. These assays serve as proxies for target engagement of cell surface IL-33R.

Statistical analysis

A sample size of 70 evaluable participants per arm was determined on the basis of the assumptions described in the Online Data Supplement. The proportion of participants with LoAC over weeks 0 to 16 (primary end point) and weeks 0 to 6 (secondary end point) was analyzed for the modified intent-to-treat LoAC population by using bayesian (primary) and frequentist (supportive) methods (see the Online Data Supplement for details of analysis populations and planned analyses). A *post hoc* analysis used rederived LoAC data to correct inconsistencies between ACQ and FEV_1 value measurements and investigator-recorded LoAC data (eg, ACQ or FEV_1 value criteria for LoAC were met but not recorded as such).

Data availability

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

RESULTS

Study population

Of the 362 participants enrolled, 168 were randomized to placebo (n = 84) or GSK3772847 (n = 84) (Fig 2). Among these, 74 and 77 participants in the placebo and GSK3772847 groups, respectively, completed the 12-week follow-up period, with fewer than half of them (23 of 84 in the placebo arm and 39 of 84 in the GSK3772847 arm) completing the study treatment (Fig 2). The proportion of female participants in the GSK3772847 arm (77%) was greater than in the placebo arm (66%) (Table I). The screening lung function test results were consistent with moderate-to-severe airflow obstruction. The baseline median FENO levels were less than 20 ppb in both arms. The baseline median blood eosinophil counts and sIL-33R concentrations (free and total) were similar between treatment arms, as was the variation in screening blood eosinophil counts (see Fig E1 in the Online Repository at www.jaci-global.org). As GSK3772847 is not present at baseline, the reported sIL-33R concentrations should theoretically be identical. However, owing to the nature of assay and variability between samples, minor differences are to be expected. Use of concomitant medications was comparable (Table I**).** Among the 164 participants using an ICS or LABA at study initiation, 98 (60%), 42 (26%), and 10 (6%) were taking FP/SAL, budesonide/formoterol, and mometasone/formoterol, respectively, with the remainder taking other ICS-LABA combinations.

Primary end point: LoAC

The proportion of participants with LoAC over weeks 0 to 16 was greater in the placebo arm than in the GSK3772847 arm for all analysis sets, with the median rate ratio from the bayesian analysis indicating a 14% to 18% reduction in LoAC for GSK3772847 versus for placebo (Table II and see Table E1 in the Online Repository at www.jaci-global.org). The 95% credible interval excluded the numerical value of 1 for the end of treatment and end of study analyses, but included 1 for the rederived LoAC analysis at the end of study (see Table E1). On the basis of the frequentist analysis, the odds of experiencing LoAC were higher with placebo than with GSK3772847 for all analysis sets; however, this was statistically significant for the end of treatment analysis only (P = .045 [Table II]). The LoAC criterion most commonly met by participants with LoAC was a prebronchodilator decrease in FEV_1 value from baseline greater than 7.5% for both treatment arms (see Table E2 in the Online Repository at www.jaci-global.org).

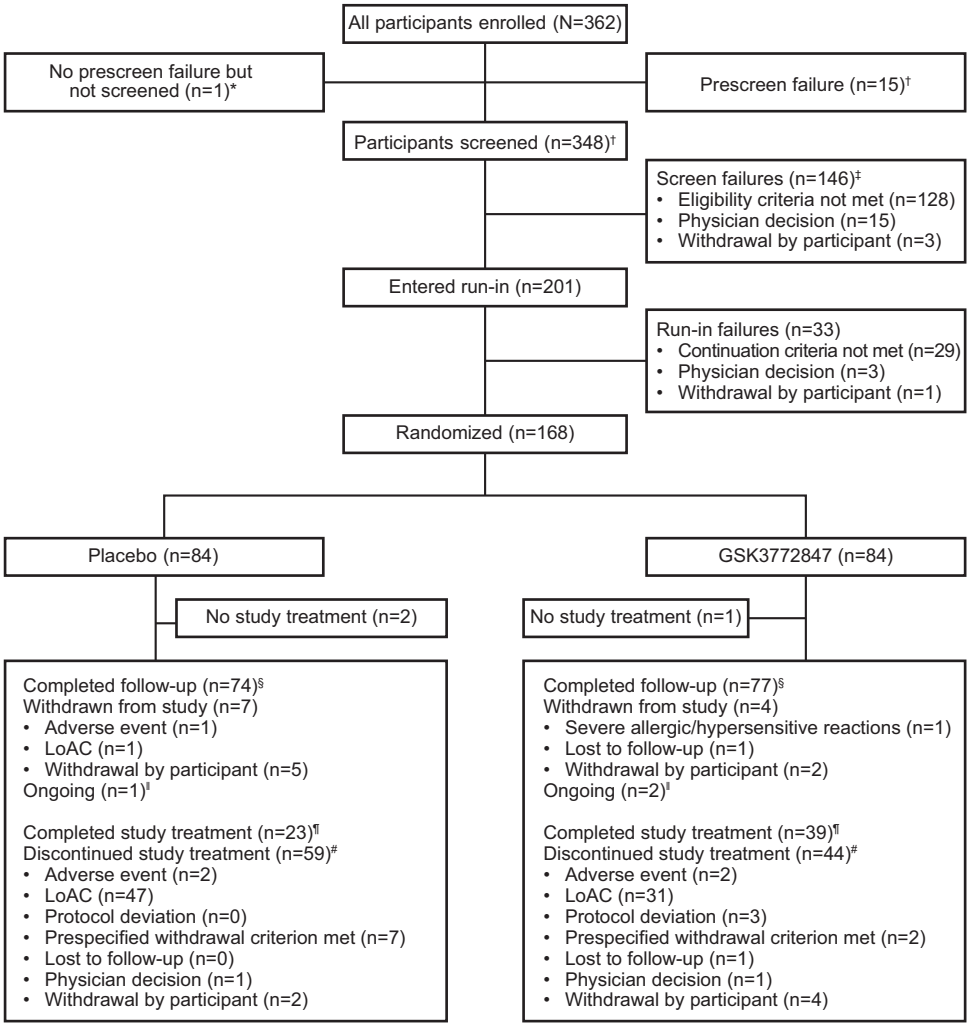

FIG 2. Study disposition. *One participant passed prescreening but was not screened, as screening was closed to enrollment. †Includes 2 participants who failed prescreening and were screened nevertheless but did not enter run-in. ‡One participant failed the inclusion criteria, was rescreened, and failed both screenings; this subject is counted twice under screen failures but only once under screened participants. §Completed follow-up is defined as a participant who completed 12 weeks of follow-up. ‖Three participants from the Good Clinical Practice–noncompliant site are included here on account of having no data recorded for withdrawal from study. ¶Treatment completion is defined as participants who completed the week 16 visit and did not prematurely withdraw from treatment. #Participants may have only 1 primary reason for withdrawal from treatment because of AEs; only participants for whom AEs were considered the primary reason for withdrawal are included here.

Secondary end points

The proportion of participants with LoAC over weeks 0 to 6 in the placebo arm was greater than in the GSK3772847 arm for the end of treatment and end of study analyses. The median rate ratio indicated a 28% to 29% reduction in LoAC for the GSK3772847 arm compared with placebo versus a 35% reduction in the median rate ratio from the *post hoc* rederived LoAC analysis at the end of study (see Table E3 in the Online Repository at www.jaci-global.org). The end of study analyses of time to LoAC indicated that participants receiving placebo had a higher probability of LoAC than did participants receiving GSK3772847 (Fig 3). The median time to LoAC was 33.5 days in the placebo arm versus 36.0 days in the GSK3772847 arm for the end of study analysis, and it was similar for the rederived data (see Fig E2 in the Online Repository at www.jaci-global.org).

One clinically significant asthma exacerbation was reported by 3 participants receiving placebo (on days 20-85) and 6 participants receiving GSK3772847 (on days 14-114, with the last 3 exacerbations occurring on days 96, 97, and 114).

No treatment differences were found with respect to change in FEV_1 value from baseline to week 4 (Fig 4, *A*), and no difference was apparent for mean change from baseline in morning or evening peak expiratory flow (PEF) during weeks 1 to 4 (see Fig E3, *A* in the Online Repository at www.jaci-global.org).

For the mixed model repeated measures analysis of FENO ratio to baseline, a significant treatment difference in favor of GSK3772847 versus placebo was noted at week 2 (GSK3772847 vs placebo change from baseline of −19.5% [95% CI = −31.0 to −6.1] [$P = .006$]), but not at weeks 1 or 4 (Fig 4, *B*).

TABLE I. Participant demographics and clinical characteristics (safety population)

Characteristic	Placebo (n = 82)	GSK3772847 (n = 83)	Total (N = 165)
Age (y), mean (SD)	54.1 (11.65)	51.8 (11.74)	52.9 (11.71)
Sex, no. (%)			
Female	54 (66)	64 (77)	118 (72)
Male	28 (34)	19 (23)	47 (28)
Hispanic/Latino, no. (%)	27 (33)	25 (30)	52 (32)
Race, no. (%)			
American Indian or Alaska Native	14 (17)	8 (10)	22 (13)
Asian	1 (1)	1 (1)	2 (1)
Black or African American	3 (4)	8 (10)	11 (7)
White	64 (78)	66 (80)	130 (79)
Body mass index (kg/m^2), mean (SD)	31.65 (6.900)	32.34 (7.007)	32.00 (6.941)
Duration of asthma (y), mean (SD)	23.7 (16.74)	24.7 (16.97)	24.2 (16.81)
Age of asthma onset (y), mean (SD)*	30.6 (19.14)	27.4 (19.15)	29.0 (19.15)
Screening smoking status, no. (%)			
Never smoked	74 (90)	71 (86)	145 (88)
Former smoker	8 (10)	11 (13)	19 (12)
Current smoker†	0	1 (1)	1 (<1)
Clinically significant exacerbations in the prior 12 mo, no. (%)			
1	70 (85)	67 (81)	137 (83)
≥2	12 (15)	16 (19)	28 (17)
Screening prebronchodilator % predicted FEV_1 value, %			
No.	75	81	156
Mean (SD)	69.8 (13.52)	71.7 (13.67)	70.8 (13.59)
Screening postbronchodilator % predicted FEV_1 value, %			
No.	57	52	109
Mean (SD)	80.7 (14.45)	82.8 (16.45)	81.7 (15.40)
Screening prebronchodilator ratio of FEV_1 value to FVC, %			
No.	75	81	156
Mean (SD)	68.1 (8.99)	69.1 (9.72)	68.6 (9.36)
Baseline blood eosinophil count ($\times 10^9$ cells/L)			-
No.	78	78	
Median (Range)	0.245 (0.01-1.71)	0.235 (0.01-1.05)	
Baseline IgE level (U/mL)			-
No.	78	78	
Median (range)	119.5 (40.0-316.0)	89.0 (50.0-403.0)	
Baseline FENO, ppb			-
n	70	70	
Median (range)	18.987 (4.47-105.50)	12.981 (3.00-162.46)	
Baseline free sIL-33R level, μg/L‡			-
n	78	78	
Median (range)	1.977 (0.43-12.87)	1.864 (0.01-5.01)	
Baseline total sIL-33R level, μg/L			-
n	78	78	
Median (range)	1.487 (0.16-19.29)	1.597 (0.16-4.84)	
Screening comorbidities, no. (%)	39 (48)	41 (49)	80 (48)
Vascular disorder	32 (39)	35 (42)	67 (41)
Hypertension	32 (39)	35 (42)	67 (41)
Metabolism and nutrition disorders	16 (20)	21 (25)	37 (22)
Diabetes mellitus	9 (11)	13 (16)	22 (13)
Hypercholesterolemia	9 (11)	12 (14)	21 (13)
Osteoporosis	0	2 (2)	2 (1)
Cardiac disorders	4 (5)	7 (8)	11 (7)
Coronary artery disease	3 (4)	3 (4)	6 (4)
Congestive heart failure	1 (1)	4 (5)	5 (3)
Arrhythmia	1 (1)	1 (1)	2 (1)
Eye disorders	3 (4)	3 (4)	6 (4)
Cataract	2 (2)	1 (1)	3 (2)
Glaucoma	1 (1)	2 (2)	3 (2)
Concomitant medication use, no. (%)	82 (100)	83 (100)	165 (100)
Corticosteroid			
Inhaled	81 (99)	83 (100)	164 (>99)
Systemic, oral, parenteral, and intraarticular	3 (4)	7 (8)	10 (6)

(Continued)

TABLE I. *(Continued)*

Characteristic	Placebo (n = 82)	GSK3772847 (n = 83)	Total (N = 165)
Depot	0	2 (2)	2 (1)
Other	1 (1)	0	1 (<1)
Long-acting β_2-agonist	82 (100)	82 (99)	164 (>99)
Short-acting β_2-agonist	72 (88)	73 (88)	145 (88)
Leukotriene receptor antagonist	9 (11)	10 (12)	19 (12)
Long-acting anticholinergic	2 (2)	3 (4)	5 (3)
Short-acting anticholinergic	4 (5)	3 (4)	7 (4)
Other asthma medication	2 (2)	0	2 (1)
Mucolytic	0	1 (1)	1 (<1)

The modified intent-to-treat population was used for blood eosinophil count, FENO level, and levels of free and total sIL-33R.
FVC, Forced vital capacity.
*Age at asthma onset is derived as age at the prescreening minus duration of asthma.
†The sole current smoker smoked for 6 years (failing the exclusion criteria); however, the number of cigarettes per day was not reported and pack years could not be calculated.
‡Values less than the lower level of quantification (LLOQ; 0.025 μg/L) are imputed by using LLOQ × 0.5.

TABLE II. LoAC over weeks 0 to 16: End of treatment (modified intent-to-treat LoAC population)

Variable	Placebo (n = 78)	GSK3772847 (n = 78)
End of treatment analysis		
No.	69	68
Participants with LoAC, no. (%)	56 (81)	45 (66)
Bayesian analysis		
Posterior for GSK3772847 vs placebo		
Median rate ratio	0.82	
95% CrI	(0.65, 0.98)	
Frequentist analysis		
GSK3772847 vs placebo		
Odds ratio	0.445	
95% CI	(0.202, 0.982)	
P value	.045	

The posterior probabilities that the ratio of the proportion of participants with LoAC on GSK3772847 compared with placebo is less than 1.0, 0.75, 0.7, 0.5, and 0.2 and greater than 0.6 are equivalent to reductions of more than 0%, 25%, 30%, 50%, and 80% and less than 40% respectively. Analyses were performed using a bayesian or frequentist logistic regression model, including treatment group and screening eosinophil count (<150 cells/μL, ≥150 cells/μL) as fixed effects. Worst-case LoAC was rederived by using both individual components and overall LoAC status to select the earliest date.
CrI, Credible interval.

During the treatment period, the ratio to baseline change in blood eosinophil count remained stable in the placebo arm. In the GSK3772847 arm, blood eosinophil count decreased from weeks 0 to 4 and remained below baseline values until week 16 (Fig 4, *C*). A significant treatment difference for blood eosinophil count in favor of GSK3772847 was observed at weeks 4, 6, 8, 10, 12, and 16; however, by week 16 only 15 participants in the placebo arm and 26 participants in the GSK3772847 arm remained in the study. During-treatment (week 16) IgE levels increased by a mean of 82.3 U/mL (SD = 216.50 U/mL) in the placebo arm and decreased by 71.8 U/mL (SD = 343.25 U/mL) with GSK3772847, but data were available from only 16 and 26 participants, respectively.

No treatment differences were observed for ACQ-5 score up to week 4 (see Fig E3, *B*) and for St. George's Respiratory Questionnaire score at week 4 (data not shown). Because of the small sample size, evaluation of the relationship between screening blood eosinophil count and LoAC or FEV_1 value (analyzed by fractional polynomial modeling) was not feasible (see Fig E4 in the Online Repository at www.jaci-global.org). Subgroup analyses (ie, eosinophil count <150/μL vs ≥150/μL) were not performed because of small sample sizes.

Safety

In all, 37 participants (45%) in the placebo arm and 32 (39%) in the GSK3772847 arm had at least 1 during-treatment AE (Table III). The incidence of AEs considered by the investigator to be related to study treatment was higher in the GSK3772847 arm (10%) than in the placebo arm (4%), although none were serious (Table III). The higher incidence of AEs considered to be related to GSK3772847 was not attributable to any specific events.

The most common AEs (preferred term) were headache (in both arms n = 9 [11%]), nasopharyngitis (in both arms, n = 4 [5%]), influenza (placebo arm, n = 4 [5%]; GSK3772847 arm, n = 1 [1%]), arthralgia (placebo arm, n = 1 [1%]; GSK3772847 arm, n = 4 [5%]), upper respiratory tract infection (placebo arm, n = 1 [1%]; GSK3772847 arm, n = 4 [5%]), nonsustained ventricular tachycardia (placebo arm, n = 3 [4%]; GSK3772847 arm, n = 1 [1%]), and cough (placebo arm, n = 1 [1%]; GSK3772847 arm, n = 3 [4%]). AEs led to permanent discontinuation of treatment by 5% of participants from both arms and to study withdrawal for 1 participant in the placebo arm.

SAEs were reported by 1 participant in the placebo arm (1%) (pneumonia) and 2 participants in the GSK3772847 arm (2%) (anaphylactic shock due to a concomitant medication [intramuscular self-injection of metamizole sodium for abdominal pain] and angioedema 13 days after the most recent dose of GSK3772847 [this participant experienced a similar episode before entering the study and self-managed it with antihistamines]). Both SAEs in the GSK3772847 arm led to permanent discontinuation of the study treatment; however, no SAEs were considered treatment-related, and all of the participants recovered (case narratives are available in the Online Supplement at www.jaci-global.org). A posttreatment SAE of asthma was reported for 1 participant in the placebo arm. There were no fatal AEs.

The most common predefined AEs of special interest (Table IV) were infections in both treatment arms. Systemic allergic/hypersensitivity and nonallergic reactions were reported for 2 participants in the placebo arm (2%) and 6 participants in the GSK3772847 arm (7%), with some participants experiencing

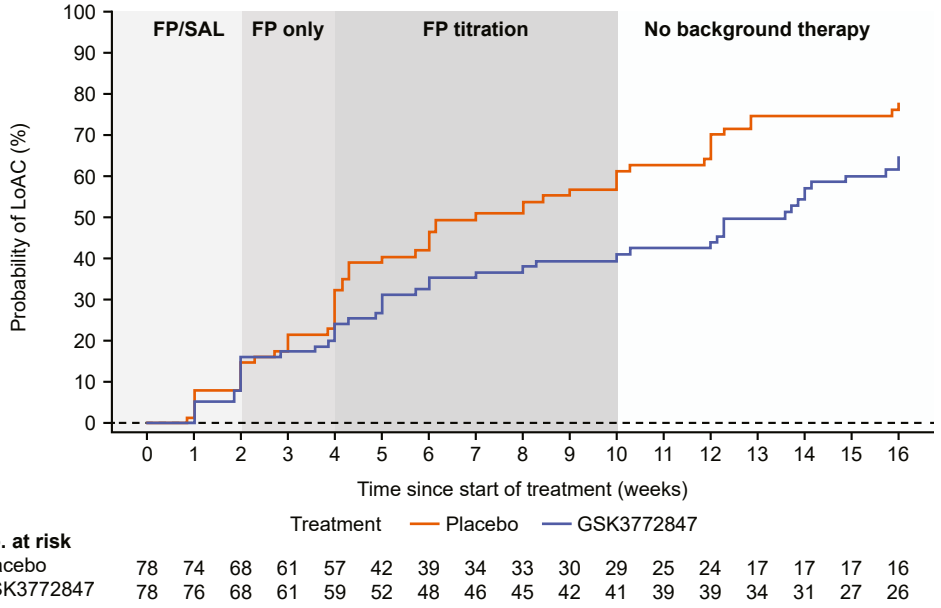

FIG 3. Time to LoAC for end of study analysis* (the modified intent-to-treat [mITT] LoAC population). *Worst case LoAC was rederived using both individual components and overall LoAC status to select the earliest date. Analysis was performed *post-hoc*.

more than 1 event. Two cardiac disorders were reported for at least 1% of the participants: nonsustained ventricular tachycardia (3 participants in the placebo arm [4%] and 1 participant in the GSK3772847 arm [1%]) and dizziness (0 participants in the placebo arm and 2 participants in the GSK3772847 arm [2%]).

For each treatment arm, at least 77% of participants had abnormal Holter test results from baseline to week 12. No differences were observed between arms, and most were not considered clinically meaningful (see Table E4 in the Online Repository at www.jaci-global.org). Sinus tachycardia was the most frequently reported Holter abnormality (in 58%-73% of participants). Nonsustained ventricular tachycardia and Mobitz type 2 second-degree heart block were reported with GSK3772847 at a frequency equal to or lower than with placebo.

Pharmacokinetics and pharmacodynamics

The serum concentration of GSK3772847 decreased in a multiphasic manner over time, consistent with the first-time-in-humans study[22] (see Fig E5 in the Online Repository at www.jaci-global.org). The mean peak serum concentration was 250 to the 269 μg/mL, and the mean trough serum concentration was 49 to 71 μg/mL. During the treatment period, free sIL-33R level decreased by more than 91% from baseline (Fig 4, *D*) and total sIL-33R level increased approximately 21- to 29-fold increase from baseline (see Fig E6 in the Online Repository at www.jaci-global.org) in the GSK3772847 arm compared with in the placebo arm. After treatment, free sIL-33R levels started to recover, and by week 28, free sIL-33R levels remained lower than baseline by 42.6% (Fig 4, *D*).

DISCUSSION

In this phase IIA proof-of-concept study, treatment with the IL-33 signaling inhibitor GSK3772847 reduced the proportion of participants with LoAC, prolonged median time to LoAC, and reduced eosinophil counts and free sIL-33R levels compared with placebo. GSK3772847 appeared to be well tolerated, and its pharmacologic activity was consistent with the expected behavior of other mAbs. These results suggest that GSK3772847 may be beneficial in the management of patients with severe asthma.

The observed reduction in LoAC with GSK3772847 versus with placebo was not as robust as anticipated when the trial was designed. Although bayesian analyses indicated a potential treatment effect with GSK3772847, a *post hoc* rederived LoAC analysis indicated no treatment difference at the end of study. Nonetheless, a concomitant decrease in free sIL-33R serum levels and increase in total sIL-33R levels provides evidence of sIL-33R engagement by GSK3772847. This was consistent with a target-mediated drug disposition profile, but true target coverage of immune cell membrane-bound IL-33R, particularly in the lungs, was not evaluated.

These results can be compared with those from a phase IIA proof-of-concept study that evaluated another anti–IL-33 mAb (itepekimab) in participants with moderate-to-severe asthma not well controlled with ICS/LABA combination therapy.[23] In contrast to our study, that study design involved the addition of blinded treatment to background ICS/LABA. Although the components constituting LoAC were also slightly different (ie, a fall in morning PEF, increase in rescue β_2-agonist or ICS use [as described in our discussion of the dupilumab trial later in this article]), the magnitude of treatment effect observed in the frequentist analysis of GSK3772847 was similar to that of itepekimab monotherapy (odds ratio = 0.42 [95% CI = 0.20-0.88]). Moreover, preliminary data from a 50-week phase IIB study that evaluated a different mAb to IL33-R (astegolimab) in participants with severe asthma uncontrolled by a medium- to high-dose ICS/LABA, showed a decrease in exacerbations with a rate ratio of 0.57 (95% CI = 0.39-0.84).[24] Together with findings from the recent phase III study of tezepelumab that reported a decrease in the annualized rate of asthma exacerbations in participants with severe, uncontrolled asthma (rate ratio = 0.44 [95%

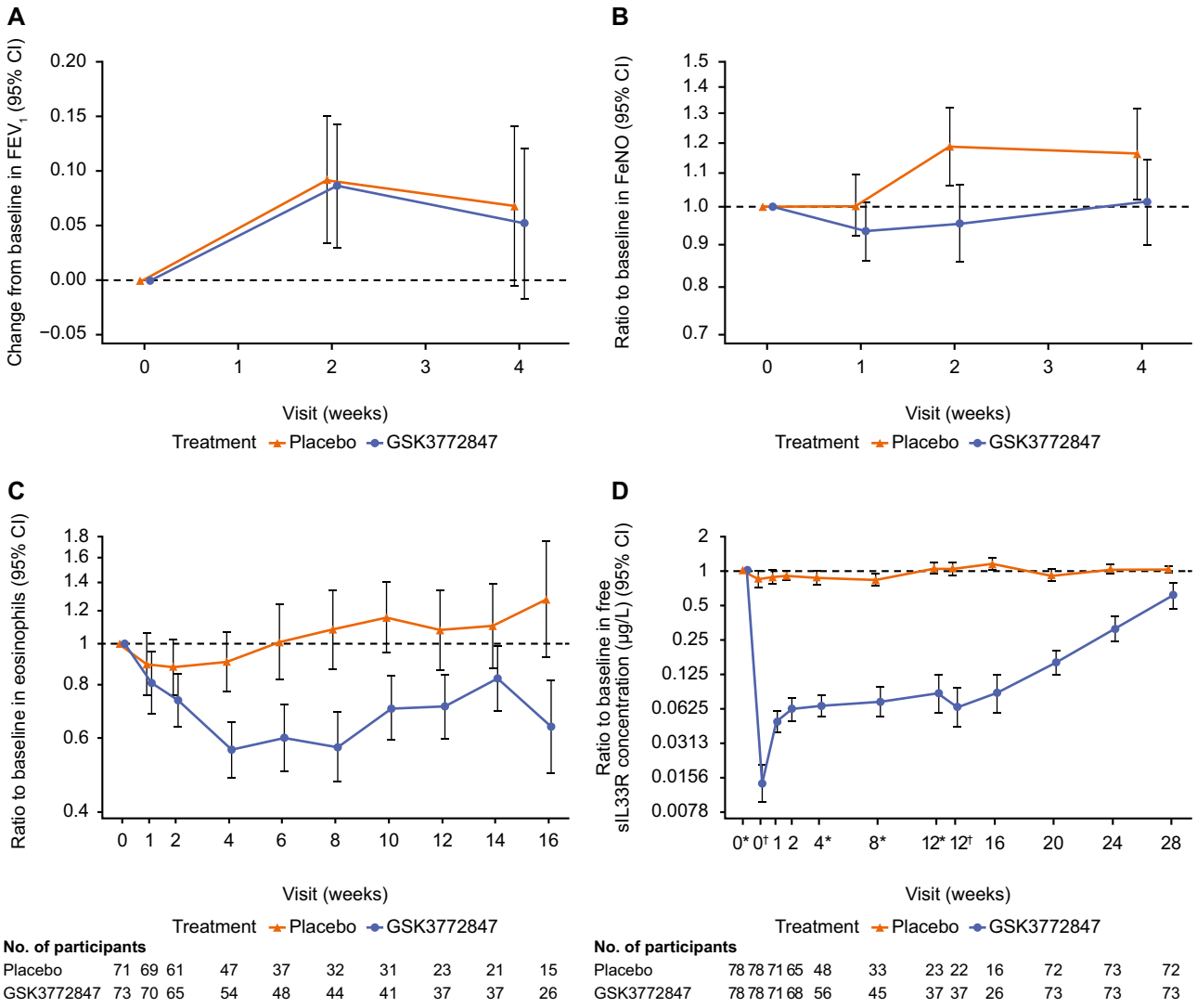

FIG 4. Change from baseline in FEV_1 value (**A**), ratio to baseline of FENO level (**B**) until week 4, ratio to baseline of eosinophil count (**C**) until week 16, and ratio of free sIL-33R concentration to baseline (**D**) until week 28 (modified intent-to-treat [mITT] population). Analysis of data beyond week 4 was performed *post hoc*. **D,** The x-axis is not on a continuous scale. The mean ratio to baseline was produced by summarizing the log-transformed ratio and back-transforming. Values below the lower level of quantification (LLOQ) (>0.025) were imputed by using LLOQ × 0.5. *Predose concentration; †Postdose concentration.

CI = 0.37-0.53]),[25] these data suggest that targeting epithelial-derived cytokines represents a new approach to managing difficult-to-treat patients.

This study was designed with the assumption that 44% of participants in the placebo arm would have LoAC on the basis of a similarly designed study using the IL-4/IL-13 signaling inhibitor dupilumab.[26] However, at end of treatment, the number of participants who discontinued study treatment due to LoAC was higher than expected (81% in the placebo arm and 66% in the GSK3772847 arm). Consequently, analyses of non-LoAC efficacy end points could not be continued beyond week 4 because of the limited sample size.

Although both the current trial and the dupilumab trial used a composite primary end point to determine LoAC and withdrew LABA treatment (at week 4 for the dupilumab study), the results differed, which may be attributable to different definitions of the LoAC end point.[26] In the dupilumab trial, the primary end point was driven mostly by 2 criteria: (1) at least a 30% reduction in morning PEF from baseline on 2 consecutive days or (2) at least 6 additional reliever inhalations of albuterol or levalbuterol in a 24-hour period relative to baseline on 2 consecutive days.[26] In the current trial, the main criterion driving treatment discontinuation was a single observation of more than a 7.5% decrease from baseline in prebronchodilator FEV_1 value, which occurred in two-thirds of participants who withdrew because of LoAC (35 of 56 participants in the placebo arm and 30 of 45 participants in the GSK3772847 arm).

Although a 7.5% increase in FEV_1 value has been used to define a clinical response in trials, such as the National Heart, Lung and Blood Institute Childhood Asthma Research and Education Network and AsthmaNet study TALC,[27,28] one cannot definitively conclude that this magnitude of reduction in FEV_1 value equates to clinical worsening. This stringent FEV_1 value criterion was also adopted to address concerns raised by ethics and regulatory bodies regarding the risk of precipitation of a severe asthma exacerbation

TABLE III. Summary of during-treatment AEs (safety population)

AE type	Placebo (n = 82)	GSK3772847 (n = 83)
AE category, no. (%)		
Any AE	37 (45)	32 (39)
Treatment-related AE	3 (4)	8 (10)
AEs leading to permanent discontinuation of study treatment*	4 (5)	4 (5)
AEs leading to study withdrawal	1 (1)	0
SAEs	1 (1)	2 (2)
Treatment-related SAEs	0	0
Fatal AEs	0	0
AEs by system organ class, no. (%)		
Infections and infestations	16 (20)	15 (18)
Nervous system disorders	9 (11)	11 (13)
Gastrointestinal disorders	5 (6)	7 (8)
Musculoskeletal and connective tissue disorders	3 (4)	7 (8)
Respiratory, thoracic, and mediastinal disorders	6 (7)	4 (5)
Cardiac disorders	6 (7)	3 (4)
Injury, poisoning and procedural complications	4 (5)	3 (4)
Skin and subcutaneous tissue disorders	2 (2)	5 (6)
General disorders and administration site conditions	0	5 (6)
Ear and labyrinth disorders	2 (2)	2 (2)
Investigations	2 (2)	2 (2)
Vascular disorders	1 (1)	1 (1)
Blood and lymphatic system disorders	0	1 (1)
Eye disorders	0	1 (1)
Immune system disorders	0	1 (1)
Psychiatric disorders	0	1 (1)
Reproductive system and breast disorders	0	1 (1)
Treatment-related AEs by system organ class and preferred term, no. (%)		
Cardiac disorders	3 (4)	3 (4)
Ventricular tachycardia	2 (2)	1 (1)
Rhythm idioventricular	1 (1)	1 (1)
Ventricular extrasystoles	0	1 (1)
Musculoskeletal and connective tissue disorders	0	3 (4)
Arthralgia	0	2 (2)
Muscle spasms	0	1 (1)
General disorders and administration site conditions	0	2 (2)
Asthenia	0	2 (2)
Chills	0	1 (1)
Nervous system disorders	0	1 (1)
Autonomic nervous system imbalance	0	1 (1)
Respiratory, thoracic, and mediastinal disorders	0	1 (1)
Bronchospasm	0	1 (1)
Skin and subcutaneous tissue disorders	0	1 (1)
Urticaria	0	1 (1)

During-treatment AE is defined as an AE the onset of which occurs from the date of initiation of the study treatment to 28 days after the study treatment has been stopped.
*Participants who discontinued the study treatment could either be withdrawn from the study or continue to complete the remaining study visits.

during LABA withdrawal and ICS downtitration. This threshold was problematic, as worsening lung function could be anticipated following withdrawal of a LABA or ICS, although any anti-inflammatory effect of anti–IL-33 therapy was hypothesized to minimize decrements in lung function. Furthermore, the decreases in FEV_1 value required to meet this criterion were far lower than the expected coefficient of repeatability for FEV_1 value in patients with asthma (GlaxoSmithKline Data on file, unpublished data, 2018). They were also lower than the published 3-month coefficient of repeatability for FEV_1 value from multicenter trials using Bland-Altman analyses for FEV_1 value for patients with chronic obstructive pulmonary disease (400 mL).[29,30] This suggests that participants in the current study may have discontinued study treatment for LoAC based on multiple factors related to LABA withdrawal and ICS downtitration rather than clinically relevant changes. Approximately 19% of participants in the placebo arm did not experience LoAC during the treatment period after ICS or LABA discontinuation, implying that some participants are symptomatic for reasons other than asthma and are being overtreated. As this was an early-phase trial, we did not require a pre-randomization titration phase to demonstrate the requirement for a moderate-to-high dose ICS or LABA.

There were 3 more exacerbations in the active treatment arm than in the placebo arm. However, these events occurred after the last observed event in the placebo arm and after most of the participants had been withdrawn for LoAC. This observed difference between arms more likely reflects an immortal time bias than a detrimental effect of GSK3772847.

Another issue was the unexpectedly low baseline FENO level (median <20 ppb for both study arms), which is lower than the

TABLE IV. Summary of during-treatment AEs of special interest (safety population*)

Special interest group (preferred term), no. (%)	Placebo (n = 82)	GSK3772847 (n = 83)
Systemic allergic/hypersensitivity and nonallergic reactions	2 (2)	6 (7)
Rhinitis allergic	2 (2)	0
Swelling face	0	2 (2)
Urticaria	0	2 (2)
Anaphylactic shock	0	1 (1)
Angioedema	0	1 (1)
Bronchospasm	0	1 (1)
Eye swelling	0	1 (1)
Rash	0	1 (1)
All infections	16 (20)	15 (18)
Nasopharyngitis	4 (5)	4 (5)
Influenza	4 (5)	1 (1)
Upper respiratory tract infection	1 (1)	4 (5)
Respiratory tract infection viral	2 (2)	2 (2)
Rhinitis	2 (2)	2 (2)
Sinusitis	2 (2)	2 (2)
Pharyngitis	2 (2)	0
Conjunctivitis	0	1 (1)
Ear infection	1 (1)	0
Pharyngotonsillitis	1 (1)	0
Pneumonia	1 (1)	0
Upper respiratory tract infection bacterial	1 (1)	0
Serious infections	1 (1)	0
Pneumonia	1 (1)	0
Cardiac disorders	6 (7)	8 (10)
Ventricular tachycardia	3 (4)	1 (1)
Dizziness	0	2 (2)
Rhythm idioventricular	1 (1)	1 (1)
Ventricular extrasystoles	1 (1)	1 (1)
Chest discomfort	0	1 (1)
Peripheral swelling	0	1 (1)
Presyncope	0	1 (1)
Sinus tachycardia	1 (1)	0
Serious cardiac, vascular, and thromboembolic events	0	1 (1)
Anaphylactic shock	0	1 (1)

During-treatment AE is defined as an AE the onset of which occurs from the date of initiation of the study treatment to 28 days after the study treatment has been stopped. *Preferred terms may contribute to more than 1 special interest group; AEs of special interest were counted for each special interest group in which they appear.

30 ppb typical for severe asthma.[31,32] The lower FENO level may in part be related to the largely clinically obese population recruited here (mean body mass index = 32.0 kg/m^2 [SD = 6.94 kg/m^2]). Obesity-associated asthma has a distinct phenotype in which patients have symptomatic but noneosinophilic asthma with lower FENO levels, despite generalized systemic inflammation.[33,34] Recruitment of participants who were using a high-dose ICS (FP, 500 μg twice daily or the equivalent) for at least 4 months may also have contributed to the low FENO levels. Following ICS downtitration after week 4, FENO levels increased, as expected, with placebo versus with GSK3772847; however, because of the small sample size after week 4, these results should be interpreted with caution.

As IL-33 may be cardioprotective,[20,21] cardiac AEs were a potential concern. However, the similar incidence of during-treatment, treatment-related cardiac AEs between study arms and few cases of nonsustained ventricular tachycardia for all postbaseline measurements from Holter monitoring suggest that GSK3772847 treatment did not lead to cardiac abnormalities.

Limitations of the current study include the stringent LoAC criteria (as already described). Importantly, this limitation precluded our ability to perform subgroup analyses for potentially responsive participants or robustly assess efficacy in participants with low T2 biomarker levels (eg, blood eosinophil counts and IgE level). Another limitation is that some participants who met the ACQ-5 or FEV_1 criteria for LoAC were not withdrawn from blinded treatment per protocol, although the *post hoc* rederived LoAC analysis was performed to correct for this. Also, the short duration of follow-up precluded the assessment of asthma exacerbations, which is an important clinical outcome.

The results of this phase IIA study suggest that treatment with GSK3772847 may benefit patients with uncontrolled asthma and is generally tolerable. However, because restrictive LoAC criteria led to many participants discontinuing study treatment, future studies should investigate prevention of exacerbations as the primary end point to confirm these preliminary positive results and should also evaluate biomarkers that may identify patients with asthma who will benefit from anti–IL-33 treatment with GSK3772847.

We would like to thank 2 GlaxoSmithKline team members, Alex Androulidakis and Marie Duggan, who contributed greatly during the study. Editorial support was provided by Liz Morgan, PhD, at Fishawack Indicia Ltd of Fishawack Health, United Kingdom.

Clinical implications: This phase IIA proof-of-concept study demonstrates that subjects with uncontrolled asthma may benefit from GSK37772847, a human mAb that binds to the IL33R, thereby inhibiting IL-33 signaling.

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