

Inhibition of the early asthmatic response to inhaled allergen by the 5-lipoxygenase activating protein inhibitor GSK2190915: a dose–response study

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Background: GSK2190915, a 5-lipoxygenase activating protein inhibitor, inhibits the production of cysteinyl leukotrienes and leukotriene B₄ and 5-oxo-6,8,11,14-eicosatetraenoic acid. We have previously reported that GSK2190915 100 mg daily inhibits early and late asthmatic responses to inhaled allergen; the effects of lower doses have not been reported. This study assessed the dose–response effects of GSK2190915 10 mg and 50 mg on the early asthmatic response (EAR) to inhaled allergen.

Methods: Nineteen subjects with mild asthma and an EAR were enrolled in a randomized, double-blind, three-way crossover study of GSK2190915 10 mg, 50 mg, and placebo orally once-daily for 3 days. Allergen challenge was performed 2 hours after the third dose.

Results: Compared with placebo, GSK2190915 10 mg and 50 mg caused significant, dose-dependent attenuation of the minimum forced expiratory volume at 1 second (FEV₁) absolute change from baseline; mean treatment differences were 0.21 L (95% confidence interval [CI] 0.04 L, 0.38 L) and 0.41 L (95% CI 0.24 L, 0.58 L), respectively. GSK2190915 50 mg was more effective than 10 mg; mean difference between treatments was 0.20 L, (95% CI 0.03 L, 0.36 L). Compared with placebo, GSK2190915 50 mg, but not 10 mg, significantly inhibited the weighted mean FEV₁ absolute change from baseline.

Conclusion: GSK2190915 50 mg attenuated the EAR similarly to GSK2190915 100 mg in our previous study, suggesting 50 mg is at the top of the dose–response curve. GSK2190915 10 mg is a suboptimal dose. The EAR can be used to assess the therapeutic dose of a new treatment for asthma.

Keywords: GSK2190915, FLAP inhibitor, early asthmatic response

Introduction

Arachidonic acid (AA) within the cell membrane is metabolized by the enzyme 5-lipoxygenase (5-LO) to produce leukotrienes.^{1,2} The 5-LO activating protein (FLAP) binds to 5-LO in this process, enabling transfer of AA to 5-LO. AA metabolism produces leukotriene A₄ (LTA₄), which is subsequently converted to either LTB₄ or the cysteinyl leukotrienes (cysLTs) LTC₄, LTD₄, and LTE₄. CysLTs bind to cysLT1 and cysLT2 receptors, causing bronchoconstriction and eosinophilic inflammation, while LTB₄ promotes the chemotaxis and activation of immune cells including neutrophils and lymphocytes through BLT1 and BLT2 receptors. AA metabolism by 5-LO also produces 5-hydroxyeicosatetraenoic acid (5-HETE), which is further metabolized to

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5-oxo-6,8,11,14-eicosatetraenoic acid (5-oxo-EETE); this activates neutrophils and eosinophils.³

CysLTs levels are elevated in the lungs of patients with asthma.^{4,5} CysLT receptor antagonists are used for the treatment of asthma,¹ but do not inhibit LTB₄ or 5-HETE activity. The 5-LO inhibitor zileuton is approved for the treatment of asthma, but the doses used in clinical practice only partially inhibit leukotriene production, and the therapeutic index is limited by side effects.¹ There is no available drug that completely inhibits the actions of all of the mediators produced by the 5-LO pathway.

GSK2190915 is a novel potent FLAP inhibitor currently in development for the treatment of asthma (the FLAP pathway is detailed in Figure 1).⁶ It inhibits pulmonary cysLTs and LTB₄ production in animal models,⁸ and inhibits LTB₄ production by whole blood stimulated ex vivo and urine LTE₄ excretion in healthy subjects.⁹

The inhaled allergen challenge model is widely used to characterize potential new treatments for asthma; inhibition of the early asthmatic response (EAR) demonstrates the ability to prevent acute allergic bronchoconstriction, whereas inhibition of the late asthmatic response (LAR) suggests effective

anti-inflammatory properties.^{7,10–15} We have recently shown that GSK2190915 100 mg daily inhibits both the EAR and LAR in subjects with mild asthma.⁷ Other FLAP inhibitors also attenuate both the EAR and LAR.^{12,13}

The therapeutic dose of a new treatment for asthma is usually established by assessing its effect on pulmonary function tests and symptoms. Such studies require large numbers of subjects to discriminate between doses.^{16,17} We have employed an alternative approach; we used the EAR to study the dose response effects of GSK2190915 in subjects with asthma. We have previously reported that GSK2190915 100 mg inhibits the EAR,⁷ but have not reported the effects of lower doses. We knew that GSK2190915 50 mg almost completely suppresses urinary LTE₄ levels in healthy subjects, whereas 10 mg causes incomplete suppression, ranging from 40% to 60%.⁹ Therefore, we chose to assess the effect of GSK2190915 10 mg and 50 mg on the EAR in subjects with mild asthma, and to compare the results with those of the effect of GSK2190915 100 mg daily on the EAR from our previously reported study.⁷

Materials and methods

Subjects

Nineteen nonsmoking subjects, aged 18 to 55 years, with mild asthma were recruited. Males and females of non-childbearing potential were included; females of childbearing potential were not included as the appropriate reproductive toxicology studies had not been conducted at the time of the study. Other inclusion criteria were: body mass index within the range 18.5–35.0 kg/m²; forced expiratory volume in 1 second (FEV₁) >70% predicted; current nonsmoker with a pack history of ≤10 pack years; current asthma treatment with an inhaled short-acting beta agonist only; no use of inhaled corticosteroids for at least 1 month before screening; and asthma diagnosis confirmed by provocative methacholine or histamine concentration causing a 20% fall in FEV₁ (provocative concentration 20 [PC₂₀]) <8 mg/mL (or <60 mg/mL for adenosine monophosphate challenge) within 6 months before screening or at the screening visit. Subjects were required to demonstrate an EAR at screening, defined as a fall in FEV₁ of at least 20% from baseline during the 2 hours after allergen challenge. Exclusion criteria were: a respiratory tract infection and/or asthma exacerbation within 4 weeks of randomization; and the possibility of symptoms of hay fever at any time during the study. The study received ethical and regulatory approval before commencement (GSK Study Number LPA112356; clinicaltrials.gov: NCT00812773). Written informed consent was obtained from each subject,

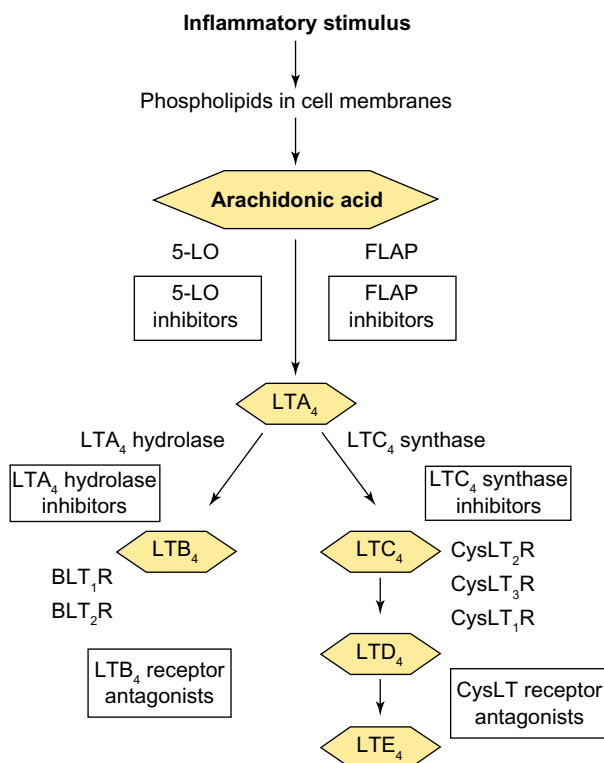


Figure 1 The 5-lipoxygenase activating protein (FLAP) pathway.

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Abbreviations: BLT, G-protein-coupled receptor for LT; Cys, cysteinyl; FLAP, 5-lipoxygenase activating protein; LO, lipoxygenase; LT, leukotriene.

and the study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice Guideline and Declaration of Helsinki.

Study design

The design was double-blind, three-way crossover, in three centers in the United Kingdom. Subjects were screened at least 14 days before the first treatment period. Eligible subjects received GSK2190915 10 mg and 50 mg and matching placebo solutions by mouth with 100 mL water, once-daily for 3 days, in randomized order. Subjects fasted for at least 8 hours before dosing. Allergen challenge was performed at 2 hours after the third dose in each treatment period (Day 3). Treatment periods were separated by a minimum 14-day washout, to allow time for recovery from any allergen-induced hyperresponsiveness, which can persist for 2 weeks in subjects who have a LAR in addition to an EAR. The 14-day washout also exceeds five half-lives of GSK2190915 ($t_{1/2}$ ~20 hours). There was a follow-up visit 5–21 days after the last dose of treatment.

Allergen challenge

Skin prick tests were performed on the volar aspect of the forearm using solutions of grass mix, house dust mite, and cat hair (ALK Abelló, Hørsholm, Denmark). A wheal of at least 3 mm diameter compared with the negative control solution (sodium chloride 0.9%) was deemed positive. Generally, the allergen that produced the largest positive response was used for the allergen challenge test at screening, using incremental doses as described previously.⁷ Allergen challenge at screening was stopped when a 20% decrease in FEV₁ was observed, indicating a positive EAR. The cumulative inhaled allergen dose that had produced an EAR at screening was subsequently administered as a single bolus dose on Day 3 of each treatment period. FEV₁ was recorded every 5 minutes until 20 minutes, then at 30, 45, 60, 90, and 180 minutes after bolus allergen challenge. Subjects were monitored for safety for at least 4 hours after allergen challenge.

Methacholine challenge

Subjects with no documented result for methacholine, histamine, or adenosine monophosphate challenge within 6 months of screening completed a methacholine challenge at the screening visit to confirm study eligibility. FEV₁ was recorded before and after the inhalation of five breaths of nebulized phenol-saline control to ensure that the control did not cause a fall in FEV₁ >10% from the pre-saline measurement. The post-phenol saline FEV₁ was the baseline value. Subjects

then proceeded to inhale methacholine (Provocholine[®]; Methapharm Europe, Geneva, Switzerland), starting at a concentration of 0.0625 mg/mL, and increasing two-fold until the PC₂₀ was reached. The concentration of methacholine did not exceed 8 mg/mL. Subjects were monitored until lung function returned to within 10% of resting FEV₁.

Pharmacokinetics

A 3 mL blood sample was taken on Day 3 at 2 hours after dosing, and plasma was separated by centrifugation (4°C, 1,500 × g, 15 minutes), then stored (–20°C) for subsequent analysis of GSK2190915 (lower limit of qualification of 5 ng/mL) by a validated method based on protein precipitation, followed by high-performance liquid chromatography tandem mass spectrometry analysis, as described previously.⁹

Safety

Adverse events (AEs), clinical laboratory tests, physical examination, vital signs, 12-lead electrocardiogram, and pulmonary function tests, were recorded throughout the study. The severity and causality of AEs were assessed before study was unblinded.

Statistical analysis

Study completion by at least 16 subjects provided at least 90% power to detect a 40% attenuation of the placebo response in the minimum FEV₁ absolute change from baseline within the 2-hour period following allergen challenge on Day 3; using a two-sided 5% significance level, assuming a within-subject standard deviation of 0.27 L and a mean placebo response of –0.87 L. The primary endpoint was the minimum FEV₁ absolute change from baseline within the 2-hour period after allergen challenge on Day 3 of each treatment. The change from allergen challenge baseline FEV₁ over time on Day 3 was analyzed using a repeated-measures model (including time point, period, treatment, treatment-by-time). The minimum FEV₁ absolute change from baseline within the 2-hour period following allergen challenge on Day 3 was analyzed using a mixed-effects model (including period, treatment, and covariates for pre-dose FEV₁ on Day 1). A similar analysis was performed for the weighted mean FEV₁ within the 2-hour period after allergen challenge on Day 3. Pharmacokinetic and safety data were summarized and listed by treatment group.

Results

Subject demographics

Nineteen subjects (18 males and 1 female, mean age 35 years, mean FEV₁ 3.80 L, mean FEV₁ predicted 92.8%) were

enrolled in the study (patient demographics and characteristics are shown in Table 1). The mean FEV₁ percentage fall from baseline during the screening allergen challenge was 33.4% (range 20.8% to 56.5%). Three subjects were withdrawn from the study due to AEs. All available data from subjects who received at least one dose of study medication were included in the analysis of efficacy, pharmacokinetics, and safety. There were no major protocol deviations.

Efficacy

Figure 2 shows the time profile of the EAR after treatment with GSK2190915 and placebo on Day 3 following allergen challenge; GSK2190915 10 mg and 50 mg attenuated the placebo response in a dose-dependent manner.

The primary endpoint analysis of minimum FEV₁ absolute change from baseline showed statistically significant attenuation of the fall in FEV₁ for GSK2190915 10 mg and 50 mg compared with placebo (Figure 3); the mean treatment differences were 0.21 L (95% confidence interval [CI] 0.04 L, 0.38 L) and 0.41 L (95% CI 0.24 L, 0.58 L), respectively, corresponding to a mean attenuation of 18.6% and 36.0% of the placebo response to allergen challenge, respectively. There was a significant difference between GSK2190915 50 mg and 10 mg in the minimum FEV₁ absolute change from baseline; the mean treatment difference was 0.20 L (95% CI 0.03 L, 0.36 L).

Compared with placebo, GSK2190915 50 mg, but not GSK2190915 10 mg, significantly attenuated the weighted mean FEV₁ absolute change from baseline (Figure 3).

Table 1 Patient demographics and characteristics (all subjects population)

Number of subjects	Total (n=19)
Number of subjects planned, n	18
Number of subjects randomized and administered first dose, n	19
Number of subjects completed as planned, n (%)	16 (84)
Number of subjects withdrawn, n (%)	
AE	3 (16)
Other reason	0
Subject demographics and characteristics	
Age (years), mean (SD)	35.0 (10.32)
Male, n (%)	18 (95)
BMI (kg/m ²), mean (SD)	25.24 (3.78)
Race, n (%)	
White	16 (84)
Other	3 (16)
FEV ₁ (L), mean (SD)	3.8 (0.75)
% predicted FEV ₁ , mean (SD)	92.8 (12.76)

Abbreviations: AE, adverse event; BMI, body mass index; FEV₁, forced expiratory volume in 1 second; SD, standard deviation; n, number.

The mean treatment differences were 0.12 L (95% CI -0.01 L, 0.24 L) and 0.30 L (95% CI 0.18 L, 0.43 L) for GSK2190915 10 mg and 50 mg compared with placebo, respectively, corresponding to mean attenuation of 21.5% and 56.2% of the placebo response, respectively.

Pharmacokinetics

On Day 3, at 2 hours after dosing with GSK2190915 10 mg and 50 mg, the mean (95% CI) plasma concentrations were 83.4 ng/mL (62.3, 104.5) and 418.9 ng/mL (311.0, 526.7), respectively.

Safety

There were 19 mild-to-moderate AEs (Table 2), all of which resolved spontaneously. Eight were deemed at least possibly related to treatment; of those eight, four occurred on GSK2190915 10 mg, one on GSK2190915 50 mg, and three on placebo. The most frequent AE was headache. There were no serious AEs.

Three subjects were withdrawn from the study due to AEs. One subject had high fasting blood glucose before dosing on Day 1 of the first treatment period, which was not noted until after dosing and could not have been due to treatment. A second subject had a flu-like illness during the third treatment period (placebo), and was withdrawn as it was not considered safe to perform the allergen challenge. A third subject received GSK2190915 50 mg during the first treatment period and subsequently completed a 25-day washout period. Alanine aminotransferase (ALT) was increased in his pre-dose sample from the second treatment period. He received a single GSK2190915 10 mg dose before being withdrawn from the study; subsequent monitoring showed a decline in ALT. The raised ALT was deemed by the investigator to be possibly related to treatment.

Discussion

GSK2190915 caused dose-related inhibition of the EAR in subjects with mild asthma. We have shown that 50 mg administered once-daily had a significantly greater effect than 10 mg once-daily. This study shows the utility of the EAR for investigating the pharmacological dose-response effects of novel drugs in humans.

Compared with placebo, GSK2190915 50 mg once-daily for 3 days caused 36% and 56% mean attenuation of the minimum and weighted mean FEV₁ change from baseline, respectively, in subjects with mild asthma; both changes were statistically significant. In our previously reported study,⁷ GSK2190915 100 mg once-daily caused 33% and 63%

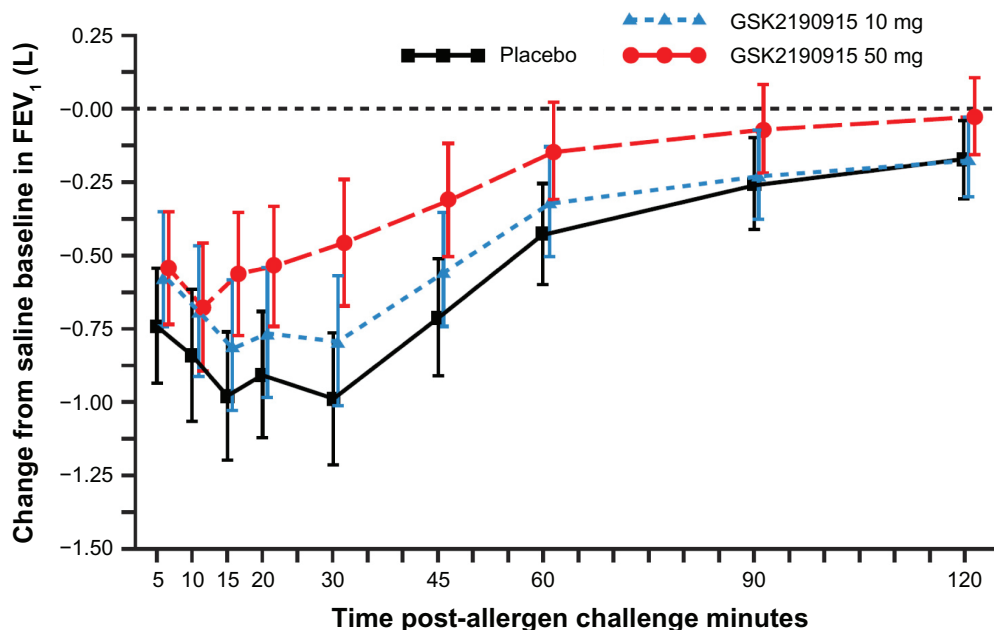


Figure 2 Adjusted mean (95% CI) absolute change in FEV₁ versus time on Day 3 (efficacy population).
Abbreviations: CI, confidence interval; FEV₁, forced expiratory volume in 1 second.

mean attenuation of the minimum and weighted mean FEV₁ change from baseline compared with placebo, respectively. Thus, 50 and 100 mg had very similar effects, suggesting both of the doses were at the top of the dose response curve for EAR.

As the 50 mg dose was shown to have a similar effect on EAR to that reported with a 100 mg dose,⁷ it would be of interest to assess whether the lower doses of GSK2190915

used in this study also protect against LAR. Assessment of other efficacy outcomes, such as airway hyperresponsiveness to methacholine, and airway or blood markers of inflammation, would also have been useful. However, such assessments would have required a more complex study design; as the priority of the study was to measure the dose response effect on the EAR, additional assessments were not included. The effect of GSK2190915 50 mg and 100 mg once-daily on the EAR

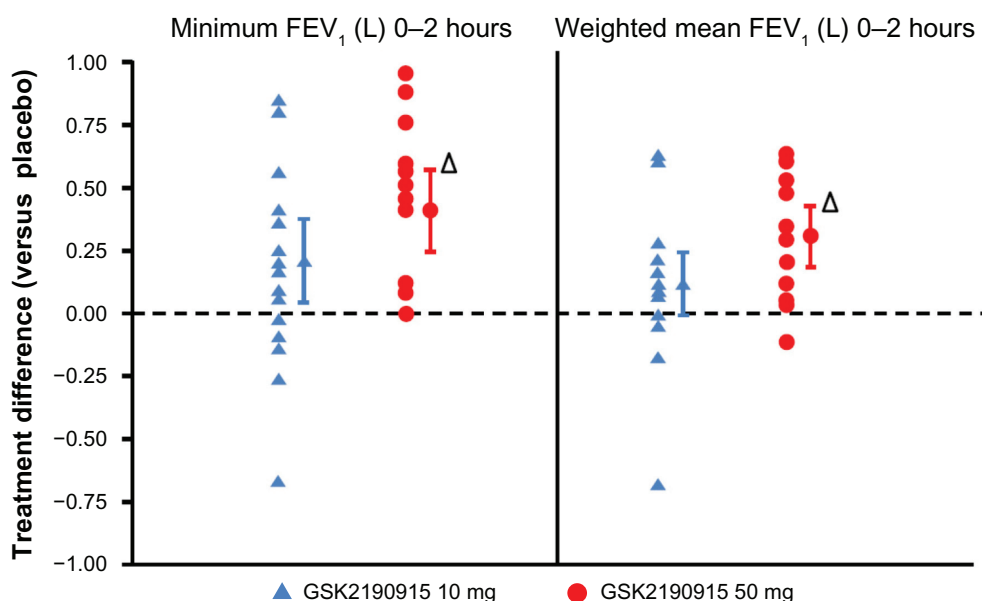


Figure 3 Adjusted mean treatment differences (95% CI) for allergen challenge: absolute change from saline baseline in minimum and weighted mean EAR on Day 3 (efficacy population).

Note: ^ΔDifference between 50 mg and 10 mg statistically significant ($P < 0.05$).

Abbreviations: CI, confidence interval; EAR, early asthmatic response; FEV₁, forced expiratory volume in 1 second.

Table 2 Adverse events (all subjects population)

Preferred term, n (%)	Placebo (n=17)	GSK2190915	
		10 mg (n=18)	50 mg (n=19)
Headache	2 (12)	4 (22)	0
Dizziness	0	0	1 (5)
Oropharyngeal pain	0	1 (6)	1 (5)
Cough	0	0	1 (5)
Influenza	1 (6)	0	0
Nasopharyngitis	0	1 (6)	0
Arthralgia	0	1 (6)	0
Myalgia	0	1 (6)	0
Dental caries	1 (6)	0	0
Nausea	1 (6)	1 (6)	0
Chest pain	0	1 (6)	0
Alanine aminotransferase increased	0	0	1 (5)

is similar to that previously reported for the clinical dose of the leukotriene antagonist montelukast.^{10,11} Furthermore, this effect is also similar to that observed in studies using FLAP inhibitors.^{12,13} These studies confirm the role of cysLTs in acute allergic bronchoconstriction; however, it would be useful to compare the magnitude of the effect of the GSK2190915 50 mg dose with other classes of drugs, although such studies have not been performed to date.

Compared with placebo, GSK2190915 10 mg once-daily for 3 days caused 18% and 21% mean attenuation of the minimum and weighted mean FEV₁ change from baseline, respectively; only the minimum mean change was significantly different from placebo. Thus, 10 mg appears to be a suboptimal therapeutic dose.

The effects of GSK2190915 10 mg and 50 mg doses on the EAR correlate well with those of the same doses on urinary LTE₄ suppression in healthy subjects;⁹ 10 mg suppressed LTE₄ by 40%, and 50 mg suppressed LTE₄ almost completely. We did not include urine LTE₄ in this study; however, the plasma concentrations were similar to those in healthy volunteers.⁹ The data suggest that the use of urine LTE₄ measurements to assess the effects of drugs on leukotriene production could be a good predictor of the likely effects on allergic bronchoconstriction.

In our previously reported study on asthma, the geometric mean peak concentration (C_{max}) for 100 mg of GSK2190915 was 671 (95% CI: 494, 910) ng/mL,⁷ compared with the observed C_{max} values for 10 mg (83.4 [95% CI: 62.3, 104.5] ng/mL) and 50 mg (418.9 [95% CI: 311.0, 526.7] ng/mL) doses in this study. These dose-related increases in GSK2190915 pharmacokinetics in patients with asthma have also been observed in healthy subjects using GSK2190915 doses up to 1,000 mg.

Ideally, we could have studied more doses of GSK2190915 in the current study, but there is a limit to the number of allergen challenges that subjects with asthma are willing to tolerate. We therefore chose not to include a dose of 100 mg, but to use results from our previously reported study⁷ for comparison. Although the two studies used different subjects, they all had mild asthma, the procedure for allergen challenge was identical, the clinical sites were the same, the two studies were conducted at the same time, and the inclusion criteria were the same, except that subjects in our previously reported study were also required to have a LAR. Therefore, comparison of the two sets of results seems reasonable. In retrospect, a dose between 10 mg and 50 mg would have yielded useful information about the therapeutic dose. Nevertheless, the EAR data from our previous⁷ and current studies provide a guide for doses that can be included in larger and longer dose-ranging studies on clinical endpoints such as lung function and asthma control.

While allergen challenge studies of more than one dose have been conducted with other drugs such as inhaled corticosteroids, these studies have included both the EAR and LAR. We are unaware of any other studies that have used the EAR alone to study the dose–response effects of novel drugs. We have demonstrated that the EAR is a model that can be used in relatively small numbers of subjects to define the dose–response effects. This approach is faster and more efficient than alternatives such as longer studies of FEV₁.

In general, GSK2190915 was well-tolerated in this short study. Of the three subjects who were withdrawn from the study because of AEs, two had abnormal blood results in pre-dose blood samples and the other was withdrawn during placebo treatment. Studies with longer duration of dosing and larger numbers of subjects are required to define the potential adverse effects of GSK2190915.

Conclusion

In conclusion, GSK2190915 caused dose-dependent attenuation of the EAR response to inhaled allergen. GSK2190915 50 mg attenuated the EAR similarly to GSK2190915 100 mg in our previous study,⁷ suggesting that 50 mg is at the top of the dose–response curve. This study shows how the EAR can be used to assess the therapeutic dose of a new treatment for allergic asthma.

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Disclosure

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References

1. Montuschi P, Peters-Golden ML. Leukotriene modifiers for asthma treatment. *Clin Exp Allergy*. 2010;40(12):1732–1741.
2. Peters-Golden M, Henderson WR. Leukotrienes. *N Engl J Med*. 2007;357(18):1841–1854.
3. Grant GE, Rokach J, Powell WS. 5-Oxo-ETE and the OXE receptor. *Prostaglandins Other Lipid Mediat*. 2009;89(3–4):98–104.
4. Gaber F, Daham K, Higashi A, et al. Increased levels of cysteinyl-leukotrienes in saliva, induced sputum, urine and blood from patients with aspirin-intolerant asthma. *Thorax*. 2008;63(12):1076–1082.
5. Pavord ID, Ward R, Woltmann G, Wardlaw AJ, Sheller JR, Dworski R. Induced sputum eicosanoid concentrations in asthma. *Am J Respir Crit Care Med*. 1999;160(6):1905–1909.
6. Evans JF, Ferguson AD, Mosley RT, Hutchinson JH. What's all the FLAP about?: 5-lipoxygenase-activating protein inhibitors for inflammatory diseases. *Trends Pharmacol Sci*. 2007;29(2):72–78.
7. Kent SE, Boyce M, Diamant Z, et al. The 5-lipoxygenase activating protein inhibitor, GSK2190915, attenuates the early and late responses to inhaled allergen in mild asthma. *Clin Exp Allergy*. 2013;43(2):177–186.
8. Lorrain DS, Bain G, Correa LD, et al. Pharmacology of AM803, a novel selective five-lipoxygenase-activating protein (FLAP) inhibitor in rodent models of acute inflammation. *Eur J Pharmacol*. 2010;640(1–3):211–218.
9. Bain G, King CD, Schaab K, et al. Pharmacodynamics, pharmacokinetics and safety of GSK2190915, a novel oral anti-inflammatory 5-lipoxygenase-activating protein inhibitor. *Br J Clin Pharmacol*. 2013;75(3):779–790.
10. Singh D, Richards D, Knowles RG, et al. Selective inducible nitric oxide synthase inhibition has no effect on allergen challenge in asthma. *Am J Respir Crit Care Med*. 2007;176(10):988–993.
11. Diamant Z, Grootendorst DC, Veselic-Charvat M, et al. The effect of montelukast (MK-0476), a cysteinyl leukotriene receptor antagonist, on allergen-induced airway responses and sputum cell counts in asthma. *Clin Exp Allergy*. 1999;29(1):42–51.
12. Hamilton AL, Watson RM, Wyile G, O'Byrne PM. Attenuation of early and late phase allergen-induced bronchoconstriction in asthmatic subjects by a 5-lipoxygenase activating protein antagonist, BAYx 1005. *Thorax*. 1997;52(4):348–354.
13. Diamant Z, Timmers MC, van der Veen H, et al. The effect of MK-0591, a novel 5-lipoxygenase activating protein inhibitor, on leukotriene biosynthesis and allergen-induced airway responses in asthmatic subjects in vivo. *J Allergy Clin Immunol*. 1995;95(1 Pt 1):42–51.
14. Hui KP, Taylor IK, Taylor GW, et al. Effect of a 5-lipoxygenase inhibitor on leukotriene generation and airway responses after allergen challenge in asthmatic patients. *Thorax*. 1991;46(3):184–189.
15. Nasser SM, Bell GS, Foster S, et al. Effect of the 5-lipoxygenase inhibitor ZD2138 on aspirin-induced asthma. *Thorax*. 1994;49(8):749–756.
16. Busse WW, Brazinsky S, Jacobson K, et al. Efficacy response of inhaled beclomethasone dipropionate in asthma is proportional to dose and is improved by formulation with a new propellant. *J Allergy Clin Immunol*. 1999;104(6):1215–1222.
17. Bleecker ER, Bateman ED, Busse WW, et al. Once-daily fluticasone furoate is efficacious in patients with symptomatic asthma on low-dose inhaled corticosteroids. *Ann Allergy Asthma Immunol*. 2012;109(5):353–358. e4.

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