

The effect of GSK2190915, a 5-lipoxygenase-activating protein inhibitor, on exercise-induced bronchoconstriction

Sandra E. Kent, M.Sc.,¹ Jane H. Bentley, M.Sc.,¹ David Miller, M.D.,² Richard Sterling, M.D.,³ Rogelio Menendez, M.D.,⁴ Martha Tarpay, M.D.,⁵ David S. Pearlman, M.D.,⁶ and Virginia Norris, M.D.¹

ABSTRACT

Exercise-induced bronchoconstriction (EIB) describes the condition whereby exercise causes airflow obstruction that lasts for up to 90 minutes without treatment. This double-blind, placebo-controlled, five-way crossover study investigated the dose response and duration of action of a 5-lipoxygenase-activating protein inhibitor, GSK2190915, to inhibit EIB in subjects with asthma. Forty-seven subjects with EIB were enrolled. Exercise challenge testing was scheduled at 2, 9.5, and 24 hours after receiving a single dose of GSK2190915 (10, 50, 100, and 200 mg) or placebo in randomized order. GSK2190915 at 200 and 100 mg significantly attenuated the response to exercise at 2 and 9.5 hours postdose, respectively, compared with placebo. The adjusted mean maximum percentage change from baseline forced expiratory volume at 1 second within 60 minutes postexercise challenge ($FEV_{1(0-60)}$) treatment difference for GSK2190915 at 200 mg compared with placebo at 2 hours postdose was 6.30% (95% CI, 3.06, 9.54), corresponding to a 40% attenuation of the placebo response to exercise; the treatment difference between GSK2190915 at 100 mg and placebo at 9.5 hours postdose was 3.49% (95% CI, 1.02, 5.95), corresponding to a 41% attenuation of the placebo response to exercise. No significant effect was seen at 24 hours postdose with any dose; however, investigation of statistically significant treatment-related effects at this time point was limited because of the small fall in adjusted mean $FEV_{1(0-60)}$ (−7.61%; 95% CI, −10.23, −4.99) after placebo. GSK2190915 may be of benefit in EIB prevention. GSK Clinical Study LPA112025; ClinicalTrials.gov identifier number: NCT00812929.

(Allergy Asthma Proc 35:126–133, 2014; doi: 10.2500/aap.2014.35.3723)

Exercise-induced bronchoconstriction (EIB) describes the condition whereby exercise causes airflow obstruction that lasts for up to 90 minutes without treatment.¹ It is hypothesized that a change in airway fluid osmolarity, caused by airway drying during exercise, induces inflammatory mediator release, including cysteinyl leukotrienes (cysLTs), into the airways of susceptible individuals.^{2,3} The cysLTs recruit inflammatory cells into the airways, such as eosinophils,^{4–6} leading to edema, mucus secretion,⁷ and smooth muscle constriction.⁸ In EIB subjects, the concentration of cysLTs is increased relative to the bronchoprotective eicosanoid prostaglandin E_2 after exercise.⁹

CysLT antagonists are successfully used in the prophylactic treatment of EIB.¹⁰ Cell activation by mechanical injury, infection, allergens, cytokines, or growth factors triggers leukotriene synthesis, which commences when cytosolic phospholipase A_2 hydrolyzes membrane phospholipids to release arachidonic acid (AA) at the leukocyte nuclear envelope; in the presence of the integral nuclear membrane protein 5-lipoxygenase-activating protein (FLAP), AA metabolizes 5-lipoxygenase to leukotriene A_4 (LTA_4); LTA_4 hydrolase converts LTA_4 to LTB_4 ; LTC_4 synthase converts LTA_4 to the cysLTs C_4 , D_4 , or E_4 (LTC_4 , LTD_4 , or LTE_4 , respectively).^{11,12} In addition to the leukotriene synthesis pathway, potent activation of neutrophils and eosinophils by 5-oxo-6, 8, 11, 14-eicosatetraenoic acid may be the result of AA reduction by 5-lipoxygenase to, then, metabolism of 5-hydroxyeicosatetraenoic acid.¹³

GSK2190915, 3-[3-*tert*-butylsulfanyl-1-[4-(6-ethoxy-pyridin-3-yl)-benzyl]-5-(5-methyl-pyridin-2-ylmethoxy)-1*H*-indol-2-yl]-2,2-dimethyl-propionic acid,^{14–16} is a high-affinity FLAP inhibitor currently in development for the treatment of asthma. Given the evidence supporting the role of cysLTs in EIB pathophysiology and the prophylactic effects of cysLT antagonists, we investigated the effect, dose response, and duration of action of GSK2190915 in mild asthmatic subjects who experience EIB. To our knowledge, this is the first study to

From ¹GlaxoSmithKline, London, United Kingdom, ²Northeast Medical Research Associates, Inc., North Dartmouth, Massachusetts, ³Sterling ENT, PA, Orangeburg, South Carolina, ⁴Allergy and Asthma Research Center of El Paso, El Paso, Texas, ⁵Allergy, Asthma and Clinical Research Center, Oklahoma City, Oklahoma, and ⁶Colorado Allergy and Asthma Centers, PC, Denver, Colorado

Funded by GlaxoSmithKline

The employers of D Miller, R Sterling, R Menendez, M Tarpay, and DS Pearlman had support from GlaxoSmithKline for the submitted work (they received funding to conduct the clinical trial; D Miller, R Sterling, R Menendez, M Tarpay, and DS Pearlman were investigators). D Miller, R Sterling, R Menendez, and M Tarpay have no personal competing interests to declare. V Norris and JH Bentley are employed by and own shares in GlaxoSmithKline. SE Kent was contracted by GlaxoSmithKline. Address correspondence to Virginia Norris, M.D., GlaxoSmithKline, Brentford, Middlesex TW8 9GS, U.K.

E-mail address: virginia.h.norris@gsk.com

Copyright © 2014, OceanSide Publications, Inc., U.S.A.

investigate an FLAP inhibitor in an exercise challenge model.

METHODS

Study Design

This five U.S. center, double-blind, randomized, five-way crossover study was completed in accordance with the International Conference of Harmonization Guideline for Good Clinical Practice from December 2, 2008 to July 15, 2009 (GSK Clinical Study LPA112025; ClinicalTrials.gov Identifier: NCT00812929). Investigational Review Board (IRB) approval was granted (Great Lakes IRB, Peotone, IL). Written informed consent was obtained before subject enrollment.

Subjects completed a screening visit within 28 days of first dose for study eligibility assessments, including one exercise challenge test (ECT). During each treatment period, overnight-fasted subjects drank a single dose of oral solution GSK2190915 (10, 50, 100, or 200 mg) or matched placebo with 100 mL of water in accordance with a computer-generated randomization schedule; ECTs were completed at 2, 9.5, and 24 hours postdose; 10 subjects at one site also provided blood and urine samples for measurement of LTB₄ and LTE₄, respectively. Treatment periods were separated by at least 7 days washout.

Subjects

Key inclusion criteria included healthy, nonsmoking, mild asthmatic, male or non-child-bearing potential (because reproductive toxicology had not been conducted) female subjects (18–50 years); prebronchodilator forced expiratory volume at 1 second (FEV₁) of at least 70% predicted¹⁷; a fall in FEV₁ between 20 and 40% of baseline after a screening exercise challenge¹⁸; and being capable of withholding short- and long-acting β_2 -agonists for 6 and 48 hours, respectively, before ECT, lung function testing (LFT), and study medication dosing. The study did not require subjects to be tested for atopic or inhalant allergies.

Key exclusion criteria included upper respiratory tract infection within 2 weeks of first study medication dosing, hay fever symptoms during study, use of oral/injectable corticosteroids within 5 weeks of study start, and use of intranasal/topical steroids within 4 weeks of start.

Safety Assessments

Samples for hematology, chemistry, and urinalysis were collected (predose, 25 hours postdose). Adverse events (AEs) were recorded using open-ended questions; causality and intensity were assessed by the investigator. Medical occurrences that resulted in death; were life-threatening; or caused hospitalization,

disability, or congenital anomaly were to have been deemed serious AEs.

Exercise Challenge Testing

One ECT methodology for motor-driven treadmill with adjustable speed and gradient was selected by the investigator at screening for each subject's study duration, either in an air-conditioned (20–25°C) and humidity-controlled (<50%) room with a nose clip in place, or by inspiring compressed cold, dry air through a two-way nonbreathing valve and a mouth piece or face mask. The methodology was kept consistent within subject and within center. ECTs required a target heart rate of at least 80% of the predicted maximum (220-age in years) for 6 consecutive minutes in accordance with published guidelines.^{18,19} Triplicate FEV₁ readings (KOKO Peak Pro, Louisville, CO) were recorded predose; pre-ECT; and 5, 10, 30, 45, 60, 90 minutes post-ECT.

Urine LTE₄ Assay

Urine collected during treatment periods (predose, pre-ECT, and 90 minutes post-ECT) was frozen (8 mL/sample, –70°C) before analysis using a validated analytical method liquid chromatography-tandem mass spectrometry with creatinine correction²⁰; lower limit of quantification for urine creatinine was 1 pg/mg (Autoanalyzer technique; Technicon, BuValo, Grove, IL).

Blood LTB₄ Assay

Blood was collected (4 mL/sample, sodium heparin-coated Vacutainer) during treatment periods (predose and pre-ECT). LTB₄ synthesis was stimulated *ex vivo* in whole blood by incubation in the presence of calcium ionophore A23187, as previously described.¹⁴ Plasma supernatant from centrifuged incubated samples was frozen (–70°C) before analysis using a validated analytical method based on enzyme immunoassay (lower limit of quantification, 11.7pg/mL). The LTB₄ value for a time point was derived from the difference between the values for stimulated and unstimulated samples.

Data Analysis and Statistics

The primary end point was the mean maximum percentage change from baseline in FEV₁ within 60 minutes post-ECT [FEV_{1(0–60)}] 24 hours postdose. The maximum percentage change from baseline FEV_{1(0–60)} after ECT at screening and 2, 9.5, and 24 hours postdose was analyzed using a mixed effects model (including period, treatment, and covariates for predose FEV₁). The adjusted mean maximum percentage change from baseline FEV_{1(0–60)} values and corresponding 95% CIs, as well as adjusted mean treatment differences between each active dose and placebo, were obtained from the model. The sample size pro-

Table 1 Patient demographics and characteristics

	Total
No. of patients administered first dose, <i>n</i>	47
Demographics	
Age (yr), mean (SD)	28.4 (8.57)
Gender, M/F	41/6
BMI (kg/m ²), mean (SD)	26.62 (4.61)
Height (cm), mean (SD)	176.7 (9.15)
Weight (kg), mean (SD)	83.60 (18.48)
Race, <i>n</i> (%)	
African American/African heritage	6 (13)
Asian	3 (6)
White	38 (81)
Reasons for patient withdrawal, <i>n</i> (%)	
AEs	1 (2)
Positive DOAs test	2 (4)

AEs = adverse events; BMI = body mass index; DOAs = drugs of abuse.

vided at least 90% power to detect a difference of 8% between treatment groups in maximum percentage change from baseline FEV₁₍₀₋₆₀₎, using a two-sided 5% significance level, assuming a within subject standard deviation of 10.9%.²¹

Post hoc analyses were performed in two subgroups of interest and the heterogeneity of the treatment effect within the subgroups was assessed using treatment-by-subgroup interaction tests for ECT at 2 and 9.5 hours postdose. The first subgroup was defined by the ECT methodology. The second subgroup was defined by disease severity using the mean maximum percentage change from baseline FEV₁₍₀₋₆₀₎ at screening and assessed the most severe 25% of subjects (having a maximum fall in FEV₁ of at least 30.9%) compared with the remaining 75% of subjects.

RESULTS

Subject Characteristics

Oral GSK2190915 was administered to 47 subjects (Table 1); 44 completed the study; three were withdrawn due to positive drug of abuse (DOA) test (*n* = 1), positive DOA/ineligible screening ECT (*n* = 1), and elevated LFTs (*n* = 1). Random population sampling for this study resulted in a majority of participants being white adult male subjects.

Safety analyses included 47 subjects. Efficacy analysis included 46 subjects, because data from the subject withdrawn because of positive DOA/ineligible screening ECT (failure to maintain target heart rate at minimum 80% predicted maximum for 6 minutes) was excluded.

Safety

All AEs (five GSK2190915 at 10 mg, seven GSK2190915 at 50 mg, four GSK2190915 at 200 mg, and four placebo) were resolved before study completion. No SAEs occurred. Dizziness was reported most frequently, either immediately before or after ECT 2 hours postdose (two placebo, one GSK2190915 at 10 mg, and two GSK2190915 at 50 mg).

Six AEs were considered GSK2190915 related by the investigator (placebo: one diarrhea and one dizziness; GSK2190915 at 10 mg: one dizziness and one hyperhidrosis; GSK2190915 at 50 mg: one dizziness and one hyperhidrosis); elevated LFTs (predose Period 3) in one withdrawn subject were considered not GSK2190915 related but caused by the subject's alcohol consumption.

Exercise Challenge Testing

Table 2 presents the adjusted mean maximum percentage change from baseline FEV₁₍₀₋₆₀₎ results. At 24 hours postdose, no GSK2190915 dose was statistically significant for the maximum percentage change from baseline FEV₁₍₀₋₆₀₎ compared with placebo. At 2 hours postdose, the maximum percentage change from baseline FEV₁₍₀₋₆₀₎ was statistically significant for GSK2190915 at 200 mg compared with placebo, corresponding to a mean attenuation of 40% of the placebo response to ECT; the 2-hour postdose FEV₁₍₀₋₆₀₎ increased with escalating GSK2190915 dose. The 9.5-hour postdose maximum percentage change from baseline FEV₁₍₀₋₆₀₎ was statistically significant for GSK2190915 at 100 mg compared with placebo, corresponding to a mean attenuation of 41% of the placebo response to ECT; at this time point, GSK219015 at 200 mg attenuated the placebo response to ECT by 30%, although this effect was not statistically significant.

Figure 1, A–C, presents the mean (95% CI) percentage change from baseline for FEV₁ within 90 minutes post-ECT for screening and treatment groups. A lower ECT response was evident at all placebo time points versus screening for the maximum percentage change from baseline FEV₁₍₀₋₆₀₎; this reduced response was most notable at 24-hour postdose ECTs after placebo compared with screening (Table 2).

Post hoc analysis of the relationship between ECT methodology and the extent of EIB attenuation by GSK2190915 2-hour postdose found no evidence that the treatment effect differed by ECT method (*p* = 0.5856). However, this analysis was limited by the small number of subjects who completed ECT in an air-conditioned (20–25°C) and humidity-controlled (<50%) room with a nose clip in place (*n* = 9) compared with those completing the challenge inspiring compressed cold, dry air through a two-way nonrebreathing valve and a mouth piece or face mask

Table 2 Adjusted mean maximum percentage change from baseline FEV₁₍₀₋₆₀₎

	Screening (n = 46)			Placebo (n = 44)			GSK2190915			
							10 mg (n = 45)	50 mg (n = 46)	100 mg (n = 45)	200 mg (n = 45)
Adjusted mean FEV ₁₍₀₋₆₀₎ (95% CI)	Screening	-27.23% (-28.68, -25.78)	-15.55% (-18.39, -12.72)	-13.04% (-15.85, -10.23)	-12.95% (-15.75, -10.16)	-12.76% (-15.57, -9.95)	-9.25% (-12.06, -6.44)			
	2 hr postdose		-8.45% (-10.88, -6.03)	-8.33% (-10.73, -5.93)	-7.69% (-10.09, -5.30)	-4.96% (-7.37, -2.56)	-6.18% (-8.59, -3.77)			
	9.5 hr postdose		-7.61% (-10.23, -4.99)	-6.33% (-8.92, -3.73)	-7.09% (-9.67, -4.50)	-7.28% (-9.98, -4.68)	-5.09% (-7.69, -2.49)			
	24 hr postdose			2.52% (-0.72, 5.75)	2.60% (-0.64, 5.84)	2.79% (-0.45, 6.03)	6.30% (3.06, 9.54)			
Adjusted mean FEV ₁₍₀₋₆₀₎ treatment difference GSK2190915 vs placebo (95% CI)	2 hr postdose		0.12% (-2.34, 2.58)	0.12% (-2.34, 2.58)	0.76% (-1.70, 3.22)	3.49% (1.02, 5.95)	2.27% (-0.19, 4.73)			
	9.5 hr postdose		1.29% (-1.56, 4.13)	1.29% (-1.56, 4.13)	0.53% (-2.32, 3.37)	0.33% (-2.52, 3.18)	2.53% (-0.31, 5.37)			
	24 hr postdose									

FEV₁₍₀₋₆₀₎ = forced expiratory volume at 1 s 60 min postexercise challenge.

(n = 37), and, consequently, the lack of power to adequately detect any heterogeneity of treatment effects.

Post hoc analyses examining subgroups defined by disease severity using the maximum percentage change from baseline FEV₁₍₀₋₆₀₎ at screening showed evidence of a statistically significant treatment-by-subgroup interaction ($p < 0.01$) for ECT at 2 hours postdose. For the more severe subjects, the adjusted mean maximum percentage change from baseline FEV₁₍₀₋₆₀₎ was -9.19% (95% CI, -15.80%, -2.57%) for GSK2190915 at 200 mg and -20.68% (95% CI, -27.28%, -14.07%) for placebo, corresponding to a mean attenuation of 56% of the placebo response to ECT. For the remaining subjects, the maximum percentage change from baseline FEV₁₍₀₋₆₀₎ adjusted means were -9.19% (95% CI, -13.08%, -5.30%) for GSK2190915 at 200 mg and -13.52% (95% CI, -17.43%, -9.61%) for placebo, corresponding to a mean attenuation of 32% of the placebo response to ECT.

The *post hoc* analyses showed no evidence of a difference between the subgroups with respect to treatment effects for ECT 9.5-hour postdose, although this analysis was underpowered to adequately detect any heterogeneity of treatment effects.

GSK2190915 Pharmacodynamics

Plasma LTB₄ (Fig. 2) was notably suppressed by GSK2190915 at 50 mg and higher doses at 2, 9.5, and 24 hours postdose. Greater than 95% LTB₄ suppression was evident at 24 hours postdose in at least 75% of subjects with GSK2190915 at 200 mg.

Urine LTE₄ (Fig. 3) was also suppressed by GSK2190915 at 50 mg and higher doses at 9.5 and 24 hours postdose. Maximum median urine LTE₄ suppression compared with predose baseline was evident for GSK2190915 at 200 (~80%) and 100 mg (~64%) at 11 hours postdose, and was at least 77% for GSK2190915 at 50 mg and higher doses at 24 hours postdose.

DISCUSSION

To our knowledge, this is the first study to report that an FLAP inhibitor is effective in attenuating EIB. There were limitations of the assessment at 24 hours postdose; however, we have shown that GSK2190915 at 200 and 100 mg attenuates EIB at 2 and 9.5 hours postdose, respectively. Our findings indicate that the extent of GSK2190915 EIB attenuation appears dose related, the doses effective on EIB correlating with doses effective at suppressing leukotrienes.

The rapid onset of EIB attenuation with GSK2190915 at 200 mg is consistent with GSK2190915 pharmacokinetics ($T_{max} \sim 2$ hours). The broadly similar magnitude of EIB attenuation 9.5 hours postdose for GSK2190915 at 100- and 200-mg doses suggests that these two doses are at the top of the dose-response curve. Our results

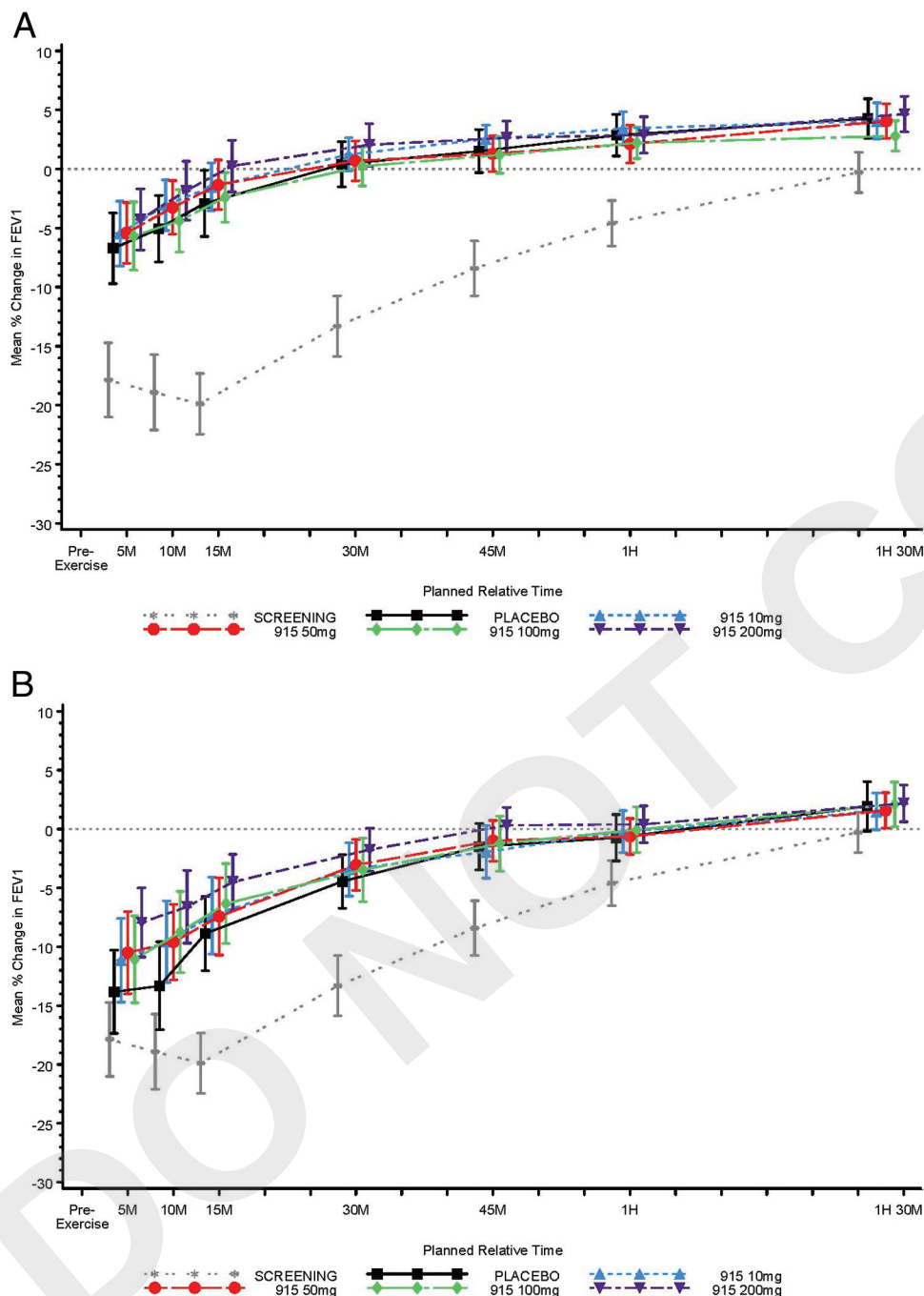


Figure 1. Mean (95% CI) percent change from baseline FEV1 within 90 minutes post ECT (A) 24 hours, (B) 9.5 hours, (C) 2 hours.

concur with previous clinical findings that single GSK2190915 doses above 150 mg provided no clear increase in LTE_4 suppression.¹⁴ Furthermore, the comparable effect on both EIB severity and the magnitude of LTE_4 suppression by GSK2190915 support the reported link between these two parameters.²²

It is evident from our data that a study designed in accordance with ECT guidelines does not guarantee a consistent and reproducible effect on FEV_1 . This is most apparent at 24 hours postdose in the difference in EIB attenuation for placebo compared with screening. The water content of inhaled air for both exercise chal-

lenge methodologies in our study was clearly defined. *Post hoc* analysis of the relationship between the exercise challenge methodology and the extent of EIB attenuation by GSK2190915 2 hours postdose cautiously found no evidence that the treatment effect differed by exercise challenge methodology.

We conjecture that natural subject variability influenced the reproducibility of ECT data. Pathophysiological factors attributed to the severity and duration of EIB include the extent of inflammatory mediator release at or around the airways²³ and sensory nerves, which are known to react to fluctuations in airway

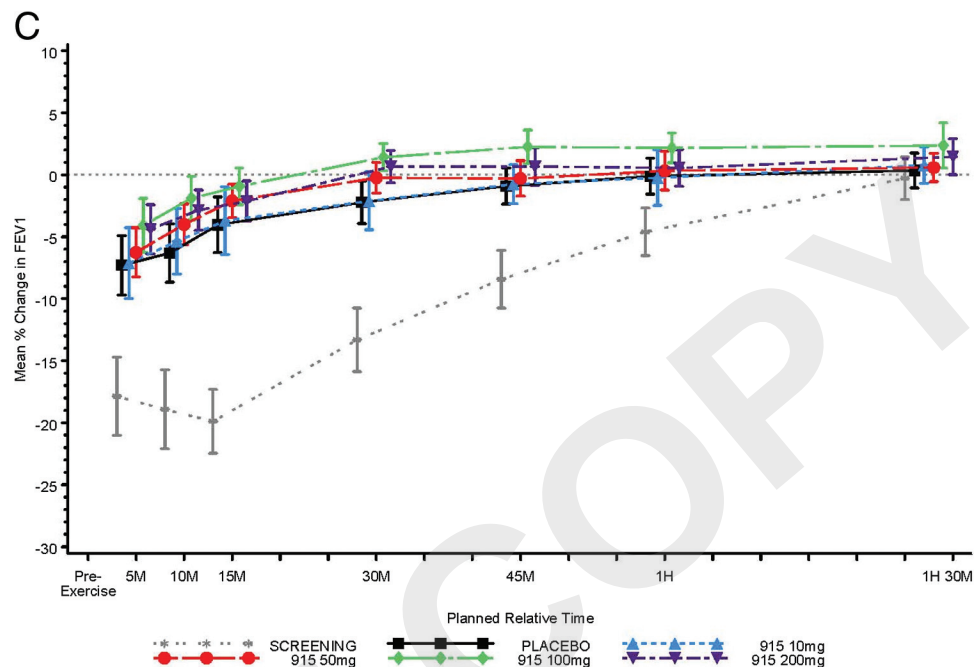


Figure 1.

surface osmolarity and levels of cysLTs.²⁴ The degree to which the airways manage the transfer of heat and water during exercise is one aspect of laboratory ECT that is difficult to manage, especially if repeat ECT assists in improving the fitness of an individual. Our results suggest some degree of a training effect; a subject may have become accustomed to the ECT protocol, thereby reducing the amount of ventilation required on repeat exercise perhaps accounting for a marked reduction in EIB compared with screening.

Our study design might have limited ECT data variability during treatment periods by requiring two

screening ECTs to assess subject eligibility. In a clinical investigation of the leukotriene receptor antagonist montelukast, 81 of the 169 adult subjects assessed were deemed ineligible because of a fall in FEV₁ that was <20% of baseline after repeat screening ECT.²⁵ Although this observation has not been validated, it implies the importance of confirming the reproducibility of exercise challenges in study designs.

The mechanism of action for GSK2190915 is evident in the suppression of urine LTE₄ and plasma LTB₄, which also is consistent with previous reports that this FLAP inhibitor is a potent inhibitor of leukotriene syn-

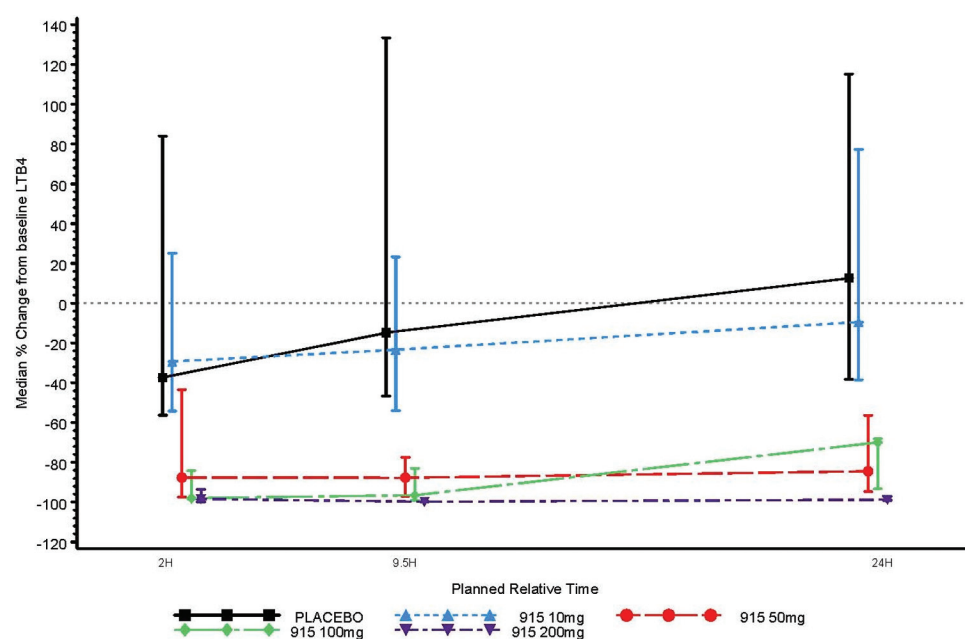


Figure 2. Percentage change from baseline LTB₄.

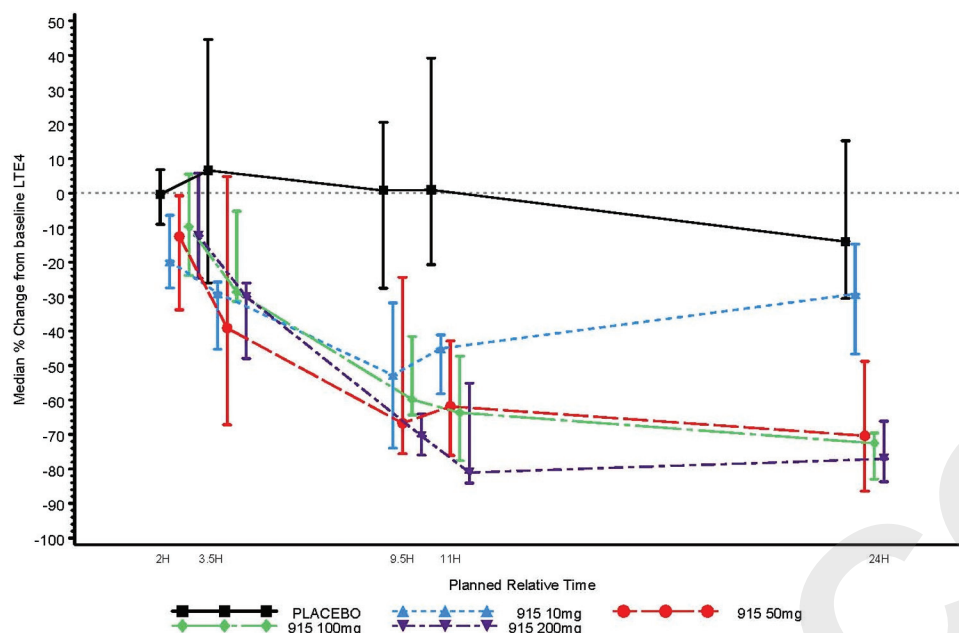


Figure 3. Percentage change from baseline LTE4.

thesis. Furthermore, GSK2190915 single doses up to 200 mg appear well tolerated in subjects with EIB. Notwithstanding cautions previously discussed, the results reported support that GSK2190915 may have usefulness in EIB; additional studies are required to validate the potential usefulness of GSK2190915 in a clinical setting.

ACKNOWLEDGMENTS

The authors are grateful to Dr. Ginger Milne for technical expertise and analysis of cysLTs in urine, Edwin Smith and Chang-Qing Zhu for data management and statistical and programming support, Dr. Claire Ambery for pharmacokinetic analysis, and the staff and subjects of the five investigative sites.

REFERENCES

- Weiler JM, Anderson SD, Randolph C, et al. Pathogenesis, prevalence, diagnosis, and management of exercise-induced bronchoconstriction: A practice parameter. *Ann Allergy Asthma Immunol* 105:S1–S47, 2010.
- Hallstrand TS, and Henderson WR Jr. Role of leukotrienes in exercise-induced bronchoconstriction. *Curr Allergy Asthma Rep* 9:18–25, 2009.
- Kippelen P, and Anderson SD. Pathogenesis of exercise-induced bronchoconstriction. *Immunol Allergy Clin North Am* 33:299–312, 2013.
- Broide DH, Eisman S, Ramsdell JW, et al. Airway levels of mast cell-derived mediators in exercise-induced asthma. *Am Rev Respir Dis* 141:563–568, 1990.
- Venge P, Henriksen J, and Dahl R. Eosinophils in exercise-induced asthma. *J Allergy Clin Immunol* 88:699–704, 1991.
- Crimi E, Balbo A, Milanese M, et al. Airway inflammation and occurrence of delayed bronchoconstriction in exercise-induced asthma. *Am Rev Respir Dis* 146:507–512, 1992.
- Reiss TF, Hill JB, Harman E, et al. Increased urinary excretion of LTE4 after exercise and attenuation of exercise-induced bronchospasm by montelukast, a cysteinyl leukotriene receptor antagonist. *Thorax* 52:1030–1035, 1997.
- Meltzer SS, Hasday JD, Cohn J, and Bleecker ER. Inhibition of exercise-induced bronchospasm by zileuton: A 5-lipoxygenase inhibitor. *Am J Respir Crit Care Med* 153:931–935, 1996.
- Hallstrand TS, Moody MW, Wurfel MM, et al. Inflammatory basis of exercise-induced bronchoconstriction. *Am J Respir Crit Care Med* 172:679–686, 2005.
- Spector S, and Tan R. Exercise-induced bronchoconstriction update: Therapeutic management. *Allergy Asthma Proc* 33:7–12, 2012.
- Funk CD. Leukotriene modifiers as potential therapeutics for cardiovascular disease. *Nat Rev Drug Discov* 4:664–672, 2005.
- Murphy RC, and Gijón MA. Biosynthesis and metabolism of leukotrienes. *Biochem J* 405:379–395, 2007.
- Grant GE, Rokach J, and Powell WS. 5-Oxo-ETE and the OXE receptor. *Prostaglandins Other Lipid Mediat* 89:98–104, 2009.
- 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* 75:779–790, 2013.
- 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* 43:177–186, 2013.
- Stock NS, Bain G, Zunic J, et al. 5-Lipoxygenase-activating protein (FLAP) inhibitors. Part 4: Development of 3-[3-tert-butylsulfanyl-1-[4-(6-ethoxypyridin-3-yl)benzyl]-5-(5-methylpyridin-2-ylmethoxy)-1H-indol-2-yl]-2,2-dimethylpropionic acid (AM803), a potent, oral, once daily FLAP inhibitor. *J Med Chem* 54:8013–8029, 2011.
- Hankinson JL, Odencrantz JR, and Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 159:179–187, 1999.
- Crapo RO, Casaburi R, Coates AL, et al. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med* 161:309–329, 2000.
- Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Guidance for industry exercise-induced

- bronchospasm (EIB)—Development of drugs to prevent EIB. Draft Guidance, 2002.
20. Milne G, Amin W, Sanchez S, and Preece A. Quantitative assessment of cysteinyl leukotrienes in human sputum during the allergen-induced asthmatic response and the effect of GSK2190915, a 5-lipoxygenase activating protein (FLAP) inhibitor. Poster presented at the Annual congress of the European Respiratory Society, Amsterdam, The Netherlands, September 24–28, 2011.
 21. Bronsky EA, Kemp JP, Zhang J, et al. Dose-related protection of exercise bronchoconstriction by montelukast, a cysteinyl leukotriene-receptor antagonist, at the end of a once-daily dosing interval. *Clin Pharmacol Ther* 62:556–561, 1997.
 22. Kippelen P, Larsson J, Anderson SD, et al. Acute effects of beclomethasone on hyperpnea-induced bronchoconstriction. *Med Sci Sports Exerc* 42:273–280, 2010.
 23. Anderson SD. The prevention of exercise-induced bronchoconstriction: What are the options? *Expert Rev Respir Med* 6:355–357, 2012.
 24. Hallstrand TS. New insights into pathogenesis of exercise-induced bronchoconstriction. *Curr Opin Allergy Clin Immunol* 12:42–48, 2012.
 25. Pearlman DS, van Adelsberg J, Philip G, et al. Onset and duration of protection against exercise-induced bronchoconstriction by a single oral dose of montelukast. *Ann Allergy Asthma Immunol* 97:98–104, 2006. □

Copyright of Allergy & Asthma Proceedings is the property of OceanSide Publications Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.