Synopsis

Identifier: GM2008/00215/00 **Study Number:** IPR110982

Title: A randomised, double blind, 2-way crossover trial of 8 days repeat dosing with intranasal GSK256066 and azelastine hydrochloride in the [redacted] in subjects with seasonal allergic rhinitis (SAR).

Investigator: Professor [redacted]

Study centre: [redacted] Austria [redacted]

Publication: None at the time of this report.

Study period:

Initiation Date: 18 FEB 2008

Completion Date: 21 MAY 2008

Phase of development: IIa

Objectives:

Primary

- Investigate effect of repeat intranasal doses of azelastine hydrochloride (AZ) alone versus GSK256066 + AZ on nasal symptoms of allergic rhinitis provoked by spending 4 hour (h) in the [redacted] after morning dosing on Day 8.

Secondary

- Explore effects of repeat doses of AZ alone versus GSK256066 + AZ on eye and global symptoms, nasal obstruction and secretions in allergic rhinitis provoked by spending 4 h in the [redacted] post morning dose on Day 8.
- Explore the safety and tolerability of repeat doses of GSK256066 in combination with AZ in mild to moderate allergic rhinitic subjects.

Methodology:

The aim of this randomised, double blind, two-way crossover study was to evaluate whether co-administration of GSK256066 can impart any additional effect to that of AZ in a model of SAR, in particular after eight days of repeated dosing.

All the subjects underwent screening 7 to 28 days prior to first dose. There was minimum 7 day wash-out between the challenge session at screening and the start of treatment.

Study comprised of two treatment periods, each lasting for 8 days, with the last dose on the morning of Day 8. Subjects were randomised to their allocated study medication on Day 1 of each treatment period. Dosing was supervised at the Clinical Unit on the mornings of Day 1 and Day 8 of each treatment period, with the remainder of dosing administered by the subject at home. Diary cards were provided to the subjects to document the date and time the study medication was taken. During the dosing periods subjects took either GSK256066 200 µg + azelastine hydrochloride 280 µg twice daily or GSK256066 matched placebo + azelastine hydrochloride 280 µg twice daily, with the exception of Day 8 where only the morning dose was taken.

Subjects returned to the Clinical Unit on Day 8 for an allergen challenge. Immediately following morning dosing on Day 8, subjects were exposed to allergens in the [redacted] for a 4 h period.

The wash-out period between the two treatment periods was at least 14 days. Subjects were requested to return to the Clinical Unit for a follow-up visit 14 to 21 days after the wash-out week had ended.

The total study duration for each subject was a maximum of 86 days. The details are given in the Time and Events table (Attachment 1).

Number of subjects:

A total of 70 subjects were planned to be randomised into the study. 70 subjects were randomised and 66 completed the study. There were 4 withdrawals in the study, 1 due to an adverse event and 3 due to withdrawn consent.

Subject Disposition and Demographics:

Number of Subjects	Total
Number of subjects planned, N:	70
Number of subjects randomized, N:	70
Number of subjects included in All subjects (safety) population, n (%):	70 (100)
Number of subjects completed as planned, n (%):	66 (94)
Number of subjects withdrawn (any reason), n (%):	4 (6)
Number of subjects withdrawn for AE, n (%):	1 (3)
Reasons for subject withdrawal, n (%)	
Adverse events	1 (3)
Other(Withdrew consent)	3 (4)
Demographics	Total
Age in Years, Mean (Range)	28.1 (19-48)
Sex, n (%)	
Female:	34 (49)
Male:	36 (51)
BMI (kg/m^2), Mean (Range)	22.54 (17.30-28.41)
Height (cm), Mean (Range)	174.7 (158-192)
Weight (kg), Mean (Range)	69.2 (50-94)
Ethnicity, n (%)	
Hispanic or Latino:	2 (3)
Not Hispanic or Latino:	68 (97)
Race, n (%)	
African American/African Heritage	1 (1)
White – White/Caucasian/European Heritage	67 (96)
Mixed race	2 (3)

Data Source: Table 9.1, Table 9.2, Table 9.3
BMI= Body mass index

Diagnosis and main criteria for inclusion:

Healthy non-smoking males and females aged 18 to 50 years inclusive, with a history of SAR, a moderate response to 1500 grass pollen grains /m^3 after 2 h in the [redacted] (total nasal symptom score of ≥ 6), positive skin prick test (wheal ≥4 mm) and a positive Radioallergosorbent Test (≥class 2) for grass pollen at or within the 12 months preceding the Screening visit.

Exclusion criteria states subjects were not to be eligible for inclusion if their supine heart rate was outside the range 40 to 90 beats per minute (bpm) at screening. [redacted]

[redacted]

No other subjects deviated from the inclusion/exclusion criteria.

Treatment administration:

Subjects were assigned to their allocated treatments in accordance with the randomisation schedule. The allocated treatments were as follows:

Treatment GSK256066 + AZ: Twice daily = GSK256066 200 µg (1x100 µg puff per nostril) + AZ 280 µg (1x140 µg puff per nostril).

Treatment AZ + GSK256066 matched placebo: Twice daily = AZ 280 µg (1x140 µg per puff per nostril) + GSK256066 matched placebo (1 puff per nostril).

AZ 280 µg was administered immediately before GSK256066 200 µg or GSK256066 matched placebo.

GSK256066 (batch number: 071131146) and GSK256066 matched placebo (batch number: 071147220) where administered using aqueous nasal sprays. Commercially available Rhinolast Nasal Spray of Meda Pharmaceuticals Ltd was used as open label AZ.

Criteria for evaluation:

Primary endpoint:

- Weighted mean total nasal symptom score (TNSS) (sneeze, itch, rhinorrhoea and obstruction) 1 to 4 h post morning dose period spent in the [redacted] on Day 8.

Secondary endpoints:

- Weighted mean eye symptom score (watery eyes, itchy eyes, and red eyes) over 1 to 4 h on Day 8.
- Weighted mean global symptom score (sneeze, itch, rhinorrhoea, obstruction, cough, itchy throat, itchy ears, watery eyes, itchy eyes and red eyes) over 1 to 4 h on Day 8.
- Weighted mean nasal airflow (measured using active anterior rhinomanometry) and secretion weight (measured by weighing tissues) over 1 to 4 h on Day 8.
- Weighted mean components of TNSS (sneeze, itch, rhinorrhoea and obstruction) over 1 to 4 h on Day 8.
- Forced expiratory volume at 1 second (FEV1), electrocardiograms (ECGs), vital signs, adverse events (AEs), and laboratory safety parameters.

Statistical methods:

Sample size considerations:

The sample size was based on the primary endpoint. Several environmental chamber studies have been previously conducted by GSK. Designs and duration of exposure varied across the studies, but based on the closest endpoint from each study to TNSS derived over 1 to 4 h, estimates of within-subject variance in weighted mean TNSS during exposure in the chamber after 7 or 8 days repeated dosing were 2.04 (IPR107498, [GlaxoSmithKline Document Number GM2007/0051/00]), 3.61 (IPR101987, [GlaxoSmithKline Document Number GM2006/00280/00]), 3.69 (ODN10003, [GlaxoSmithKline Document Number GM2005/00334/00]) and 4.62 (FFR10007, [GlaxoSmithKline Document Number GM2004/00170/00]). A difference in weighted mean TNSS between positive control and placebo of 1 is deemed to be clinically significant. The observed difference in TNSS over 1 to 4 h between GSK256066 and placebo on Day 7 was 1.3 in IPR101987 (GSK256066 200 µg) (IPR101987, [GlaxoSmithKline Document Number GM2006/00280/00]) and 0.9 in IPR107498 (GSK256066 50 µg) (IPR107498, [GlaxoSmithKline Document Number GM2007/0051/00]).

Based on the average estimate of within-subject variance of 3.26, a sample size of 58 subjects has 90% power to detect a difference of 1 in weighted mean TNSS (1 to 4 h) between GSK256066 + AZ and AZ alone at the 5% one-sided significance level. To ensure approximately 58 subjects completed the study, 70 subjects were recruited.

Interim Analyses:

No interim analyses were performed.

Final Analyses:

The final analyses were performed after unblinding. Unblinding happened after the database had frozen. Database freeze happened when all subjects had completed the study, all data had been entered onto the database and all queries had been resolved.

All displays were generated in the HARP (Harmonisation of Analysis and Reporting Program) environment which uses SAS version 8.2 on a UNIX platform.

The primary analysis was the comparison of weighted mean (1 to 4 h) of TNSS between GSK256066 + AZ compared to AZ on Day 8. The data were analysed using a mixed effects analysis of variance model adjusting for terms due to period and treatment fitted as fixed effects, with subject fitted as a random effect. An estimate of the treatment comparisons on Day 8 was calculated between the adjusted means (Least Square means) along with the associated 90% Confidence intervals (CIs). A sensitivity analysis including subject-level and period-level baseline in the model as covariates was also carried out. The distribution of the data of subjects with pre-chamber TNSS was expected to be skewed to zero; therefore baseline was not included in the main analysis and was only listed in the sensitivity analysis.

All secondary efficacy endpoints (components of TNSS, eye symptom score, global symptom score, nasal airflow and nasal secretion) were analysed in a similar fashion to the primary endpoint.

Mean profile plots showing the mean at all time points were produced for each efficacy endpoint. To obtain the estimates at each time point over 0 to 4 h a mixed effects analysis of variance model was used fitting subject-level and period-level baseline, period, time, treatment, period-level baseline*time and time*treatment interaction as fixed effects, with subject as a random effect and time as a repeated effect. Looking at each end point separately, if too many subjects had no symptoms pre-challenge or the distribution was too skewed or the residuals from the model adjusting for baseline indicated a poor goodness of fit baseline values were not included in the model as covariates. In this case, the response included the pre-challenge values and they were displayed in the plot as a 0 h time-point.

All safety and tolerability endpoints (AEs, ECG, vital signs, laboratory tests, pulmonary function and nasal examinations) were listed and summarised. No formal statistical analyses had been carried out.

Changes in conduct of the study or planned analyses:

The reporting and analysis plan (RAP) (Attachment 2) states that for the purpose of all data displays the treatment groups were to be ordered and labelled with the descriptor as follows:

Randomisation		Final Data Display (i.e. HARP / other)
Code	Treatment Description	Treatment Description
A	GSK256066 + AZ	GSK256066 200 µg BID + AZ
B	AZ + GSK256066 placebo	AZ

This treatment group order was incorrect, as the reference treatment group i.e. AZ alone, needed to be displayed first:

Randomisation		Final Data Display (i.e. HARP / other)
Code	Treatment Description	Treatment Description
B	AZ + GSK256066 placebo	AZ
A	GSK256066 + AZ	GSK256066 200 µg BID + AZ

Summary:

Efficacy:

Efficacy data are summarised in Data Source Figure 10.1 to Figure 10.15 and Data Source Table 10.1 to Table 10.7

A summary of the statistical comparisons of all efficacy endpoints is described in the following table.

Summary of Statistical Comparisons of Efficacy Endpoints

Endpoint (Weighted Mean)	LS Means		Difference	90% CI
	AZ	GSK256066 200 µg + AZ		
TNSS	4.39	3.98	-0.41	(-0.79, -0.02)
Nasal Blockage	1.52	1.44	-0.09	(-0.21, 0.04)
Nasal Itching	1.04	0.93	-0.11	(-0.24, 0.02)
Rhinorrhea	1.11	1.06	-0.06	(-0.18, 0.07)
Sneezing	0.71	0.56	-0.15	(-0.26, -0.04)
Eye Symptom Score	1.27	1.04	-0.23	(-0.51, 0.05)
Global Symptom Score	6.48	5.82	-0.67	(-1.31, -0.03)
Nasal Airflow (cm^3/s)	347.78	368.77	20.99	(0.73, 41.25)
Nasal Secretion Weight (g)	1.29	0.97	-0.33	(-0.55, -0.11)

Data Source: Table 10.1, Table 10.2, Table 10.4, Table 10.5, Table 10.6 and Table 10.7

Hypothesis tests were performed at the 5% one-sided level (which is equivalent to a 10% two-sided level). For all endpoints other than nasal airflow, superiority was demonstrated if the upper confidence limit of the 90% CI for the difference between treatment groups is smaller than zero. For nasal airflow superiority was demonstrated if the lower limit is greater than zero.

There was a statistically significant decrease in weighted mean TNSS over 1 to 4 h for GSK256066 200 µg BID + AZ compared to AZ alone, with an average reduction of -0.41 (90% CI -0.79, -0.02) in weighted mean score. This reduction is smaller than 1 that was used in the sample size calculations, it is therefore not deemed to be clinically meaningful.

The components of TNSS (nasal blockage, nasal itching, rhinorrhea and sneezing) over 1 to 4 h all decreased for GSK256066 200 µg BID + AZ compared to AZ alone, with the upper limit of confidence interval for the sneezing component of TNSS being below zero.

Weighted mean eye symptom scores, global symptoms scores and nasal secretion rate over 1 to 4 h were lower for GSK256066 200 µg BID + AZ compared to AZ alone. The upper limit of the CIs for global symptom scores and nasal secretion rate were below zero.

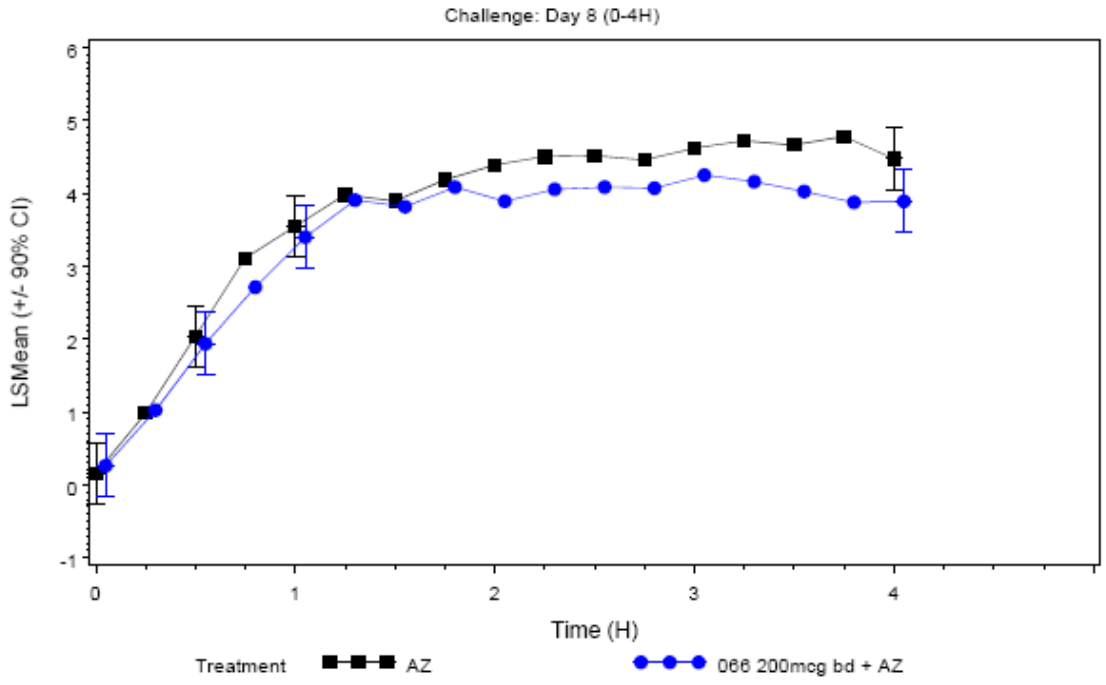
Weighted mean nasal airflow over 1 to 4 h was higher for GSK256066 200 µg BID + AZ compared to AZ alone, with the lower limit of the confidence interval being above zero.

A sensitivity analysis including subject-level and period-level baseline in the model as covariates was also carried out. For the analysis of TNSS, global symptom score and eye symptom score there were a high number of subjects with a score of zero at baseline; in addition, a skewed distribution of these parameters at baseline was observed. For the analysis of nasal airflow, the model fit was adequate with subject-level and period-level baseline in the model as covariates.

A mean profile plot showing the mean at all time points over 0 to 4 h has been created for all efficacy endpoints. As with the sensitivity analysis of the weighted mean endpoints a high number of subjects with scores of zero at baseline and a skewed distribution for TNSS, global symptom score and eye symptom score were observed. Therefore subject-level and period-level baselines were not included in the repeated measures model as covariates other than for nasal airflow where the model fit was reasonable.

The mean profile plot for TNSS, eye symptom score, global symptom score, nasal airflow and nasal secretion weight is presented in the following figures.

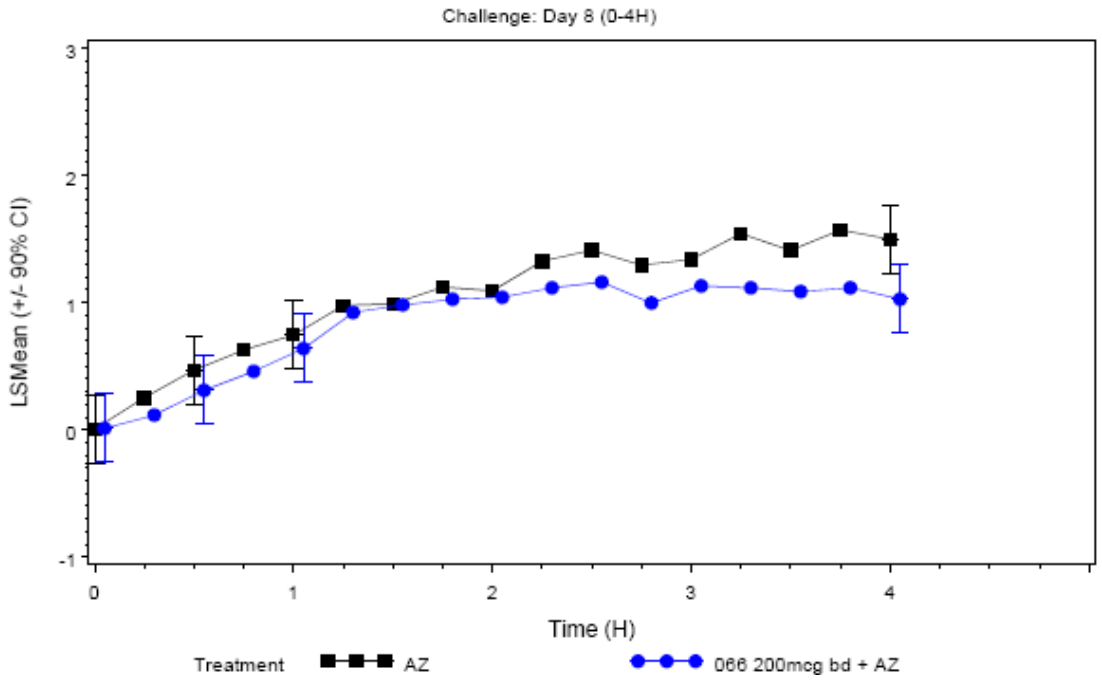
Adjusted Mean Profile Plot for TNSS



Data Source: Figure 10.2

The adjusted mean profile plot for TNSS generally shows lower scores for GSK256066 200 µg BID + AZ compared to AZ alone throughout the 0 to 4 h challenge.

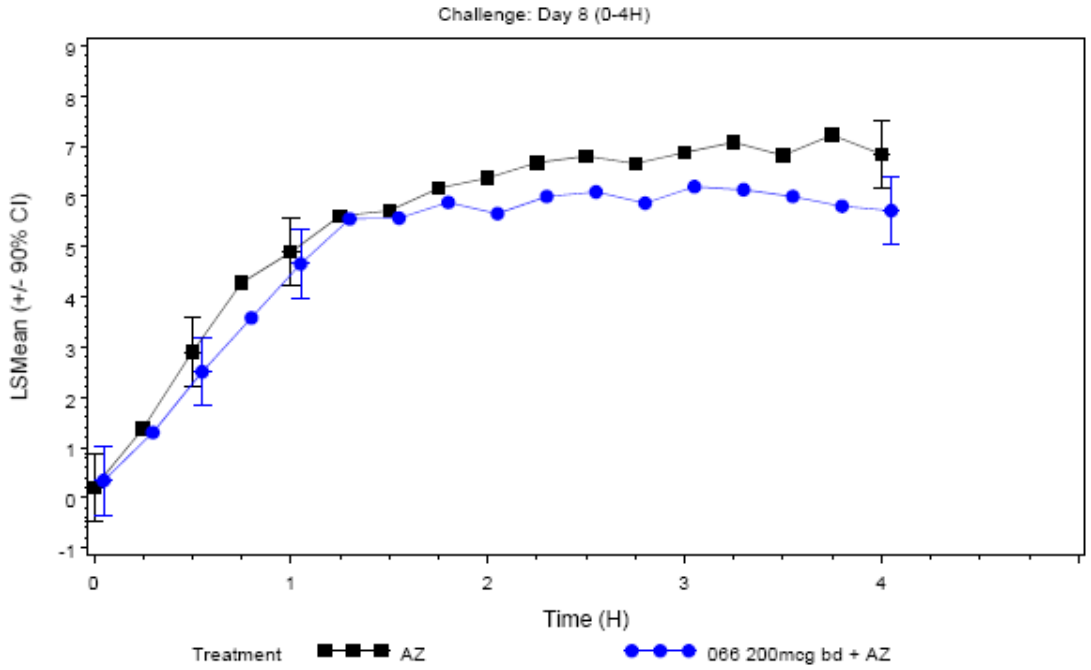
Adjusted Mean Profile Plot for Eye Symptom Score



Data Source: Figure 10.9

The adjusted mean profile plot for eye symptom scores shows lower scores for GSK256066 200 µg BID + AZ compared to AZ alone throughout the 0 to 4 h challenge.

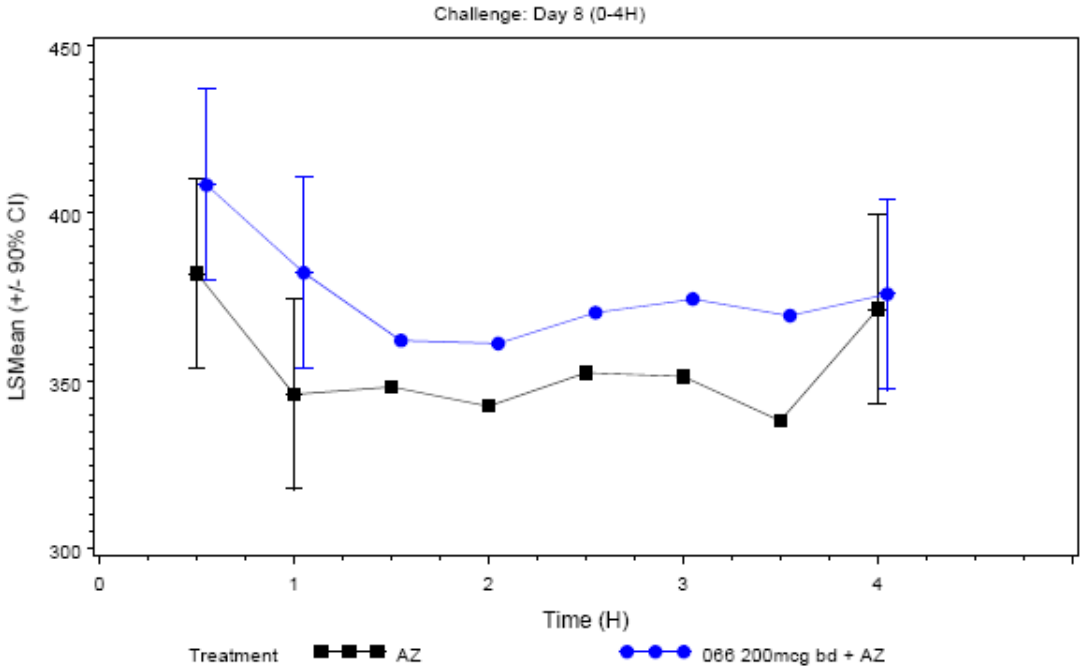
Adjusted Mean Profile Plot for Global Symptom Score



Data Source: Figure 10.11

The adjusted mean profile plot for global symptom scores shows lower scores for GSK256066 200 µg BID + AZ compared to AZ alone throughout the 0 to 4 h challenge.

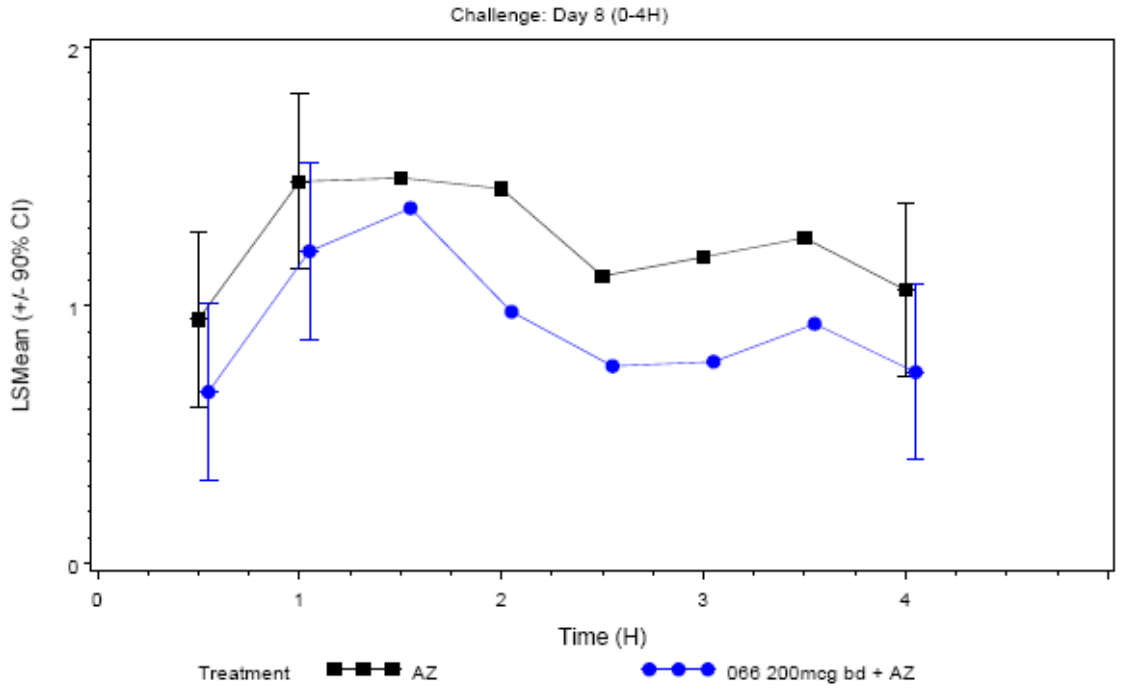
Adjusted Mean Profile Plot for Nasal Airflow



Data Source: Figure 10.13

The adjusted mean profile plot for nasal airflow shows higher scores for GSK256066 200 µg BID + AZ compared to AZ alone throughout the 0 to 4 h challenge.

Adjusted Mean Profile Plot for Nasal Secretion Weight



Data Source: Figure 10.15

The adjusted mean profile plot for nasal secretion weight shows lower scores for GSK256066 200 µg BID + AZ compared to AZ alone throughout the 0 to 4 h challenge.

Safety:

There were no deaths, non fatal serious adverse events or pregnancies reported in this study. A total of 11 (16%) subjects experienced 26 individual AEs during both treatment periods of the study. The most common AE experienced in both treatment groups was dysgeusia. All AEs were mild to severe in intensity.

[redacted] AE was of severe intensity and not considered to be related to investigational product by the Investigator.

A summary of all AEs is presented in the table below.

Summary of all Adverse Events

Adverse Events	AZ N=70	GSK256066 200 µg + AZ N=69
Any AE, n (%)	7(10)	8(12)
Any AE related to investigational product	5(7)	5(7)
All AEs:		
Dysgeusia	4(6)	2(3)
Headache	1(1)	2(3)
Nasal dryness	2(3)	1(1)
Nasal discomfort	2(3)	1(1)
Rhinorrhoea	2(3)	-
Nasal Congestion	1(1)	-
Pharyngolaryangeal pain	-	1(1)
Tonsillitis	-	2(3)
Nasopharyngitis	1(1)	
Nausea	-	1(1)
Pyrexia	-	1(1)

Data Source: Table 11.1 and Table 11.2

Drug related AEs are summarised in the following table.

Drug Related Adverse Events

Drug Related Adverse Events	AZ N=70	GSK256066 200 µg + AZ N=69
Any drug related AEs, n(%)	5(7)	5(7)
Dysgeusia	4(6)	2(3)
Headache	-	1(1)
Nasal dryness	2(3)	1(1)
Nasal discomfort	2(3)	1(1)
Rhinorrhoea	1(1)	-
Pharyngolaryangeal pain	1(1)	-
Nausea	-	1(1)

Data Source: Table 11.2

Concomitant Medications

The concomitant medications administered during this study are summarised in Data Source Table 9.4. These medications were considered not likely to affect the outcome of the study or safety of the subject by the Investigator.

Vital Signs:

Vital signs measurements comprised heart rate, systolic and diastolic blood pressure. None of these vital signs parameters were reported to be clinically significant by the Investigator.

12-Lead ECGs:

[redacted]

None of these ECG findings were reported to be clinically significant by the Investigator.

Laboratory findings:

Laboratory findings comprised of haematology, clinical chemistry and urinalysis.

The following subjects had potential clinical importance (PCI) values for haematology; 10 subjects had a high platelet count, 4 subjects had low haemoglobin, 3 subjects had a low white blood cell count and segmented neutrophil count separately, 2 subjects had a low red blood cell count and 1 subject each had a low haematocrit value and eosinophil count separately.

The following subjects had PCI values for clinical chemistry; 31 subjects had high creatine kinase- MB, 7 subjects had high creatine kinase, 13 subjects had low glucose, 5 subjects had high C-reactive protein and total bilirubin separetaly, 4 subjects had high gamma glutamyl transferase and 2 subjects had high creatinine. [redacted] In all instances of elevated creatine kinase or creatine kinase-MB, the troponin levels were negative, suggesting life style changes.

[redacted] This subject was menstruating at the time of the urine measurement.

None of these PCI values were considered to be clinical significant or related to study drug by the Investigator.

Conclusions:

- There was a statistically significant decrease in weighted mean TNSS over 1 to 4 h for GSK256066 200 μg BID + AZ compared to AZ alone, with an average reduction of -0.41 (90% CI -0.79, -0.02) in weighted mean score. This reduction is smaller than 1 that was used in the sample size calculations, it is therefore not deemed to be clinically meaningful.
- The components of TNSS (nasal blockage, nasal itching, rhinorrhea and sneezing) over 1 to 4 h all were lower for GSK256066 200 μg BID + AZ compared to AZ alone, with the upper limit of confidence interval for the sneezing component of TNSS being below zero.
- Weighted mean eye symptom scores, global symptoms scores and nasal secretion rate over 1 to 4 h were lower for GSK256066 200 μg BID + AZ compared to AZ alone. The upper limit of the confidence intervals for global symptom scores and nasal secretion rate were below zero.
- Weighted mean nasal airflow over 1 to 4 h was higher for GSK256066 200 μg BID + AZ compared to AZ alone, with the lower limit of the confidence interval being above zero.
- Eight days repeat dosing of GSK256066 200 μg BID and AZ were found to be safe and well tolerated by SAR subjects in this study.

Date of Report:

September 2008