1. SYNOPSIS

Name of Sponsor Company	Shionogi & Co., Ltd.	Individual Study Table Referring to Part _____ of the Dossier Volume: _____ Page: _____	(For National Authority Use Only)
Name of Finished Product	S-555739		
Name of Active Ingredient	DP-antagonist		
Title of Study	A randomised, double-blind, placebo-controlled, 2-period crossover study to evaluate effects of S-555739 on prostaglandin D2 (PGD2) induced nasal airway resistance in healthy adult volunteers		
Principal Investigator	[redacted]		
Study Sites	This study was conducted at [redacted]		
Publication(s)	This data has not been published to date.		
Study Period	First subject dosed: [redacted] 2009 Date last follow up: [redacted] 2009	Phase IIa	
Objectives	**Primary objectives:** • To evaluate the effects of multiple oral doses of S-555739 once daily on prostaglandin D2 (PGD2) induced total nasal airway resistance (NAR). **Secondary objectives:** • To evaluate the effects of a single oral dose of S-555739 on PGD2 induced total NAR. • To evaluate the effects of S-555739 on the changes in nasal cross sectional area and volume following challenge with a range of doses of PGD2. • To measure the effects of S-555739 on the nasal symptoms resulting from challenge with PGD2, including rhinorrhea, nasal congestion, sneezing and pruritis. • To evaluate the general safety and tolerability of multiple oral doses of S-555739 100 mg once daily. **Exploratory objectives** • To evaluate the relationship between the plasma level of S-555739 and the pharmacodynamic endpoints.		
Methodology	This randomised double-blind, placebo-controlled, 2-period crossover study was designed to evaluate the effects of multiple oral doses of S-555739 on PGD2 induced NAR in healthy adult volunteers. Each subject was to undergo the following: **Screening**: Within 3 weeks prior to treatment subjects provided demographic		

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	data, medical history, informed consent and underwent physical examination, vital signs, electrocardiogram (ECG), laboratory tests, alcohol test, urine drug abuse screen test, nasal medical examination, and provocative dose which results in a 75% increase in NAR (PD_{75}) was obtained or assessed. **During treatment:** Period 1: Subjects took S-555739 or placebo orally on Days 1, 3, 4, 5, 6 and 7. Subjects visited the study site on Day 1, 2 and 8. A PGD2 challenge test was performed on Day 2 and 8 as well as the other study assessments as shown on the study flow sheet. Period 2: After a minimum 14-day washout from the last dose of period 1, subjects took S-555739 or placebo orally on Days 1, 3, 4, 5, 6 and 7. The subjects visited the study site on Day 1, 2 and 8 and a PGD2 challenge test was performed on Day 2 and 8 as well as the other study assessments as shown on the study flow sheet. Administration and procedures were performed as in period 1. Follow-up visit was conducted 14 (± 2) days after the last dose in the period 2. Physical examination, vital signs, ECG, laboratory tests were assessed. Safety follow-up: An end of study phone call was made 30 days after last dose of S-555739 or placebo (either at end of treatment period 2 or at withdrawal) for safety follow-up (Adverse events [AEs]/Serious adverse events [SAEs]).
Number of Patients (planned and analysed)	Sixteen healthy adult subjects were recruited and randomised into the study.
Criteria for Inclusion and Exclusion	To be included, subjects were required to meet eligibility criteria. Key inclusion criteria were: 1. Those who understood the procedures of the study and agree to participate in the study by providing written informed consent. 2. Male between 18 and 55 years of age at screening. 3. Those with a body mass index (BMI) of ≥ 18.0 to < 29 kg/m^2. 4. Those judged to be in generally good health and with no clinically significant findings on the basis of the medical history, physical examination and laboratory evaluation. 5. Those who had positive responses to PGD2 induced NAR (PD_{75} ≤ 32 µg) at the screening visit. 6. Provide written (signed) informed consent to participate in the trial

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prior to any trial specific screening procedures, with the understanding that the subject has the right to withdraw from the trial at any time, without prejudice.

Key exclusion criteria were:

1. Current or recent past abusers of alcohol (alcohol consumption > 40 grams/day), or those with a positive alcohol breath test at screening or current users or recent past abuser of illicit drugs (amphetamines, benzodiazepines, barbiturates, cannabis, cocaine, opiates).
2. Smokers within 6 months before the study.
3. Those who have participated in a clinical trial involving an investigational or marketed drug within 4 weeks of screening.
4. Those in a situation or any condition which, in the opinion of the investigator, may interfere with optimal participation in the study.
5. Those not willing to discontinue grapefruit whole or juice consumption during the study.
6. Those with active allergic rhinitis within 3 weeks prior to randomisation.
7. Those with perennial allergic rhinitis history who presented current symptoms or within 3 weeks prior to randomisation.
8. Those receiving medications for allergic rhinitis and/or asthma within 3 weeks prior randomisation.
9. Those with an upper respiratory tract infection (URI), sinusitis, infectious rhinitis, ocular infection, or history of any of these within 3 weeks prior to the randomisation.
10. Those unable to tolerate the active posterior rhinomanometry and/or acoustic rhinometry procedures.
11. Those with a baseline total NAR > 0.4 $Pa/cm^3/s$.
12. Those who responded to intranasal control solution provocation with a > 30% increase in total NAR.
13. Those who underwent major surgical (requiring general anaesthetic) procedures or procedures to the nasopharynx within 4 weeks of randomisation.
14. Those with a history of an anaphylactic allergic reaction related to food or administration of either a marketed or investigational drug.
15. Those who were using any prescription or non-prescription drugs on a regular basis or within 2 weeks prior to randomisation.
16. Those who had received immunotherapy within 6 months of randomisation.
17. Those who had donated 400 mL of blood within 12 weeks before randomisation or 200 mL or more, within the 4 weeks before randomisation or any amount from screening to first visit.

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Schedule of treatment and visits

The following procedures were conducted during each visit.
At screening: eligibility of the subjects were judged on their medical history, informed consent, physical examination, demography, vital signs, ECG, laboratory tests, alcohol test, urine drug abuse screen test, nasal medical examination, and PD_{75} was obtained or assessed.

PERIOD 1:
Subjects took S-555739 or placebo orally on Days 1, 3, 4, 5, 6 and 7. The subjects visited the study site on Day 1, 2 and 8. A PGD2 challenge test was performed on Day 2 and 8 as well as the other study assessments as shown on the study flow sheet.

Day 1:

- Allocation of subject number.
- Vital signs, physical examination, ECG, nasal allergic rhinitis symptoms and laboratory tests, medical interview.
- Drug intake of 100 mg of S-555739 or matched placebo (within 30 minutes after breakfast or lunch).

Day 2:

- Medical interview, vital signs and urinalysis.
- Nasal allergic rhinitis symptom scores 60 minutes before PGD2 challenge test.
- Nasal medical examination.
- Ten minutes before challenge, blood samples were collected for laboratory tests and to measure S-555739 concentration.
- PGD2 challenge test: PGD2 administrations were conducted approximately every 15 minutes, following the administration of vehicle solution.
- Active posterior rhinomanometry 4, 8, and 12 minutes after each administration.
- Acoustic rhinometry 4, 8, and 12 minutes after each administration.
- Nasal allergic rhinitis symptoms 10 minutes after every PGD2 challenge dose.
- Vital signs were evaluated after the PGD2 challenge test completion.

Days 3 to 7:

- Drug intake of 100 mg of S-555739 or matched placebo (within 30 minutes after breakfast or lunch); subjects were provided with a 5-day supply to be dosed once daily.
- Diary card was provided to record AEs during all periods (both treatments, washout and follow up periods).

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	Day 8: • Medical interview, physical examination, vital signs, ECG and urinalysis. • Nasal allergic rhinitis symptom scores 60 minutes before PGD2 challenge test. • Nasal medical examination. • Ten minutes before challenge, blood samples were collected for laboratory tests and to measure S-555739 concentration. • PGD2 challenge test (see Day 1). • Active posterior rhinomanometry 4, 8, and 12 minutes after each administration. • Acoustic rhinometry 4, 8, and 12 minutes after each administration. • Nasal allergic rhinitis symptoms 10 minutes after every PGD2 challenge dose. • Vital signs were evaluated after the PGD2 challenge test completion. PERIOD 2: Following a minimum 14-day washout from the last dose of period 1, subjects took S-555739 or placebo orally on Days 1, 3, 4, 5, 6 and 7 (within 30 minutes after breakfast or lunch). Subjects visited the study site on Day 1, 2 and 8 and a PGD2 challenge test was performed on Day 2 and 8 as well as the other study assessments as shown on the study flow sheet. Administration and procedures were performed as in period 1. The follow-up visit was conducted 14 (± 2) days after the last dose in the period 2. Medical interview, physical examination, vital signs, ECG, laboratory tests were assessed. Safety follow-up: an end of study phone call was made 30 days after last dose of S-555739 or placebo (either at end of treatment period 2 or at withdrawal) for safety follow-up (AEs/SAEs).		
Treatment (dose, mode of administration and duration)	The study drug S-555739 (two tablets of 50 mg) or the comparator (placebo) were administered orally, within 30 minutes after a meal (breakfast or lunch according to challenge schedule).		
Challenge agent	The challenge agent (PGD2) was stored at - 20ºC as a stock solution in methanol at 25 mg/mL. Immediately prior to administration solutions were prepared by dilution in 0.9% sodium chloride to appropriate concentrations and were kept at room temperature.		

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	During the challenge procedure PGD2 was administered approximately every 15 minutes by metered dose spray to both nostrils in serial escalating sequence in amounts starting at 2 µg per nostril until the total NAR increases by 75% over the maximum control baseline value or the maximum dose of PGD2 (512 µg per nostril) was administered. Baseline values were determined by administering 0.9% sodium chloride before PGD2 administration.		
Duration of treatment	Both study drug or the comparator was administered on Day 1 at the study site, and Days 3, 4, 5, 6, and 7 at home for each treatment period.		
Reference Therapy	S-555739 matching placebo		

Criteria for Evaluation

Efficacy endpoints

Primary Endpoint

- Proportion of subjects with a higher PD_{75} at Day 8 of the S-555739 period than at Day 8 of the placebo period. (PD_{75} is a dose of PGD2 required to induce a 75% increase in total NAR by the PGD2 challenge agent).

Secondary Endpoints

- Proportion of subjects with a higher PD_{75} at Day 2 of the S-555739 period than at Day 2 of the placebo period.
- Changes in nasal cross sectional area and volume following challenge with a range of doses of PGD2 a) following a single dose of S-555739/placebo and b) following multiple doses of S-555739/placebo.
- Nasal symptom scores resulting from challenge with PGD2 a) following a single dose of S-555739/placebo and b) following multiple doses of S-555739/placebo.

Safety endpoints

AEs and adverse drug reactions, vital signs, physical examinations, ECG's, and laboratory parameters including urinalysis, exposure and reasons for withdrawal from study.

PK Endpoint

Plasma concentration before PDG2 challenge.

Statistical method

Populations analysed are described in terms of 'summary statistics', which refers to the mean, standard deviation, median, minimum, maximum for quantitative variables and to frequency and percentages (referring to filled data) for qualitative variables.

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Analyses of efficacy are based on all populations (Evaluable-for-Response, per-protocol and intention-to-treat). Analyses of safety data are based on the intention-to-treat population.

All individual data are presented in listings in the statistical appendix of the clinical study report. Results of statistical analysis, descriptive summary statistics, and supportive listings/figures are be presented in the statistical appendix of the clinical study report.

Results Summary

Efficacy Results

This study did not demonstrate a statistically significant difference between the treatment groups in the primary end point (proportion of subjects with a higher PD_{75} at Day 8 of the S-555739 period than at Day 8 of the placebo period). There was however, a consistent trend for a reduction in PGD2-induced changes in NAR, nasal area and volume and allergic rhinitis symptom scores at both Day 8 and 2. The proportions of subjects having a higher PD_{75} between the treatments did not appear evenly distributed between the sequence groups, indicating that the order in which subjects received treatments may have influenced the NAR.

Analyses of between-treatment differences at each subject's maximum dose administered on both treatments indicated differences between the treatments in terms of changes in total NAR at Day 2, percentage changes in nasal cross-sectional area and volume at both Days 2 and 8 and total symptom scores at Day 2.

Mean total NAR was lower following treatment with S-555739 than placebo across the range of PGD2 doses both at Day 8 and 2. The between treatment difference in change in total NAR was statistically significant at PGD2 dose of 64 µg/nostril at Day 8, and between 8 and 32 µg/nostril at Day 2.

At Day 8 and 2, treatment with S-555739 resulted in a larger nasal cross-sectional area and nasal volume, compared with placebo across the PGD2 challenge doses. At Day 8, the difference in nasal area was statistically significant at 64, 256 and 512 µg/nostril ($p < 0.05$). The differences in nasal volume were also statistically significant between 8 and 256 µg/nostril ($p < 0.05$) except at 128 µg/nostril. At Day 2, the difference in nasal area was statistically significant at 32 µg/nostril ($p < 0.05$). The differences in nasal volumes were also statistically significant at a PGD2 dose of 16 and 64 µg/nostril ($p < 0.05$).

Safety and Tolerability Results

Multiple oral doses of S-555739 100 mg once daily were well tolerated with only mild to moderate TEAEs. There were no SAEs in any group and all AEs were either mild or moderate in intensity.

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PK profile

The mean C24 on Day 2 and 8 were almost same as those of single and 14-day multiple dose of 100 mg in phase I multiple dose study [redacted] respectively.

The mean C24 on Day 8 was almost same as that of 6-day multiple dose of 100 mg in nasal allergen challenge study (Protocol No. 0818D1521).

Conclusions

This study did not demonstrate a statistically significant difference at the primary endpoint of proportion of subjects with a higher PD_{75} at Day 8 of the S-555739 period than at Day 8 of the placebo period. There was however, a consistent trend for a reduction in PGD2-induced changes in NAR, nasal area and volume and allergic rhinitis symptom scores at both Day 2 and 8.

Multiple oral doses of S-555739 100 mg once daily was well tolerated with few TEAEs, no SAEs and no severe AEs. Fewer AEs were recorded during the S-555739 period than during the placebo period. Six AEs during the S-555739 period were considered possibly related to treatment. Seven AEs in the placebo phase were considered possibly related. The most frequent AE in each treatment period was headache with 8 events in the S-555739 period and 7 events in the placebo period. No notable differences in laboratory values, vital signs or ECG's were detected between treatments.

There seemed to be a possible treatment sequence effect in both the proportion of subjects with a between-treatment difference in PD_{75} and reporting of TEAEs, although not apparent in all measurements.

Date of Report	5th March 2010