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 multiple oral doses of S-555739 on nasal allergen challenge in subjects with intermittent grass pollen sensitive allergic rhinitis.		
Principal Investigator:	[redacted]		
Study Sites:	This study was conducted at [redacted]		
Publication(s):	This data has not been published to date.		
Study Period:	First patient dosed: [redacted] 2009 Date last visit: [redacted] 2009	Phase IIa	
Objectives:	**Primary objectives:** • To evaluate the effects of multiple oral doses of S-555739 100 mg once daily on allergen challenge induced total nasal airway resistance (NAR) between active and placebo treatments at Day 7. **Secondary objectives:** • To evaluate the effects of multiple oral doses of S-555739 100 mg once daily on allergen challenge induced total NAR between active and placebo treatments at Day 9. • To evaluate the effects of multiple oral doses of S-555739 100 mg once daily on nasal peak inspiratory flow, internal nasal luminal volume and minimum cross sectional area between active and placebo treatments. • To evaluate the effects of multiple oral doses of S-555739 100 mg once daily on nasal symptoms of allergic rhinitis between active and placebo treatments. • 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 trough plasma levels of S-555739 and the pharmacodynamic endpoints. • To evaluate the effects of multiple oral doses of S-555739 100 mg once daily on inflammatory cell counts in nasal lavage.		

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		
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 nasal allergen challenge in subjects with intermittent grass pollen sensitive allergic rhinitis. Subjects were randomised into 2 groups. The first group of subjects took S-555739 in period 1 and placebo in period 2, once daily for 6 days. The second group of subjects took placebo in period 1 and S-555739 in period 2 once daily for 6 days. Each subject was to undergo the following: **Screening**: Within 2 weeks prior to treatment, eligible patients provided informed consent, demographic data, medical history, and underwent the following assessments: ECG, serology, serum pregnancy test (for women of child bearing potential), urine drug screen/alcohol breath test, laboratory tests (haematology, biochemistry, urinalysis), nasal airway challenge (NAC) test to identify optimal allergen dose, skin prick allergen test, nasal medical examination, height and weight, anterior rhinomanometry, physical examination, vital signs, nasal and ocular allergic rhinitis scores, AEs and concomitant medications. **During treatment**: During period 1 the subjects visited the study site at Day 1 for baseline assessments and then on Day 7 and Day 9 (after an overnight stay) to have an allergen challenge test. A ≥ 14-day washout period occurred from the last dosing in period 1, after which the same procedures as period 1 were implemented in period 2. A follow-up assessment was conducted 14 days (±2) after the last dosing of period 2.		
Number of Patients (planned and analyzed):	Twenty adult subjects with a history or present evidence of grass pollen sensitive allergic rhinitis were recruited and randomised in the study.		

<table>
<tr><td>Name of Sponsor Company:</td><td>Shionogi & Co., Ltd.</td><td rowspan="3">Individual Study Table Referring to Part _____ of the Dossier

Volume: _____

Page: _____</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:</td><td>S-555739</td></tr>
<tr><td>Name of Active Ingredient:</td><td>DP-antagonist</td></tr>
<tr><td>Criteria for Inclusion and Exclusion:</td><td colspan="3">
<u>Inclusion Criteria</u>

Subjects must meet all of the following to be included in the study:
1) Those who understand the procedures of the study and agree to participate in the study by providing written informed consent.
2) Men and women between 18 and 55 years of age at screening.
3) Those with body mass index (BMI) of ≥ 18.0 to < 29 kg/m^2.
4) Current non-smokers from at least 6 months before the study initiation.
5) Those judged to be in generally good health and without any clinically significant findings on the basis of the medical history, physical and nasal examination, and laboratory evaluation.
6) Have a positive response to allergen-induced NAC at the screening visit.
7) Those with at least a documented history, (from the data collected at the screening visit), of seasonal allergic rhinitis during the grass season but are currently asymptomatic.
8) Those demonstrating a positive percutaneous allergen skin test response to grass pollens (timothy (Phleum pratense), orchard (Dactylis glomerata), ryegrass (lolium perenne), Kentucky blue grass (poa pratensis) and/or sweet vernal grass (anthoxanthum odoratum)).
9) Must be affiliated with, or a beneficiary of, a French social security system.
10) The investigator must consult the "Fichier des Volontaires pour la Recherche Biomédicale" (the "National Index of volunteers") to register each volunteer in the index and to ensure that the exclusion period is respected and that the maximum annual compensation is not exceeded.

<u>Exclusion Criteria</u>

Subjects were not eligible for inclusion in this trial if they fulfil one or more of the following criteria:
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 user or recent past abuser of illicit drugs (amphetamines, benzodiazepines, barbiturates, cannabis, cocaine, opiates).
2) Those who have participated in a clinical trial involving an investigational or marketed drug within 3 months of screening.
3) Those in a situation or any condition which, in the opinion of the investigator, may interfere with optimal participation in the study.
4) Those not willing to discontinue grapefruit whole or juice consumption during the study.
</td></tr>
</table>

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		

5) Female patients of childbearing potential (defined as pre-menopausal or with menstruation in the last 12 months in the absence of either hysterectomy or surgical sterilisation) without acceptable contraceptive measures (i.e. barrier methods of contraception with or without oral contraceptives, implanted contraceptive device), or male patients who have not agreed to use barrier contraceptives (condoms) to prevent pregnancy from first dose until 12 weeks after last dose.
6) Those with a documented evidence of perennial allergic rhinitis at screening.
7) Those with active allergic rhinitis within 3 weeks prior to randomisation.
8) Those receiving medications for allergic rhinitis and/or asthma prior to the screening within 3 weeks prior to randomisation.
9) Those with a history of exclusively seasonal allergic asthma.
10) Those with a positive skin prick test for at least one of the tree pollens Alder, Hazel tree and Cypressus ashei.
11) Those with an upper respiratory tract infection (URI), sinusitis, infectious rhinitis, ocular infection, or history of any of these within 3 weeks prior to randomisation.
12) Those unable to perform the active anterior rhinomanometry procedure.
13) Those with a baseline total NAR > 0.4 $Pa/cm^3/s$.
14) Those who respond to an intranasal control solution provocation with a > 30% increase in total NAR.
15) Those who do not show NAR increases from baseline by 100% (PD100) at a 100 IR (or maximum) allergen dose at screening test.
16) Those who have undergone major surgical (requiring general anaesthetic) procedures or procedures to the nasopharynx within 4 weeks of screening.
17) Those with a history of an anaphylactic allergic reaction related to food or administration of either a marketed or investigational drug.
18) Those currently using any prescription or non-prescription drugs (except for hormonal contraceptive drugs) on a regular basis or within 2 weeks prior to screening.
19) Those who have a positive reaction to any of the following tests: HBs antigen, anti-HCV antibodies, anti-HIV_1 antibodies, anti-HIV_2 antibodies.
20) Those who had used any of the following drugs within the specified period of time: parenteral corticosteroids within 90 days; oral corticosteroids within 30 days prior to randomisation.
21) Those who have donated 400 ml of blood within 12 weeks before randomisation or 200 ml or more within 4 weeks before randomisation or of any amount from screening to first visit.

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		

	22) Those who have received immunotherapy within 6 months of screening. 23) Subject being the investigator or any sub-investigator, research assistant, pharmacist, study coordinator, or other staff directly involved in the conduct of the protocol. 24) Volunteers without health insurance. 25) Volunteers unable to be contacted in case of emergency. 26) The participants belonging to any of the following categories: incarcerated persons, patients in an emergency situation, in-patients with mental disorders. 27) Female who are pregnant, lactating or planning to become pregnant during the study.
Schedule of treatment and visits	The following procedures were conducted during each visit. Visits were ambulatory, except for the night prior to a challenge test when an overnight stay was required. <u>Screening</u>: • Medical history, informed consent, physical examination, height and weight, demographics, AEs, concomitant medications, nasal medical examination, nasal and ocular allergic rhinitis scores, serum pregnancy test (for women of child bearing potential (WOCBP) only), vital signs, ECG, haematology, biochemistry and urinalysis, urine drug screen, alcohol breath test, serology (HBs antigen, anti-HCV antibodies, anti-HIV_1 antibodies, anti-HIV_2 antibodies), anterior rhinomanometry were obtained or assessed. • Skin prick tests were performed with a standardised five-grass-pollen extract to confirm reactivity. Subjects were challenged with the diluent for the allergen extract to establish the level of non-specific reactivity. When the reactivity was confirmed, the standardised five-grass-pollen extract was used for a skin prick titration; the first dilution in each subject to elicit a negative skin response was used as the starting nasal allergen dilution in the nasal allergen challenge. • An escalating dose NAC test using increasing concentrations of allergen was administered to each subject, in order to obtain the optimal individualised dose of allergen – i.e. at 15 minutes intervals until PD100. Baseline total NAR was determined by administering vehicle control solution. • Eligibility of the subjects was judged by comparison with the study inclusion and exclusion criteria in the protocol.

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		

PERIOD 1:
Day 1 (P1D1)

- Ambulatory visit for WOCBP the afternoon before for serum pregnancy test.
- Vital signs, physical examination, ECG, concomitant medications, AEs, nasal medical examination, questionnaire for symptoms scores, urine drug screen, alcohol breath test and laboratory tests (haematology, biochemistry and urinalysis) was performed within 2 hours of study drug administration.
- These assessments were performed at the same time of day on each visit, if at all possible, to avoid circadian variation.
- Study drug was administered.

Subjects were provided with a 6-day supply of S-555739 or matching placebo to be dosed once daily every morning.

From Day 2 to Day 5 (P1D2 to P1D5)

- Subjects were contacted by phone by the site once a day to check their compliance to treatment.

Day 6 (P1D6)

- Subjects came to the Clinical Unit for an overnight stay.
- Nasal lavage samples were taken for baseline evaluation of inflammatory cells.

Day 7 (P1D7)
Prior to the allergen challenge

- Vital signs, physical examination, concomitant medications, ECG, nasal medical examination and laboratory tests including urinalysis were performed.
- Nasal and ocular allergic rhinitis symptom scores were assessed 60 min before each allergen challenge.
- Prior to initiation of administration of the challenge test, a plasma sample was collected to measure S-555739 concentration.
- Each subject sat quietly for 30 min in a room where the challenge took place.
- Anterior rhinomanometry and acoustic rhinometry were performed prior to challenge with the first dose (baseline).

Nasal allergen challenge

- Escalation of allergen doses up to the dose which achieved PD100 during the screening test was performed.

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		

- Anterior rhinomanometry was performed at 4, 8, and 12 minutes after each dose of allergen.After the dose which achieved PD100 during the screening test, anterior rhinomanometry was performed at 4 min, 8 min, 12 min, 20 min, 30 min, 60 min, 2 hr, 4 hr, 6 hr and 8 hr.
- Acoustic rhinometry was performed after the dose which achieved PD100 during the screening test, acoustic rhinometry was performed at 20 min, 30 min, 60 min, 2 hr, 4 hr, 6 hr, 8 hr.
- Nasal allergic rhinitis symptoms were noted 12 min, 20 min, 30 min, 60 min, 2 hr, 4 hr, 6 hr and 8 hr after the PD100 allergen challenge dose.
- Nasal lavage samples were collected 8 hours after the PD100 dose and after the other evaluations for collection of inflammatory cells.
- Nasal Peak Inspiratory Flow was measured using a nasal peak flow meter at 20 min, 30 min, 60 min, 2 hr, 4 hr, 6 hr and 8 hr post challenge.

Day 8 (P1D8)

- Subject visited the Clinical Unit for an overnight stay.

Day 9 (P1D9)

The procedures undertaken at Day 7 were repeated on Day 9.

WASHOUT OF PERIOD 1:

A minimum of a 14-day washout occurred from the last dosing of period 1, after which the subject returned to the clinic for period 2. Information on nasal symptoms, adverse events and concomitant medications was collected by phone call (except for sneezing) on Day 7 after last dose (+/- 2 days).

PERIOD 2:

Day 1(P2D1)

- The same procedures as P1D1 were performed.
- The subject received a further 6-day treatment with the second randomised treatment.

From Day 2 to Day 5 (P2D2 to P2D5)

- Subjects were contacted by phone once a day by the site to check their compliance to treatment.

Day 6 (P2D6)

- Subject visited the Clinical Unit for an overnight stay.

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		
	• Nasal lavage samples were taken for baseline evaluation of inflammatory cells. **Day 7: (P2D7)** • The same procedures as P1D7 were performed. **Day 8 (P2D8)** • Subject visited the Clinical Unit for an overnight stay. **Day 9 of period 2 (P2D9)** The procedures undertaken at Day 7 were repeated on Day 9. **FOLLOW-UP:** This visit was conducted 14 (± 2 days) days after the last dosing day in period 2. Physical examination, concomitant medications, serum pregnancy test (WOCBP only), vital signs, ECG and laboratory tests including urinalysis were performed. 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):	Both the study drug and the comparator were administered orally within 30 minutes after taking breakfast from Day 1 to Day 6 in each treatment period.		
Reference Therapy (dose, mode of administration):	S-555739 matching placebo.		

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		

Criteria for Evaluation

Efficacy endpoints:

Primary Endpoint:

- Change in total NAR after PD100 challenge at Day 7 on active and placebo treatments.

Secondary Endpoints

- Change in total NAR after PD100 challenge at Day 9 on active and placebo treatments.
- Change in total nasal allergic rhinitis symptom scores (total symptom score) after PD100 challenge at Days 7 and 9 on active and placebo treatments.
- Changes in nasal cross-sectional area, nasal volume and nasal inspiratory flow after PD100 challenge at Days 7 and 9 on active and placebo treatments.

Exploratory Endpoints

Change in inflammatory cell counts in nasal lavage after PD100 challenge at Days 7 and 9 on active and placebo treatments.

PK Endpoints

Plasma levels of S-555739 at Day 7: 24 hr and Day 9: 72 hr post dose.

Safety endpoints:

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

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.

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

Results Summary:

Efficacy Results

The primary efficacy analysis demonstrated a higher maximum mean change from pre-challenge in total NAR at Day 7 after treatment with S-555739 compared with placebo. However, the mean difference between treatments was not significantly different. At Day 9, the maximum mean change in total NAR between treatments was not significantly different, either.

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		

Within 120 min following allergen, a trend for lower NAR following S-555739 than placebo was clear at Day 9. At Day 9, at 20 min following allergen challenge, the difference in NAR was statistically significant in favour of S-555739.

Following S-555739, nasal allergic rhinitis symptoms at both Day 7 and Day 9 displayed a generally consistent pattern of reduced symptom scores in the first 120 minutes following allergen challenge. The trend of difference was noted in total score, obstruction and rhinorrhoea. At Day 7, at 60 min following allergen challenge, the difference in obstruction was statistically significant in favour of S-555739.

Nasal pruritis, nasal cross-sectional area and volume, nasal inspiratory flow, inflammatory cells from nasal lavage were also assessed in the study. At Day 7, the difference in nasal volume at 20 min and that in nasal inspiratory flow at 480 min were statistically significant. At Day 9, the difference in nasal inspiratory flow at 360 min was statistically significant.

Although significant treatment effect was demonstrated only at some time points, the trend of a reduction in nasal airway resistance and allergic rhinitis symptom scores was noted receiving S-555739 in this study.

Safety and Tolerability Results

Multiple oral doses of S-555739 100 mg once daily were well tolerated and no specific safety concerns were raised. Almost all AEs were mild and no severe AEs or SAEs were observed in any group.

PK profile

The PK levels observed at C24 and C72 time points were consistent with the levels achieved in the multiple dose pharmacokinetic study.

Conclusions

Although significant treatment effect was demonstrated only at some time points, the trend of a reduction in nasal airway resistance and allergic rhinitis symptom scores was noted receiving S-555739 in this study. Multiple oral doses of S-555739 100 mg once daily were well tolerated.

Date of Report:	22 January 2010