SMP-028

PROTOCOL NUMBER: D4050169

STUDY TITLE: AN EXPLORATORY, RANDOMISED, DOUBLE-BLIND, PLACEBO CONTROLLED, 14-DAY, TWO-WAY CROSSOVER, INHALED ALLERGEN CHALLENGE (IAC) STUDY TO EVALUATE THE EFFECTS OF SMP-028 IN SUBJECTS WITH MILD TO MODERATE ASTHMA

EUDRACT NUMBER: 2009-012675-10

Indication studied:	*Mild to moderate asthma*
Developmental phase of study:	*Phase 2*
First subject enrolled:	*29 October 2009*
Last subject completed:	*11 June 2010*
Release date of report:	*23 March 2011*

Company/Sponsor signatory:

Research and Development
Director, Dainippon Sumitomo
Pharma Europe Ltd.

Telephone: 0207 821 2858

Fax: 0207 821 2841

This trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline.

Co-ordinating Principal Investigator: Heart Lung Centre (HLC), London, UK.

2. SYNOPSIS

Name of Sponsor/Company: Dainippon Sumitomo Pharma Europe Ltd	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: SMP-028		
Name of Active Ingredient: N-{2-[(2Z)-2-[(3-fluorophenyl)imino]-4-(4-morpholin-4-ylphenyl)-1,3-thiazol-3(2H)-yl]ethyl}-N'-methylurea		

Title of Study: An exploratory, randomised, double-blind, placebo controlled, 14 day, 2-way crossover, Inhaled Allergen Challenge (IAC) study to evaluate the effects of SMP-028 in subjects with mild to moderate asthma.

Principal Investigators: Site 1 - Site 2 -

Study centres: Site 1 - Heart Lung Centre (HLC), Queen Anne Street Medical Centre, 18-20 Queen Anne Street, London, W1G 8HU, UK; Site 2 - Medicines Evaluation Unit (MEU), The Langley Building, Wythenshawe Hospital, Southmoor Road, Manchester, M23 9QZ, UK.

Publications (reference): None at the time of this report.

Studied period (years):	**Phase of development:**
Date first subject enrolled: 29 October 2009 Date last subject completed: 11 June 2010	II

Objectives:

Primary:

- To evaluate the effect of treatment with repeat doses of SMP-028 on the late asthmatic response (LAR) to Inhaled Allergen Challenge in mild to moderate asthmatic subjects.

Secondary:

- To evaluate the effect of treatment with repeat doses of SMP-028 on the early asthmatic response (EAR) to Inhaled Allergen Challenge in mild to moderate asthmatic subjects.
- To evaluate the effect of treatment with repeat doses of SMP-028 on lung function as measured by FEV_1 (Forced Expiratory Volume in 1 second) on Day 13 in subjects with mild to moderate asthma.
- To evaluate the effect of treatment with repeat doses of SMP-028 on exhaled nitric oxide (eNO) on Days 13 and 14 in subjects with mild to moderate asthma.
- To evaluate the effect of treatment with repeat doses of SMP-028 on bronchial hyper-reactivity as measured by adenosine monophosphate (AMP) challenge on Day 14 in mild to moderate asthmatic subjects.
- To evaluate the effect of treatment with repeat doses of SMP-028 on induced sputum post-allergen challenge on Day 14.
- To assess the safety and tolerability of treatment with repeat doses of SMP-028 in mild to moderate asthmatic subjects.
- To evaluate the multiple dose pharmacokinetics (PK) of SMP-028 and its M3 and M5 metabolites in subjects with mild to moderate asthma.

Name of Sponsor/Company: Dainippon Sumitomo Pharma Europe Ltd	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: SMP-028		
Name of Active Ingredient: N-{2-[(2Z)-2-[(3-fluorophenyl)imino]-4-(4-morpholin-4-ylphenyl)-1,3-thiazol-3(2H)-yl]ethyl}-N'-methylurea		

Methodology: This was an exploratory, randomised, double-blind, placebo-controlled, 14-day, 2-way crossover, IAC study to evaluate the effects of SMP-028 in approximately 24 subjects with mild to moderate asthma. Subjects were sequentially enrolled into the study if they fulfilled the study entry criteria and then randomly allocated to a treatment sequence. Subjects were randomised to receive either SMP-028 80 mg twice daily (b.i.d) or placebo in Treatment Period 1 followed by the other treatment in Treatment Period 2. In each Treatment Period the subject received the treatment twice daily on Days 1 to 13 and once daily on Day 14 (morning dose only). The allergen and AMP challenges were performed at Screening (21-35 days prior to the start of dosing on Study Day 1) and on Day 13 (for the allergen challenge) and Day 14 (for the AMP challenge). Subjects also attended the centres on Days 7, 15 and 16 for PK samples (also taken on Day 14) and for a follow-up safety visit 10±3 days after the last dose on Day 14 of Period 2. The effects of treatment on eNO were assessed at Screening, and on Days 1, 13 and 14. A washout period of 21-35 days was required between Periods 1 and 2.

Number of subjects (planned and analysed):

Planned: approximately 24 subjects in order to ensure 20 completed subjects.
Analysed: 24 subjects
Completed: 24 subjects

Diagnosis and main criteria for inclusion:

The inclusion criteria for this study were designed to define a population of healthy mild to moderate asthmatics aged between 18 and 65 years. Subjects had to have a documented history of bronchial asthma, first diagnosed at least 6 months prior to Screening, and being treated only with intermittent short-acting beta-agonist therapy by inhalation. Pre-bronchodilator FEV_1 had to be >65% of predicted at Screening and subjects had to demonstrate a positive wheal reaction (≥ 3 mm relative to negative control) to at least 1 of 3 allergens (house dust mite, grass pollen, cat hair and dander) on skin prick testing at Screening, or within 12 months of study start. Subjects also had to demonstrate both an early and a late asthmatic response to the Screening allergen challenge. The early asthmatic response had to include a fall in FEV_1 of ≥ 20% from the post-saline or diluent value on at least 1 occasion, between 5 and 30 minutes after the final concentration of allergen. The late asthmatic response had to include a fall in FEV_1 of ≥ 15% from the post-saline or diluent value, on at least 3 occasions, 2 of which had to be consecutive, between 4 and 10 hours after the final concentration of allergen. Subjects were also required to have sensitivity to AMP, with a provocative concentration of AMP resulting in a 20% fall in FEV_1 (PC_{20} AMP) of < 80 mg/mL at Screening.

Test product, dose and mode of administration, batch number:

On Days 1-13, the dose of SMP-028 was 80 mg (4 x 20 mg tablets) twice a day administered orally with 240 mL water at room temperature (total daily dose of 160 mg). A single morning dose of 80 mg SMP-028 (4 tablets) was taken on Day 14. Batch number: 08033.

Name of Sponsor/Company: Dainippon Sumitomo Pharma Europe Ltd	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: SMP-028		
Name of Active Ingredient: N-{2-[(2Z)-2-[(3-fluorophenyl)imino]-4-(4-morpholin-4-ylphenyl)-1,3-thiazol-3(2H)-yl]ethyl}-N'-methylurea		

Duration of treatment:

The maximum duration of subject participation was 111 days, based on the following:

- 35 days from Screening to Day 1.
- 16 days each for Period 1 and Period 2 (14 days of dosing per period).
- 33 day washout period between Period 1 and Period 2 (35 days from Day 14 of Period 1 to Day 1 of Period 2).
- Follow-Up Visit 11 days after the end of period 2 (13 days after last dose).

Reference therapy, dose and mode of administration, batch number:

On Days 1-13, the dose of matching placebo was 4 tablets, administered orally with 240 mL water at room temperature. A single morning dose of matching placebo (4 tablets) was taken on Day 14. Batch number: 08036.

Criteria for evaluation:

Pharmacodynamics (PD): Baseline-corrected FEV_1 $AUC_{4\text{-}10h}$ on Day 13 of each Treatment Period; mean minimum FEV_1 and mean baseline-corrected FEV_1 $AUC_{0\text{-}4h}$ and $AUC_{0\text{-}10h}$ after allergen challenge on Day 13 of each Treatment Period; maximum eNO and $AUC_{0\text{-}24h}$ of eNO on Day 13 and 14 of each Treatment Period; AMP PC_{20} FEV_1 on Day 14 of each Treatment Period; induced sputum cell count on Day 14 of each Treatment Period; and induced sputum biomarkers (cysteinyl leukotriene and prostaglandin D2) and inflammatory mediators (epithelial neutrophil-activating peptide 78, eotaxin-1, interferon gamma, monocyte chemotactic protein 1, macrophage inflammatory protein 1-alpha, macrophage inflammatory protein 1-beta, regulated upon activation normal T-cell expressed and secreted, tumour necrosis factor, IL-1-beta, IL-4, IL-5, IL-6, IL-8, IL-13 and IL-17) on Day 14 of each treatment period).

Pharmacokinetics: PK parameters were evaluated from plasma samples taken in both Treatment Periods at Day 1, Day 7, Day 14, Day 15, and Day 16. Urine samples were also taken and analysed to assist with assay development, but this was not a formal analysis of the study and so is not reported in the Clinical Study Report.

Safety: Safety was evaluated through monitoring of adverse events (AEs), laboratory tests, hormone monitoring, electrocardiograms (ECGs), vital signs and body weight/height, and physical examinations.

Statistical methods: Descriptive summaries were presented using summary statistics (e.g. number (n), mean, geometric mean, standard deviations (SD), coefficient of variance as a percentage (%CV), median, minimum, maximum) and 95% confidence intervals (CI) for continuous parameters or frequency distributions (n, %) for categorical parameters. Since this was an exploratory study, no inferential statistical testing was conducted.

Name of Sponsor/Company: Dainippon Sumitomo Pharma Europe Ltd	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: SMP-028		
Name of Active Ingredient: N-{2-[(2Z)-2-[(3-fluorophenyl)imino]-4-(4-morpholin-4-ylphenyl)-1,3-thiazol-3(2H)-yl]ethyl}-N'-methylurea		

Efficacy data were summarised by treatment and timepoint using descriptive statistics. The change from baseline was calculated and summarised. Areas under the curve (AUC_{0-10h}, AUC_{0-4h}, AUC_{4-10h}) were derived for all applicable primary and secondary endpoints for each Treatment Period. The difference between treatments was calculated. The data were summarised using summary statistics and the 95% CI given for the differences between treatments.

PK parameters were estimated for SMP-028 and its M3 and M5 metabolites using a non-compartmental approach and summarised by treatment using descriptive statistics e.g. geometric mean, geometric SD, and 95% CI.

The incidence of AEs was summarised by system organ class (SOC), preferred term (PT) and maximum severity or strongest relationship to study treatment for each treatment. Serious adverse events (SAEs) and AEs leading to early withdrawal from the study were listed. Clinical safety laboratory tests data were listed by subject and visit, with values falling outside the normal range flagged. Shifts from abnormally low/normal/abnormally high at baseline to the end of the study were shown. Data on vital signs and ECGs were summarised.

SUMMARY – CONCLUSIONS

PHARMACODYNAMIC RESULTS:

The primary endpoint in this study was the mean baseline-corrected area under the FEV_1 reduction curve from 4 to 10 hours after allergen challenge (AUC_{4-10h}) on Day 13 of each treatment period. A mean difference of -0.38 L*h was seen between the SMP-028 and placebo treatment periods on Day 13, with a 95% CI of (-1.22, 0.47). No notable differences were seen for any of the secondary endpoints (see table below).

PD endpoint	**Mean (SD) difference (SMP-028 – Placebo)**	**95% CI**
Late Asthmatic Response (AUC_{4-10h}), L*h	-0.38 (1.998)	-1.22, 0.47
Early Asthmatic Response (AUC_{0-4h}), L*h	-0.43 (1.107)	-0.89, 0.04
Total Asthmatic Response (AUC_{0-10h}), L*h	-0.80 (2.782)	-1.98, 0.37
Minimum $FEV_{1\ (4-10h)}$, L	-0.06 (0.295)	-0.19, 0.06
Minimum $FEV_{1\ (0-4h)}$, L	-0.14 (0.511)	-0.36, 0.07
Minimum $FEV_{1\ (0-10h)}$, L	-0.09 (0.289)	-0.22, 0.03
eNO $AUC_{(0-24h)}$ (ppb*h)	-0.19 (230.713)	-97.61, 97.23
Maximum eNO (ppb)	-8.95 (25.089)	-19.54, 1.64
Sputum cell count: sputum (g)	0.06 (0.358)	-0.24, 0.36
Sputum cell count: Eosinophils (%)	-7.31 (36.720)	-38.00, 23.39
Sputum cell count: Macrophages (%)	0.26 (13.870)	-11.34, 11.85
Sputum cell count: Neutrophils (%)	14.45 (40.361)	-19.30, 48.19
Sputum cell count: Leukocytes (% viability)	6.30 (11.928)	-3.67, 16.28
	Median (range) difference (SMP-028 – Placebo)	**CV%**
Bronchial AMP PC_{20} (mg/mL)	0.39 (-2.41, 4.20)	357.29

Name of Sponsor/Company: Dainippon Sumitomo Pharma Europe Ltd	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: SMP-028		
Name of Active Ingredient: N-{2-[(2Z)-2-[(3-fluorophenyl)imino]-4-(4-morpholin-4-ylphenyl)-1,3-thiazol-3(2H)-yl]ethyl}-N'-methylurea		

No significant differences were seen for any of the exploratory efficacy endpoints, with the exception of percentage maximum fall from baseline in $FEV_{1\ (0\text{-}10h)}$, where a difference of 2.20% was seen between the two treatment periods (95% CI: 0.50, 5.80).

No trends were seen in any of the biomarker or inflammatory mediator data and no notable differences were seen between the SMP-028 and placebo groups for any of the parameters assessed.

PHARMACOKINETIC RESULTS:

Summary statistics for serum PK parameters of SMP-028 and its metabolites M3 and M5 on Day 14 following repeated oral administration of 80 mg SMP-028 twice daily are presented in the following table:

Parameter	**SMP-028 (N=23)**		**M3 (N=23)**		**M5 (N=23)**	
	Day 1	**Day 14**	**Day 1**	**Day 14**	**Day 1**	**Day 14**
AUC_τ (ng.h/mL)	2566[b] (45.7)	4324 (49.7)	79.4[b] (31.7)	144 (36.4)	297[b] (52.0)	758 (47.8)
C_{max} (ng/mL)	437 (47.3)	656 (44.2)	10.6 (34.7)	18.3 (32.4)	33.6 (51.9)	83.7 (47.5)
C_{min} (ng/mL)	79.3[b] (67.8)	155 (81.9)	3.67[b] (47.5)	6.97 (57.5)	18.9[b] (57.6)	46.1 (55.5)
t_{max}[a] (h)	1.90 (0.500-4.05)	3.87 (0.500-4.57)	2.07 (0.500-4.13)	3.97 (0.500-4.57)	2.15 (0.500-8.05)	4.00 (1.00-4.57)
$t_{½}$ (h)	4.25[d] (25.6)	7.09 (24.1)	6.52[b] (36.9)	8.46 (18.0)	9.80[c] (42.2)	10.7 (21.0)
λ_z (h^{-1})	0.163[d] (25.6)	0.0978 (24.1)	0.106[b] (36.9)	0.0819 (18.0)	0.0707[c] (42.2)	0.0645 (21.0)
$RAC_{AUC\tau}$	NA	1.74[b] (28.4)	NA	1.88[b] (22.7)	NA	2.64[b] (32.3)
RAC_{Cmax}	NA	1.50 (37.4)	NA	1.73 (31.8)	NA	2.49 (35.1)
RAC_{Cmin}	NA	2.00[b] (37.7)	NA	1.95[b] (23.5)	NA	2.50[b] (33.6)
RL	NA	1.44[d] (25.5)	NA	1.26[b] (18.9)	NA	1.25[c] (33.4)
CL/F (mL/min)	440[d] (51.1)	308 (49.7)	NA	NA	NA	NA
V_z/F (L)	162[d] (41.0)	189 (57.3)	NA	NA	NA	NA
MR_{AUC}	NA	NA	0.0401 (22.2)	0.0353 (17.2)	0.215[c] (30.4)	0.181 (35.4)
MR_{Cmax}	NA	NA	0.0256[b] (31.7)	0.0296 (17.6)	0.0793 (34.7)	0.132 (35.3)

Geometric mean (Geometric CV%) data are presented. N = Number of subjects studied; NA = Not applicable;
[a] Median (min-max); [b] N=21; [c] N=16; [d] N=22

The absorption of SMP-028 was rapid with a median t_{max} of 1.9 and 3.9 hours on Days 1 and 14, respectively. Following C_{max}, serum concentration decreased in a bi-phasic manner, having a shallow and short distribution phase and an apparent terminal elimination half-life of approximately 7 hours on Day 14. SMP-028 reached steady state by Day 7 of b.i.d dosing, with up to 2-fold accumulation in exposure following 14 days of dosing. The metabolites M3 and M5 were both rapidly formed in serum, with median t_{max} of approximately 2 hours on Day 1 and approximately 4 hours on Day 14 for both metabolites. Total systemic exposure to the metabolites was much lower than the parent drug, representing up to 4% and 22% of SMP-028 exposure for M3 and M5, respectively, as assessed by

Name of Sponsor/Company: Dainippon Sumitomo Pharma Europe Ltd	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: SMP-028		
Name of Active Ingredient: N-{2-[(2Z)-2-[(3-fluorophenyl)imino]-4-(4-morpholin-4-ylphenyl)-1,3-thiazol-3(2H)-yl]ethyl}-N'-methylurea		

MR_{AUC}. The PK of SMP-028 and its metabolites M3 and M5 appeared linear over time, with the metabolic ratios being similar following single and repeated dosing and accumulation ratios being similar for all analytes. Inter-subject variability was high for SMP-028 and its metabolites M3 and M5, assessed from the geometric coefficient of variation (CV%) with estimates ranging from 31.7 to 52.0% for AUC_{τ}, 32.4 to 51.9% for C_{max} and 47.5 to 81.9% for C_{min}.

SAFETY RESULTS:

The incidence of TEAEs reported during SMP-028 dosing was similar to that reported during placebo dosing (54.2% and 62.5%, respectively), as was the incidence of treatment-related TEAEs (25.0% in both groups). Only one severe TEAE was reported (in the placebo group).

Summary of AEs, n (%)		**SMP-028 (N=24)**	**Placebo (N=24)**
Number of subjects with TEAEs		13 (54.2)	15 (62.5)
Number of subjects with SAEs		0	0
Number of subjects withdrawing due to an AE		0	0
Maximum severity			
	Mild	11 (45.8)	10 (41.7)
	Moderate	2 (8.3)	4 (16.7)
	Severe	0	1 (4.2)
Strongest Causality			
	Related[1]	6 (25.0)	6 (25.0)
	Probably related	0	1 (4.2)
	Possibly related	6 (25.0)	5 (20.8)
	Unlikely to be related	5 (20.8)	6 (25.0)
	Unrelated	2 (8.3)	3 (12.5)

[1]Related included categories probably and possibly related

The most common TEAE was headache, which was reported in 11 (45.8%) subjects (5 [20.8%] subjects during SMP-028 dosing and 9 [37.5%] subjects during placebo dosing). No subjects experienced an SAE or withdrew from the study due to an AE. No changes in laboratory parameters, vital signs, ECGs or physical examinations indicated any adverse effects of SMP-028 dosing.

CONCLUSION:

- The effect of SMP-028 on modifying the responses to an inhaled allergen challenge in subjects with mild to moderate asthma were comparable to those seen with placebo, with the effects of SMP-028 on FEV_1, eNO, sputum cell counts, biomarkers, and inflammatory mediators also being comparable to those seen with placebo.

Name of Sponsor/Company: Dainippon Sumitomo Pharma Europe Ltd	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: SMP-028		
Name of Active Ingredient: N-{2-[(2Z)-2-[(3-fluorophenyl)imino]-4-(4-morpholin-4-ylphenyl)-1,3-thiazol-3(2H)-yl]ethyl}-N'-methylurea		

- The PK of SMP-028 and its M3 and M5 metabolites appeared linear over time, with the metabolic ratios being similar following single and repeated dosing and accumulation ratios being similar for all analytes, although inter-subject variability was high. PK of SMP-028 reached steady state by Day 7 of 80 mg b.i.d. dosing, with up to 2-fold accumulation in exposure following 14 days of dosing.
- The safety and tolerability profile of SMP-028 was good and was comparable to placebo.

Date of the report: 23 March 2011