SYNOPSIS

Name of Sponsor/Company: Ono Pharmaceutical Co., Ltd. Name of Finished Product: ONO-4053 Name of Active Ingredient: ONO-4053	Individual Study Table Referring to Part of the Dossier Volume: Page:
Title of Study: A randomised, double-blind, placebo controlled, double dummy, four period crossover study to evaluate the efficacy, safety and tolerability of oral repeat doses of ONO-4053 and cetirizine in subjects with seasonal allergic rhinitis in the Vienna Challenge Chamber.	
Studied period (years): First subject enrolled: 12-NOV-2012 Last subject completed: 12-MAR-2013	Phase of Development: Phase IIa
Objectives: Primary Objectives: • To investigate the effect of repeat oral doses of ONO-4053 versus placebo on nasal symptoms (Total Nasal Symptom Score; TNSS) elicited by allergen chamber challenge in subjects with allergic rhinitis • To investigate the safety and tolerability of repeat oral doses of ONO-4053 versus placebo in subjects with allergic rhinitis Secondary Objectives: • To investigate the effect of repeat oral doses of ONO-4053 versus cetirizine on nasal symptoms (TNSS) elicited by allergen chamber challenge in subjects with allergic rhinitis • To investigate the effect of repeat oral doses of ONO-4053 versus placebo and cetirizine on individual nasal symptoms, eye and other symptoms, nasal obstruction (active anterior rhinomanometry) and nasal secretion weight elicited by allergen chamber challenge in subjects with allergic rhinitis • To investigate pharmacokinetics of ONO-4053 following repeat oral doses in subjects with allergic rhinitis	
Methodology: This was a randomised, double-blind, placebo controlled, repeat dose, four period crossover study. Subjects were randomised to receive oral placebo, ONO-4053 60 mg, ONO-4053 300 mg and cetirizine 10 mg once daily for 8 days. The order of treatments was randomised. The ratio of randomisation was to be 1:1:1:1 in each sequence and all sequences were to include the same number of subjects. Treatment periods were separated by a washout of at least 6 days. Immediately after dosing on Day 8, subjects entered the Vienna Challenge Chamber (VCC) and were exposed to allergen for a period of 6 h during which symptoms of seasonal allergic rhinitis (SAR) were assessed. In addition, objective measurements of SAR were undertaken during this period to determine the effectiveness of treatment.	
Number of subjects (planned and analysed): Up to 60 subjects were to be randomised to achieve at least 46 evaluable subjects. Fifty-eight subjects were randomised and dosed; 56 completed all four periods.	
Diagnosis and main criteria for inclusion: Male and female subjects aged 18–65 years inclusive, and healthy with the exception of SAR were enrolled. Only subjects who exhibited a moderate to severe response (TNSS ≥6 and nasal obstruction subscore ≥2) to approximately 1500 grass pollen grains/m^3 within the first 2 h in the VCC at the screening visit, and who had a positive skin prick and radioallergosorbent test for grass pollen were included. Subjects with mild asthma that did not require treatment were eligible for the study. Subjects were excluded if they had any conditions or factors which would have made them unlikely to be able to stay in the chamber for 6 h. Subjects with nasal structural abnormalities or nasal polyps, a history of frequent nosebleeds, nasal biopsy, nasal trauma or nasal surgery were not eligible.	
Test product, dose and mode of administration, batch number: Oral ONO-4053 10 mg tablet (Lot No. J243) and ONO-4053 100 mg tablet (Lot No. J244). Placebo tablets to match ONO-4053 (Lot Nos. J241,	

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J242).

Duration of treatment: Once daily for 8 days at an ONO-4053 dose of 60 mg or 300 mg (or placebo).

Reference therapy, dose and mode of administration, batch number: Oral cetirizine 10 mg encapsulated tablet (Lot No. X282). Placebo encapsulated tablet to match cetirizine (Lot No. X281).

Criteria for evaluation: The primary study endpoints were as follows:

- Area under the pharmacodynamic (PD) effect time curves (AUE0-2h, 2-6h and 0-6h) of TNSS on Day 8 (nasal obstruction, rhinorrhoea, nasal itching and sneezing were scored on a categorical scale from 0 to 3. Individual scores were summed to produce the TNSS)
- Adverse events (AEs), physical examination, vital signs, 12-lead electrocardiogram (ECG), lung function test and safety laboratory evaluations

Secondary endpoints were as follows:

- AUE (0-2h, 2-6h and 0-6h) of individual nasal symptom scores of TNSS: nasal obstruction, rhinorrhoea, nasal itching and sneezing (scored on a categorical scale of 0 to 3)
- AUE (0-2h, 2-6h and 0-6h) of Total Ocular Symptom Score (TOSS): watery eyes, itchy eyes and red eyes were scored on a categorical scale of 0 to 3. Individual scores were summed to produce the TOSS
- AUE (0-2h, 2-6h and 0-6h) of Miscellaneous Allergy Symptom Score (MASS): cough, itchy throat and itchy ears were scored on a categorical scale of 0 to 3. Individual scores were summed to produce the MASS
- AUE (0-2h, 2-6h and 0-6h) of Global Symptom Score (sum of TNSS, TOSS and MASS)
- AUE (0-2h, 2-6h and 0-6h) of active anterior rhinomanometry (the sum of left and right nostril for evaluation)
- AUE (0-2h, 2-6h and 0-6h) of nasal secretion weight
- AUE(0-2h, 2-6h and 0-6h) of sum of three nasal symptom scores on Day 8 (nasal obstruction, rhinorrhoea and sneezing were scored on a categorical scale from 0 to 3. Individual scores were summed to produce the sum score)
- Pharmacokinetics of plasma ONO-4053: concentration prior to dosing on Day 1 (Treatment Periods 2, 3 and 4 only) and trough concentration prior to dosing on Day 8; Day 8 post-allergen challenge (6 h post-dose)

Treatment Assignment: During implementation of the randomisation, subjects were misassigned investigational product. The error occurred due to different investigational product treatment kit labelling information being provided to the drug packaging vendor compared with that implemented in the Interactive Web Response (IWR) system that was used for randomisation and kit allocation. As a result, in each treatment period, subjects received one of four treatments at random rather than the planned treatments, and most subjects received at least one treatment regimen for more than one treatment period. This summary presents data for the actual treatments administered. A description of the number of subjects who received each treatment is presented in the safety section of this report.

Statistical Methods: A sample size of 60 subjects (46 evaluable) would have provided 80% power to detect a difference in TNSS score between placebo and ONO-4053 at a 0.05 level (two-sided). The statistical analysis plan was revised before data unblinding to take account of the misassignment of study medication described above. The primary analysis used analysis of variance (ANOVA) to compare TNSS AUE (0-2h, 2-6h, 0-6h) between treatment regimens: ONO-4053 60 mg and 300 mg vs. placebo; ONO-4053 60 mg and 300 mg vs. cetirizine; and cetirizine vs. placebo. Adjusted least squares (LS) means, 95% confidence intervals (CI) and p-values were reported. Analysis of covariance (ANCOVA) was used to assess the effect of

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baseline on TNSS AUE treatment comparisons. Additional analyses were performed for each period separately, and also using only the first period in which a subject received a given treatment. Secondary efficacy analyses of all other AUE endpoints were conducted using similar ANOVA and ANCOVA models to those used in the primary analysis.

The primary analysis was to be based on a Per-Protocol Set (PPS); however, due to the misassignment of study medication the PPS was no longer valid and therefore a new analysis population, the Efficacy Set (EFF), was defined prior to unblinding the treatment allocations. In addition to identifying subjects who were not eligible for the study and would be excluded from the EFF, specific study periods were identified for exclusion by identifying protocol violations that could potentially affect safety or efficacy evaluation of the study drug(s) during that period. These study periods were excluded from the EFF analyses. The Full Analysis Set (FAS) comprised all subjects who received at least one dose of study medication and had at least one non-missing PD evaluation. Safety data were summarised descriptively for the Safety Set and pharmacokinetic data for the Pharmacokinetic Analysis Set (PAS).

The present summary reports PD results in the form of treatment comparisons from the ANOVA of all data for each primary and secondary endpoint in the EFF.

Summary – Conclusions:

Subject Disposition and Demographic Data:

Fifty-eight subjects were randomised and 56 (97%) completed the study. Two subjects withdrew for personal reasons after completing dosing in Period 2 (Subject 018 [placebo] and Subject 043 [cetirizine 10 mg]). Subjects were predominantly White (93%) and male (55%). All women were pre-menopausal.

Subject disposition and demographic data for all subjects are summarised below.

Disposition	All Subjects
Subjects Randomised	58
Full Analysis Set, n (%)	58 (100.0)
Efficacy Set, n (%)	57 (98.3)
Safety Set, n (%)	58 (100.0)
Pharmacokinetic Analysis Set, n (%)	55 (94.8)
Subjects completed all four periods, n (%)	56 (96.6)
Subjects withdrawn early from study, n (%)	2 (3.4)
Reason for early withdrawal: Other	2 (3.4)

Demographics (FAS)	Placebo (N=41)	ONO-4053 60 mg (N=38)	ONO-4053 300 mg (N=41)	Cetirizine 10 mg (N=41)	Total (N=58)
Age in years, mean [range]	30.2 [18–48]	30.7 [19–53]	29.2 [18–53]	30.8 [18–53]	30.1 [18–53]
Sex, n (%)					
Male	21 (51.2)	21 (55.3)	24 (58.5)	23 (56.1)	32 (55.2)
Female	20 (48.8)	17 (44.7)	17 (41.5)	18 (43.9)	26 (44.8)
Race, n (%)					
White	38 (92.7)	35 (92.1)	40 (97.6)	39 (95.1)	54 (93.1)
Asian	1 (2.4)	0	0	1 (2.4)	1 (1.7)
Other	2 (4.9)	3 (7.9)	1 (2.4)	1 (2.4)	3 (5.2)
Height in cm, mean [range]	172 [157–197]	173 [158–194]	173 [158–197]	173 [157–197]	172 [157–197]
Weight in kg, mean [range]	68.9 [49–98]	70.3 [50–98]	70.1 [50–98]	70.3 [49–98]	69.8 [49–98]
Body Mass Index in kg/m^2,	23.2 [19–30]	23.5 [19–30]	23.2 [19–29]	23.5 [19–30]	23.3 [19–30]

mean [range]					

Pharmacodynamic Results:

TNSS results: Statistical analysis of TNSS AUE(0-2h) post-allergen challenge on Day 8 showed significant decreases following ONO-4053 60 mg, ONO-4053 300 mg and cetirizine 10 mg compared with placebo (p=0.0049, p=0.0424 and p<0.0001, respectively). Statistically significant decreases in TNSS AUE(2-6h) and AUE(0-6h) were observed for ONO-4053 60 mg, ONO-4053 300 mg and cetirizine 10 mg versus placebo (p<0.0001 for all comparisons; see table below).

A statistically significant increase in TNSS AUE(0-2h) was observed for ONO-4053 60 mg and 300 mg versus cetirizine (p=0.0113 and p=0.0007, respectively). There was no statistically significant difference in TNSS AUE(2-6h) for ONO-4053 60 mg or 300 mg versus cetirizine 10 mg. A statistically significant increase in TNSS AUE(0-6h) was observed for ONO-4053 300 mg compared with cetirizine (p=0.0334). There was no significant difference in TNSS AUE(0-6h) between ONO-4053 60 mg and cetirizine 10 mg.

Treatment comparisons for the ANOVA of TNSS AUE (0-2h, 2-6h and 0-6h) in the EFF are summarised in the table below.

TNSS AUE (score*h)	Placebo (N=39)	ONO-4053 60 mg (N=37)	ONO-4053 300 mg (N=39)	Cetirizine 10 mg (N=39)
AUE(0-2h)				
n	53	54	53	54
Adjusted LS mean (95% CI)	10.6 (9.3, 11.8)	8.5 (7.3, 9.7)	9.1 (7.8, 10.3)	6.6 (5.4, 7.9)
Diff. vs. placebo (95% CI)	NA	-2.1 (-3.5, -0.6)	-1.5 (-2.9, -0.1)	-3.9 (-5.3, -2.5)
P-value	NA	0.0049	0.0424	<0.0001
Diff. vs. cetirizine (95% CI)	NA	1.8 (0.4, 3.3)	2.4 (1.0, 3.8)	NA
P-value	NA	0.0113	0.0007	NA
AUE(2-6h)				
n	53	54	53	54
Adjusted LS mean (95% CI)	27.0 (24.4, 29.6)	20.2 (17.6, 22.8)	20.1 (17.5, 22.7)	18.1 (15.5, 20.6)
Diff. vs. placebo (95% CI)	NA	-6.8 (-9.8, -3.7)	-6.9 (-10.0, -3.9)	-8.9 (-11.9, -5.9)
P-value	NA	<0.0001	<0.0001	<0.0001
Diff. vs. cetirizine (95% CI)	NA	2.2 (-0.9, 5.2)	2.0 (-1.0, 5.0)	NA
P-value	NA	0.1653	0.1883	NA
AUE(0-6h)				
n	53	54	53	54
Adjusted LS mean (95% CI)	37.6 (34.0, 41.2)	28.7 (25.1, 32.3)	29.1 (25.5, 32.7)	24.7 (21.1, 28.3)
Diff. vs. placebo (95% CI)	NA	-8.9 (-13.0, -4.7)	-8.5 (-12.6, -4.3)	-12.9 (-17.0, -8.8)
P-value	NA	<0.0001	<0.0001	<0.0001
Diff. vs. cetirizine (95% CI)	NA	4.0 (-0.2, 8.2)	4.4 (0.4, 8.5)	NA
P-value	NA	0.0587	0.0334	NA

Diff.=difference of adjusted LS means; NA=not applicable.
Note: subjects receiving the same treatment in multiple treatment periods are counted more than once within the treatment group, therefore n may be greater than N.

Statistical analysis of AUE(0-2h) post-allergen challenge on Day 8 for the TNSS subscore of nasal obstruction showed no significant changes versus placebo. Statistically significant decreases in nasal obstruction AUE(2-6h) were observed following ONO-4053 60 mg, ONO-4053 300 mg and cetirizine 10 mg versus placebo (p=0.0282, p=0.0032 and p=0.0341, respectively). Statistically significant decreases in nasal obstruction AUE(0-6h) were observed following ONO-4053 60 mg, ONO-4053 300 mg and cetirizine 10 mg

compared with placebo (p=0.0248, p=0.0135 and p=0.0340, respectively). Statistically significant decreases in AUE(0-2h) were observed for rhinorrhoea and nasal itching following ONO-4053 60 mg and cetirizine 10 mg, and for sneezing following all three treatments compared with placebo. Statistically significant decreases in rhinorrhoea, nasal itching and sneezing AUE(2-6h and 0-6h) were observed following ONO-4053 60 mg, ONO-4053 300 mg and cetirizine 10 mg compared with placebo.

Treatment comparisons versus placebo from the ANOVA for individual TNSS subscore AUEs in the EFF are summarised below.

Parameter	AUE(0-2h)		AUE(2-6h)		AUE(0-6h)	
(score*h)	Diff. (95% CI)	P-value	Diff. (95% CI)	P-value	Diff. (95% CI)	P-value
TNSS subscore						
Nasal obstruction						
ONO-4053 60 mg	-0.5 (-0.9, 0.0)	0.0624	-1.0 (-2.0, -0.1)	0.0282	-1.5 (-2.8, -0.2)	0.0248
ONO-4053 300 mg	-0.2 (-0.7, 0.2)	0.3149	-1.4 (-2.3, -0.5)	0.0032	-1.6 (-2.9, -0.3)	0.0135
Cetirizine 10 mg	-0.4 (-0.9, 0.1)	0.1057	-1.0 (-1.9, -0.1)	0.0341	-1.4 (-2.6, -0.1)	0.0340
Rhinorrhoea						
ONO-4053 60 mg	-0.5 (-0.9, -0.0)	0.0309	-2.2 (-3.1, -1.2)	<0.0001	-2.6 (-4.0, -1.3)	<0.0001
ONO-4053 300 mg	-0.4 (-0.8, 0.1)	0.0893	-2.1 (-3.1, -1.2)	<0.0001	-2.5 (-3.8, -1.2)	0.0002
Cetirizine 10 mg	-1.0 (-1.4, -0.6)	<0.0001	-2.3 (-3.2, -1.3)	<0.0001	-3.3 (-4.5, -2.0)	<0.0001
Nasal Itching						
ONO-4053 60 mg	-0.4 (-0.8, -0.0)	0.0489	-1.6 (-2.4, -0.7)	0.0007	-2.0 (-3.2, -0.8)	0.0011
ONO-4053 300 mg	-0.4 (-0.8, 0.1)	0.0882	-1.8 (-2.7, -0.9)	0.0001	-2.2 (-3.3, -1.0)	0.0004
Cetirizine 10 mg	-1.3 (-1.7, -0.9)	<0.0001	-2.9 (-3.8, -2.1)	<0.0001	-4.2 (-5.4, -3.1)	<0.0001
Sneezing						
ONO-4053 60 mg	-0.7 (-1.1, -0.3)	0.0004	-2.1 (-2.9, -1.2)	<0.0001	-2.8 (-3.9, -1.6)	<0.0001
ONO-4053 300 mg	-0.5 (-0.9, -0.1)	0.0081	-1.7 (-2.6, -0.8)	0.0002	-2.3 (-3.4, -1.1)	0.0001
Cetirizine 10 mg	-1.3 (-1.6, -0.9)	<0.0001	-2.8 (-3.7, -2.0)	<0.0001	-4.1 (-5.2, -3.0)	<0.0001

MASS results: Statistical analysis of MASS AUE (0-2h, 2-6h and 0-6h) post-allergen challenge on Day 8 showed significant decreases following cetirizine 10 mg compared with placebo. The decreases in MASS were primarily due to decreases in throat itching.

Treatment comparisons versus placebo from the ANOVA for MASS AUEs in the EFF are summarised below.

Parameter	AUE(0-2h)		AUE(2-6h)		AUE(0-6h)	
(score*h)	Diff. (95% CI)	P-value	Diff. (95% CI)	P-value	Diff. (95% CI)	P-value
MASS						
ONO-4053 60 mg	-0.2 (-0.8, 0.3)	0.4347	-0.8 (-2.3, 0.7)	0.2976	-1.0 (-2.9, 1.0)	0.3192
ONO-4053 300 mg	-0.3 (-0.8, 0.3)	0.3095	-0.8 (-2.3, 0.7)	0.2792	-1.1 (-3.0, 0.8)	0.2711
Cetirizine 10 mg	-0.6 (-1.1, -0.0)	0.0479	-1.5 (-3.0, -0.1)	0.0383	-2.1 (-4.0, -0.2)	0.0317
Cough						
ONO-4053 60 mg	0.0 (-0.2, 0.2)	0.9134	0.0 (-0.5, 0.6)	0.8939	0.1 (-0.6, 0.7)	0.8756
ONO-4053 300 mg	-0.0 (-0.2, 0.2)	0.8434	0.0 (-0.5, 0.5)	0.9947	-0.0 (-0.7, 0.7)	0.9768
Cetirizine 10 mg	-0.2 (-0.4, 0.1)	0.1430	-0.1 (-0.7, 0.4)	0.5877	-0.3 (-1.0, 0.4)	0.4067
Itchy Ears						
ONO-4053 60 mg	-0.1 (-0.3, 0.1)	0.5318	-0.2 (-0.7, 0.4)	0.5079	-0.2 (-0.9, 0.5)	0.5167
ONO-4053 300 mg	-0.1 (-0.3, 0.1)	0.2829	-0.2 (-0.8, 0.3)	0.3661	-0.3 (-1.0, 0.3)	0.3216
Cetirizine 10 mg	-0.1 (-0.3, 0.1)	0.3744	-0.4 (-0.9, 0.1)	0.1378	-0.5 (-1.2, 0.2)	0.1625
Itchy Throat						

ONO-4053 60 mg	-0.2 (-0.6, 0.1)	0.2058	-0.7 (-1.5, 0.1)	0.1088	-0.9 (-1.9, 0.2)	0.1169
ONO-4053 300 mg	-0.2 (-0.5, 0.1)	0.2504	-0.6 (-1.4, 0.2)	0.1509	-0.8 (-1.9, 0.3)	0.1586
Cetirizine 10 mg	-0.4 (-0.7, -0.0)	0.0321	-1.0 (-1.8, -0.2)	0.0125	-1.4 (-2.4, -0.3)	0.0123

TOSS results: Statistical analysis of TOSS AUE(0-2h) post-allergen challenge on Day 8 showed significant decreases following ONO-4053 300 mg and cetirizine 10 mg compared with placebo. Statistically significant decreases in TOSS AUE(2-6h and 0-6h) were observed following ONO-4053 60 mg, ONO-4053 300 mg and cetirizine 10 mg compared with placebo. The TOSS subscores of watery eyes and red eyes showed statistically significant decreases in AUE (0-2h, 2-6h and 0-6h) following all three treatments compared with placebo. For itchy eyes, statistically significant decreases were observed in AUE(2-6h) following all three treatments compared with placebo, and in AUE(0-6h) for ONO-4053 300 mg and cetirizine 10 mg.

Treatment comparisons versus placebo from the ANOVA for TOSS AUEs in the EFF are summarised below.

Parameter	AUE(0-2h)		AUE(2-6h)		AUE(0-6h)	
(score*h)	Diff. (95% CI)	P-value	Diff. (95% CI)	P-value	Diff. (95% CI)	P-value
TOSS						
ONO-4053 60 mg	-0.7 (-1.5, 0.1)	0.0822	-3.4 (-5.7, -1.1)	0.0034	-4.1 (-7.0, -1.2)	0.0062
ONO-4053 300 mg	-0.9 (-1.7, -0.1)	0.0228	-3.4 (-5.7, -1.1)	0.0033	-4.3 (-7.2, -1.4)	0.0038
Cetirizine 10 mg	-1.2 (-2.0, -0.5)	0.0018	-5.1 (-7.3, -2.8)	<0.0001	-6.3 (-9.1, -3.5)	<0.0001
Watery Eyes						
ONO-4053 60 mg	-0.3 (-0.6, -0.1)	0.0137	-1.3 (-2.0, -0.5)	0.0013	-1.6 (-2.5, -0.6)	0.0016
ONO-4053 300 mg	-0.4 (-0.6, -0.1)	0.0046	-1.3 (-2.1, -0.5)	0.0009	-1.7 (-2.6, -0.7)	0.0008
Cetirizine 10 mg	-0.5 (-0.7, -0.2)	0.0005	-1.7 (-2.5, -1.0)	<0.0001	-2.2 (-3.2, -1.3)	<0.0001
Itchy Eyes						
ONO-4053 60 mg	-0.1 (-0.4, 0.3)	0.6468	-1.0 (-1.9, -0.0)	0.0401	-1.0 (-2.2, 0.2)	0.0888
ONO-4053 300 mg	-0.2 (-0.6, 0.1)	0.2261	-1.0 (-1.9, -0.1)	0.0280	-1.2 (-2.4, -0.1)	0.0411
Cetirizine 10 mg	-0.3 (-0.7, 0.0)	0.0616	-1.7 (-2.6, -0.8)	0.0003	-2.0 (-3.2, -0.8)	0.0009
Red Eyes						
ONO-4053 60 mg	-0.3 (-0.6, -0.0)	0.0345	-1.2 (-2.0, -0.4)	0.0037	-1.5 (-2.5, -0.5)	0.0047
ONO-4053 300 mg	-0.3 (-0.6, -0.0)	0.0211	-1.1 (-1.9, -0.3)	0.0084	-1.4 (-2.4, -0.4)	0.0072
Cetirizine 10 mg	-0.4 (-0.7, -0.2)	0.0012	-1.6 (-2.4, -0.9)	<0.0001	-2.1 (-3.1, -1.1)	<0.0001

Global Symptom Score: Statistical analysis of global symptom score AUE (0-2h, 2-6h and 0-6h) post-allergen challenge on Day 8 showed significant decreases following ONO-4053 60 mg, ONO-4053 300 mg and cetirizine 10 mg compared with placebo.

Treatment comparisons versus placebo from the ANOVA for global symptom score AUEs in the EFF are summarised below.

Parameter	AUE(0-6h)		AUE(0-2h)		AUE(2-6h)	
(score*h)	Diff. (95% CI)	P-value	Diff. (95% CI)	P-value	Diff. (95% CI)	P-value
Global Symptom Score						
ONO-4053 60 mg	-3.0 (-5.2, -0.9)	0.0067	-11.2 (-16.6, -5.9)	<0.0001	-14.3 (-21.5, -7.1)	0.0001
ONO-4053 300 mg	-2.7 (-4.9, -0.6)	0.0140	-11.4 (-16.8, -6.0)	<0.0001	-14.1 (-21.3, -7.0)	0.0001
Cetirizine 10 mg	-5.8 (-7.9, -3.6)	<0.0001	-15.7 (-21.0, -10.4)	<0.0001	-21.6 (-28.6, -14.5)	<0.0001

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Rhinomanometry results: Statistical analysis of rhinomanometry AUE (0-2h, 2-6h and 0-6h) post-allergen challenge on Day 8 showed no significant differences versus placebo for any of the treatments.

Treatment comparisons versus placebo from the ANOVA for rhinomanometry AUEs in the EFF are summarised below.

Parameter ($3600*cm^3$)	AUE(0-2h)		AUE(2-6h)		AUE(0-6h)	
	Diff. (95% CI)	P-value	Diff. (95% CI)	P-value	Diff. (95% CI)	P-value
Rhinomanometry (sum of left and right)						
ONO-4053 60 mg	54.4 (-31.9, 140.7)	0.2149	96.2 (-41.1, 233.5)	0.1686	150.9 (-54.1, 355.8)	0.1479
ONO-4053 300 mg	76.4 (-9.3, 162.1)	0.0803	74.5 (-61.9, 210.9)	0.2822	148.5 (-55.0, 352.0)	0.1515
Cetirizine 10 mg	22.0 (-62.1, 106.1)	0.6063	-28.7 (-162.6, 105.1)	0.6720	-10.6 (-210.3, 189.1)	0.9167
Rhinomanometry (resistance)						
ONO-4053 60 mg	0.0 (-0.2, 0.3)	0.7705	-0.3 (-0.9, 0.4)	0.4126	-0.2 (-1.1, 0.6)	0.6038
ONO-4053 300 mg	-0.0 (-0.3, 0.2)	0.8257	-0.3 (-0.9, 0.4)	0.4204	-0.3 (-1.1, 0.6)	0.4967
Cetirizine 10 mg	0.1 (-0.2, 0.4)	0.4707	-0.2 (-0.8, 0.5)	0.6055	-0.1 (-0.9, 0.8)	0.8847

Nasal secretion weight: Statistical analysis of nasal secretion weight AUE(0-2h) post-allergen challenge on Day 8 showed significant decreases following ONO-4053 60 mg and cetirizine 10 mg compared with placebo. Statistically significant decreases in nasal secretion weight AUE(2-6h and 0-6h) were observed following ONO-4053 60 mg, ONO-4053 300 mg and cetirizine 10 mg compared with placebo.

Treatment comparisons versus placebo from the ANOVA for nasal secretion weight AUEs in the EFF are summarised below.

Parameter (g*h)	AUE(0-2h)		AUE(2-6h)		AUE(0-6h)	
	Diff. (95% CI)	P-value	Diff. (95% CI)	P-value	Diff. (95% CI)	P-value
Nasal Secretion Weight						
ONO-4053 60 mg	-1.8 (-2.8, -0.8)	0.0004	-3.6 (-5.1, -2.2)	<0.0001	-5.4 (-7.6, -3.3)	<0.0001
ONO-4053 300 mg	-0.7 (-1.7, 0.3)	0.1581	-2.8 (-4.2, -1.3)	0.0002	-3.5 (-5.7, -1.3)	0.0017
Cetirizine 10 mg	-2.3 (-3.3, -1.4)	<0.0001	-3.7 (-5.2, -2.3)	<0.0001	-6.1 (-8.2, -4.0)	<0.0001

Comparisons versus cetirizine: Statistical analysis of the TNSS subscore of nasal obstruction AUE (0-2h, 2-6h and 0-6h) post-allergen challenge on Day 8 showed no significant differences between ONO-4053 60 mg or 300 mg and cetirizine. Adjusted LS mean values for nasal obstruction AUE(2-6h and 0-6h) were numerically lower for ONO-4053 60 mg and 300 mg than for cetirizine, but the p-values for the treatment differences were >0.05. Statistically significant increases in rhinorrhoea AUE(0-2h) were observed following ONO-4053 60 mg and ONO-4053 300 mg compared with cetirizine 10 mg. Statistically significant increases in nasal itching AUE (0-2h, 2-6h and 0-6h) and sneezing AUE (0-2h and 0-6h) were observed following both ONO-4053 dose levels compared with cetirizine. A statistically significant increase in sneezing AUE(2-6h) was seen for ONO-4053 300 mg versus cetirizine.

Treatment comparisons versus cetirizine from the ANOVA for individual TNSS subscore AUEs in the EFF are summarised below.

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Parameter (score*h)	AUE(0-2h)		AUE(2-6h)		AUE(0-6h)	
	Diff. (95% CI)	P-value	Diff. (95% CI)	P-value	Diff. (95% CI)	P-value
TNSS subscore						
Nasal obstruction						
ONO-4053 60 mg	-0.1 (-0.5, 0.4)	0.7841	-0.1 (-1.0, 0.9)	0.9098	-0.1 (-1.4, 1.2)	0.8708
ONO-4053 300 mg	0.1 (-0.3, 0.6)	0.5443	-0.4 (-1.3, 0.5)	0.3686	-0.3 (-1.5, 1.0)	0.6900
Rhinorrhoea						
ONO-4053 60 mg	0.5 (0.1, 0.9)	0.0289	0.1 (-0.8, 1.1)	0.8074	0.6 (-0.7, 1.9)	0.3527
ONO-4053 300 mg	0.6 (0.2, 1.0)	0.0069	0.1 (-0.8, 1.0)	0.8005	0.7 (-0.6, 2.0)	0.2660

Parameter (score*h)	AUE(0-2h)		AUE(2-6h)		AUE(0-6h)	
	Diff. (95% CI)	P-value	Diff. (95% CI)	P-value	Diff. (95% CI)	P-value
TNSS subscore (contd.)						
Nasal Itching						
ONO-4053 60 mg	0.8 (0.4, 1.3)	<0.0001	1.4 (0.5, 2.3)	0.0024	2.2 (1.1, 3.4)	0.0002
ONO-4053 300 mg	0.9 (0.5, 1.3)	<0.0001	1.2 (0.3, 2.0)	0.0082	2.1 (0.9, 3.2)	0.0005
Sneezing						
ONO-4053 60 mg	0.6 (0.2, 0.9)	0.0049	0.8 (-0.1, 1.6)	0.0871	1.3 (0.2, 2.5)	0.0209
ONO-4053 300 mg	0.7 (0.4, 1.1)	0.0001	1.1 (0.3, 2.0)	0.0107	1.9 (0.7, 3.0)	0.0011

Statistical analysis of MASS and TOSS AUE (0-2h, 2-6h and 0-6h) post-allergen challenge on Day 8 showed no significant differences between ONO-4053 and cetirizine overall or for individual symptom subscores.

Treatment comparisons versus cetirizine from the ANOVA for MASS and TOSS AUEs in the EFF are summarised below.

Parameter (score*h)	AUE(0-2h)		AUE(2-6h)		AUE(0-6h)	
	Diff. (95% CI)	P-value	Diff. (95% CI)	P-value	Diff. (95% CI)	P-value
MASS						
ONO-4053 60 mg	0.3 (-0.2, 0.9)	0.2466	0.7 (-0.7, 2.2)	0.3196	1.1 (-0.8, 3.0)	0.2650
ONO-4053 300 mg	0.3 (-0.3, 0.8)	0.3365	0.7 (-0.7, 2.2)	0.3228	1.0 (-0.9, 2.9)	0.2945
Cough						
ONO-4053 60 mg	0.2 (-0.0, 0.4)	0.1234	0.2 (-0.3, 0.7)	0.5064	0.3 (-0.4, 1.0)	0.3330
ONO-4053 300 mg	0.1 (-0.1, 0.3)	0.2021	0.1 (-0.4, 0.7)	0.5800	0.3 (-0.4, 0.9)	0.4198
Itchy Ears						
ONO-4053 60 mg	0.0 (-0.2, 0.2)	0.8081	0.2 (-0.3, 0.8)	0.4277	0.3 (-0.4, 1.0)	0.4720
ONO-4053 300 mg	-0.0 (-0.2, 0.2)	0.8354	0.2 (-0.4, 0.7)	0.5668	0.1 (-0.5, 0.8)	0.6939
Itchy Throat						
ONO-4053 60 mg	0.1 (-0.2, 0.5)	0.3974	0.4 (-0.5, 1.2)	0.3892	0.5 (-0.6, 1.6)	0.3668
ONO-4053 300 mg	0.2 (-0.2, 0.5)	0.3205	0.4 (-0.4, 1.2)	0.2875	0.6 (-0.5, 1.6)	0.2726
TOSS						
ONO-4053 60 mg	0.5 (-0.2, 1.3)	0.1781	1.7 (-0.6, 3.9)	0.1511	2.2 (-0.7, 5.1)	0.1303
ONO-4053 300 mg	0.3 (-0.4, 1.1)	0.4047	1.7 (-0.5, 3.9)	0.1401	2.0 (-0.8, 4.8)	0.1623
Watery Eyes						
ONO-4053 60 mg	0.1 (-0.1, 0.4)	0.3258	0.5 (-0.3, 1.2)	0.2034	0.6 (-0.3, 1.6)	0.2034
ONO-4053 300 mg	0.1 (-0.2, 0.3)	0.5230	0.4 (-0.3, 1.2)	0.2341	0.5 (-0.4, 1.5)	0.2680
Itchy Eyes						
ONO-4053 60 mg	0.3 (-0.1, 0.6)	0.1678	0.7 (-0.2, 1.6)	0.1286	1.0 (-0.2, 2.2)	0.1081

ONO-4053 300 mg	0.1 (-0.2, 0.5)	0.5157	0.6 (-0.2, 1.5)	0.1566	0.8 (-0.4, 1.9)	0.1912
Red Eyes						
ONO-4053 60 mg	0.2 (-0.1, 0.4)	0.2715	0.5 (-0.3, 1.3)	0.2567	0.6 (-0.4, 1.6)	0.2111
ONO-4053 300 mg	0.1 (-0.1, 0.4)	0.3482	0.6 (-0.2, 1.4)	0.1461	0.7 (-0.3, 1.7)	0.1506

Statistical analysis of global symptom score AUE(0-2h and 0-6h) post-allergen challenge on Day 8 showed significant increases following both ONO-4053 dose levels compared with cetirizine.

Treatment comparisons versus cetirizine from the ANOVA for global symptom score AUEs in the EFF are summarised below.

Parameter	AUE(0-2h)		AUE(2-6h)		AUE(0-6h)	
(score*h)	Diff. (95% CI)	P-value	Diff. (95% CI)	P-value	Diff. (95% CI)	P-value
Global Symptom Score						
ONO-4053 60 mg	2.7 (0.6, 4.9)	0.0137	4.5 (-0.9, 9.8)	0.1040	7.3 (0.1, 14.5)	0.0469
ONO-4053 300 mg	3.0 (0.9, 5.2)	0.0051	4.3 (-0.9, 9.6)	0.1067	7.4 (0.4, 14.4)	0.0382

Statistical analysis of rhinomanometry AUE (0-2h, 2-6h and 0-6h) post-allergen challenge on Day 8 showed no significant differences compared with cetirizine.

Treatment comparisons versus cetirizine from the ANOVA for rhinomanometry AUEs in the EFF are summarised below.

Parameter	AUE(0-2h)		AUE(2-6h)		AUE(0-6h)	
($3600*cm^3$)	Diff. (95% CI)	P-value	Diff. (95% CI)	P-value	Diff. (95% CI)	P-value
Rhinomanometry (sum of left and right)						
ONO-4053 60 mg	32.4 (-54.0, 118.8)	0.4596	124.9 (-12.5, 262.3)	0.0745	161.5 (-43.7, 366.6)	0.1220
ONO-4053 300 mg	54.4 (-28.9, 137.7)	0.1991	103.3 (-29.3, 235.8)	0.1260	159.1 (-38.7, 356.9)	0.1141
Rhinomanometry (resistance)						
ONO-4053 60 mg	-0.1 (-0.3, 0.2)	0.6793	-0.1 (-0.8, 0.6)	0.7530	-0.2 (-1.0, 0.7)	0.7060
ONO-4053 300 mg	-0.1 (-0.4, 0.1)	0.3405	-0.1 (-0.7, 0.5)	0.7593	-0.2 (-1.1, 0.6)	0.5810

Statistical analysis of nasal secretion weight AUE (0-2h, 2-6h and 0-6h) post-allergen challenge on Day 8 showed no significant differences between ONO-4053 60 mg and cetirizine 10 mg. Statistically significant increases in nasal secretion weight AUE(0-2h and 0-6h) were observed following ONO-4053 300 mg compared with cetirizine.

Treatment comparisons versus cetirizine from the ANOVA for nasal secretion weight AUEs in the EFF are summarised below.

Parameter	AUE(0-2h)		AUE(2-6h)		AUE(0-6h)	
(g*h)	Diff. (95% CI)	P-value	Diff. (95% CI)	P-value	Diff. (95% CI)	P-value
Nasal Secretion Weight						
ONO-4053 60 mg	0.6 (-0.4, 1.5)	0.2651	0.1 (-1.3, 1.5)	0.8773	0.7 (-1.5, 2.8)	0.5353
ONO-4053 300 mg	1.6 (0.7, 2.6)	0.0008	1.0 (-0.4, 2.4)	0.1713	2.6 (0.5, 4.7)	0.0148

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Pharmacokinetic Results:

Mean Day 8 plasma ONO-4053 concentrations in the PAS are summarised below.

Plasma ONO-4053 Concentration (ng/mL)	Placebo (N=38)	ONO-4053 60 mg (N=38)	ONO-4053 300 mg (N=41)	Cetirizine 10 mg (N=38)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
n	50	56	56	52
Pre-dose on Day 8	<LLOQ (0.00)	409.7 (272.40)	2251.8 (1937.15)	<LLOQ (0.00)
6 h post-dose on Day 8	<LLOQ (0.00)	1787.6 (630.63)	7531.8 (2723.07)	<LLOQ (0.00)

SD=standard deviation; LLOQ=lower limit of quantification.

Safety Results:

A risk-benefit assessment indicated no known subject safety concern arising from the misassignment of treatment considering that cumulative exposure to ONO-4053 was greater than expected in some subjects. Exposure to study medication was as follows: 41 subjects received placebo, 38 subjects ONO-4053 60 mg, 41 subjects ONO-4053 300 mg and 41 subjects cetirizine 10 mg once daily for 8 days. Because of the misassignment of treatment, 54 subjects received the same treatment in more than one period and only two subjects received all four treatments. Two subjects received ONO-4053 300 mg three times in three separate periods, and 11 further subjects received this regimen twice. Mean [range] cumulative exposure was 2940 [480–7200] mg for total ONO-4053 and 111 [80–240] mg for cetirizine.

Thirty-five treatment-emergent AEs (TEAEs) were reported in 20 subjects (34%). The most frequently reported TEAE was nasopharyngitis, with 12 AEs reported in 10 subjects (17%). Gastrointestinal disorders were reported in a greater percentage of subjects following ONO-4053 60 mg dosing (three subjects, 8%) than with other treatment regimens (two subjects who received placebo [5%], and one subject each following ONO-4053 300 mg and cetirizine 10 mg [2%]). Most of the AEs were of mild or moderate intensity. There were two AEs of severe intensity in two subjects: headache and upper abdominal pain, both following ONO-4053 60 mg. Both of these AEs were considered possibly related to study medication by the Investigator. In addition to the AEs of severe intensity, two other drug-related AE were reported: abdominal pain following placebo and headache following ONO-4053 60 mg. All AEs had resolved by the end of the study. No serious adverse events (SAEs) or premature study discontinuations due to AEs were reported. All TEAEs are summarised in the table below.

Adverse event	Placebo (N=41)	ONO-4053 60 mg (N=38)	ONO-4053 300 mg (N=41)	Cetirizine 10 mg (N=41)	Total (N=58)
	n (%)	n (%)	n (%)	n (%)	n (%)
Any AE	7 (17.1)	8 (21.1)	4 (9.8)	6 (14.6)	20 (34.5)
Nasopharyngitis	4 (9.8)	2 (5.3)	3 (7.3)	2 (4.9)	10 (17.2)
Headache	1 (2.4)	3 (7.9)	1 (2.4)	2 (4.9)	6 (10.3)
Oropharyngeal pain	0	1 (2.6)	1 (2.4)	0	2 (3.4)
Vomiting	0	1 (2.6)	0	1 (2.4)	2 (3.4)
Abdominal pain	1 (2.4)	0	0	0	1 (1.7)
Abdominal pain upper	0	1 (2.6)	0	0	1 (1.7)
Flatulence	1 (2.4)	0	0	0	1 (1.7)

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Gastritis	0	1 (2.6)	0	0	1 (1.7)
Nausea	0	0	1 (2.4)	0	1 (1.7)
Pyrexia	0	1 (2.6)	0	0	1 (1.7)
Dysmenorrhoea	0	0	1 (2.4)	1 (2.4)	1 (1.7)
Cough	0	0	0	1 (2.4)	1 (1.7)

No clinically significant vital signs, ECG, physical examination, safety laboratory or lung function test findings were reported. No QTcB or QTcF values >480 msec or changes from baseline >60 msec were reported.

Conclusions:

ONO-4053 demonstrated clinical efficacy at both the 60 mg and 300 mg dose levels in this model of SAR. Alleviation of symptoms compared with placebo was observed for TNSS scores over 0-2 h, 2-6 h and 0-6 h post-allergen challenge and for all TNSS subscores over 2-6 h and 0-6 h post-challenge. ONO-4053 also reduced TOSS, global symptom score and nasal secretion weight compared with placebo. The active comparator cetirizine showed clinical efficacy as expected. Cetirizine demonstrated greater symptom decreases than ONO-4053 on the TNSS over 0-2 h (both dose levels) and 0-6 h (300 mg only) post-allergen challenge; no difference was observed between cetirizine and ONO-4053 for TNSS over 2-6 h (both dose levels) or 0-6 h (60 mg only). No statistically significant improvements compared with placebo were observed in nasal airflow as measured by rhinomanometry following ONO-4053 or cetirizine administration, although a trend for increased nasal airflow was observed with ONO-4053 300 mg compared with ONO-4053 60 mg and cetirizine.

ONO-4053 was well tolerated following repeat dose oral administration (60 mg and 300 mg once daily for 8 days) in subjects with SAR.

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