SYNOPSIS

Name of Sponsor/Company: RespiVert Ltd	Individual Study Table Referring to Part of the Dossier	(*For National Authority Use Only*)
Name of Finished Product: RV568	Volume:	
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Title of Study: A two day, randomised, single blind, parallel group trial of repeat doses of intranasal RV568 in the Vienna Challenge Chamber in subjects with seasonal allergic rhinitis (SAR).	
Investigator: Prof Friedrich Horak, MD.	
Study Centre: Vienna Challenge Chamber, Institute for Allergy Research, Hütteldorferstr. 44, 1150 Vienna, Austria.	
Publication (reference): None at the time of report writing.	
Studied period (years): Date of first enrolment: 18-OCT-2010 Date of last completed: 29-NOV-2010	Phase of Development: Phase IIa

Objectives:

Primary Objective:

- To investigate the effect of repeat intranasal doses of RV568 vs. placebo on nasal symptoms of allergic rhinitis provoked by spending 6 hours (h) in the Vienna Challenge Chamber after morning dosing on Day 2.

Secondary Objectives:

- To explore the effects of repeat doses of RV568 vs. placebo on eye and global symptoms, nasal obstruction and secretions in allergic rhinitis provoked by spending 6 h in the Vienna Challenge Chamber post morning dose on Day 2.
- To assess the safety and tolerability of RV568 in mild to moderate allergic rhinitic subjects.

Methodology: This was a randomised, single-blind, placebo-controlled, parallel group, repeat dose study. Subjects were randomised to receive one of the following intranasal treatments:

- RV568 – Day 1, 400 μg twice daily; Day 2, 800 μg single dose.
- Placebo – Day 1, 200 μL twice daily; Day 2, 400 μL single dose.

Within 1 h after dosing on Day 2 subjects entered the Challenge Chamber and were exposed to allergen for a period of 6 h.

Number of subjects (planned and analysed): A minimum of 70 and up to 90 subjects were planned. Seventy-five subjects were enrolled: 33 were randomised to receive placebo and 42 were randomised to receive RV568 800 μg. All 75 subjects completed the study and all 75 were included in the Safety and modified Intent-to-Treat (ITT) populations.

Diagnosis and main criteria for inclusion: Non-smoking male subjects with seasonal allergic rhinitis (otherwise healthy) aged 18–55 years, inclusive, with a 4 h Challenge Chamber grass pollen nasal symptom score ≥6. Subjects were required to have a baseline forced expiratory volume over 1 second (FEV_1) ≥80% and FEV_1/forced vital capacity (FVC) ≥70% of predicted.

Test product, dose and mode of administration, batch number: RV568 suspension, unit dose strength 2.0 mg/mL (RX50584.013). Placebo solution (RX50584.014).

Duration of treatment: 2 days.

Criteria for evaluation: The primary study endpoint was weighted mean total nasal symptom score (TNSS) (congestion, rhinorrhoea, nasal itching and sneezing) over 1–6 h on Day 2.

Secondary endpoints were as follows:

- Weighted mean eye symptom score (watery eyes, itchy eyes, red eyes) over 1–6 h on Day 2.
- Weighted mean global symptom score (congestion, rhinorrhoea, nasal itching, sneezing, watery eyes, itchy

eyes, red eyes, cough, itchy throat and itchy ears) over 1–6 h on Day 2.

- Weighted mean nasal airflow (measured using active anterior rhinomanometry) and secretion weight (measured by weighing tissues) over 1–6 h on Day 2.
- Weighted mean components of TNSS (congestion, rhinorrhoea, nasal itching and sneezing) over 1–6 h on Day 2.
- Safety parameters: lung function parameters (FEV_1); adverse events (AEs); 12-lead electrocardiogram (ECG) parameters; clinical laboratory evaluations (haematology, clinical chemistry, urinalysis).

Exploratory endpoints comprised inhibition of cytokines in nasal tissue samples (interleukin [IL]-8, IL-6, IL-1β, IL-13).

Statistical Methods: A sample size of 45 subjects per treatment arm would provide 80% power to detect a difference in TNSS weighted mean of 1.5 at a 0.05 level (two- sided). The primary analysis used two sample t-tests to compare weighted mean TNSS (1–6 h) between treatment groups. Nominal p-value, standard error (SE) and 95% confidence intervals (CIs) for treatment difference (Diff) were reported. The following sensitivity analyses were performed: complete case analysis (only subjects who had non-missing TNSS at all planned time points); nonparametric analysis (Wilcoxon's Rank Sum test, included all subjects in primary analysis); and baseline adjusted analysis (analysis of covariance model: adjusted least square means and 95% CIs were reported). Secondary efficacy analyses comprised subgroup analysis of TNSS weighted mean, similar to the primary analysis, based on age and baseline TNSS. Eye, global and individual symptom scores were also analysed. All of the above efficacy analyses used the modified ITT population. Safety data were summarised descriptively for the Safety population. Pharmacodynamic data were summarised descriptively for the modified ITT population.

Summary – Conclusions:

Efficacy Results: Statistical analysis of weighted mean TNSS (1–6 h) post-allergen challenge on Day 2 showed no statistically significant difference between RV568 800 μg and placebo: p-values for the treatment difference were greater than 0.05 for the primary, complete case, non-parametric and baseline adjusted analyses.

Analysis	Placebo (N=33)		RV568 800 μg (N=42)		RV568–Placebo			
	n	Estimate[1]	n	Estimate[1]	Diff	SE	95% CI	p-value
Primary analysis	33	6.34	42	6.22	-0.12	0.472	-1.06, 0.83	0.8058
Complete case analysis	33	6.34	42	6.22	-0.12	0.472	-1.06, 0.83	0.8058
Non-parametric analysis	33	6.00	42	6.76	0.77	-	-	0.8900
Baseline adjusted analysis	33	6.34	42	6.22	-0.12	0.476	-1.06, 0.83	0.8072

1. Mean for primary analysis and complete case analysis; median for non-parametric analysis; adjusted least squares means for baseline adjusted analysis. Unit is score/h.

Statistical analysis of subgroups for weighted mean TNSS (1–6 h) post-allergen challenge on Day 2 (score/h) showed no statistically significant difference between RV568 800 μg and placebo when analysed by age and by baseline TNSS.

Subgroup	Placebo (N=33)		RV568 800 μg (N=42)		RV568–Placebo			
	n	Mean	n	Mean	Diff	SE	95% CI	p-value
≤ median age	17	6.01	26	6.04	0.03	0.616	-1.21, 1.28	0.9570
> median age	16	6.70	16	6.52	-0.17	0.750	-1.70, 1.36	0.8199
≤ median baseline TNSS	22	6.50	26	6.29	-0.21	0.553	-1.32, 0.90	0.7048
> median baseline TNSS	11	6.03	16	6.13	0.09	.899	-1.76,1.95	0.9171

Statistical analysis of weighted mean (1–6 h) eye, global and individual symptom scores post-allergen challenge on Day 2 (score/h) showed no statistically significant difference between RV568 800 μg and placebo: p-values for the treatment difference were greater than 0.05 for each of the parameters.

Symptom score parameter	Placebo (N=33)		RV568 800 μg (N=42)		RV568–Placebo			
	n	Mean	n	Mean	Diff	SE	95% CI	p-value
Eye symptom score	33	1.52	42	1.69	0.18	0.381	-0.58, 0.94	0.6473
Global symptom score	33	8.56	42	8.79	0.22	0.845	-1.46, 1.91	0.7936
Congestion symptom score	33	1.68	42	1.74	0.06	0.126	-0.20, 0.31	0.6593
Rhinorrhoea symptom score	33	1.65	42	1.70	0.05	0.127	-0.20, 0.30	0.7043
Nasal itching symptom score	33	1.63	42	1.45	-0.19	0.163	-0.51, 0.14	0.2524
Sneezing symptom score	33	1.37	42	1.34	-0.03	0.143	-0.32, 0.25	0.8174

Weighted mean (1–6 h) nasal airflow and nasal secretion weight post-allergen challenge on Day 2 showed no statistically significant difference between RV568 800 μg and placebo.

Parameter	Placebo (N=33)		RV568 800 μg (N=42)		RV568–Placebo			
	n	Mean	n	Mean	Diff	SE	95% CI	p-value
Mean nasal airflow (units/h)	33	137.85	42	126.29	-11.57	12.688	-36.85, 13.72	0.3650
Secretion weight (g/h)	33	2.27	42	2.27	-0.01	0.349	-0.70, 0.69	0.9855

Safety Results: RV568 was well tolerated following repeated intranasal dosing for 2 days (400 μg twice daily on Day 1 and 800 μg single dose on Day 2). There were no serious adverse events and no AEs leading to withdrawal. The numbers of subjects with treatment-emergent AEs (TEAEs) are summarised below.

System organ class	Preferred term	Placebo (N=33)	RV568 800 μg (N=42)
Number of subjects with TEAEs n (%)		5 (15.2)	5 (11.9)
Number of subjects with drug-related TEAEs n (%)		4 (12.1)	4 (9.5)
All TEAEs irrespective of causality n (%):			
Nervous system disorders	Total number of subjects	1 (3.0)	4 (9.5)
	Dizziness	1 (3.0)	1 (2.4)
	Headache	0	3 (7.1)
Respiratory, thoracic and mediastinal disorders	Total number of subjects	3 (9.1)	1 (2.4)
	Nasal discomfort	2 (6.1)	0
	Nasal dryness	1 (3.0)	0
	Oropharyngeal pain	0	1 (2.4)
General disorders and administration site conditions	Total number of subjects	1 (3.0)	0
	Fatigue	1 (3.0)	0
Infections and infestations	Total number of subjects	1 (3.0)	0
	Nasopharyngitis	1 (3.0)	0

No clinically significant ECG, vital signs or safety laboratory values were reported. There were no notable differences between placebo and RV568 for mean ECG interval, vital signs or laboratory values. There were no notable differences between placebo and RV568 with regard to the number of subjects with laboratory abnormalities. There was no evidence of a difference between RV568 and placebo with regard to FEV_1 or visual nasal assessment.

Study Number: RVH002	**Document No.:** RV2011-SR002/00
	Compound No.: RV568
Clinical Study Report	Version: Final

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Pharmacodynamic Results:

Summary statistics for pharmacodynamic parameters are presented in the table below.

Parameter	Placebo (N=33)			RV568 800 μg (N=42)		
	n	Mean	SD	n	Mean	SD
IL-8 (RFC)	33	0.696	(0.687)	42	0.649	(0.633)
IL-1β (RFC)	33	0.248	(0.354)	42	0.477	(0.942)
IL-6 (RFC)	33	0.0024	(0.0035)	42	0.0025	(0.0039)
IL-13 (RFC)	33	0.026	(0.071)	42	0.067	(0.179)
MUC5AC (RFC)	33	5.904	(9.336)	42	4.115	(4.637)
CCL5 (RFC)	33	0.184	(0.164)	42	0.184	(0.213)

MUC5AC = mucin 5, subtypes A and C; CCL5 = chemokine (C-C motif) ligand 5; RFC = relative fold change vs. housekeeping gene, GNB2L1.

Conclusions: Intranasal RV568 800 μg administered for 2 days did not demonstrate clinical efficacy in this model of seasonal allergic rhinitis. No alleviation of symptoms was observed compared with the placebo group for TNSS scores, eye, global or individual symptom scores over 1 to 6 h post-allergen challenge. There was no evidence of a difference between RV568 and placebo for nasal airflow or nasal secretion weights.

RV568 was well tolerated following intranasal repeat dose administration (400 μg twice on Day 1 and 800 μg once on Day 2) in male subjects with seasonal allergic rhinitis.

RV568 did not show any significant inhibitory effects on IL-1β, IL-6, IL-8, IL-13, MUC5AC and CCL5 gene expression in *ex vivo* nasal scrape samples compared with placebo.

Date of the Report: 27-APR-2011.