RespiVert Ltd

Clinical Study Report

A randomised, double-blind, placebo-controlled, parallel group study to evaluate the safety and tolerability of treatment with repeat doses of inhaled RV568 in patients with COPD

Protocol RVH006; Phase 2a

RV568

EudraCT Number: 2011-004031-31

PRINCIPAL INVESTIGATOR: Leonard Siew, MB ChB

SPONSOR'S RESPONSIBLE MEDICAL OFFICER: William Garth Rapeport, MB, BCh

DATE STUDY INITIATED: 09 January 2012

DATE STUDY COMPLETED: 24 April 2012

Status: Approved
Date: 29 January 2013
Prepared by: Niche Science & Technology Ltd.

GCP Compliance: This study was conducted in compliance with Good Clinical Practice, including the archival of essential documents.

SYNOPSIS

Name of Sponsor/Company	RespiVert Ltd
Name of Finished Product	To be determined
Name of Active Ingredient(s)	RV568

Status: Approved

Date: 29 January 2013

Prepared by: Niche Science & Technology Ltd.

Protocol No.: RVH006

Title of Study: A randomised, double-blind, placebo-controlled, parallel group study to evaluate the safety and tolerability of treatment with repeat doses of inhaled RV568 in patients with COPD

EudraCT Number: 2011-004031-31

NCT No.: NCT01475292

Clinical Registry No.: 2011-004031-31

Principal Investigators: Leonard Siew, MB ChB, Quintiles Drug Research Unit at Guy's Hospital, London, United Kingdom (UK). S. Dave Singh, MD, Medicines Evaluation Unit (MEU), Manchester, UK.

Study Centres: Two centres in the UK (subjects were recruited at MEU only).

Publication (Reference): None at the time of this report.

Study Period: 09-Jan-2012 to 24-Apr-2012.

Phase of Development: 2a

Objectives: The primary objective was to evaluate the safety and tolerability of repeat inhaled doses of RV568 for 14 days in subjects with moderate to severe stable chronic obstructive pulmonary disease (COPD).

Secondary objectives:

- To characterise the pharmacokinetic parameters of RV568 following repeat administration of inhaled RV568 for 14 days in subjects with moderate to severe stable COPD
- To evaluate the effect of treatment with repeat inhaled doses of RV568 for 14 days on pharmacodynamic markers (plethysmography) in patients with moderate to severe COPD

Exploratory objectives:

- To evaluate the effect of treatment with repeat inhaled doses of RV568 for 14 days on markers of inflammation in induced sputum and sputum cells
- To evaluate the effect of treatment with repeat inhaled doses of RV568 for 14 days on exploratory markers of inflammation in serum

Methodology: This was a Phase IIa randomised, double-blind, parallel-group study that evaluated RV568 in subjects with moderate to severe, stable COPD, as defined by the 'Global initiative for chronic

obstructive lung disease' guidelines. Subjects were randomised (using a 1:1:1 ratio) to receive one of the following three nebulised inhaled treatments:

- RV568 50 µg once daily for 14 days
- RV568 100 µg once daily for 14 days
- Placebo once daily for 14 days

Number of Subjects (planned and analysed): Thirty subjects were randomised, as planned: 10 subjects in the placebo group, 10 in the RV568 50 µg group and 10 in the RV568 100 µg group. All 30 subjects were included in the Safety population.

Diagnosis and Main Criteria for Inclusion: Male or female (aged 40–75 years) current or previous smokers with a diagnosis of COPD of at least 1 year. Subjects were required to have a baseline post-salbutamol forced expiratory volume over 1 second (FEV_1) ≥40 % and ≤80 % of predicted and a FEV_1/ forced vital capacity (FVC) ratio of ≤0.70.

Test Product, Dose and Mode of Administration, Batch No.: RV568 suspension, unit dose strength 0.4 mg/mL (RX50584.18).

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo solution (RX50584.015).

Duration of Treatment: 14 days.

Criteria for Evaluation: Primary endpoints were as follows:

- Adverse events (AEs)
- Twelve-lead electrocardiogram (ECG) parameters on Day 1 and Day 14
- Clinical laboratory evaluations (haematology, clinical chemistry, urinalysis) on Day 1 and Day 14
- Lung function parameters on Days 1, 2, 4, 7, 9, 12 and 14
- Mucus and cough monitoring
- Withdrawals for worsening COPD

Statistical Methods: No formal hypothesis testing was performed. Descriptive statistics (e.g., mean, median, standard deviation, coefficient of variation) were used to summarise the key data. *Post-hoc* analyses of FEV_1 and sputum biomarker data were conducted using analysis of covariance.

RESULTS:

STUDY POPULATION:

- Twenty-eight of 30 subjects completed the study as planned. Two subjects were withdrawn from the study, one subject after 6 days of RV568 50 µg dosing following a physician decision (due to a decrease in FEV_1) and one subject following 1 day of RV568 100 µg dosing after meeting the withdrawal criteria on FEV_1
- Subject demographic characteristics were similar in the placebo and RV568 groups except gender, weight and height. The differences in weight and height were considered not to affect the results of the study; median body mass index (BMI) was similar between the groups. Demographic characteristics were as follows:
  - Men and women were included in equal numbers overall, although there were more men in the placebo group than in the RV568 groups
  - Most subjects were White (96.7%)

- The median age was 63 years
- Median BMI was similar across treatment groups at 26.8 kg/m^2

- Baseline pulmonary function test results are summarised in the table below:

Summary of Baseline Characteristics (Study RVH006: Safety Population)

	Placebo N=10	RV568 50 µg N=10	RV568 100 µg N=10
Post-bronchodilator FEV_1 (% predicted)			
Mean (Standard deviation)	67 (10)	65 (9)	62 (11)
Median (Range)	67 (49–81[a])	65 (49–80)	60 (46–79)
Post-bronchodilator FEV_1/FVC ratio (%)			
Mean (Standard deviation)	52.2 (10.2)	49.2 (12.5)	48.1 (11.6)
Median (Range)	52.5 (35.8–66.1)	50.6 (25.7–65.0)	47.1 (31.3–68.0)

[a] One subject had a screening FEV_1 >80% predicted (81%), and a repeat screening visit was conducted (repeat value was 78%).

- Thirty subjects received study medication: 10 subjects received once daily doses of placebo, 10 subjects once daily doses of RV568 50 µg (nine subjects for 14 days and one subject for 6 days prior to withdrawal), and 10 subjects once daily dose(s) of RV568 100 µg (nine subjects for 14 days and one subject for 1 day prior to withdrawal)

SAFETY RESULTS:

There were no AEs leading to discontinuation of treatment or withdrawal from the study. There were no deaths. One subject in the placebo group had an exacerbation of COPD that resulted in hospitalisation and was classed as a serious adverse event (SAE). The onset of the SAE was on Day 28, 14 days after the last dose of study medication, and the event did not result in withdrawal. The event had a duration of 21 days, was moderate in intensity, and had resolved by the end of the study. The Investigator considered the SAE to have a possible relationship to study medication.

A summary of AEs reported in more than one subject is presented in the table below.

Summary of TEAEs Reported in More Than One Subject (Study RVH006: Safety Population)

System Organ Class	Preferred Term	Placebo (N=10) n (%)	RV568 50 µg (N=10) n (%)	RV568 100 µg (N=10) n (%)	All RV568-Treated Subjects (N=20) n (%)
Number of subjects with TEAEs		6 (60)	8 (80)	8 (80)	16 (80)
Gastrointestinal disorders					
	Toothache	0	1 (10)	1 (10)	2 (10)
General disorders and administration site conditions					
	Catheter site haematoma	0	0	2 (20)	2 (10)
	Chest discomfort	1 (10)	1 (10)	0	1 (5)
Infections and infestations					
	Oral herpes	0	1 (10)	1 (10)	2 (10)
Musculoskeletal and connective tissue disorders					
	Arthralgia	0	1 (10)	1 (10)	2 (10)
	Back pain	1 (10)	0	2 (20)	2 (10)
Nervous system disorders					
	Headache	2 (20)	3 (30)	3 (30)	6 (30)
	Dizziness	0	2 (20)	2 (20)	4 (20)
Respiratory, thoracic and mediastinal disorders					
	Cough	2 (20)	5 (50)	2 (20)	7 (35)
	Rhinorrhoea	0	2 (20)	1 (10)	3 (15)
	Chronic obstructive pulmonary disease	3 (30)	1 (10)	1 (10)	2 (10)

Notes: TEAE=Treatment-emergent adverse event. A subject experiencing multiple occurrences of an adverse event was counted, at most, once per system organ class and preferred term.

There were no clinically significant clinical laboratory, vital signs or ECG abnormalities. Mucus and cough monitoring raised no safety concerns.

In the *post-hoc* statistical analysis of Day 14 change from baseline FEV_1 data (n=28 subjects who completed 14 days of dosing), RV568 treatment resulted in a statistically significant ($p<0.05$) increase in pre-bronchodilator FEV_1 (50 µg and 100 µg dose groups) and post-bronchodilator FEV_1 (50 µg group only) compared with placebo.

Two subjects were withdrawn from the study after meeting the withdrawal criteria on FEV_1. The first subject was withdrawn following 1 day of RV568 100 µg administration; no AEs were reported for this subject. The second subject was withdrawn from the study following a physician decision after 6 days of RV568 50 µg treatment. The investigator site confirmed that the stopping criterion of decrease in FEV_1 by more than 20% from baseline had been met. The subject also had flu-like symptoms. This subject went on to have a COPD exacerbation that was considered possibly related to study medication by the Investigator. The exacerbation resolved on treatment with concomitant medication.

EFFICACY RESULTS: Per protocol, no efficacy measures were assessed in this study.

PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS:

Pharmacokinetics summary

- Pharmacokinetic parameters of RV568 following single (Day 1) and repeated (Day 14) inhaled doses of RV568 to subjects are presented in the tables below
- The apparent shorter half-lives after single dosing (compared with repeat dosing) were most probably due to plasma concentrations in the terminal phase falling below the limit of quantification; however, estimation of apparent terminal half-lives was considered to be unreliable on both Days 1

and 14 because the period over which half-lives were calculated was less than two-fold the half-life itself

Summary of Pharmacokinetic Parameters on Day 1 (Study RVH006: Pharmacokinetic Population)

Pharmacokinetic Parameters	Geometric Mean (CV (%))	
	RV568 50 µg dose (N=10)	RV568 100 µg dose (N=10)
t_{max} [a] (h)	0.330 (0.270, 0.370)	0.360 (0.300, 0.770)
C_{max} (pg/mL)	50.4 (61.4)	67.2 (62.7)
$AUC_{0-\tau}$ (pg.h/mL)	85.4 (95.0)	149 (52.2)
$AUC_{0-\infty}$ (pg.h/mL)	131 (69.2)	195 (49.8)
$t_{1/2}$ (h)	4.07 (50.4)	5.02 (67.1)

[a] Presented as median and range.

CV=coefficient of variation; t_{max}=time to maximum observed plasma concentration; Cmax=maximum observed plasma concentration; $AUC_{0-\tau}$=area under the concentration-time curve over the dosing interval; $AUC_{0-\infty}$=AUC from time zero extrapolated to infinity; $t_{1/2}$=apparent terminal half-life.

Summary of Pharmacokinetic Parameters on Day 14 (Study RVH006: Pharmacokinetic Population)

Pharmacokinetic Parameters	Geometric Mean (CV (%))	
	RV568 50 µg dose (N=9)	RV568 100 µg dose (N=9)
t_{max} [a] (h)	0.350 (0.280, 0.730)	0.330 (0.300, 0.400)
C_{max} (pg/mL)	49.3 (52.6)	72.6 (53.3)
$AUC_{0-\tau}$ (pg.h/mL)	190 (91.3)	278 (48.5)
$t_{1/2}$ (h)	22.6 (64.2)	18.9 (82.2)
R_o	2.31 (81.7)	1.72 (27.9)

[a] Presented as median and range.

CV=coefficient of variation; t_{max}=time to maximum observed plasma concentration; Cmax=maximum observed plasma concentration; $AUC_{0-\tau}$=area under the concentration-time curve over the dosing interval; $t_{1/2}$= apparent terminal half-life; R_o=observed extent of accumulation in plasma.

- Following single and repeated inhaled doses of 50 or 100 µg RV568, systemic exposure (area under the curve from time zero to time of last quantifiable concentration [AUC_{0-t}] and maximum observed plasma concentration [C_{max}]) in female subjects was not appreciably different to that in males. The between-subject variability in systemic exposure to RV568 in males and females was generally high with coefficients of variation of geometric mean C_{max} and AUC over the dosing interval ($AUC_{0-\tau}$) of 48.5 to 95.0 %
- The extent of systemic exposure to RV568 (C_{max} and AUC_{0-t}) increased with a doubling in dose; however, the increase was less than dose proportional. The exponent of the power model was less than unity (0.415 to 0.844). For a doubling in dose, C_{max} and AUC_{0-t} were predicted to increase 1.33- to 1.79-fold based on the estimate of the exponent of the power model. The 95% confidence interval of the estimate included unity indicating that the non-proportionality was not statistically significant; however, the confidence intervals were wide, consistent with high between-subject variability in systemic exposure to RV568
- The extent of systemic exposure to RV568 (AUC_{0-24h}) on Day 14 was, on average, 2.31- and 1.72-fold greater than that on Day 1 at 50 µg and 100 µg RV568, respectively. This extent of accumulation in plasma (R_O) is consistent with an effective half-life of 19 to 29 hours; i.e., not appreciably different to the estimated half-lives after repeated dosing (i.e., 18.9 to 22.6 hours)
- The value of the effective half-life indicated that >95% of steady state would be reached in the order of 6 days; visual inspection of pre-dose concentrations of RV568 indicated that steady state appeared to be reached by 7 days of dosing. The observed extent of accumulation of RV568 in plasma, and apparent time to reach steady state, was consistent with linear, time-invariant kinetics of RV568

Pharmacodynamics summary

- Whole body plethysmography data suggested no consistent treatment-related changes in lung volumes. In the placebo group, there was a modest increase in both FRC (0.24 L) and RV (0.11 L) but no change in TLC after 14 days of treatment compared with baseline. As a result, IC was slightly decreased (0.16 L). For the RV568 50 µg group, there was no change in FRC but an increase in TLC (0.27 L), resulting in an increase in IC (0.14 L). Mean RV was also slightly increased in this group (0.29 L). For the RV568 100 µg group, there was no change in FRC or TLC and as a result, there was no change in IC. There was a minor decrease in RV in the 100 µg group (0.12 L)
- In 17 paired induced sputum samples, RV568 treatment resulted in a statistically significant ($p<0.05$) decrease in malondialdehyde (MDA; both dose groups) and matrix metalloproteinase 1 (MMP1; 50 µg group only) levels in supernatant on Day 14 compared with pre-treatment levels
- In serum, RV568 treatment resulted in a statistically significant ($p<0.05$) reduction of myeloperoxidase (MPO; for both doses) and macrophage inflammatory protein (MIP-1β; 100 µg only) on Day 14 compared with pre-treatment levels. However, decreases from baseline were also observed in the placebo group; therefore, it cannot be concluded that RV568 caused the reduction
- In a *post-hoc* statistical analysis, RV568 treatment resulted in a statistically significant ($p<0.05$) decrease in Day 14 sputum MDA levels (50 µg and 100 µg dose groups) compared with placebo
- Biomarker gene expression analysis of sputum cell RNA showed no apparent significant differential effect of RV568 compared with placebo

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

CONCLUSIONS:

- RV568 was well tolerated in the COPD population at both doses tested with no clinically meaningful differences in safety between the 50 µg and 100 µg dose groups
- There was no evidence of a post-treatment change in mucus production in the placebo or RV568 groups
- *Post-hoc* analysis of Day 14 change from baseline FEV_1 data showed a statistically significant ($p<0.05$) increase in pre-bronchodilator FEV_1 (RV568 50 µg and 100 µg dose groups) and post-bronchodilator FEV_1 (50 µg group only) compared with placebo in completed subjects
- The observed extent of accumulation of RV568 in plasma, and apparent time to reach steady state, were consistent with linear, time-invariant kinetics of RV568
- There were no consistent treatment-related changes in lung volume parameters, measured by whole body plethysmography
- There was evidence of a reduction in sputum MDA and MMP1, and in serum MPO and MIP-1β after RV568 dosing compared with pre-treatment, although reductions in serum MPO and MIP-1β were also seen in the placebo group. A *post-hoc* statistical analysis showed a statistically significant ($p<0.05$) decrease in Day 14 sputum MDA levels in RV568 50 µg and 100 µg dose groups compared with placebo.