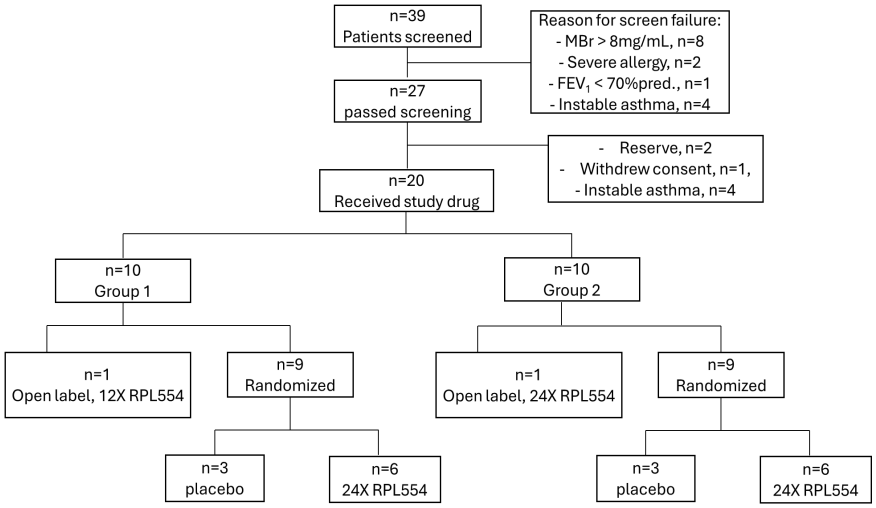
Summary of Study Results

Sponsor	Verona Pharma plc
Protocol number	2010-021349-36
Title	Randomised, double-blind, placebo-controlled evaluation of the safety and duration of action of 2 single inhaled doses, 0.036 mg/kg (12X) and 0.072 mg/kg (24X), of RPL554, a dual PDE-3/4 inhibitor, in allergic asthmatics
Study start/end dates	11 November 2010 to 6 January 2011
Study design /Methodology	This was a single-centre trial. The study used a randomised, double-blind, placebo-controlled design assessing the safety of single inhaled doses of RPL554 0.036 mg/kg (12X) and, subsequently, if safe, RPL554 0.072 mg/kg (24X) in clinically stable allergic asthmatics, not on controller medication. This study also explored the bronchodilator effectiveness of RPL554 at both doses as assessed by changes in FEV_1. To ensure subject safety, the two doses were explored in a sequential, dose-escalating study design. The first group (12X dose group) consisted of 10 subjects: the first subject received open label 0.036 mg/kg RPL554 and the remaining 9 subjects were randomised in 2:1 ratio to 0.036 mg/kg RPL554, or placebo treatment, respectively. The reason for studying the first subject in an open label fashion was to confirm operational feasibility, and to assess safety of 0.036 mg/kg RPL554 before starting the double-blind phase. After the 12X dose had shown to be safe and tolerable, a similar procedure was followed in the second group (24X dose group; 10 subjects) with RPL554 0.072 mg/kg. Again, the first subject received open-label RPL554 0.072 mg/kg and 9 remaining subjects were randomised in a 2:1 ratio to 0.072 mg/kg RPL554 and placebo treatment, respectively.
Test product, Dose(s), Mode(s) of administration	RPL554 nebulized solution, 12X group: 0.036 mg/kg, 24X group: 0.072 mg/kg, aerosol via nasal inhalation.
Statistical methods	This study was informed by a previous trial (2008-005048-17) that tested RPL554 with a similar sample size and study design. Each dose group (12X and 24X) included 10 subjects, ensuring enough data to assess safety and pharmacodynamics — 6 receiving RPL554 and 3 receiving a placebo.
Inclusion/exclusion criteria	Main Inclusion Criteria: • Men and women aged between 18 and 55 years • No clinically relevant history of cardiovascular (including arrhythmias) disease • No clinically relevant history of chronic or malignant diseases • Healthy body weight, with a BMI between 18 and 33. • Normal physical exam results, except for mild asthma or allergies.

	• Clinically stable asthma, i.e. stable asthma symptoms and baseline pre-bronchodilator FEV_1 values within 10% (i.e. study day 1 compared to screening) • Documented bronchial hyperresponsiveness to inhaled Methacholine • Documented allergy by a standardized Skin Prick Test Main Exclusion Criteria: • Desensitization therapy in the past 5 years • Unstable/uncontrolled disease within 3 weeks of participation in the study • Treatment with another investigational drug within 3 months prior to screening. • Known hypersensitivity to any excipients of the drug formulations • History or clinical evidence of alcoholism within the 3-year period prior to screening
Participant Flow:	

Baseline Characteristics:

Stable asthmatics	n=20	Average Placebo	Average RPL554 12X*	Average RPL554 24X**
	Age	24.5	26.8	26.2
	BMI (kg/m^2)	23.7	24.2	24.9
Screening	FEV_1 (L)	3.91	4.21	4.06
	FEV_1 pred (%)	87.4	92.2	89.8
	FVC (L)	5.77	6.19	5.98
	FEV_1/FVC (%)	70.3	72.0	71.2
	PEF (L/s)	8.41	9.08	8.75
Study day	FEV_1 (L) -15 min pre dose	3.73	4.03	3.88
	FEV_1 (L) -5 min pre dose	3.71	3.91	3.90

*Average calculated without subject nr 1
**Average calculated without subject nr 11
FEV_1 = forced expiratory volume in 1 s. BMI=body-mass index. FVC= forced vital capacity.

Outcome Measures:

Conclusions

Safety

Single inhaled dose, 0.036 and 0.072 mg/kg of nebulized RPL554, were well tolerated in allergic asthmatics. Only a few, mild short lasting and self-limiting, adverse events were noted, with a similar distribution for active drug and placebo. Across the three dosing groups, the most frequent reported adverse event was nasal congestion. The only exception is the significant increase in heart rate which lasted for a period of approximately 2 hours, after the highest dose (0.072 mg/kg).

Pharmacodynamics

Bronchodilator effects were observed for both dose groups with a mean maximum increase for FEV_1 reached between 60-120 minutes for 12X and at approximately 90 minutes for 24X. The maximum effect compared to placebo at one hour after dosing was 420 mL and 310 mL for the 12X and 24X respectively. The bronchodilation remained on average different from placebo up to approximately 9 hours for 12X and 7½ hours for 24X.

Pharmacokinetics

A 2 fold increase in RPL554 dose, from 12X to 24X, resulted in a 1.7 fold increase in plasma exposure (based on AUC_{inf}). For the 12X dose, given over 12 minutes, the mean C_{max} was 4.3 x103 pg/mL and mean terminal half life was 4.2 hours. For the 24X dose, given over a period of 24 minutes, the mean C_{max} was 4.2 x103 pg/mL and the mean terminal half life was 4.1 hours.

Adverse Events:

Type of AE	Placebo	RPL554	
		12X	24X
Nr subjects	n=6	n=7	n=7
Nausea	1	0	0
Fatigue	1	0	1
Headache	1	1	2
Somnolence	1	0	1
Nasal congestion	2	5	4
Rhinorrhoea	2	1	0
Respiratory tract irritation	0	1	1
Increased bronchial secretion	0	1	0
Sneezing	0	0	1
Dizziness	1	2	0
Presyncope	0	0	1

AE=adverse events.

Date of clinical trial report	20 July 2011