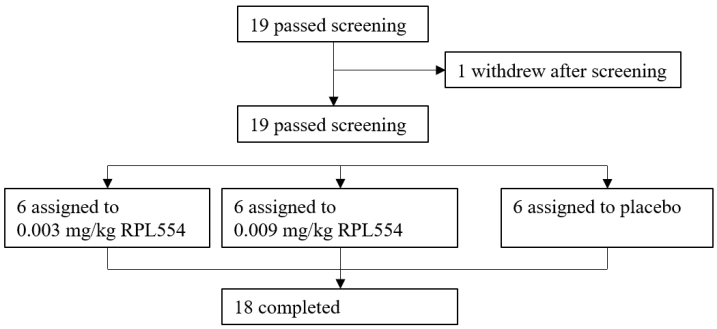
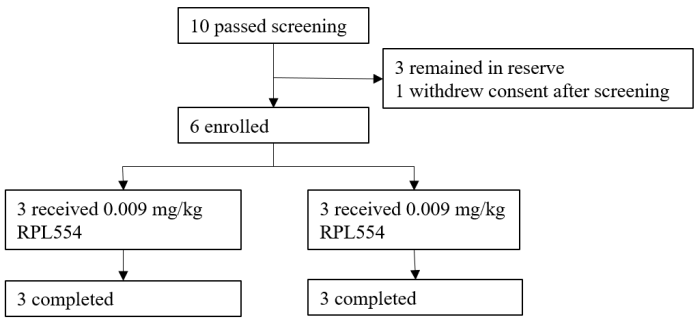
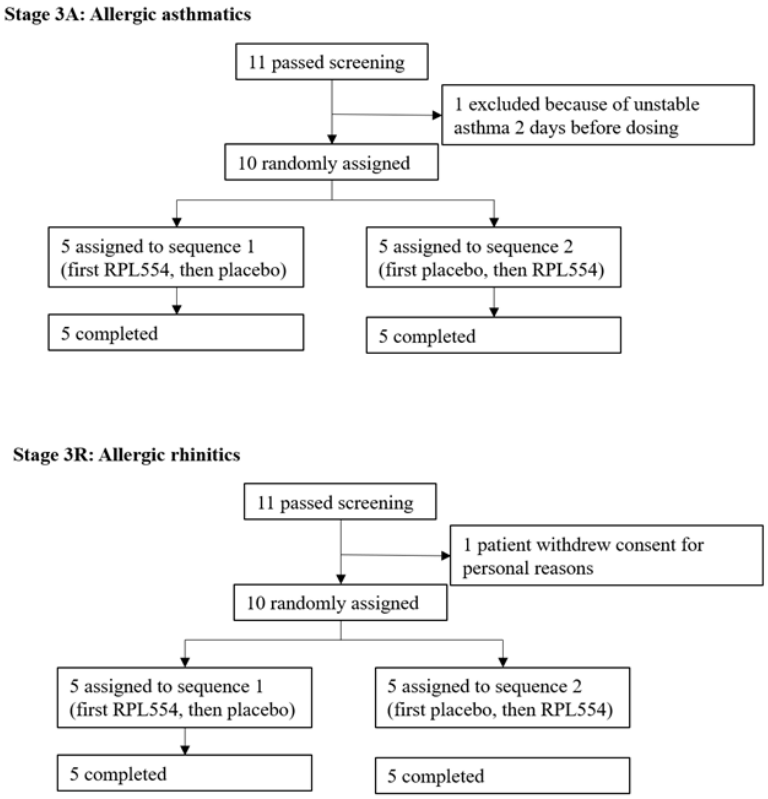
Summary of Study Results

Sponsor	Verona Pharma plc
Protocol number	2008-005048-17
Title	A combined Clinical Phase I/IIa Study of the Safety and Efficacy of nebulized RPL554 in Healthy Subjects, Asthmatics and Allergic Rhinitics
Study start/end dates	03 February 2009 to 05 August 2009
Study design /Methodology	A single-dose study that was split into three stages. Stage 1 was a double-blind, parallel group, placebo-controlled, randomised study in healthy volunteers. Stage 2 was an open-label study in allergic asthmatics. Stage 3 was a randomised, double-blind, crossover, placebo-controlled study. Stage 3 consisted of two groups. The first group (Stage 3A) consisted of mild allergic asthmatics. The second group (Stage 3R) consisted of allergic rhinitics.
Test product, Dose(s), Mode(s) of administration	Nebulised RPL554 solution. Stage 1: The first group received a single dose of 0.003 mg/kg of while the second group received a single dose of 0.009 mg/kg RPL554. Stage 2: The first group received a single dose of 0.009 mg/kg while the second group received a single dose of 0.018 mg/kg RPL554. Stage 3: All subjects received a single dose of 0.018 mg/kg RPL554.
Statistical methods	In order to estimate the sample size for a study that has 80% power of detecting a 1.5 times doubling dose in PC20MCh, the standard deviation (SD) of the difference of two treatments was obtained from a former study in which PC20MCh was measured. With this log SD of 0.72 it was calculated for a 2-sided paired t-test, alpha=0.05 that 11 subjects were needed to establish a one time doubling dose (100% difference) and 6 subjects for a 1.5 doubling dose (200% difference). Ten subjects therefore were adequate to establish a 200% rise in the dose of methacholine.

Inclusion/exclusion criteria	Main Inclusion criteria: • Male or female (non-child bearing potential) subjects 18 years to 55 years • Healthy volunteers, allergic asthmatic subjects, allergic rhinitis subjects • Non-smokers or ex-smokers Main Exclusion criteria: • Clinically relevant history of cardiovascular, chronic or malignant diseases • Clinically relevant abnormalities in 12-lead ECG, including congenital or pre-existing arrhythmias • Clinically significant findings on physical examination Other protocol defined inclusion/exclusion criteria applied.
Participant Flow:	**Stage 1: Healthy volunteers**  **Stage 2: Allergic asthmatics** 

Participant Flow (contd.):



Baseline Characteristics:

	Stage 1 (n=18)	Stage 2 (n=6)	Stage 3 A (n=10)	Stage 3 R (n=11)
	Mean (SD)			
Age (years)	23.6 (5.7)	25.3 (2.9)	28.7 (10.6)	29.4 (9.7)
BMI (kg/m^2)	22.8 (2.6)	22.9 (2.7)	24.9 (3.5)	25.2 (2.6)
FEV_1 (L)	4.83 (0.6)	4.42 (1)	4.09 (6)	4.50 (1)
Increase in FEV_1 after 200 µg salbutamol (%)	N/A	Not tested	Not tested	
Present smokers	0	0	0	
Former smokers	Not measured, but none smoked in previous 6 months	Not measured, but none smoked in previous 6 months	Not measured, but none smoked in previous 6 months	
Cigarette pack-years	<10	<10	<10	

BMI = Body Mass Index, FEV_1 = Forced expiratory volume in 1 s

Outcome Measures:	The primary objective of the study was to assess the safety of RPL554 solution in healthy subjects,allergic asthmatics and allergic rhinitics. Single ascending inhaled doses (0.003, 0.009 and 0.018 mg/kg) of nebulised RPL554 were well-tolerated by healthy volunteers, asthmatics and subjects with allergic rhinitis. Only few AEs occurred throughout the course of the study. All AEs were mild, short-lasting and self limiting. Across all study stages, the most frequently reported AEs included fatigue, somnolence, headache and upper respiratory tract (nasal) irritation. These events occurred after both RPL554 and placebo administration, and hence, were generally regarded as not RPL554-related. ln Stage 3A, the number of AEs reported in the placebo group was greater than those which occurred after RPL554 exposure. There were no clinically important changes in vital signs, ECG parameters and laboratory results. ln conclusion, over the dose-range explored (0.003 to 0.018 mg/kg) RPL554 was generally well tolerated and did not raise any specific safety concerns.

Adverse Events:

Adverse Event	Stage 1: healthy			Stage 2: asthmatics		Stage 3 A: allergic asthmatics		Stage 3 R: allergic rhinitics	
	RPL554		Placebo	RPL554		RPL554	Placebo	RPL554	Placebo
	0.003 mg/kg (n=6)	0.009 mg/kg (n=6)	0.003 mg/kg (n=6)	0.009 mg/kg (n=3)	0.018 mg/kg (n=3)	0.018 mg/kg (n=10)	n=10	0.018 mg/kg (n=10)	n=10
Allergic rhinitis	0	1	0	0	0	0	1	0	1
Asthma	0	0	0	3	0	0	2	1	0
Back pain	0	0	0	0	0	1	0	0	1
Cough	0	0	0	0	0	0	1	0	0
Dizziness	0	1	1	0	0	0	0	0	1
Dyspnoea	0	0	0	0	0	1	0	0	0
Fatigue	0	0	1	0	0	0	2	2	1
Food poisoning	1	0	0	0	0	0	0	0	0
Headache	0	1	3	0	0	2	2	2	2
Hypotension	0	0	0	0	1	0	0	0	0
Nasal congestion	0	1	0	0	0	1	0	0	1
Nausea	0	0	1	0	1*	0	0	0	0
Palpitations	0	0	0	0	0	1	0	0	0
Paresthesia	0	0	0	0	0	1	0	0	0
Pre-syncope	0	0	1	0	0	0	0	0	0
Respiratory tract infection	0	0	0	1	0	0	0	0	0
Rhinorrhea	0	1	0	1	0	1	0	0	1
Skin irritation	1	1	0	0	0	0	2	0	0
Sneezing	0	0	0	1	0	0	0	0	0
Somnolence	0	0	1	0	0	2	2	4	1
Sputum retention	0	0	0	0	0	0	1	0	0
Upper respiratory infection	0	1	0	0	0	0	0	0	0
Vasodilatation	0	1	1	0	1	0	0	0	0
Viral rhinitis	0	0	0	1	0	0	0	0	0

*Nausea was reported more than 1 day after the drug administration and was regarded as a non-drug-related event.

Date of clinical trial report	21 Mar 2013