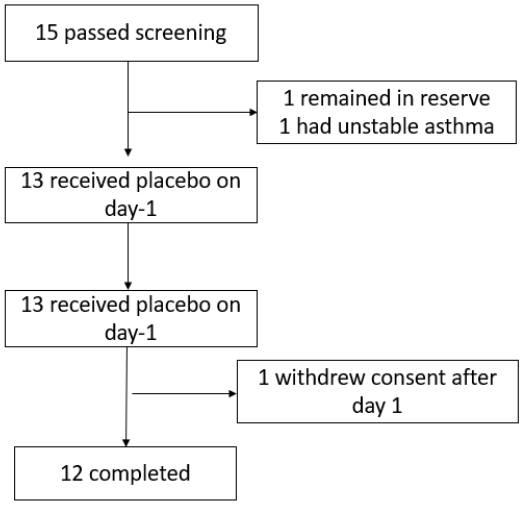
Summary of Study Results

Sponsor	Verona Pharma plc
Protocol number	2011-001698-22
Title	Evaluation of the efficacy and safety of 6 repeated daily doses of nebulised RPL554 0.018 mg/kg (6X) in Allergic Asthmatics
Study start/end dates	03 May 2011 to 01 July 2011
Study design /Methodology	Single-blind, non-randomised, single-arm, placebo (day-1) followed by RPL554, phase II study in allergic asthmatics.
Test product, Dose(s), Mode(s) of administration	RPL554 solution, 0.018 mg/kg once daily for 6 days, nebulization via oral/nasal mask
Statistical methods	The number of subjects needed was determined based on how much lung function (FEV_1) varied in individuals in the study reference EudraCT 2008-005048-17. Using these estimates, it was calculated that 14 participants would give an 80% chance of detecting a difference of 0.150 liters in lung function, assuming a potential difference of 0.179 liters. Data from the first eight subjects were used to adjust the calculations. The new estimate of lung function variability was 97 mL, lower than the original estimate of 179 mL. Based on this, it was found that only 12 subjects would be enough to detect a difference of 87 mL.
Inclusion/exclusion criteria	Main Inclusion Criteria • Healthy men aged 18 to 55. • Clinically stable mild to moderate asthma. • No clinically relevant history of cardiovascular (including arrhythmias) disease. • No clinically relevant history of chronic or malignant diseases. • BMI between 18 and 33. • Normal blood pressure (100-155/50-90 mmHg) and heart rate (45-90 bpm) after resting. • No major concerns found in a physical exam or ECG (other than asthma and allergies). • Non-smokers or ex-smokers

<table>
<tr><td></td><td>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</td></tr>
<tr><td>Participant Flow:</td><td> 
</td></tr>
<tr><td>Baseline Characteristics:</td><td>
<table>
<tr><th colspan="2">Study 2011-001698-22 (n=13)</th></tr>
<tr><td>Disease stages (GINA/GOLD)</td><td>Healthy, mild-to-moderate asthma</td></tr>
<tr><td>Men</td><td>13</td></tr>
<tr><td>Age (years)</td><td>26.0 (8.2)</td></tr>
<tr><td>Body-mass index (kg/m^2)</td><td>23.0 (1.8)</td></tr>
<tr><td>FEV_1 (%)</td><td>88.1% (8.5)</td></tr>
<tr><td>FEV_1 (L)</td><td>3.99 (0.66)</td></tr>
<tr><td>Increase in FEV_1 after 200 µg salbutamol (%)</td><td>13.0% (2.9)</td></tr>
<tr><td>Present smokers</td><td>0</td></tr>
<tr><td>Former smokers</td><td>5, but none smoked in previous 6 months</td></tr>
<tr><td>Cigarette pack-years</td><td><10</td></tr>
</table>
Data are number or mean (SD). FEV_1 = forced expiratory volume in 1 s. GINA = Global initiative for asthma. GOLD = Global initiative for Chronic Obstructive Lung Disease.
</td></tr>
</table>

Outcome Measures:

Primary Endpoint:

The primary endpoint of the study was maximum FEV_1 reached during 6 h after dose on days –1, 1, 3, and 6. Repeated daily doses of nebulised 0·018 mg/kg RPL554 for 6 days resulted in a reproducible, maintained bronchodilator effect as shown in Table 2 below. Tachyphylaxis was not observed. The change from baseline after 200 µg salbutamol, which is in line with the maximum response of RPL554 of 555 mL from baseline on day 1.

Table 2: Maximum forced expiratory volume in 1 s on each day

	Mean (mL)	95% CI
Day -1 (placebo)	3990.0	3547.6-4432.4
Day 1 (RPL554)	4352.5	3907.4-4797.6
Day 3 (RPL554)	4304.2	3867.9-4740.4
Day 6 (RPL554)	4272.5	3816.6-4728.4

These data are the mean and 95% CI of the maximum value from FEV_1 measurements taken at 15 min, 30 min, 45 min, 60 min, and then every 30 min until 6 h post dose.

Secondary Endpoint – Safety and Tolerability:

Assessment of the safety of RPL554 solution in subjects with asthma was a secondary endpoint in the study. Inhaled RPL554 (0·018 mg/kg) once daily for 6 days was well tolerated. 16 mild, short-lasting, and self-limiting AEs occurred during the study (see table in Adverse Events section). The most frequently reported AEs were headache, irritation of the larynx, and dizziness. Blood pressure did not change during the study. There were a mean 3.2 beats per min increase in heart rate over 360 min on day 6 compared with day 1 (95% CI 1.9–4.4) and a mean 2.9 beats per min increase on day 6 compared with day 3 (1.6–4.2). There were no clinically important changes in vital signs, ECG variables, and laboratory results.

<table>
<tr>
<td></td>
<td>The mean maximum plasma concentration of RPL554 in this study was 1.706 pg/mL at day 1 and 1.904 pg/mL at day 6. Additionally, the pharmacokinetics after six daily inhaled doses showed no evidence of accumulation of RPL554 (Figure 1 below). Median accumulation values estimated on day 3 and day 6 suggested no accumulation of RPL554 (C_{min} ratios were 0.85 and 1.26 on days 3 and 6, respectively, and AUCτ ratios were 0.90 and 1.27).

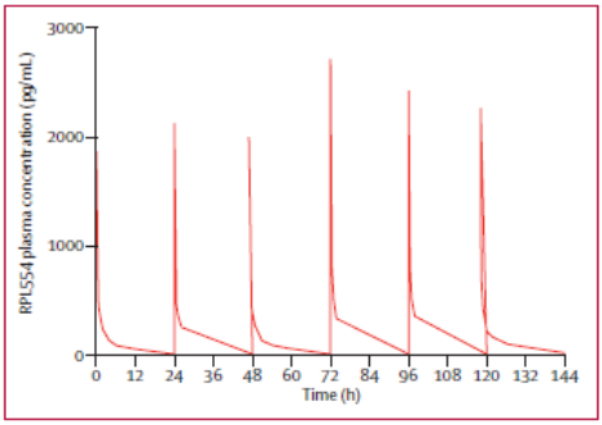
 

Figure 1: Plasma concentration of RPL554 overtime after six inhaled daily doses of RPL554 in asthmatics</td>
</tr>
<tr>
<td>Adverse Events:</td>
<td>
<table>
<tr><th colspan="2">Number of adverse events with more than 5% occurrence in any treatment group</th></tr>
<tr><th></th><th>RPL554 0.018 mg/kg (n=13)*</th></tr>
<tr><td>Dizziness</td><td>3</td></tr>
<tr><td>Dry throat</td><td>1</td></tr>
<tr><td>Fatigue</td><td>2</td></tr>
<tr><td>Headache</td><td>4</td></tr>
<tr><td>Larynx irritation</td><td>3</td></tr>
<tr><td>Nasal congestion</td><td>1</td></tr>
<tr><td>Nausea</td><td>1</td></tr>
<tr><td>Rhinorrhoea</td><td>1</td></tr>
</table>
*These are numbers of participants who received placebo and RPL554.
</td>
</tr>
<tr>
<td>Date of clinical trial report</td>
<td>31 October 2011</td>
</tr>
</table>