Clinical trial results:
A Phase IIA randomized, double-blind, placebo controlled, cross-over study to evaluate the effects of multiple doses of inhaled RNS60 and Budesonide on the late phase asthmatic response to allergen challenge in patients with mild asthma.

Note:
Following Protocol Amendment 2.1, this study was conducted as a randomised, double-blind, placebo-controlled, parallel (RNS60/Placebo) 1 period study and no longer involves the administration of budesonide.

Summary

EudraCT number	2014-003846-29
Trial protocol	GB
Global end of trial date	10 November 2015

Results information

Result version number	v1 (current)
This version publication date	03 July 2022
First version publication date	03 July 2022

Trial information

Trial identification

Sponsor protocol code	01.1.1.H3

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Revalesio Corporation
Sponsor organisation address	1202 East D Street, Tacoma, United States, 98421
Public contact	Clinical trial manager, Revalesio Corporation, 1 253 922 2600, info@revalesio.com
Scientific contact	Clinical trial manager, Revalesio Corporation, 1 253 922 2600, info@revalesio.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 May 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1) Assess the effect of treatment with RNS60 on the response to allergen challenge compared with placebo (0.9% saline), in subjects with mild asthma.

2) Assess the safety and tolerability of multiple doses of RNS60 in subjects with mild asthma.

The efficacy of nebulized RNS60 was investigated through the assessment of forced expiratory volume in 1 second (FEV1) responses during the late asthmatic response (LAR) after inhaled allergen challenge in subjects with mild allergic asthma. The allergen challenge model allowed the evaluation of several features of the physiology of mainly Th2 cell-driven asthma in relation to the kinetics of the underlying airway pathology during the allergen-induced late response.

RNS60 is an electrokinetically altered aqueous fluid consisting of 0.9% sodium chloride and dissolved oxygen, generated using modified Taylor-Couette-Poiseuille (TCP) flow under elevated oxygen pressure, hypothesized to produce oxygen nanobubbles.

Protection of trial subjects:

The study was conducted in accordance with Good Clinical Practice (GCP) as required by the International Council on Harmonisation (ICH) guidelines and in accordance with country-specific laws and regulations governing clinical studies of investigational products. Compliance with these requirements also constitutes conformity with the ethical principles of the Declaration of Helsinki.

Background therapy:

Background therapy - Not applicable

Additional relevant information regarding study conduct:

Due to the Protocol Amendment 2.1, introduced after the study start, there were 2 cohorts in the study. Cohort 1 (comprised of 12 subjects) and Cohort 2 (comprised of 18 subjects).

Subjects in Cohort 1 were enrolled prior to the change in study design described in Protocol Amendment 2.1. After screening and a baseline allergen challenge, these subjects received either RNS60 or placebo, twice daily for 20 days (Day 1 to Day 20) and a single dose in the morning of Day 21. The subjects received an allergen challenge on Day 21. Cohort 1 subjects then received a second allergen challenge on Day 42; the study design was amended prior to these subjects commencing the crossover portion of the original protocol. Post Day 21 data were excluded from the primary and secondary efficacy endpoint analyses for Cohort 1 subjects. Thus, the follow-up visit for Cohort 1 occurred after approval of the amended study design and was scheduled according to the availability of the subjects.

Subjects in Cohort 2 were enrolled as per Protocol Amendment 2.1. After screening and a baseline allergen challenge, these subjects received either RNS60 or placebo, twice daily for 20 days (Day 1 to Day 20) and a single dose in the morning of Day 21. The subjects received an allergen challenge on Day 21 after the final treatment.

The final overall data analysis was performed on subject groups, i.e. subjects who received the study drug RNS60 (N= 16) or placebo (N=14).

Evidence for comparator: -	
Actual start date of recruitment	07 April 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 30
Worldwide total number of subjects	30
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	30
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 30 subjects (male and female) diagnosed with mild asthma were recruited according to the study inclusion and exclusion criteria.

Pre-assignment

Screening details:

Eligible subjects had to show a positive methacholine with a provocative concentration of methacholine, leading to a 20% fall in FEV1 (PC20 methacholine) of equal to or less than 8 mg/mL. Subject or legal representative gave written consent prior to any treatment procedures after receiving detailed information about the study.

Period 1

Period 1 title	Overall study period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

This was a randomized, double-blind, placebo-controlled study with limited access to the randomization code.
Study medication and placebo were identical in physical appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	RNS60

Arm description:

Subjects received RNS60 twice daily for 20 days (Day 1 to Day 20) and a single dose in the morning of Day 21. The subjects received an allergen challenge on Day 21 after the final treatment.

Arm type	Experimental
Investigational medicinal product name	RNS60
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

RNS60 chemically is a 0.9% sodium chloride for irrigation with added USP Oxygen, processed using modified Taylor-Couette-Poiseuille (TCP) flow under elevated oxygen pressure. RNS60 drug product was supplied as a sterile solution for nebulized inhalation.

Treatments were administered as a nebulized dose using a Pari Mini nebulizer system with Pari LC Sprint reusable, disposable nebulizers.

4 mL dose, twice daily dosing for 20 days (Day 1 to Day 20) with a single dose on Day 21.

Treatment was administered under supervision in the clinical unit and self-administered by the subjects when they were not attending the clinical unit. The subjects entered the details of self-administration into diary cards. Diary cards were reviewed by the clinical staff when the subjects returned to the clinic.

Arm title	Placebo

Arm description:

Subjects received placebo (0.9% saline) twice daily for 20 days (Day 1 to Day 20) and a single dose in the morning of Day 21. The subjects received an allergen challenge on Day 21 after the final treatment.

Arm type	Placebo

Investigational medicinal product name	Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Placebo:

Normal saline placebo was 0.9% sodium chloride for irrigation. Normal saline drug product was supplied as a sterile solution for nebulized inhalation

Treatments were administered as a nebulized dose using a Pari Mini nebulizer system with Pari LC Sprint reusable, disposable nebulizers.

4 mL, twice daily dosing for 20 days (Day 1 to Day 20) with a single dose on Day 21.

Treatment was administered under supervision in the clinical unit and self-administered by the subjects when they were not attending the clinical unit. The subjects entered the details of self-administration into diary cards. Diary cards were reviewed by the clinical staff when the subjects returned to the clinic.

Number of subjects in period 1	RNS60	Placebo
Started	16	14
Completed	16	14

Baseline characteristics

Reporting groups	
Reporting group title	RNS60
Reporting group description:	
Subjects received RNS60 twice daily for 20 days (Day 1 to Day 20) and a single dose in the morning of Day 21. The subjects received an allergen challenge on Day 21 after the final treatment.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo (0.9% saline) twice daily for 20 days (Day 1 to Day 20) and a single dose in the morning of Day 21. The subjects received an allergen challenge on Day 21 after the final treatment.	

Reporting group values	RNS60	Placebo	Total
Number of subjects	16	14	30
Age categorical Units: Subjects			
Adults (18-64 years)	16	14	30
Age continuous Units: years			
arithmetic mean	33	31	
standard deviation	± 9	± 9	-
Gender categorical Units: Subjects			
Female	3	4	7
Male	13	10	23
Race Units: Subjects			
Asian	1	4	5
Black	2	1	3
White	13	9	22
Body mass index Units: kg/m²			
arithmetic mean	25.63	24.91	
standard deviation	± 2.88	± 2.02	-

End points

End points reporting groups

Reporting group title	RNS60

Reporting group description:

Subjects received RNS60 twice daily for 20 days (Day 1 to Day 20) and a single dose in the morning of Day 21. The subjects received an allergen challenge on Day 21 after the final treatment.

Reporting group title	Placebo

Reporting group description:

Subjects received placebo (0.9% saline) twice daily for 20 days (Day 1 to Day 20) and a single dose in the morning of Day 21. The subjects received an allergen challenge on Day 21 after the final treatment.

Primary: 1_Emax(3-8) -- Allergen-induced late asthmatic response (LAR)

End point title	1_Emax(3-8) -- Allergen-induced late asthmatic response (LAR)

End point description:

Emax(3-8)

Evaluate the allergen-induced late asthmatic response (LAR), as measured by maximal percent decrease in forced expiratory volume in 1 second (FEV1) from the baseline (pre-allergen challenge) to the period beginning 3 hours and ending 8 hours post allergen challenge.

Inhaled methacholine was used as the challenge agent, to cause airway tightening (bronchospasm), followed by measurement of FEV1 using established spirometry methods.

Emax(3-8) = The maximal percentage decrease (% change from baseline/baseline) from the pre-allergen challenge (i.e., baseline was the post-diluent value) in FEV1 between 3 hours and 8 hours after allergen challenge

Efficacy analysis set included all subjects who received at least one dose of study medication (RNS60 or placebo) and had at least one scheduled post-dose efficacy measurement. Subjects in this analysis set were used for all efficacy analyses.

End point type	Primary

End point timeframe:

Baseline (screening, pre-allergen challenge), and after 21 days of treatment i.e. on Day 21: at 10, 15, 20, 30, and 45 min and at 1, 2, 3, 4, 5, 6, 7, and 8 h after allergen challenge.

End point values	RNS60	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16[1]	13[2]		
Units: Percent (%)				
arithmetic mean (standard deviation)	28.0 (± 16.80)	26.51 (± 15.05)		

Notes:

[1] - Efficacy analysis set

[2] - Efficacy analysis set

Statistical analyses

Statistical analysis title	Emax(3-8)

Statistical analysis description:

The primary efficacy endpoints for FEV1 were compared between RNS60 and placebo using an analysis of covariance (ANCOVA) model with treatment as a fixed effect and baseline value as a covariate. Least-squares (LS) means for each treatment with 95% confidence intervals (CIs) and LS mean differences for comparison with 95% CI between the two treatments are presented.

Comparison groups	RNS60 v Placebo
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8371
Method	ANCOVA
Parameter estimate	least-squares mean difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.03
upper limit	13.5

Secondary: 2_Emax(0-3) -- Allergen-induced early asthmatic response (EAR)

End point title	2_Emax(0-3) -- Allergen-induced early asthmatic response (EAR)

End point description:

Emax(0-3)

Evaluate the allergen-induced early phase asthmatic response (EAR) as measured by maximal percent decrease in the FEV1 from the baseline (pre-allergen diluent challenge) during the first 3 hours post-allergen challenge (0 to 3 hours).

Emax(0-3) = Maximal percentage decrease from the pre-allergen challenge (i.e., baseline was the post-diluent value) in FEV1 during the first 3 hours post-allergen challenge (0 to 3 hours)

EAR: The inhalation of allergens by allergic asthmatics leads to the early asthmatic response (EAR), which is characterized by acute airway obstruction beginning within a few minutes.

End point type	Secondary

End point timeframe:

Baseline (screening, pre-allergen challenge), and after 21 days of treatment i.e. Day 21: at 10, 15, 20, 30, and 45 min and at 1, 2, 3, 4, 5, 6, 7, and 8 h after allergen challenge.

End point values	RNS60	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16[3]	13[4]		
Units: Percent (%)				
arithmetic mean (standard deviation)	27.66 (± 6.17)	27.3 (± 9.51)		

Notes:

[3] - Efficacy analysis set

[4] - Efficacy analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: 3_AUEC(0-3) -- Area under the effect curve post-allergen challenge (between 0 and 3 h post-allergen challenge)

End point title	3_AUEC(0-3) -- Area under the effect curve post-allergen challenge (between 0 and 3 h post-allergen challenge)

End point description:

AUEC(0-3)

The AUEC between 0 hours and 3 hours post-allergen challenge (using change-from-baseline FEV1 values, with the post-diluent challenge value in FEV1 as baseline), was calculated using the linear trapezoidal method.

AUEC=Area under the effect curve

End point type	Secondary

End point timeframe:

Baseline (screening, pre-allergen challenge), and after 21 days of treatment i.e. Day 21: at 10, 15, 20, 30, and 45 min and at 1, 2, 3, 4, 5, 6, 7, and 8 h after allergen challenge.

End point values	RNS60	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16[5]	13[6]		
Units: h*L				
arithmetic mean (standard deviation)	1.234 (± 0.521)	1.077 (± 0.536)		

Notes:

[5] - Efficacy analysis set

[6] - Efficacy analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: 4_AUEC(3-8) -- Area under the effect curve post-allergen challenge (between 3 and 8 h post-allergen challenge)

End point title	4_AUEC(3-8) -- Area under the effect curve post-allergen challenge (between 3 and 8 h post-allergen challenge)

End point description:

AUEC(3-8)

Evaluate the AUEC between 3 hours and 8 hours post-allergen challenge (using change-from-baseline FEV1 values, with post-diluent challenge value in FEV1 as the baseline), using the linear trapezoidal method.

AUEC=Area under the effect curve

End point type	Secondary

End point timeframe:

Baseline (screening, pre-allergen challenge), and after 21 days of treatment i.e. on Day 21: at 10, 15, 20, 30, and 45 min and at 1, 2, 3, 4, 5, 6, 7, and 8 h after allergen challenge.

End point values	RNS60	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16[7]	13[8]		
Units: h*L				
arithmetic mean (standard deviation)	3.12 (± 2.176)	2.991 (± 1.518)		

Notes:

[7] - Efficacy analysis set

[8] - Efficacy analysis set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time of study information consent signature to the end of the study (follow-up visit). Follow-up: Cohort 1=about 28 - 46 days after the allergen challenge on Day 42; Cohort 2=about 7 days after the final study drug administration (Day 28).

Adverse event reporting additional description:

Treatment-emergent adverse events (TEAEs) are reported and defined as AEs that started or worsened in severity on or after the first dose of study medication.

The Safety Analysis Set was used to evaluate adverse events (AE). The Safety Analysis Set included all subjects who received at least one dose of study medication (RNS60 or placebo).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	RNS60
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	RNS60	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 14 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	RNS60	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 16 (50.00%)	9 / 14 (64.29%)	
Investigations			
Weight decreased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Limb injury			

subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 16 (18.75%)	3 / 14 (21.43%)	
occurrences (all)	3	3	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 16 (6.25%)	2 / 14 (14.29%)	
occurrences (all)	1	2	
Cough			
subjects affected / exposed	1 / 16 (6.25%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Asthma			
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Wheezing			
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Infections and infestations			
Rhinitis			

subjects affected / exposed	2 / 16 (12.50%)	1 / 14 (7.14%)	
occurrences (all)	2	1	
Nasopharyngitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Oral herpes			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 June 2015	Protocol Amendment 2 Amending the study design (submitted for approval to the MHRA and EC). The MHRA approved the amendment, with additional changes requested by the EC.
15 July 2015	Protocol Amendment 2.1 After incorporating the changes requested by EC for amendment 2.0, amendment 2.1 was submitted and approval was granted by the EC. Summary of the main changes to the study protocol is provided below. The original study design, a randomized, placebo controlled, 3-period crossover design was amended to a randomized, placebo controlled, 1-period parallel design. The delay in the start of the study meant that patients would be crossing over between treatment arms during the season of peak tree and grass pollen levels. After consultation with experts in the asthma field and allergen stress tests it was determined that the study would be more reliable if modified to a simple 2 arm randomized, placebo controlled trial and the study design was amended prior to any subjects entering the crossover arms. The amended study design did not include the active control arm (budesonide); the original protocol was not powered to compare the efficacy of RNS60 versus budesonide. As the original protocol was powered to detect a difference between RNS60 and placebo, removal of the budesonide arm did not impact the essential objective of the study. The secondary objective of the study, to assess the persistency of effect of twice daily dosing with RNS60 for 21 days, was removed from the amended study design.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

No limitations and caveats applicable to this summary of results were used.

Notes: