Clinical trial results:
Demonstration of therapeutic equivalence/non-inferiority as well as early onset of action of the novel water-soluble budesonide nasal spray (Budesolv) compared with marketed Rhinocort® aqua 64 in patients suffering from grass pollen induced allergic rhinitis/rhinoconjunctivitis with or without controlled asthma.

Summary

EudraCT number	2018-001324-19
Trial protocol	AT
Global end of trial date	05 April 2019
Results information	
Result version number	v1 (current)
This version publication date	23 May 2021
First version publication date	23 May 2021
Summary attachment (see zip file)	Fast effectiveness of solubilized low-dose budesonide nasal spray in allergic rhinitis (2020-zieglmayer-fast-effectiveness-of-a-solubilized-low-dose-budesonide-nasal-spray-in-allergic-rhinitis.pdf)

Trial information

Trial identification	
Sponsor protocol code	BDS_18_01
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03755557
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Marinomed Biotech AG
Sponsor organisation address	Hovengasse 25, Korneuburg, Austria, 2100
Public contact	Project manager, Marinomed Biotech AG, +43 1250774460, andreas.goessl@marinomed.com
Scientific contact	Project manager, Marinomed Biotech AG, +43 1250774460, andreas.goessl@marinomed.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	20 November 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 April 2019
Global end of trial reached?	Yes
Global end of trial date	05 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial is to demonstrate therapeutic equivalence/non-inferiority between Budesolv 10 and Rhinocort® aqua 64, a marketed comparator containing the same compound (budesonide), in patients suffering from grass pollen induced allergic rhinitis/rhinoconjunctivitis with or without controlled asthma on day 8 of treatment.

Protection of trial subjects:

This study was performed in compliance with the ICH E6 Guideline for Good Clinical Practice, the principles that have their origin in the Declaration of Helsinki and local laws and regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 September 2018
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	Austria: 83
Worldwide total number of subjects	83
EEA total number of subjects	83

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)	83

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from one study site in Austria.

Pre-assignment

Screening details:

Patients were screened for appropriate allergic response. A Total Nasal Symptom Score (TNSS) of at least 6 points out of 12 within the first two hours in the grass pollen challenge chamber was required to be included into the study.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Rhinocort aqua 64

Arm description:

Rhinocort aqua 64 nasal spray - budesonide suspension
83 subjects were randomised. 8 subjects were lost to follow up.75 subjects completed the trial per protocol.

Arm type	Active comparator
Investigational medicinal product name	Rhinocort aqua 64 nasal spray
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray, suspension
Routes of administration	Intranasal use

Dosage and administration details:

once daily 2 puffs per nostil; for 8 days

Arm title	Budesolv 10 micrograms

Arm description:

Budesolv nasal spray, solution, 200mg/ml budesonide
83 subjects were randomised. 8 subjects were lost to follow up.75 subjects completed the trial per protocol.

Arm type	Experimental
Investigational medicinal product name	Budesonide 10 micrograms, nasal spray
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Intranasal use

Dosage and administration details:

once daily two puffs per nostril; for 8 days

Arm title	Placebo nasal spray

Arm description:

Matching Placebo to Budesolv 10 nasal spray
83 subjects were randomised. 8 subjects were lost to follow up.75 subjects completed the trial per protocol.

Arm type	Placebo

Investigational medicinal product name	Placebo nasal spray
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Intranasal use

Dosage and administration details:

once daily two puffs per nostril; for 8 days

Number of subjects in period 1	Rhinocort aqua 64	Budesolv 10 micrograms	Placebo nasal spray
Started	75	75	75
wash-out 1	75	75	75
wash-out 2	75	75	75
Completed	75	75	75

Baseline characteristics

Reporting groups	
Reporting group title	Rhinocort aqua 64
Reporting group description:	
Rhinocort aqua 64 nasal spray - budesonide suspension 83 subjects were randomised. 8 subjects were lost to follow up.75 subjects completed the trial per protocol.	
Reporting group title	Budesolv 10 micrograms
Reporting group description:	
Budesolv nasal spray, solution, 200mg/ml budesonide 83 subjects were randomised. 8 subjects were lost to follow up.75 subjects completed the trial per protocol.	
Reporting group title	Placebo nasal spray
Reporting group description:	
Matching Placebo to Budesolv 10 nasal spray 83 subjects were randomised. 8 subjects were lost to follow up.75 subjects completed the trial per protocol.	

Reporting group values	Rhinocort aqua 64	Budesolv 10 micrograms	Placebo nasal spray
Number of subjects	75	75	75
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	75	75	75
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
median	31	31	31
full range (min-max)	20 to 61	20 to 61	20 to 61
Gender categorical Units: Subjects			
Female	45	45	45
Male	30	30	30

Reporting group values	Total		
Number of subjects	75		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	75		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
median			
full range (min-max)	-		
Gender categorical			
Units: Subjects			
Female	45		
Male	30		

Subject analysis sets

Subject analysis set title	Non-inferiority assessment on Day 8
Subject analysis set type	Per protocol

Subject analysis set description:

In the randomised placebo controlled cross-over non-inferiority trial efficacy analysis was done on day 8 of treatment

Subject analysis set title	Early onset of action on day 1
Subject analysis set type	Intention-to-treat

Subject analysis set description:

In the randomised placebo controlled cross-over trial early onset of action was measured after initial single treatment.

Reporting group values	Non-inferiority assessment on Day 8	Early onset of action on day 1	
Number of subjects	75	78	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	75	78	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
median	31	31	
full range (min-max)	20 to 61	20 to 61	
Gender categorical			
Units: Subjects			
Female	44	46	
Male	31	32	

End points

End points reporting groups

Reporting group title	Rhinocort aqua 64
Reporting group description:	
Rhinocort aqua 64 nasal spray - budesonide suspension 83 subjects were randomised. 8 subjects were lost to follow up.75 subjects completed the trial per protocol.	
Reporting group title	Budesolv 10 micrograms
Reporting group description:	
Budesolv nasal spray, solution, 200mg/ml budesonide 83 subjects were randomised. 8 subjects were lost to follow up.75 subjects completed the trial per protocol.	
Reporting group title	Placebo nasal spray
Reporting group description:	
Matching Placebo to Budesolv 10 nasal spray 83 subjects were randomised. 8 subjects were lost to follow up.75 subjects completed the trial per protocol.	
Subject analysis set title	Non-inferiority assessment on Day 8
Subject analysis set type	Per protocol
Subject analysis set description:	
In the randomised placebo controlled cross-over non-inferiority trial efficacy analysis was done on day 8 of treatment	
Subject analysis set title	Early onset of action on day 1
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
In the randomised placebo controlled cross-over trial early onset of action was measured after initial single treatment.	

Primary: Total nasal symptom score

End point title	Total nasal symptom score[1]
End point description:	
The TNSS was the sum of the symptoms “nasal congestion”, “rhinorrhea”, “itchy nose” and “sneezing”. Each individual symptom was scored on a 4-point categorical scale from 0-3 (where “0”= none, “1”=mild, “2”=moderate, “3”=severe).	
End point type	Primary
End point timeframe:	
Mean 2-6 h assessed on day 8	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to the cross-over setting and the non-inferiority assessment statistics for all the arms in the baseline period can not be indicated. Please refer to the uploaded publication to see the study setting and the results.

End point values	Rhinocort aqua 64	Budesolv 10 micrograms		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	75		
Units: TNSS points				
arithmetic mean (confidence interval 95%)	5.05 (4.41 to 5.68)	4.98 (4.39 to 5.57)		

Statistical analyses

Statistical analysis title	Non-inferiority Rhinocort/Budesolv

Statistical analysis description:

As it is not foreseen to enter such a complex trial setting, we uploaded already published results in Clinical Experimental Allergy 2020.

The total number of subjects analysed were 75 but as this is a cross-over trail the subjects analysed below are featuring as 150 as the number of subjects adds up on selecting the two arms that are being compared.

Comparison groups	Rhinocort aqua 64 v Budesolv 10 micrograms
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	< 0.05
Method	ANOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	1-sided
upper limit	1.15

Notes:

[2] - A 95% confidence interval was calculated for the mean difference between the two active treatments. Non-inferiority could be stated if the upper limit of the confidence interval did not exceed mean reference plus 15%.
The upper limit of the 95% confidence interval of the individual differences (Rhinocort® aqua 64 – Budesolv 10) was 0.64. Mean sum of scores (Budesolv) + 0.64 is 5.62. This value is below 5.80 ([mean Rhinocort® aqua 64] +15%). Non-inferiority was shown.

Secondary: Active anterior rhinomanometry

End point title	Active anterior rhinomanometry[3]

End point description:

Active anterior rhinomanometry was measured as objective parameter to support recorded subjective symptoms scores.
Non-inferiority margin: Mean of active control (Rhinocort® aqua 64) - 15% = 319.0
Non-inferiority margin*: Lower 95% confidence interval of active control (Rhinocort® aqua 64) - 15% = 331.8. Mean difference (Rhinocort® aqua 64 – Budesolv 10) was -8.58 ± 116.60. The lower limit of the 95% confidence interval of the difference was -35.41. Mean sum of scores of test treatment (Budesolv 10, 383.87) -35.41 is 348.46, and thus falls above both margins (319.0 and 331.8). Hence, non-inferiority was shown for Nasal Airflow measured by rhinomanometry.

End point type	Secondary

End point timeframe:

mean 2-6h on day 8

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to the cross-over setting and the non-inferiority assessment statistics for all the arms in the baseline period can not be indicated. Please refer to the uploaded publication to see the study setting and the results.

End point values	Rhinocort aqua 64	Budesolv 10 micrograms		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	75		
Units: ml/sec				
arithmetic mean (confidence interval 95%)	375.29 (337.51 to 413.06)	383.87 (345.64 to 422.10)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Adverse events were reported during the whole study period.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0
Reporting groups	
Reporting group title	Budesolv 10 micrograms
Reporting group description: Budesonide 10 nasal spray	
Reporting group title	Rhinocort aqua 64
Reporting group description: Rhinocort nasal spray	
Reporting group title	Placebo
Reporting group description: Placebo nasal spray	

Serious adverse events	Budesolv 10 micrograms	Rhinocort aqua 64	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 78 (0.00%)	0 / 78 (0.00%)	0 / 78 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Budesolv 10 micrograms	Rhinocort aqua 64	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 78 (23.08%)	15 / 78 (19.23%)	18 / 78 (23.08%)
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 78 (3.85%)	2 / 78 (2.56%)	3 / 78 (3.85%)
occurrences (all)	8	8	8
Migraine			
subjects affected / exposed	1 / 78 (1.28%)	0 / 78 (0.00%)	0 / 78 (0.00%)
occurrences (all)	1	1	1
Immune system disorders			

Allergy to animal			
subjects affected / exposed	2 / 78 (2.56%)	0 / 78 (0.00%)	0 / 78 (0.00%)
occurrences (all)	2	2	2
Drug hypersensitivity			
subjects affected / exposed	0 / 78 (0.00%)	1 / 78 (1.28%)	0 / 78 (0.00%)
occurrences (all)	1	1	1
Hypersensitivity			
subjects affected / exposed	1 / 78 (1.28%)	1 / 78 (1.28%)	2 / 78 (2.56%)
occurrences (all)	4	4	4
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 78 (1.28%)	1 / 78 (1.28%)	1 / 78 (1.28%)
occurrences (all)	3	3	3
Dysphonia			
subjects affected / exposed	0 / 78 (0.00%)	0 / 78 (0.00%)	1 / 78 (1.28%)
occurrences (all)	1	1	1
Epistaxis			
subjects affected / exposed	3 / 78 (3.85%)	1 / 78 (1.28%)	0 / 78 (0.00%)
occurrences (all)	4	4	4
Nasal congestion			
subjects affected / exposed	0 / 78 (0.00%)	0 / 78 (0.00%)	2 / 78 (2.56%)
occurrences (all)	2	2	2
Nasal discomfort			
subjects affected / exposed	0 / 78 (0.00%)	0 / 78 (0.00%)	2 / 78 (2.56%)
occurrences (all)	2	2	2
Nasal pruritus			
subjects affected / exposed	0 / 78 (0.00%)	0 / 78 (0.00%)	1 / 78 (1.28%)
occurrences (all)	1	1	1
Oropharyngeal pain			
subjects affected / exposed	0 / 78 (0.00%)	2 / 78 (2.56%)	0 / 78 (0.00%)
occurrences (all)	2	2	2
Throat irritation			
subjects affected / exposed	1 / 78 (1.28%)	0 / 78 (0.00%)	1 / 78 (1.28%)
occurrences (all)	1	1	1
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	1 / 78 (1.28%)	2 / 78 (2.56%)	1 / 78 (1.28%)
occurrences (all)	4	4	4
Pain in extremity			
subjects affected / exposed	0 / 78 (0.00%)	1 / 78 (1.28%)	0 / 78 (0.00%)
occurrences (all)	1	1	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 78 (0.00%)	0 / 78 (0.00%)	1 / 78 (1.28%)
occurrences (all)	1	1	1
Nasopharyngitis			
subjects affected / exposed	3 / 78 (3.85%)	4 / 78 (5.13%)	3 / 78 (3.85%)
occurrences (all)	10	10	10
Tonsillitis			
subjects affected / exposed	2 / 78 (2.56%)	0 / 78 (0.00%)	0 / 78 (0.00%)
occurrences (all)	2	2	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported