Clinical trial results:
A double blind, placebo controlled randomized study of nasal steroid spray treatment on the quality of life and objective sleep parameters in children with sleep disorder breathing.

Summary

EudraCT number	2013-004620-10
Trial protocol	SE
Global end of trial date	18 October 2016

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021

Trial information

Trial identification

Sponsor protocol code	719-13

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Västra Götalandsregionen, Sahlgrenska Universitetssjukhus
Sponsor organisation address	Gröna stråket 9, Gothenburg, Sweden, 41320
Public contact	Johan Hellgren, Västra Götalandsregionen, Sahlgrenska Universitetssjukhus, 0046 313429147, johan.hellgren@gu.se
Scientific contact	Johan Hellgren, Västra Götalandsregionen, Sahlgrenska Universitetssjukhus, 0046 313429147, johan.hellgren@gu.se

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	18 October 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2016
Global end of trial reached?	Yes
Global end of trial date	18 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study is to evaluate the effect of nasal budesonide spray compared to placebo on health related quality of life in children with sleep disorder breathing (SDB) as well as symptoms of SDB such as snoring, apneas and nasal obstruction and the adenoid size. The aim was also to compare AHI in children in the two treatment groups, so all children underwent at-home respiratory polygraphy before and after 6 weeks treatment.

Protection of trial subjects:

The study was designed and conducted in accordance with the Helsinki statement. The guardians of each child and the child, when appropriate, received both written and oral informations and gave their informed consent to participate in the study. It was approved by the Regional Ethical Board, Gothenburg (Dnr 719-13), and the Swedish Medical Products Agency (Dnr 5.1-2014-84538)

Background therapy:

None

Evidence for comparator:

Previous research showis that nasal steroid treatment reduces the size of the adenoids, alleviates symptoms (snoring, apneas, and nasal obstruction), and improves polysomnography (PSG) results. To our knowledge, there is no previous randomized, placebo-controlled study of the effect of intranasal steroid treatment on the HRQoL of children with SDB. The placebo spray consisted of a solution identical to the budesonide spray, except for the active substance.

Actual start date of recruitment	15 January 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 60
Worldwide total number of subjects	60
EEA total number of subjects	60

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	60
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Children aged 4-10 that were referred to us for snoring and suspected sleep apnea during the 18 month trial period were screened and asked to participate in the trial if they fulfilled the inclusion criteria and none of the exclusion criteria.

Pre-assignment

Screening details:

134 patients were screened, 27 did not meet the inclusion criteria, 43 declined participation and 4 were excluded for other reasons.

Pre-assignment period milestones

Number of subjects started	60
Number of subjects completed	60

Period 1

Period 1 title	Overall Trial (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:

The study drugs were manufactured by APL (Apotek Produktion & Laboratorier AB, Gothenburg, Sweden) and were delivered in identical coded glass bottles in identical sealed containers, placebo was also delivered in identical packaging. Investigators and Monitor were blinded as to which child received wich treatment until after the trial period. The sleep physician was blinded to the treatment group allocation and the order of registration.

Arms

Are arms mutually exclusive?	Yes
Arm title	Budesonide treament group

Arm description:

30 children allocated to treatment with budesonide nasal spray (64 µg/mL; Rhinocort Aqua) twice daily for 6 weeks.

Arm type	Experimental
Investigational medicinal product name	Budesonide nasal spray
Investigational medicinal product code	
Other name	Rhinocort Aqua
Pharmaceutical forms	Nasal spray
Routes of administration	Nasal use

Dosage and administration details:

Budesonide nasal spray (64 µg/mL) 1 spray in each nostril twice daily

Arm title	Placebo

Arm description:

Placebo nasal spray treatment twice daily for 6 weeks

Arm type	Placebo

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

Dosage and administration details:

Placebo nasal spray, one spray in each nostril twice daily for 6 weeks

Number of subjects in period 1	Budesonide treament group	Placebo
Started	30	30
Completed	30	25
Not completed	0	5
Consent withdrawn by subject	-	3
Lost to follow-up	-	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Budesonide treament group
Reporting group description:	
30 children allocated to treatment with budesonide nasal spray (64 µg/mL; Rhinocort Aqua) twice daily for 6 weeks.	
Reporting group title	Placebo
Reporting group description:	
Placebo nasal spray treatment twice daily for 6 weeks	

Reporting group values	Budesonide treament group	Placebo	Total
Number of subjects	30	30	60
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)	30	30	60
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	5.2	5.2	
inter-quartile range (Q1-Q3)	4.7 to 5.8	4.7 to 5.7	-
Gender categorical Units: Subjects			
Female	16	11	27
Male	14	19	33

End points

End points reporting groups

Reporting group title	Budesonide treament group
Reporting group description:	
30 children allocated to treatment with budesonide nasal spray (64 µg/mL; Rhinocort Aqua) twice daily for 6 weeks.	
Reporting group title	Placebo
Reporting group description:	
Placebo nasal spray treatment twice daily for 6 weeks	

Primary: OSA-18 total score

End point title	OSA-18 total score
End point description:	
Quality of life was assessed with the Swedish version of the OSA-18, a validated 18-item questionnaire with proven test-retest reliability, construct validity, and internal consistency. It contains questions across 5 domains (sleep disturbance, physical symptoms, emotional distress, daytime function, caregivers' concerns). Each item is scored in relation to its frequency from "never" to "all the time" on a scale of 1 to 7 with a maximum score of 126. A total score <60 suggests a small impact on HRQoL; 60 to 80, a moderate impact; and >80, a large impact.10 The OSA-18 also includes a direct global rating of the child's general HRQoL based on a 10-point visual analog scale (VAS; 0 = poorest, 10 = best).	
End point type	Primary
End point timeframe:	
OSA-18 total score difference before and after 6 weeks treatment.	

End point values	Budesonide treament group	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	25		
Units: Points				
arithmetic mean (confidence interval 95%)				
Baseline	65.2 (58.8 to 71.7)	54.8 (50.1 to 59.5)		
Mean Difference After Treatment	-19.5 (-24.6 to -14.4)	-7.5 (-12.5 to -2.5)		

Statistical analyses

Statistical analysis title	OSA-18 Total Score Analysis
Comparison groups	Placebo v Budesonide treament group

Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0014
Method	Fisher Permutation Test

Secondary: OSA-18 subgroup Sleep Disturbance

End point title	OSA-18 subgroup Sleep Disturbance

End point description:

Questions regarding snoring, apnea, choking sounds and restless sleep. Possible points 4-28.

End point type	Secondary

End point timeframe:

Before and after 6 weeks treatment

End point values	Budesonide treament group	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	25		
Units: Points				
arithmetic mean (confidence interval 95%)				
Baseline	16.7 (14.7 to 18.6)	15.0 (13.2 to 16.8)		
Mean Difference After Treatment	-6.5 (-8.4 to -4.6)	-2.0 (-4.0 to 0.0)		

Statistical analyses

Statistical analysis title	OSA-18 Sleep Disturbance Analysis
Comparison groups	Budesonide treament group v Placebo
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Fisher Permutation Test

Secondary: OSA-18 subgroup Physical suffering

End point title	OSA-18 subgroup Physical suffering

End point description:

Qestions regarding mouth breathing, respiratory obstruction, nasal discharge or dysphagia. Possible points 4-28

End point type	Secondary

End point timeframe:

Before and after 6 weeks treatment

End point values	Budesonide treament group	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	25		
Units: Points				
arithmetic mean (confidence interval 95%)				
Baseline	14.7 (13.0 to 16.4)	11.9 (10.3 to 13.5)		
Mean difference after treatment	-3.9 (-5.6 to -2.3)	-2.0 (-4.1 to 0.1)		

Statistical analyses

Statistical analysis title	Physical symptoms Analysis
Comparison groups	Budesonide treament group v Placebo
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.17
Method	Fishers permutation test

Secondary: OSA-18 subgroup Emotional distress

End point title	OSA-18 subgroup Emotional distress

End point description:

Questions about moodswings, behavior and disciplin problems. Possible points 3-21.

End point type	Secondary

End point timeframe:

Before and after 6 weeks treatment

End point values	Budesonide treament group	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	25		
Units: Score				
arithmetic mean (confidence interval 95%)				
Baseline Emotional Distress	10.3 (8.4 to 12.2)	8.8 (7.1 to 10.4)		
Difference after treatment - Emotional distress	-2.0 (-3.7 to -0.4)	-1.0 (-2.8 to 0.9)		

Statistical analyses

Statistical analysis title	Physical symptoms analysis
Comparison groups	Budesonide treament group v Placebo
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.44
Method	Fishers permutation test

Secondary: OSA-18 subgroup Daytime function

End point title	OSA-18 subgroup Daytime function
End point description:	
Questions about daytime sleepiness, concentration problems and problems getting out of bed in the morning. Possible points 3-21.	
End point type	Secondary
End point timeframe:	
Before and after 6 weeks treatment	

End point values	Budesonide treament group	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	25		
Units: score				
arithmetic mean (confidence interval 95%)				
Baseline	10.3 (8.4 to 12.2)	8.7 (7.5 to 10.0)		
Mean difference after treatment	-2.2 (-3.6 to -0.8)	-1.8 (-2.8 to -0.6)		

Statistical analyses

Statistical analysis title	Daytime function analysis
Comparison groups	Budesonide treament group v Placebo

Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.71
Method	Fishers permutation test

Secondary: OSA-18 subgroup Caregivers' concerns

End point title	OSA-18 subgroup Caregivers' concerns

End point description:

Questions about caregivers concerns and frustration regarding the child's health problems. Possible points 4-28.

End point type	Secondary

End point timeframe:

Before and after 6 weeks treatment

End point values	Budesonide treament group	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	25		
Units: Score				
arithmetic mean (confidence interval 95%)				
Baseline	13.3 (11.2 to 15.3)	10.4 (8.7 to 12.1)		
Mean difference after treatment	-4.8 (-6.7 to -2.9)	-0.8 (-2.8 to 1.3)		

Statistical analyses

Statistical analysis title	Caregivers' concerns analysis
Comparison groups	Placebo v Budesonide treament group
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0057
Method	Fishers permutation test

Secondary: VAS Quality of life

End point title	VAS Quality of life

End point description:

Quality of life VAS scale from 1-10, (VAS; 0 = poorest, 10 = best)

End point type	Secondary

End point timeframe: Before and after 6 weeks treatment

End point values	Budesonide treament group	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	25		
Units: points				
arithmetic mean (confidence interval 95%)				
Baseline	6.4 (5.6 to 7.2)	7.1 (6.4 to 7.7)		
Mean difference after treatment	1.4 (0.8 to 1.9)	-0.6 (-1.3 to 0.1)		

Statistical analyses

Statistical analysis title	VAS Quality of lifa analysis
Comparison groups	Budesonide treament group v Placebo
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fishers permutation test

Secondary: Adenoid size	
End point title	Adenoid size
End point description: Grade of obstruction of the choanae by the adenoid seen with flexible fiberoptic endoscope.	
End point type	Secondary
End point timeframe: Before and after 6 weeks treatment	

End point values	Budesonide treament group	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	30		
Units: percent volume/volume				
number (confidence interval 95%)				
Baseline	75 (69 to 81)	73 (66 to 81)		
Mean difference after treatment	-9.8 (-16.3 to -3.4)	-4.1 (-10.7 to 2.6)		

Statistical analyses

Statistical analysis title	Adenoid size analysis
Comparison groups	Budesonide treament group v Placebo
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Fishers permutation test

Secondary: Tonsil size

End point title	Tonsil size
End point description: Brodski score	
End point type	Secondary
End point timeframe: Tonsil size at baseline and difference after treatment	

End point values	Budesonide treament group	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	25		
Units: Score				
arithmetic mean (standard deviation)				
Baseline	2.47 (± 0.7)	2.93 (± 0.8)		
Mean difference after treatment	-0.1 (± 0.5)	0.1 (± 0.5)		

Statistical analyses

Statistical analysis title	Tonsil size analysis
Comparison groups	Placebo v Budesonide treament group
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Fishers permutation test

Secondary: AHI

End point title	AHI

End point description:

End point type	Secondary

End point timeframe:

AHI measured with at-home respiratory polygraphy at baseline and after treatment.

End point values	Budesonide treament group	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	10		
Units: Score				
arithmetic mean (standard deviation)				
Baseline	3.33 (± 4.14)	3.27 (± 3.92)		
Mean difference after treatment	-2.84 (± 4.58)	-1.04 (± 3.49)		

Statistical analyses

Statistical analysis title	AHI analysis
Comparison groups	Budesonide treament group v Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Fishers permutation test

Adverse events

Adverse events information	
Timeframe for reporting adverse events: January 2015 to October 2106	
Assessment type	Systematic
Dictionary used	
Dictionary name	SNOMED CT
Dictionary version	2
Reporting groups	
Reporting group title	Budesonide treatment group
Reporting group description: Budesonide treatment group	
Reporting group title	Placebo group
Reporting group description: Placebo group	

Serious adverse events	Budesonide treatment group	Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Budesonide treatment group	Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 30 (10.00%)	2 / 30 (6.67%)	
Nervous system disorders			
Headache	Additional description: One child admitted to hospital over-night due to headeche and dizziness.		
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Epistaxis	Additional description: Mild nosebleed (epistaxis) that improved in all subjects when the treatment was stopped for 2 days and then commenced again.		
subjects affected / exposed	3 / 30 (10.00%)	1 / 30 (3.33%)	
occurrences (all)	3	1	

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

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29161199