Clinical trial results:
A randomized, multicenter, double-blind, placebo-controlled, parallel group study of the 12 month effect of treatment with once daily triamcinolone acetonide (NASACORT® AQ Nasal Spray 110 g) on the growth velocity of children, 3 to 9 years of age, with perennial allergic rhinitis (PAR)

Summary

EudraCT number	2014-004645-27
Trial protocol	Outside EU/EEA
Global end of trial date	12 October 2011

Results information

Result version number	v1 (current)
This version publication date	01 April 2016
First version publication date	15 May 2015

Trial information

Trial identification

Sponsor protocol code	XRG5029C_3503

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00449072
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi U.S Services Inc.
Sponsor organisation address	55 Corporate Drive Bridgewater, New Jersey, United States, NJ 08807
Public contact	Trial Transparency Team, Sanofi Aventis Recherche & Developpement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi Aventis Recherche & Developpement, Contact-US@sanofi.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 November 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 October 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to characterize the difference in prepubescent growth velocity in children 3 to 9 years of age with perennial allergic rhinitis (PAR) treated with triamcinolone acetonide (TAA) nasal spray (NASACORT® AQ 110 µg treatment group) or placebo (NASACORT® AQ placebo group) for 12-months.

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of pediatric subjects. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimized. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anesthesia may have been used to minimize distress and discomfort.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	14 March 2007
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 States: 299
Worldwide total number of subjects	299
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)	299
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:

The study was conducted between 14 March 2007 (first subject enrolled) and 12 October 2011 (last subject last visit) at 69 active centers located in the US.

Pre-assignment

Screening details:

299 subjects were randomized, 298 were treated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

3 to 9 year old subjects with PAR administered.
- Placebo (once to demonstrate IP administration in the baseline/screening period).
- Placebo in the double-blind treatment period.
All subjects were provided Children's Claritin® Syrup as a rescue medication.

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

Dosage and administration details:

Placebo to TAA-AQ was administered once at the study site in each nostril during the baseline/screening period to demonstrate intranasal IP administration. Placebo to TAA-AQ was administered intranasally once daily in each nostril during the double-blind period.

Investigational medicinal product name	Claritin® Syrup
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Syrup
Routes of administration	Oral use

Dosage and administration details:

Subjects were provided Children's Claritin® Syrup (5 mg of loratadine per 5 mL), as rescue medication for the relief of allergic rhinitis (AR) symptoms, and could be used throughout the study on an as needed basis according to the Food and Drug Administration-approved manufacturer's label.

Arm title	TAA-AQ

Arm description:

3 to 9 year old subjects with Perennial Allergic Rhinitis (PAR) administered.
- Placebo in the baseline/screening period to demonstrate administration of IP with the nasal spray bottle.
- Triamcinolone acetonide (TAA-AQ) in the double-blind treatment period. All subjects were provided Children's Claritin® Syrup as a rescue medication.

Arm type	Experimental

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

Dosage and administration details:

Placebo to TAA-AQ was administered once at the study site in each nostril during the baseline/screening period to demonstrate intranasal IP administration.

Investigational medicinal product name	Triamcinolone acetonide aqueous (TAA-AQ) nasal spray (NASACORT AQ)
Investigational medicinal product code	XRG5029
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Nasal use

Dosage and administration details:

110 µg TAA-AQ was administered once daily intranasally (1 spray delivering 55 µg of TAA-AQ in each nostril) during the double-blind treatment period.

Investigational medicinal product name	Claritin® Syrup
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Syrup
Routes of administration	Oral use

Dosage and administration details:

Subjects were provided Children's Claritin® Syrup (5 mg of loratadine per 5 mL), as rescue medication for the relief of allergic rhinitis (AR) symptoms, and could be used throughout the study on an as needed basis according to the Food and Drug Administration-approved manufacturer's label.

Number of subjects in period 1	Placebo	TAA-AQ
Started	148	151
Completed	107	109
Not completed	41	42
Relocation	3	2
Physician decision	1	-
Excluded medication	-	2
Adverse event	3	1
Non-compliance	2	5
Protocol Violation	14	12
'Withdrawal by subject '	11	8
Sponsor decision	1	3
Lost to follow-up	5	7
Lack of efficacy	1	1
Not treated	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
3 to 9 year old subjects with PAR administered. - Placebo (once to demonstrate IP administration in the baseline/screening period). - Placebo in the double-blind treatment period. All subjects were provided Children's Claritin® Syrup as a rescue medication.	
Reporting group title	TAA-AQ
Reporting group description:	
3 to 9 year old subjects with Perennial Allergic Rhinitis (PAR) administered. - Placebo in the baseline/screening period to demonstrate administration of IP with the nasal spray bottle. - Triamcinolone acetonide (TAA-AQ) in the double-blind treatment period. All subjects were provided Children's Claritin® Syrup as a rescue medication.	

Reporting group values	Placebo	TAA-AQ	Total
Number of subjects	148	151	299
Age categorical			
Age group at screening			
Units: Subjects			
<=3 to <6 years	64	65	129
<=6 to <10 years	84	86	170
Age continuous			
Age at screening			
Units: years			
arithmetic mean	6.24	6.12	
standard deviation	± 1.55	± 1.62	-
Gender categorical			
Units: Subjects			
Female	62	64	126
Male	86	87	173
Race			
Units: Subjects			
Caucasian/White	114	111	225
Black	22	28	50
Asian/Oriental	4	1	5
American Indian or Alaska Native	0	1	1
Native Hawaiian or other Pacific Island	0	0	0
Other	8	10	18
Ethnicity			
Units: Subjects			
Hispanic or Latino	23	33	56
Not Hispanic or Latino	125	118	243
Tanner classification at randomization			
Tanner classification distinguishes stages of puberty. Each stage differentiates the extent of breast, genitalia and pubic hair growth. Tanner Stage I represents the preadolescent stage where breast, genitalia and pubic hair growth are of the same size and shape as in early childhood; and in Tanner Stage 5 breasts and genitalia are of adult shape and size, and pubic hair is adult in quantity (mature			

stage). Stages 2, 3 and 4 are intermediate stages.			
Units: Subjects			
Stage 1	148	151	299
Stage 2	0	0	0
Stage 3	0	0	0
Stage 4	0	0	0
Stage 5	0	0	0

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

3 to 9 year old subjects with PAR administered.
- Placebo (once to demonstrate IP administration in the baseline/screening period).
- Placebo in the double-blind treatment period.
All subjects were provided Children's Claritin® Syrup as a rescue medication.

Reporting group title	TAA-AQ

Reporting group description:

3 to 9 year old subjects with Perennial Allergic Rhinitis (PAR) administered.
- Placebo in the baseline/screening period to demonstrate administration of IP with the nasal spray bottle.
- Triamcinolone acetonide (TAA-AQ) in the double-blind treatment period. All subjects were provided Children's Claritin® Syrup as a rescue medication.

Primary: Growth Velocity

End point title	Growth Velocity

End point description:

Individual subject's growth velocity over double-blind treatment period was calculated using a linear regression of height over time. Height was measured on the same wall-mounted Harpenden stadiometer with the subject barefoot and in light clothing. The modified intent-to-treat (mITT) population included all intent-to-treat subjects who had at least 3 postrandomization visits with recorded height measurements during the double-blind treatment period, excluding those from Good Clinical Practice (GCP) noncompliant sites.

End point type	Primary

End point timeframe:

Day 1 to end of treatment (Day 360)

End point values	Placebo	TAA-AQ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	134		
Units: centimeter/year				
least squares mean (standard error)	6.09 (± 0.122)	5.65 (± 0.122)		

Statistical analyses

Statistical analysis title	TAA-AQ vs Placebo

Statistical analysis description:

The treatment arm, age group (at Visit 1) and sex were fixed effects, and baseline growth velocity was a covariate in the ANCOVA model.

Comparison groups	Placebo v TAA-AQ

Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0096
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	-0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.78
upper limit	-0.11

Secondary: Change From Baseline in Instantaneous Total Nasal Symptom Score (TNSS)

End point title	Change From Baseline in Instantaneous Total Nasal Symptom Score (TNSS)

End point description:

PAR symptoms nasal stuffiness, nasal discharge, sneezing, and nasal itching were scored upon arising in the morning according to the following 4point scale:
0 = symptom absent,
1 = mild (present but not annoying to self),
2 = moderate (annoying to self but not interfering with sleep or daily living),
3 = severe (interfered with daily living and/or sleep) TNSS was the sum of the individual symptom scores (ranging 0-3), and TNSS ranged from 0 (best outcome) to 12 (worst outcome). A negative value for change represents an improvement in symptoms. mITT population with scores available for TNSS: All randomized and treated subjects with at least 3 post-randomization height measurements during the double-blind treatment period with scores available for TNSS, excluding those from GCP noncompliant sites.

End point type	Secondary

End point timeframe:

For 7 days prior to randomization (Baseline) and everyday for 7 days prior to Day 360 (end of treatment)

End point values	Placebo	TAA-AQ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	104		
Units: score on a scale				
least squares mean (standard error)	-2.68 (± 0.26)	-2.8 (± 0.25)		

Statistical analyses

Statistical analysis title	TAA-AQ vs Placebo

Statistical analysis description:

The treatment arm, sex and age group were fixed effects, and baseline value was a covariate in the ANCOVA model.

Comparison groups	Placebo v TAA-AQ

Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7341
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.83
upper limit	0.58

Secondary: Change From Baseline in Four Individual Nasal Symptom Scores at the End of Treatment

End point title	Change From Baseline in Four Individual Nasal Symptom Scores at the End of Treatment

End point description:

PAR symptoms - nasal stuffiness, nasal discharge, sneezing, and nasal itching were scored upon arising in the morning according to the following 4-point scale:
0 = symptom absent
1 = mild (present but not annoying to self)
2 = moderate (annoying to self but not interfering with sleep or daily living)
3 = severe (interfered with daily living and/or sleep)
Individual symptom scores ranged from 0 (best outcome) to 3 (worst outcome). A negative value for change represents an improvement in symptoms. mITT population with available nasal symptom scores: All randomized and treated participants with at least 3 post-randomization height measurements during the double-blind treatment period with available nasal symptom scores, excluding those from GCP noncompliant sites.

End point type	Secondary

End point timeframe:

For 7 days prior to randomization (Baseline) and everyday for 7 days prior to Day 360 (end of treatment)

End point values	Placebo	TAA-AQ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	134		
Units: score on a scale				
least squares mean (standard error)				
Nasal stuffiness (N=101, N=104)	-0.68 (± 0.08)	-0.83 (± 0.08)		
Nasal discharge (N=102, N=103)	-0.67 (± 0.07)	-0.71 (± 0.07)		
Sneezing (N=102, N=103)	-0.64 (± 0.07)	-0.55 (± 0.07)		
Nasal itching (N=101, N=104)	-0.69 (± 0.08)	-0.71 (± 0.08)		

Statistical analyses

Statistical analysis title	Change in nasal stuffiness
Statistical analysis description:	
The treatment arm, sex and age group were fixed effects, and baseline value was a covariate in the ANCOVA model.	
Comparison groups	Placebo v TAA-AQ
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1963
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	0.08

Statistical analysis title	Change in Nasal Discharge
Statistical analysis description:	
The treatment arm, sex and age group were fixed effects, and baseline value was a covariate in the ANCOVA model.	
Comparison groups	TAA-AQ v Placebo
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7193
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	0.17

Statistical analysis title	Change in Sneezing
Statistical analysis description:	
The treatment arm, sex and age group were fixed effects, and baseline value was a covariate in the ANCOVA model.	
Comparison groups	Placebo v TAA-AQ

Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.402
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.29

Statistical analysis title	Change in Nasal Itching

Statistical analysis description:

The treatment arm, sex and age group were fixed effects, and baseline value was a covariate in the ANCOVA model.

Comparison groups	Placebo v TAA-AQ
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8854
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.2

Secondary: Global Efficacy as Assessed by the Subject (With the Help of a Parent/Guardian/Caregiver) During and at the End of the Double-blind Treatment Period

End point title	Global Efficacy as Assessed by the Subject (With the Help of a Parent/Guardian/Caregiver) During and at the End of the Double-blind Treatment Period

End point description:

Global efficacy was assessed by the subject (with the help of a parent/guardian/caregiver) using the following scale:
0 = no relief (symptoms unchanged or worse than before),
1 = slight relief (symptoms were present and only minimally improved)
2 = moderate relief (symptoms were present and could have been troublesome but were noticeably improved)
3 = marked relief (symptoms were greatly improved and although present were scarcely troublesome)
4 = complete relief (virtually no symptom present).
mITT population: All randomized and treated subjects with at least 3 post-randomization height measurements during the double-blind treatment period, excluding those from GCP noncompliant sites.

End point type	Secondary

End point timeframe:
Day 120, Day 240 and Day 360

End point values	Placebo	TAA-AQ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	134		
Units: score on a scale				
arithmetic mean (standard deviation)				
Day 120 (N=127, N=131)	1.87 (± 1.1)	2.09 (± 1)		
Day 240 (N=115, N=116)	1.97 (± 1.04)	2.16 (± 1.03)		
Day 360 (N=125, N=125)	1.86 (± 1.08)	2.18 (± 1.19)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Day 120

Statistical analysis description:

The treatment arm, assessment visit, their interaction, sex and age group were fixed effects, and assessment visit was a repeated factor.

Comparison groups	Placebo v TAA-AQ
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0951
Method	Mixed model for repeated measures

Statistical analysis title	Statistical analysis for Day 240

Statistical analysis description:

The treatment arm, assessment visit, their interaction, sex and age group were fixed effects, and assessment visit was a repeated factor.

Comparison groups	Placebo v TAA-AQ
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1247
Method	Mixed model for repeated measures

Statistical analysis title	Statistical analysis for Day 360

Statistical analysis description:

The treatment arm, assessment visit, their interaction, sex and age group were fixed effects, and assessment visit was a repeated factor.

Comparison groups	Placebo v TAA-AQ

Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0207
Method	Mixed model for repeated measures

Secondary: Global Efficacy as Assessed by the Investigator During and at the End of the Double-blind Treatment Period

End point title	Global Efficacy as Assessed by the Investigator During and at the End of the Double-blind Treatment Period

End point description:

Global efficacy was assessed by the investigator using the following scale:
0 = no relief (symptoms unchanged or worse than before)
1 = slight relief (symptoms were present and only minimally improved)
2 = moderate relief (symptoms were present and could have been troublesome but were noticeably improved)
3 = marked relief (symptoms were greatly improved and although present were scarcely troublesome)
4 = complete relief (virtually no symptom present).
mITT population: All randomized and treated subjects with at least 3 post-randomization height measurements during the double-blind treatment period, excluding those from GCP noncompliant sites.

End point type	Secondary

End point timeframe:

Day 120, Day 240 and Day 360

End point values	Placebo	TAA-AQ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	134		
Units: score on a scale				
arithmetic mean (standard deviation)				
Day 120 (N=128, N=130)	1.89 (± 1.11)	2.04 (± 1.04)		
Day 240 (N=115, N=136)	2.11 (± 1.07)	2.21 (± 1.08)		
Day 360 (N=125, N=125)	1.8 (± 0.98)	2.14 (± 1.16)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Day 120

Statistical analysis description:

The treatment arm, assessment visit, their interaction, sex and age group were fixed effects, and assessment visit was a repeated factor.

Comparison groups	Placebo v TAA-AQ
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2445
Method	Mixed model for repeated measures

Statistical analysis title	Statistical Analysis for Day 240

Statistical analysis description:

The treatment arm, assessment visit, their interaction, sex and age group were fixed effects, and assessment visit was a repeated factor.

Comparison groups	Placebo v TAA-AQ
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4488
Method	Mixed model for repeated measures

Statistical analysis title	Statistical Analysis for Day 360

Statistical analysis description:

The treatment arm, assessment visit, their interaction, sex and age group were fixed effects, and assessment visit was a repeated factor.

Comparison groups	Placebo v TAA-AQ
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0142
Method	Mixed model for repeated measures

Secondary: Percentage of Subjects Who Used the Rescue Medication During the Double-blind Phase of the Study

End point title	Percentage of Subjects Who Used the Rescue Medication During the Double-blind Phase of the Study

End point description:

Children's Claritin® syrup was provided as a rescue medication to control allergic rhinitis (AR) symptoms and could be used throughout the study on an as needed basis. Use of rescue medication was to be documented in the subject's diary. The percentage of subjects who used the rescue medication during each of the study periods is reported. mITT population: All randomized and treated subjects with at least 3 post-randomization height measurements during the double-blind treatment period, excluding those from GCP noncompliant sites.

End point type	Secondary

End point timeframe:

Baseline (4-6 months before Day 1), double-blind treatment period (Day 1 to Day 360) and follow-up (Day 361 to Day 420)

End point values	Placebo	TAA-AQ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	134		
Units: percentage of subjects				
number (not applicable)	81.2	90.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Days Subjects Used the Rescue Medication During the Double-blind Treatment Phase of the Study

End point title	Percentage of Days Subjects Used the Rescue Medication During the Double-blind Treatment Phase of the Study

End point description:

Children's Claritin® syrup was provided as a rescue medication to control allergic rhinitis (AR) symptoms and could be used throughout the study on an as needed basis. Use of rescue medication was to be documented in the subject's diary. The percentage of days that subjects used the rescue medication during the double-blind treatment phase of the study. mITT population: All randomized and treated subjects with at least 3 post-randomization height measurements during the double-blind treatment period, excluding those from GCP noncompliant sites.

End point type	Secondary

End point timeframe:

double-blind treatment period (Day 1 to Day 360)

End point values	Placebo	TAA-AQ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	134		
Units: percentage of days				
arithmetic mean (standard deviation)	20.39 (± 28.02)	15.69 (± 21.53)		

Statistical analyses

No statistical analyses for this end point

Secondary: 24 Hour Urinary Free Cortisol Levels

End point title	24 Hour Urinary Free Cortisol Levels

End point description:

Urine cortisol levels was determined at screening, at the end of treatment, and at follow-up visit using routine laboratory testing. The normal range for urinary free cortisol for 3- to 9-year-olds was considered to be [1.4 - 21 µg/24 hours]. All randomized and treated subjects, excluding those from GCP noncompliant sites.

End point type	Secondary

End point timeframe:

Baseline (2 to 6 weeks before Day 1), end of treatment (Day 360), and at follow-up (Day 420)

End point values	Placebo	TAA-AQ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	146		
Units: µg/24 hours				
arithmetic mean (standard deviation)				
at baseline (N=146, N=141)	7.44 (± 4.23)	7.44 (± 4.04)		
at end of treatment (EOT) (N=114, N=118)	7.05 (± 5.33)	7.42 (± 5.93)		
at follow-up (N=96, N=97)	7.85 (± 5.65)	7 (± 5.28)		

Statistical analyses

No statistical analyses for this end point

Secondary: 24 Hour Cortisol/Creatinine Ratio

End point title	24 Hour Cortisol/Creatinine Ratio

End point description:

Urine cortisol and creatinine levels were determined at screening, at the end of treatment, and at follow-up visit using routine laboratory testing. The normal range for urinary free cortisol for 3- to 9-year-olds was considered to be [1.4 - 21 µg/24 hours]. No normal range is available for cortisol/creatinine ratio. All randomized and treated subjects, excluding those from GCP noncompliant sites.

End point type	Secondary

End point timeframe:

Baseline (2 to 6 weeks before Day 1), end of treatment (Day 360), and at follow-up (Day 420)

End point values	Placebo	TAA-AQ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	146		
Units: µg/g Creatinine				
arithmetic mean (standard deviation)				
at baseline (N=145, N=141)	18.94 (± 9.64)	19.44 (± 10.62)		
at end of treatment (N=114, N=118)	15.47 (± 12.6)	15.86 (± 10.77)		
at follow-up (N=96, N=97)	17.01 (± 12.63)	15.1 (± 9.54)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-emergent Adverse Events (TEAE)

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAE)

End point description:

Adverse events that developed, worsened, or became serious during the double-blind treatment period or within 7 days after the last dose of double-blind investigational product (IP) are defined as TEAEs.
A serious adverse event (SAE) was defined as any untoward medical occurrence that at any dose:
•Resulted in death
•Was life-threatening
•Required inpatient hospitalization or prolongation of existing hospitalization
•Resulted in persistent or significant disability/incapacity
•Was a congenital anomaly/birth defect
•Was a medically important event.
All randomized and treated subjects, excluding those from GCP noncompliant sites.

End point type	Secondary

End point timeframe:

From Day 1 to 7 days following end of treatment (Day 360)

End point values	Placebo	TAA-AQ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	146		
Units: subjects				
with any TEAE	113	117		
with any treatment emergent SAE	0	2		
with any TEAE leading to permanent discontinuation	3	1		
with any TEAE leading to death	0	0		
with investigational product (IP) overdose TEAE	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From treatment initiation to 7 days after the last dose of double-blind treatment (double blind treatment period)

Adverse event reporting additional description:

Adverse events that developed, worsened, or became serious during the double-blind treatment period or within 7 days after the last dose of double-blind period, i.e. Treatment-emergent adverse events.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	TAA-AQ

Reporting group description:

Placebo at screening and Triamcinolone acetonide administered in the treatment period. All subjects were provided Children's Claritin® Syrup as a rescue medication.

Reporting group title	Placebo

Reporting group description:

Placebo matched to triamcinolone acetonide at baseline and in the treatment period. All subjects were provided Children's Claritin® Syrup as a rescue medication.

Serious adverse events	TAA-AQ	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 146 (1.37%)	0 / 147 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Animal Bite			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis Ulcerative			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	TAA-AQ	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	109 / 146 (74.66%)	98 / 147 (66.67%)	
Nervous system disorders			
Headache			
subjects affected / exposed	34 / 146 (23.29%)	31 / 147 (21.09%)	
occurrences (all)	98	69	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	31 / 146 (21.23%)	37 / 147 (25.17%)	
occurrences (all)	42	62	
Ear and labyrinth disorders			
Ear Pain			
subjects affected / exposed	7 / 146 (4.79%)	14 / 147 (9.52%)	
occurrences (all)	7	15	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	19 / 146 (13.01%)	8 / 147 (5.44%)	
occurrences (all)	28	10	
Abdominal Pain Upper			
subjects affected / exposed	16 / 146 (10.96%)	15 / 147 (10.20%)	
occurrences (all)	34	21	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	10 / 146 (6.85%)	10 / 147 (6.80%)	
occurrences (all)	15	17	
Cough			
subjects affected / exposed	29 / 146 (19.86%)	30 / 147 (20.41%)	
occurrences (all)	45	51	
Oropharyngeal Pain			
subjects affected / exposed	17 / 146 (11.64%)	18 / 147 (12.24%)	
occurrences (all)	32	30	
Epistaxis			
subjects affected / exposed	16 / 146 (10.96%)	7 / 147 (4.76%)	
occurrences (all)	27	23	
Nasal Congestion			

subjects affected / exposed	6 / 146 (4.11%)	11 / 147 (7.48%)	
occurrences (all)	9	17	
Rhinorrhoea			
subjects affected / exposed	8 / 146 (5.48%)	9 / 147 (6.12%)	
occurrences (all)	17	13	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	10 / 146 (6.85%)	4 / 147 (2.72%)	
occurrences (all)	19	5	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	28 / 146 (19.18%)	18 / 147 (12.24%)	
occurrences (all)	46	32	
Otitis Media			
subjects affected / exposed	4 / 146 (2.74%)	8 / 147 (5.44%)	
occurrences (all)	5	8	
Pharyngitis Streptococcal			
subjects affected / exposed	12 / 146 (8.22%)	10 / 147 (6.80%)	
occurrences (all)	17	14	
Sinusitis			
subjects affected / exposed	12 / 146 (8.22%)	11 / 147 (7.48%)	
occurrences (all)	14	17	
Influenza			
subjects affected / exposed	10 / 146 (6.85%)	3 / 147 (2.04%)	
occurrences (all)	10	3	
Gastroenteritis Viral			
subjects affected / exposed	8 / 146 (5.48%)	6 / 147 (4.08%)	
occurrences (all)	10	7	
Upper Respiratory Tract Infection			
subjects affected / exposed	25 / 146 (17.12%)	19 / 147 (12.93%)	
occurrences (all)	34	27	
Viral Infection			
subjects affected / exposed	9 / 146 (6.16%)	3 / 147 (2.04%)	
occurrences (all)	9	4	
Viral Upper Respiratory Tract Infection			

subjects affected / exposed occurrences (all)	9 / 146 (6.16%) 11	9 / 147 (6.12%) 14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 July 2005	- Removal of the nasal spray aerosol type only. - Removal Single-blind single-blind NASACORT AQ placebo, which was planned at baseline. - Removal of stratification by age grouping. - Removal of randomization procedure, including Interactive voice response system. - Removal of statistical methods, including subset analyses. - Removal of the NASACORT AQ HFA Nasal Aerosol reference materials.
27 September 2005	- Limiting the inclusion age to 3 years of age and older. - Clarifying why mild asthma is an inclusion criterion. - Excluding children with a bone age which is different from chronological age by more than 1 year. - Withholding intranasal corticosteroids and high potency topical corticosteroids for at least 6 weeks prior to baseline assessments. - Performing an additional physical examination and Tanner staging at the final follow-up visit (Visit 11). - Use of the 12-hour urinary free cortisol and not the urinary free cortisol corrected for creatinine to assess the effect of treatment on hypothalamic-pituitary-adrenal (HPA) axis. - Repeating the PAR symptoms assessment at the end of treatment, in addition to the proposed 14-day assessment prior to randomization. - Additional analyses to be included: A subset analysis excluding any subject who exhibits >Tanner Stage 2 characteristics at the end of treatment period; An analysis of the percent of children who are below a certain percentile of growth velocity (eg, 3 rd percentile) or percent of children whose percentile of height decreases during the treatment period; A subset analysis excluding children who receive systemic corticosteroids during the double-blind treatment period. - A statistical analysis adjusting for the age factor in order to prevent variation between strata that could contribute to variation in the treatment effect. - A linear regression model as it is a better method to estimate growth velocity since it takes into account all height measurements during the treatment period (vs change from baseline in height where it does not). - Removal CLARITIN Reditabs as a rescue medication option.
09 January 2006	Corrections in typographical errors and clarification of the timing of the dose.

15 September 2006	- An administrative change in responsible medical expert and sponsor signatory. - A change in the protocol title to extend the age range from 3-8 to 3-9 (9 year old males only). - A correction in the study duration and dates. - Re-wording of the Primary and Secondary Objectives; Inclusion and Exclusion Criteria; Concomitant Treatments section for greater clarity - A change in the Study Design to remove the Single-Blind Run-In period and insert the use of demo placebo prior to randomization at Visit 3 - A change in Urinary Cortisol from 12 hour to 24 hour along with insertion of cortisol/creatinine ratio assessment in addition to urinary free cortisol; and insertion of normal ranges. - A change in the Treatments section to add demo placebo and greater detail regarding the use of the rescue medication, Claritin Syrup. - A change in study schedule at Visit 2 from -2 wks to -3 weeks to allow 1 week in which to complete the 24 urine collection and to ensure results are available to site prior to Visit 3, Randomization; also inserted early term visit procedures. - The Period of Observation extended to the time the last 24 hour urine specimen is returned after the final visit (V11 or Early Term Visit). - Inclusion of the revised NASACORT AQ package insert. - Deletion of the Appendices for the US NCHS Growth charts for boys and girls-5th to 95th percentiles, as only the 3rd to 97th percentile growth charts were to be used.
16 January 2007	- Correction in staff location and nonfunctional hyperlinks. - Acceptance of an alternative bone image for bone assessment. - Modification of the inclusion criterion for rhinitis symptom score. - Demonstration of the placebo actuator earlier. - Adjustment of rescue medication use per manufacturer's instructions. - Inclusion of a compliance measurement of partial dose administration. - Restriction of wearing shoes, socks, or head cover during height and weight measurements and allow a subject to wear light clothing or gown during height and weight measurements - Clarification that subject-reported daily diaries were to be dispensed at Visit 1 and collected, reviewed, and dispensed at Visits 2, 11, and early withdrawal Clarification of when subjects might prematurely be withdrawn - Administration of the first dose at the site - Clarification that subjects who become toilet trained after Visit 2 and did not complete the Visit 2 urine collection would not participate in the 24-hour urine collection procedure - Clarification that subjects who may have an abnormal cortisol at Visit 11 or an early withdrawal visit should either be continued for follow- up or referred to another physician – with documentation in the case report form - Permit the investigator or their designee to assess the validity of the 24-hour urine specimen - Define overdose by the sponsor - Permission of breaking of the blind by the investigator for expedited reporting or emergency medical treatment that would result in subject withdrawal.

11 September 2008	- Changed Visit 10 study day from 365 ± 5 to 360 ± 5 days after Visit 3. - Deletion of bone age Inclusion and Exclusion criteria at Visit 2. - Removal of bone age assessment from the protocol. - Addition of Inclusion criterion: subjects must be toilet-trained. - Addition of exclusion criterion: abnormal 24-hour urinary free cortisol level. - Clarification of Upper Respiratory Tract Infection, sinus infection, or nasal candidiasis. - Clarification of inclusion criterion to specify "legal guardian" and to require subjects 7 years of age and older to provide a signed assent form. - Changed the expected duration of the study from 44 months to 56 months, and the end of subject recruitment from 1st quarter 2009 to 1st quarter 2010. - Provided instructions regarding the labeling of each bottle of the investigational product and instructions to subjects and caregivers. - Provided compliance rate calculation and dosing adherence post-randomization. - Deletion of exclusion criterion regarding concomitant use of nasal or oral antihistamine or decongestant or oral leukotriene modifier prior to Visit 3. - Expanded visit window for screening (Visit 1) and baseline (Visit 2). - Added permission to allow non-randomized subject to be re-screened and re-entered into the study. - Clarification of sample size calculation. - Broadening the definition of ITT population to include all subjects who received at least 1 dose of investigational product, regardless of their randomization status. - Clarification of the End of Study follow-up period. - Changed "Early Withdrawal" to "Early Termination". - Clarification that End of Study (Follow-up/post-treatment) Visit 11 procedures should be completed at 60 ± 5 days after Visit 10 or an Early Termination visit. - Changed the 6-month visit date from 182 ± 5 days to 180 days ± 5 days and 12-month visit date from 365 ± 5 days to 360 ± 5 days. - Changed language to clarify stratification by age and sex.
01 December 2008	- Expansion the number of clinical sites (from 60 to 100). - Clarification of systemic corticosteroid exclusion criterion: Treatment with systemic corticosteroids >2 courses received up to 1 year before Visit 1 was exclusionary. Up to 2 courses of systemic corticosteroids, each course not exceeding 14 days, up to 1 year before Visit 1 was allowed.
23 April 2010	- Conduct the primary analysis in the mITT population. - Conduct sensitivity analyses in the intent-to-treat (ITT) and per-protocol (PP) populations and other defined analysis sets. - Define an mITT and PP population(s). - Broaden the desired precision for growth velocity to a total width of 2*0.45 cm/year. - Recalculate the sample size based on the desired precision . - Identify unusual individual growth velocities and discuss their impact on the results of the overall analysis of growth velocity in the clinical study report. - Perform statistical analyses that exclude questionable height measurements and include the percent of subjects who are below certain percentiles of growth velocity. - Perform descriptive statistics (comparison) on the growth velocities by sex and ethnicity. - Summarize the number of subjects at each visit (from screening to follow-up) by investigational product treatment group. - Conduct sensitivity analysis using the random-effects model accounting for repeated height measurements within subjects and for the difference in variance of the estimated individual growth slopes when the number of height measurements per subject varies across subjects

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.

Two study sites with significant GCP noncompliance were reported to the U.S. Food and Drug Administration (FDA) by the Sponsor. A total of 5 treated participants (1 placebo and 4 TAA-AQ) from these 2 study sites were excluded from the analysis.

Notes: