Clinical trial results:
A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study Evaluating the Pharmacodynamic Effect of a 6-week Treatment With Triamcinolone Acetonide Aqueous Nasal Spray 110 g and 220 g Once Daily on Basal Hypothalamic-Pituitary-Adrenal (HPA) Axis Function in Children [>=2 to < 12 Years of Age] With Allergic Rhinitis

Summary

EudraCT number	2014-004646-98
Trial protocol	Outside EU/EEA
Global end of trial date	10 October 2010

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	15 May 2015

Trial information

Trial identification

Sponsor protocol code	TRICA_L_04286

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01154153
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi U.S Services Inc.
Sponsor organisation address	55 Corporate Drive, Bridgewater, NJ, United States, 08807
Public contact	Trial Transparency Team, Sanofi Aventis recherche & Development, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi Aventis recherche & Development, 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	09 November 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 October 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the effect of a 6-week treatment with TAA-AQ (110 µg) and TAA-AQ (220 µg) once daily (QD) versus placebo on hypothalamic-pituitary-adrenal (HPA) axis function as measured by serum cortisol AUC(0-24 hr) in children (>=2 to <12 years old) with allergic rhinitis (AR).

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	16 June 2010
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: 140
Worldwide total number of subjects	140
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)	140
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 performed in 8 study centres in the United States.

Pre-assignment

Screening details:

Of 179 screened subjects, 31 subjects were screen failures and 8 subjects did not continue as the limit on the number of subjects to be randomized had been reached. 140 subjects were randomized.

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, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Children >=2 to <12 years old with AR symptoms who received placebo during the screening phase and placebo during the treatment phase. All children had the option to take rescue medication, (Claritin®) as needed to relieve symptoms of AR.

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

Dosage and administration details:

Children's Claritin® Syrup [5 mg of loratadine per 5 mL] could be taken orally for the relief of AR symptoms throughout the study on an as needed basis, according to the Food and Drug Administration-approved manufacturer's label.

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

Dosage and administration details:

1 spray/nostril, once daily in the morning, for 8 to 24 days during the screening phase.
For children who were >=2 to <6 years old, 1 spray/nostril, once daily in the morning, for 6 weeks, during the double-blind treatment phase.
For children who were >= 6 yrs to <12 years old, either 1 spray/nostril or 2 sprays/nostril, once daily in the morning, for 6 weeks, during the double-blind treatment phase.

Arm title	TAA-AQ

Arm description:

Children >=2 to <12 years old with AR symptoms who received placebo during the screening phase and TAA-AQ (Nasacort AQ) during the treatment phase. All children had the option to take rescue medication, (Claritin®) as needed to relieve symptoms of AR.

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:

1 spray/nostril, once daily in the morning, for 8 to 24 days during the screening phase.

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

Dosage and administration details:

Children's Claritin® Syrup [5 mg of loratadine per 5 mL] could be taken orally for the relief of AR symptoms throughout the study on an as needed basis, according to the Food and Drug Administration-approved manufacturer's label.

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:

Treatment assignment was randomized with stratification by sex and age group (>=2 to <6, >=6 to <12 years old).
- For children who were >=2 to <6 years old, 1 spray/nostril (110 µg TAA-AQ), once daily in the morning, for 6 weeks, during the double-blind treatment phase.
- For children who were >=6 yrs to <12 years old, either 1 spray/nostril (110 µg TAA-AQ) or 2 sprays/nostril (220 µg TAA-AQ), once daily in the morning, for 6 weeks, during the double-blind treatment phase.

Number of subjects in period 1	Placebo	TAA-AQ
Started	71	69
Completed	66	66
Not completed	5	3
Poor compliance to protocol	2	-
Unable to use labs	2	3
'Withdrew consent '	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Children >=2 to <12 years old with AR symptoms who received placebo during the screening phase and placebo during the treatment phase. All children had the option to take rescue medication, (Claritin®) as needed to relieve symptoms of AR.	
Reporting group title	TAA-AQ
Reporting group description:	
Children >=2 to <12 years old with AR symptoms who received placebo during the screening phase and TAA-AQ (Nasacort AQ) during the treatment phase. All children had the option to take rescue medication, (Claritin®) as needed to relieve symptoms of AR.	

Reporting group values	Placebo	TAA-AQ	Total
Number of subjects	71	69	140
Age categorical Units: Subjects			
>=2 to < 4 years	6	5	11
>=4 to < 6 years	15	16	31
>=6 to < 12 years	50	48	98
Age continuous Units: years			
arithmetic mean	7.3	7.1	
standard deviation	± 2.7	± 2.5	-
Gender categorical Units: Subjects			
Female	29	28	57
Male	42	41	83
Race/Ethnicity Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	0	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	22	22	44
White	43	42	85
Others	4	5	9
Region of Enrollment Units: Subjects			
United States	71	69	140
Tanner Classification			
Tanner classification distinguishes stages of puberty. Each stage represents the extent of breast, genitalia and pubic hair growth. Tanner Stage I represents the pre-adolescent 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	55	60	115
Stage 2	12	9	21
Stage 3	4	0	4

Stage 4	0	0	0
Stage 5	0	0	0
Primary Allergic Rhinitis Diagnosis			
Subjects diagnosed with perennial allergic rhinitis (PAR); and seasonal allergic rhinitis (SAR).			
Units: Subjects			
PAR only	11	12	23
SAR only	5	3	8
Both PAR and SAR	55	54	109
Time from the first Allergic Rhinitis symptom to Visit 1			
For subjects with both PAR and SAR, it is the longest time. A missing month of the first symptom start date was imputed as December and a missing day was imputed as the last date of the month.			
Units: years			
arithmetic mean	4.82	4.79	
standard deviation	± 2.7	± 2.48	-

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Children >=2 to <12 years old with AR symptoms who received placebo during the screening phase and placebo during the treatment phase. All children had the option to take rescue medication, (Claritin®) as needed to relieve symptoms of AR.

Reporting group title	TAA-AQ

Reporting group description:

Children >=2 to <12 years old with AR symptoms who received placebo during the screening phase and TAA-AQ (Nasacort AQ) during the treatment phase. All children had the option to take rescue medication, (Claritin®) as needed to relieve symptoms of AR.

Primary: Ratio of Serum Cortisol Area Under Curve [AUC(0-24 hr)] at the End of Treatment to Baseline

End point title	Ratio of Serum Cortisol Area Under Curve [AUC(0-24 hr)] at the End of Treatment to Baseline

End point description:

Blood samples were collected over a 24-hour period (at 0, 2, 4, 8, 12, 20, and 24 hours), with 0 hour being between 8:00AM to 9:00AM, immediately prior to investigational product (IP) administration. AUC (0-24hr) was calculated using the trapezoid rule, and was normalized by dividing the AUC(0-24 hr) by the actual sample collection interval between 0-hour and 24-hour blood draw times.
Ratio in Serum Cortisol AUC(0-24 hr) = (Serum Cortisol AUC[0-24 hr] at 6 weeks postrandomization)/(Serum Cortisol AUC[0-24 hr] at 1-3 days prerandomization). Log transformation was used for the analysis. The per protocol (PP) population included all randomized subjects who took at least one dose of study medication and had no major protocol violations. Major protocol violations were those deemed most likely to affect the interpretation of the results and included poor compliance, use of prohibited medication, missing blood samples.

End point type	Primary

End point timeframe:

1-3 days prerandomization and 6 weeks postrandomization

End point values	Placebo	TAA-AQ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	65		
Units: Ratio				
geometric mean (full range (min-max))	0.938 (0.39 to 1.63)	0.898 (0.48 to 4.45)		

Statistical analyses

Statistical analysis title	TAA-AQ vs Placebo

Statistical analysis description:

Missing values imputed with multiple imputation. AUC(0-24hr) was calculated for each imputation & analyzed with log-transformation using ANCOVA model with treatment (Tx), sex, age group as fixed effects & log-transformed baseline value as covariate. Mean difference in log scale between treatments & its SE were calculated by LS mean. Results from multiply imputed data were combined using SAS

procedure MIANALYZE. Tx ratio was calculated as exponential of mean difference between Tx in log scale.

Comparison groups	Placebo v TAA-AQ
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Treatment Ratio of Geometric mean
Point estimate	0.966
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.892
upper limit	1.045

Secondary: Change From Baseline in the Reflective Total Nasal Symptom Score (rTNSS)

End point title	Change From Baseline in the Reflective Total Nasal Symptom Score (rTNSS)

End point description:

Every morning, subjects rated the severity of symptoms experienced over the previous 24 hours using scale from 0-3, where 0=symptoms absent, 1=mild, 2=moderate, and 3=severe symptoms (interfere with daily living or sleep) for each symptom (nasal congestion, nasal itching, sneezing, and runny nose). The rTNSS was the sum of the individual symptom scores, ranged from 0-12 (where 12 reflected the worst symptoms).
Change from baseline in the rTNSS = mean rTNSS (double-blind treatment phase) - mean rTNSS (screening phase).The per protocol (PP) population included all randomized subjects who took at least one dose of study medication and had no major protocol violations. Major protocol violations were those deemed most likely to affect the interpretation of the results and included poor compliance, use of prohibited medication, missing blood samples.

End point type	Secondary

End point timeframe:

From 8-24 days prerandomization up to 6 weeks postrandomization

End point values	Placebo	TAA-AQ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	65		
Units: Score on a scale				
arithmetic mean (standard deviation)	-0.22 (± 1.12)	-1.07 (± 1.66)		

Statistical analyses

Statistical analysis title	TAA-AQ vs Placebo

Statistical analysis description:

For ANCOVA, treatment arm, randomization strata were fixed effects and baseline value was a covariate.

Comparison groups	Placebo v TAA-AQ

Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.34
upper limit	-0.37

Secondary: Number of Subjects by Relief Level as Evaluated by the Physician

End point title	Number of Subjects by Relief Level as Evaluated by the Physician

End point description:

Efficacy of treatment was assessed by the physician using a scale from 0-4 for relief levels, where 0 = no relief (symptoms unchanged or worsened than before), 1 = slight relief (symptoms present and only minimally improved), 2 = moderate relief (symptoms are present and may be troublesome, but are noticeably improved), 3 = marked relief (symptoms are greatly improved and although present are scarcely troublesome) and 4 = complete relief (virtually no symptom present). The per protocol (PP) population included all randomized subjects who took at least one dose of study medication and had no major protocol violations. Major protocol violations were those deemed most likely to affect the interpretation of the results and included poor compliance, use of prohibited medication, missing blood samples.

End point type	Secondary

End point timeframe:

At end of study (43-50 days after randomization)

End point values	Placebo	TAA-AQ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	65		
Units: Subjects				
Relief Level 0 (No relief)	11	9		
Relief Level 1 (Slight relief)	18	13		
Relief Level 2 (Moderate relief)	16	20		
Relief Level 3 (Marked relief)	13	17		
Relief Level 4 (Complete relief)	3	6		

Statistical analyses

Statistical analysis title	TAA-AQ vs Placebo
Comparison groups	Placebo v TAA-AQ

Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1332 [1]
Method	Cochran-Mantel-Haenszel

Notes:

[1] - Based on the ordinal evaluation score and adjusted for the randomization strata.

Secondary: Number of Subjects by Relief Level as Evaluated by the Subject

End point title	Number of Subjects by Relief Level as Evaluated by the Subject

End point description:

Efficacy of treatment was assessed by the subject using a scale from 0-4 for relief levels, where 0 = no relief (symptoms unchanged or worsened than before), 1 = slight relief (symptoms present and only minimally improved), 2 = moderate relief (symptoms are present and may be troublesome, but are noticeably improved), 3 = marked relief (symptoms are greatly improved and although present are scarcely troublesome) and 4 = complete relief (virtually no symptom present). The per protocol (PP) population included all randomized subjects who took at least one dose of study medication and had no major protocol violations. Major protocol violations were those deemed most likely to affect the interpretation of the results and included poor compliance, use of prohibited medication, missing blood samples.

End point type	Secondary

End point timeframe:

At end of study (43-50 days after randomization)

End point values	Placebo	TAA-AQ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	65		
Units: Subjects				
Relief level 0 (No relief)	9	5		
Relief level 1 (Slight relief)	17	22		
Relief level 2 (Moderate relief)	16	13		
Relief level 3 (Marked relief)	14	16		
Relief level 4 (Complete relief)	5	9		

Statistical analyses

Statistical analysis title	TAA-AQ vs Placebo
Comparison groups	Placebo v TAA-AQ
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3314 [2]
Method	Cochran-Mantel-Haenszel

Notes:

[2] - Based on the ordinal evaluation score and adjusted for the randomization strata.

Secondary: Number of Subjects Using Rescue Medication

End point title	Number of Subjects Using Rescue Medication

End point description:

The number of subjects using the rescue medication (Claritin®) during the single-blind screening phase (the time from 8-24 days before randomization up to the day before randomization) and during the double-blind treatment phase (the time from randomization to end of study). The per protocol (PP) population included all randomized subjects who took at least one dose of study medication and had no major protocol violations. Major protocol violations were those deemed most likely to affect the interpretation of the results and included poor compliance, use of prohibited medication, missing blood samples.

End point type	Secondary

End point timeframe:

From 8 to 24 days prerandomization and randomization to end of study (43-50 days postrandomization)

End point values	Placebo	TAA-AQ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	65		
Units: Subjects				
Prerandomization period	8	8		
Postrandomization period	24	19		

Statistical analyses

No statistical analyses for this end point

Secondary: The Percent of Days of Rescue Medication Use During the Double-blind Treatment Phase

End point title	The Percent of Days of Rescue Medication Use During the Double-blind Treatment Phase

End point description:

The percent of days of rescue medication used during the double-blind treatment phase was calculated. For subjects who did not use any rescue medication, the percentage of days using rescue medication was set to be 0. The per protocol (PP) population included all randomized subjects who took at least one dose of study medication and had no major protocol violations. Major protocol violations were those deemed most likely to affect the interpretation of the results and included poor compliance, use of prohibited medication, missing blood samples.

End point type	Secondary

End point timeframe:

From randomization to 43-50 days postrandomization

End point values	Placebo	TAA-AQ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	65		
Units: Percentage of days				
arithmetic mean (standard deviation)	4.02 (± 12.77)	3.07 (± 11.82)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Days 43 to 50 post-randomization) regardless of seriousness or relationship to investigational product.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	TAA-AQ

Reporting group description:

Children >=2 to <12 years old with AR symptoms who received placebo during the screening phase and TAA-AQ (Nasacort AQ) during the treatment phase. All children had the option to take rescue medication, (Claritin®) as needed to relieve symptoms of AR.

Reporting group title	Placebo

Reporting group description:

Children >=2 to <12 years old with AR symptoms who received placebo during the screening phase and placebo during the treatment phase. All children had the option to take rescue medication, (Claritin®) as needed to relieve symptoms of AR.

Serious adverse events	TAA-AQ	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 69 (0.00%)	1 / 71 (1.41%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Humerus Fracture			
subjects affected / exposed	0 / 69 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
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	7 / 69 (10.14%)	12 / 71 (16.90%)	
Nervous system disorders			
Headache			

subjects affected / exposed	2 / 69 (2.90%)	4 / 71 (5.63%)	
occurrences (all)	7	4	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 69 (5.80%)	2 / 71 (2.82%)	
occurrences (all)	4	2	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	3 / 69 (4.35%)	7 / 71 (9.86%)	
occurrences (all)	5	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 January 2010	- The primary objective of this study: To evaluate the effect of a 6-week treatment with triamcinolone acetonide aqueous nasal spray versus placebo on basal hypothalamic-pituitaryadrenal (HPA) axis function as measured by plasma cortisol area under the curve (AUC[0-24hr]). - Inclusion of children down to 2 years of age in study population. - Inclusion of the subject's diaries and assessment of global efficacy in drug compliance assessment. - Statistical analyses was to be performed with and without log transformation of the plasma cortisol (24-hour plasma cortisol and 24-hour plasma cortisol trough).
18 May 2010	- Total blood volume to be collected per subject for the study would be approximately no more than 98 mL. - Total blood volume by test would be: 84 mL for serum cortisol; 9 mL for clinical laboratoryanalytes; 5 mL for ImmunoCAP. - Cortisol measurements was to be performed on blood serum and not blood plasma.
12 July 2010	- The 24-hour blood draw schedule was revised to allow for up to 2 extra drawings of blood samples if needed. These extra samples were to be drawn only if the initial blood sample was inadequate or mishandled, as long as the ± 15 minute time frame for that pre-specified time point had not expired. - Exclusion criteria was modified for morning serum cortisol in alignment with published literature and the previous pivotal Phase 3 protocol XRG5029C/3502.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported