Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

Triamcinolone acetonide

Nasacort

CZ/W/0010/pdWS/001

Rapporteur:	Czech Republic
Finalisation procedure (day 120):	30.7.2018

TABLE OF CONTENTS

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Nasacort
INN (or common name) of the active substance(s):	Triamcinolone acetonide
MAH(s):	Sanofi Aventis
Pharmaco-therapeutic group (ATC Code):	R01AD11 – decongestants and other nasal preparations for topical use
Pharmaceutical form(s) and strength(s):	Triamcinolone 55 micrograms/dose nasal spray suspension

I. EXECUTIVE SUMMARY

This is an assessment of data for Triamcinolone acetonide. A MAH submitted paediatric studies evaluated the efficacy of the use of triamcinolone acetonide in paediatric population, in accordance with Article 45 of Regulation (EC) No1901/2006, as amended. The CZ was Rapporteur for this procedure.

Changes to the paediatric information in sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC have been proposed. A corresponding update to the PIL has also been proposed.

SmPC changes are proposed in sections:
Section 4.1: use in children 2 years and over
Section 4.2: dosage recommendation for children 2 to 5 years
Section 4.4: warning that Nasacort is not recommended for children below 2 years
Section 4.8: adverse events specific for paediatric population 2-5 years added
Section 5.1: results of studies on the influence on the HPA axis in patients 2-5 years added
Section 5.2: pharmacokinetic properties specific to paediatric patients added.

The PIL has been updated to reflect the proposed changes to the SmPC.

Overall the rapporteur considers that the submitted data are sufficient to extend the indication of triamcinolone acetonide aqueous (TAA-AQ) nasal spray for the treatment of perennial allergic rhinitis (PAR) and seasonal allergic rhinitis (SAR) for children aged over 2 years from the current indication of adults, adolescents, and children 6-11 years of age. Adequate clinical study performed in children 2-5 years of age demonstrated that the proposed dose of 110 µg of nasal spray once daily provided a statistically significant improvement in reflective total nasal symptom score (rTNSS) compared to placebo in children with PAR with or without SAR.

Summary of outcome

☐ No change

☒ Change

☐ New study data

☐ New safety information

☐ Paediatric information clarified

☒ New indication: sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2

II. RECOMMENDATION[1]

Based on the clinical information submitted by the applicant, an update to paediatric information should be implemented.

[1] *The recommendation from section V can be copied in this section.*

Paediatric wording in the SmPC:

The proposed additions are marked in **bold,** proposed deletions in ~~strikethrough~~**.**

4.1 Therapeutic indications

NASACORT is indicated for the treatment of symptoms of seasonal and perennial allergic rhinitis **in adults and children 2 years of age and over.**

4.2 Posology and method of administration

Adults
~~*Patients aged 12 years and over:*~~ The recommended starting dose is 220 micrograms as 2 sprays in each nostril once daily. Once symptoms are controlled patients can be maintained on 110 micrograms (1 spray in each nostril once daily).

Paediatric population
Children aged 12 years and over
The recommended starting dose is 220 micrograms as 2 sprays in each nostril once daily. Once symptoms are controlled patients can be maintained on 110 micrograms (1 spray in each nostril once daily).

Children aged 6 to 12 years
~~*Paediatric patients aged 6 to 12 years:*~~ The recommended dose is 110 micrograms as 1 spray in each nostril once daily. In patients with more severe symptoms, a dose of 220 micrograms may be used. But once symptoms are controlled, patients should be maintained on the lowest effective dose (see sections 4.4 and 5.1). ~~Until further evidence is available, continuous use beyond 3 months is not recommended.~~

Children aged 2 to 5 years
The recommended and maximum dose is 110 micrograms as 1 spray in each nostril once daily (see sections 4.4 and 5.1).

~~Until further evidence is available,~~ **C**ontinuous use beyond 3 months in children under 12 years is not recommended.

4.4 Special warnings and precautions for use

Paediatric population
~~As experience with NASACORT in children under 6 years of age is limited, use in this age group is not recommended~~**. NASACORT is not recommended for use in children under 2 years of age.**

Reduction in growth velocity has been reported in children receiving nasal corticosteroids, ***including NASACORT*** *at licensed doses.* ***See section 5.1.***

It is recommended that the height of children receiving ~~prolonged~~ treatment with nasal corticosteroids is regularly monitored. ~~If growth is slowed, t~~ Therapy should be managed ~~reviewed~~ with the aim of reducing the dose of nasal corticosteroid, if possible, to the lowest dose at which effective control of symptoms is maintained.
~~*In addition, consideration should be given to referring the patient to a paediatric specialist.*~~ *The long-term effects of reduction in growth velocity associated with nasal corticosteroids, including*

the impact on final adult height are unknown. ***In addition, consideration should be given to referring the patient to a paediatric specialist, especially for children under the age of 6 years this is strongly recommended****.*

5.1 Pharmacodynamic properties
In clinical studies performed in adults and children **6 years of age and above** at doses up to 440 µg/day intranasally, **and in children 2 to 5 years of age at 110 µg/day intranasally,** no suppression of the Hypothalamic-Pituitary-Adrenal (HPA) axis has been observed.

5.2 Pharmacokinetic properties

~~Following multiple doses in paediatric patients, plasma drug concentrations, AUC, Cmax and Tmax were similar to those values observed in adult patients.~~

Paediatric population

Following multiple doses intranasal administration of NASACORT, systemic exposures observed in paediatric patients 6 to 12 years of age were similar to those observed in adult patients**.**

Intranasal administration of NASACORT 110 µg once daily in paediatric patients 2 to 5 years of age exhibited similar systemic exposure to that achieved in adult patients at a dose of 220 µg once daily.

The apparent clearance and volume of distribution in paediatric patients 2 to 5 years of age were found to be approximately half of that in adults.

Paediatric wording in the PL:

Section 1, What Nasacort is and what it is used for:

Nasacort contains a medicine called triamcinolone acetonide. This belongs to a group of medicines called corticosteroids which means it is a type of steroid. It is given as a spray in the nose to treat the nasal symptoms of allergic **rhinitis in adults and children 2 years of age and over**.

Section 2, Children (under **2** ~~6~~ years):

This medicine is not recommended for use in children under **2** ~~6~~ years of age.

Section 3: How much Nasacort to use:

Children (2 to 5 years)
- **The usual dose is 1 spray in each nostril each day**

Do not use Nasacort for more than 3 months in children under 12 years old
An adult should help a young child use this medicine.
~~Children (under 6 years) Check with your doctor or pharmacist before using~~

III. INTRODUCTION

For the work-sharing procedure, data regarding paediatric use of triamcinolone acetonide were submitted in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

Nasacort 55 micrograms/dose, nasal spray, suspension contains triamcinolone acetonide as an active substance. The currently approved indication is treatment of symptoms of seasonal and perennial allergic rhinitis.
Triamcinolone acetonide is a more potent derivative of triamcinolone and is approximately 8 times more potent than prednisone. Although the precise mechanism of corticosteroid antiallergic action is unknown, corticosteroids are very effective in the treatment of allergic diseases in man.
In October 2013, the MAH submitted the paediatric package for Nasacort 55 micrograms/dose nasal spray suspension in accordance with Art. 45 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

The MAH proposed the following regulatory action:
Changes to the SmPC to reflect the available clinical data and recommend Nasacort for use in children between 2 and 5 years of age, with appropriate posology and appropriate safety information.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical studies

In all submitted studies, Nasacort (triamcinolone acetonide aqueous, TAA-AQ) nasal spray suspension 55 micrograms/dose was used.

IV.2 Non-clinical aspects

N/A

IV.3 Clinical aspects

1. Introduction

The Applicant has submitted several studies relevant for the proposed changes:

Pharmacokinetics: Studies which evaluate the PK of triamcinolone acetonide in allergic rhinitis patients 2 to 5 years of age (XRG5029/1000 and XRG5029/3502). In addition, a population pharmacokinetic model was developed from these studies (study POH0176).

Pharmacodynamics: Specific pharmacodynamics studies were conducted in children with TAA-AQ in order to assess the potential effects on the Hypothalamic-Pituitary-Adrenal (HPA) axis and on growth velocity. They are listed in Table 1.

Table 1: Clinical studies evaluating pharmacodynamics of triamcinolone

Study identification	Publication	Study Type	Study design	Subject age (year)	Treatment dose (µg)	Treatment duration (week) / N
Internal reports						
RG5029Y-125	Nayak AS et al. 1998 (14)	Adrenal function and PK in AR patients	Randomized, double-blind, placebo-controlled, parallel group, multicenter	6 - 12	TAA-AQ: 220, 440 Placebo	6 / 80
XRG5029C/3502	Weinstein et al. 2009 (15)	Adrenal function in a subset of patients with AR	4-week randomized, double-blind, placebo-controlled period followed by 6-month open-label period	2 - 5	TAA-AQ: 110 Placebo	26 / 61
RG5029Y-315	Skoner et al. 2000 (16) Skoner et al. 2003 (17)	Short-term growth in AR patients	Randomized, double-blind, 4-way cross-over, single center	4 - 10	TAA-AQ: 110, 220, placebo Flonase 200	2 / 59
XRG5029C/3503	-	Effect on growth of long-term treatment in PAR patients	Randomized, double-blind, placebo-controlled, parallel group, multicenter	3 - 9	TAA-AQ: 110, placebo	52 / 298
Trica_L_04286	-	Adrenal function in AR patients	Randomized, double-blind, placebo-controlled, parallel group, multicenter	2 - 12	TAA-AQ: 110, 220, placebo	6 / 140
Publication						
Skoner et al. 2008 (18)	-	Effect on growth in AR patients	Non-comparative, prospective	6 - 14	TAA-AQ: 110, 220	1 to 2 years / 39

Of note, two of pharmacodynamics studies (TRICA_L_04286 and XRG5029C/3503) have been already evaluated during Art. 46 paediatric worksharing procedure UK/W/0047/pdWS/001.

Clinical efficacy: Several clinical trials were conducted to assess the efficacy of TAA-AQ for the treatment of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in paediatric patients. The MAH has presented studies in adults and adolescents aged 12 to 17, children from 6 to 12 or children from 2 to 5 years (Table 2). In this assessment report studies in children between 2 and 5 years of age will be summarized and assessed only.

Table 2: Studies including children from 2 to 5 years

Study identification	Publication	Study type	Study design	Subject age (year)	Treatment dose (µg)	Treatment duration (week) / N
Internal reports						
XRG5029C/3502	Weinstein et al. 2009 (15)	Efficacy in PAR	DB period: Randomized, double-blind, placebo-controlled, parallel group, multicenter	2 - 5	TAA-AQ: 110, placebo	4 / 474
RG5029Y-314	-	Efficacy in PAR	Randomized, double-blind, placebo-controlled, parallel group, multicenter	4 - 12	TAA-AQ: 110, 220, placebo	12 / 319
Trica_L_04286	-	Efficacy in PAR or SAR (secondary evaluation)	Randomized, double-blind, placebo-controlled, parallel group, multicenter	2 - 12	TAA-AQ: 110, 220, placebo	6 / 140
XRG5029C/3503	-	Efficacy in PAR (secondary evaluation)	Randomized, double-blind, placebo-controlled, parallel group, multicenter	3 - 9	TAA-AQ: 110, placebo	52 / 298

2. Clinical studies

Pharmacokinetics

Study XRG5029C/1000: an open-label, repeat-dose, multicentre study to evaluate the safety and pharmacokinetics of single and multiple doses of intranasally administered triamcinolone acetonide (NASACORT AQ) in paediatric allergic rhinitis patients 2 to 5 years of age compared to adult patients 18 to 50 years of age.

Objectives:

- To characterize the single dose and steady state PK of triamcinolone acetonide in paediatric subjects 2 to 5 years of age compared with adult subjects 18 to 50 years of age following 5 days of intranasal dose administration.
- To evaluate the safety and tolerability of 5 days use of intranasal TAA in paediatric subjects.

Investigational plan:
This was an open-label, repeat-dose, multicenter study conducted in the US. Paediatric subjects completed one 5-day treatment period; the adult subjects completed two 5-day treatment periods, separated by a 7-day washout period. All subjects received intranasal TAA (110 µg) for 5 days. In the adult subjects, a 7-day washout period was followed by an additional 5-day treatment period with intranasal TAA (220 µg).

A peripheral venous blood sample (approximately 2.5 mL) was collected for measurement of TAA concentrations from all paediatric subjects, according to a staggered sparse sampling strategy (Table 3). Sampling strategy assignments (A or B) were made at the time of enrolment at each CRC according to site-specific assignments lists prepared by the sponsor before the study. Enrolment across the study and the balance of the sampling strategy assignments (A vs B) among the paediatric subjects were monitored by the sponsor during the study. Peripheral venous blood samples (approximately 3 mL) were collected from all adult subjects as follows:

before TAA administration and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 hours post-dose on Study days 1 and 5 of each treatment period.

Table 3: Sparse sampling strategies for paediatric patients

PK Sampling strategy	Study day 1				Study day 5			
PK Sample no.	1	2	3	4	1	2	3	4
A	1 h	3 h	5 h	8 h	Predose	2 h	4 h	6 h
B	Predose	2 h	4 h	6 h	1 h	3 h	8 h	10 h

h = Hour
PK = Pharmacokinetic
Predose was defined as a PK sample drawn no earlier than 60 minutes before investigational product administration.

The following PK variables have been evaluated: $AUC_{(0\rightarrow z)}$, $AUC_{(0\rightarrow \infty)}$, $C_{max,}$ $t_{max,}$ elimination rate constant (λ_z), terminal half-life ($t_{1/2}$), apparent clearance (CL_{nasal}).
Population pharmacokinetic parameters estimated from the plasma TAA concentration-time data obtained from both pediatric and adult subjects included:
• CL/F – Apparent body clearance
• V/F – Apparent volume of distribution

Assessor´s comment: *investigational plan is in general considered adequate to capture the PK profile of triamcinolone. Regarding the adult sampling scheme, it is considered appropriate to generate the PK profile of triamcinolone for the purpose of comparison with the paediatric population. Regarding the staggered sparse sampling scheme, it is not entirely clear why such „crossover" sampling schedule has been derived. The MAH should provide justification.*

Statistical methods:
Baseline data were descriptively summarized by treatment group and age group using mean, standard deviation, and median, as well as minimal and maximal values for continuous variables and frequencies and percentage for categorical variables.
Descriptive statistics for TAA plasma concentrations (N, mean, %CV, median, minimum, and maximum) were presented by dose group and nominal time.
TAA plasma concentrations following the first dose (Day 1) and last dose (Day 5) were analyzed using non-compartmental techniques in adult subjects. All subjects completing serial sampling were included in the non-compartmental analysis.
Population PK parameters, including intra-subject and inter-subject variability were estimated from the TAA plasma concentrations collected following the first dose and at steady state using nonlinear hierarchical models in paediatric and adult subjects. The goal of the population analysis was to examine the factors that contributed to the PK behaviour of TAA in paediatric and adult subjects using a mixed-effects modelling approach. The focus of the analysis was on estimating the typical population parameters and inter-subject variability in paediatric and adult subjects and investigating the relationship between subject demographics and exposure using mechanistically meaningful models. All subjects who completed 5 days of multiple exposure and those who had at least 2 PK samples after multiple dosing were included in the population analysis. No formal interim analysis was performed for this study.
However, TAA plasma concentration–time data from the first 5 paediatric subjects were descriptively examined against the same data obtained in adult subjects to preliminarily assess design assumptions and the appropriateness of the 110-µg dose selection for a subsequent

efficacy study (sponsor's Study 3502), prior to that study's initiation. No formal pharmaco-statistical analyses were performed.

Assessor´s comment: *since the study is exploratory in nature, descriptive statistics is an adequate approach to the data analysis. The Applicant declares that no interim analysis has been performed; however, some of the data have been analysed before the study was finished, which seems to be the interim analysis. The Applicant is requested to clarify in more details the reasons for performing this analysis and to discuss the possible influence of the analysis on overall study findings.*

Study results:

Demographic characteristics of the patients are presented in Table 4.

Table 4: Demography of the study population

Demographic variable	Pediatric subjects (n = 15)	Adult subjects (n = 15)	Total (N=30)
	Age (y)		
Mean (SD)	3.7 (1.0)	32.3 (9.7)	–
Median	4	30	–
Range	2-5	20-49	–
2 years of age? [n (%)]	2 (13.3)	--	–
3 years of age? [n (%)]	4 (26.7)	--	–
4 years of age? [n (%)]	6 (40.0)	--	–
5 years of age? [n (%)]	3 (20.0)	--	–
	Sex [n (%)]		
Male	8 (53.3)	10 (66.7)	18 (60.0)
Female	7 (46.7)	5 (33.3)	12 (40.0)
	Race [n (%)]		
White	4 (26.7)	2 (13.3)	6 (20.0)
Black	8 (53.3)	13 (86.7)	21 (70.0)
Multiracial	3 (20.0)	0	3 (10.0)
	Weight (kg)		
Mean (SD)	17.8 (2.99)	77.2 (14.1)	-
Median	16.9	79.1	-
Range	13.6 – 22.7	48.6 – 101	-
	Height (cm)		
Mean (SD)	105 (7.4)	172 (9.8)	-
Median	105	175	-
Range	93 – 119	155 – 188	-
	BMI (kg/m^2)		
Mean (SD)	16.1 (0.78)	26.2 (4.81)	-
Median	16.1	25.2	-
Range	15.0 – 17.6	17.8 – 39.9	-
	BSA (m^2)		
Mean (SD)	0.71 (0.09)	1.90 (0.20)	-
Median	0.70	1.92	-
Range	0.58 – 0.87	1.52 – 2.21	-

[a] The PK evaluable population did have 2 subjects who did not complete the study, but who did have evaluable PK data on Study day 1 (see Section 6.1).
BMI = Body mass index
BSA = Body surface area

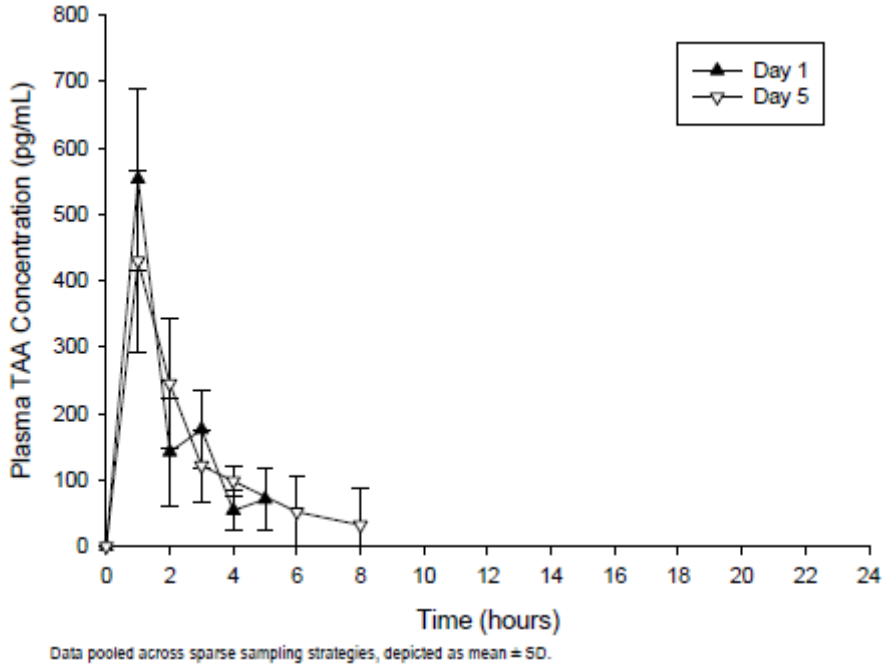
Assessor´s comment: *the demographic characteristics are well described. It is noted that the majority of patients were black. Nevertheless, the results of the population PK modelling suggest that the race does not influence the PK of triamcinolone. For this reason, it is assumed that the study results are valid also for the European population.*

Pharmacokinetics results in paediatric population:

Fourteen subjects provided evaluable TAA concentration-time data. Among the 14 subjects providing evaluable PK data, 7 were assigned to sparse sampling Strategy A and 7 were assigned to Strategy B.
Of the subjects assigned to sampling Strategy A, 2 of the 7 subjects (28.6%) had quantifiable TAA concentrations 8 hours after dose administration on Study day 1 while 5 of 7 subjects (71.4%) had quantifiable TAA concentrations 6 hours after dose administration on Study day 5.
Of the subjects assigned to sampling Strategy B, 3 of the 7 subjects (42.9%) had quantifiable TAA concentrations 6 hours after dose administration on Study day 1 while 3 of 7 subjects

(42.9%) had quantifiable TAA concentrations 8 hours after dose administration on Study day 5. No pediatric subject assigned to Strategy B had a quantifiable TAA concentration 10 hours after dose administration on Study day 5 (two 10-hour samples were missing). Additionally, one subject had no quantifiable TAA concentrations on Study day 1.

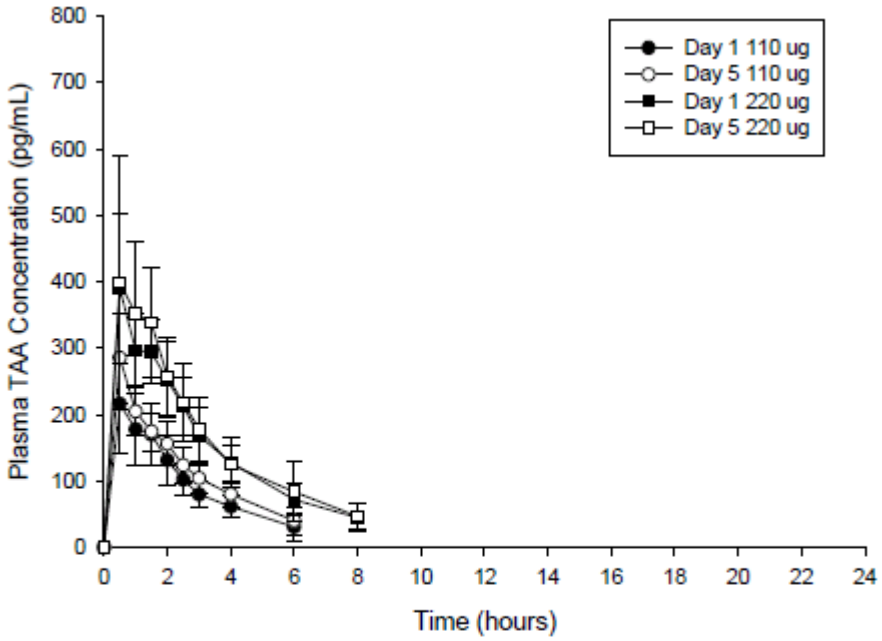
Figure 1: TAA concentration-time profile at 110 µg qd for 5 days: paediatric subjects



Pharmacokinetic results in adult subjects

Fifteen adult subjects provided evaluable TAA concentration-time data for the 110 µg dose and 14 adult subjects for the 220 µg dose. One subject withdrew her consent after completing the first study period.
Exposure to TAA increased in a dose-proportional manner, with no appreciable accumulation over 5 days of dosing. Exposure to TAA at these doses was consistent with historical data.

Figure 2: TAA plasma concentration-time profile at 110 µg qd for 5 days, followed by 220 µg qd for 5 days: adult subjects

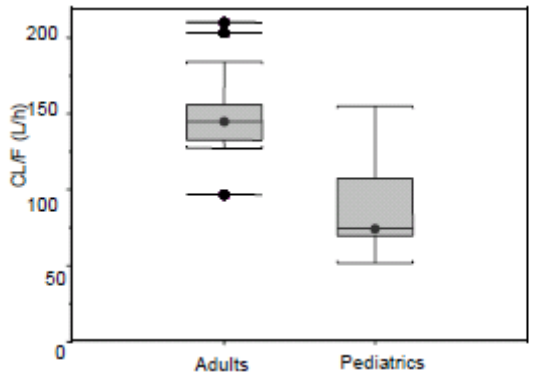


Day 1 data at 110 µg: n = 15.
Day 5 data at 110 µg: n = 15.
Day 1 data at 220 µg: n = 15.
Day 5 data at 220 µg: n = 14 (one adult subject did not complete Day 5 [see Section 6.1]).
Data depicted as mean ± SD.
TAA = Triamcinolone acetonide

Comparison of paediatric vs adult subjects

The overall time course of exposure to TAA in the paediatric subjects who received 110 µg daily was more similar to the adult subjects receiving 220 µg daily, compared with the adult subjects receiving 110 µg daily.
Plasma TAA concentration-time data for both paediatric and adult subjects were pooled and analyzed using non-linear mixed effects modelling methods. TAA disposition was well described by a one-compartment model with first order input. Inter-subject variability was described by an exponential error model on the structural PK parameters, clearance (CL/F) and volume (V/F), while the residual variability was described by a proportional error model. The NONMEM covariate analysis revealed that apparent total body clearance (CL/F) was most strongly correlated with study population (paediatric or adult). The apparent volume of distribution (V/F) was strongly correlated with body size, with body weight being the preferred covariate over BSA. Sex was not a significant covariate in the analysis. Study population (POP) was correlated with body weight, but was chosen in the final model since incorporation of this covariate resulted in a greater drop in the objective function value, compared with body weight alone.
According to the final PPK model, the CL/F in the typical paediatric subject 2 to 5 years of age was estimated as 83.6 L/h. Similarly, the CL/F in a typical adult subject was estimated as 148 L/h.

Figure 3: Relationship between clearance and study population based on the final PPK model



Descriptive statistics of the individual Bayesian POSTHOC parameter estimates from the final PPK model are summarized in Table 5.

Table 5: Summary of the individual Bayesian POSTHOC PK parameter estimates, based on the final PPK model

PPK variable	Pediatric subjects (n = 15)	Adult subjects (n = 15)
	CL/F (L/h)	
Mean (SD)	83.3 (28.0)	144.8 (29.5)
Median	86.8	150.2
Range	51.7 – 154.8	96.8 – 210.0
CV (%)	32	20
	V/F (L)	
Mean (SD)	164.0 (62.6)	445.1 (89.4)
Median	177.1	448.3
Range	114.3 – 375.0	332.6 – 623.2
CV (%)	35	20

[a] The PK evaluable population did have 2 subjects who did not complete the study, but who did have evaluable PK data on at least Study day 1 (see Section 6.1).
CL/F = Apparent total body clearance
PPK = Population pharmacokinetics
V/F = Apparent volume of distribution

Based on the study results and population PK modelling the Applicant concluded that in the paediatric subjects with allergic rhinitis, as in adults, the pharmacokinetics of TAA following intranasal administration of NASACORT AQ can be described by a one-compartment model with first order input. The estimated CL/F of TAA is lower in the 2- to 5-year olds, but the inter-subject variability in CL/F is moderate and similar between paediatric and adult subjects. A daily dose of 110 µg administered intranasally to 2- to 5-year-olds with allergic rhinitis can be expected to best target and match the systemic exposures to TAA produced by a daily dose of 220 µg administered intranasally to adults.

Assessor´s comment*: study results and results of the population PK show that elimination in patients aged 2-5 is slower than in the adults and paediatric patients aged 6-12. This finding would naturally raise the question whether the dose has been determined correctly for the youngest age groups. Triamcinolone does not accumulate after once daily dosing, and the previous studies conducted in older patients have shown that after 24 h the plasma concentrations were below the limit of detection. However, it is questionable whether the same conclusion can be applied on the youngest age group. The Applicant is therefore invited to provide additional analysis and discussion on the concentration-time profile approximately 24 h in order to confirm the adequacy of the proposed posology.*

Study XRG5029C-3502 (the PK part): A randomized, double-blind, parallel group, placebo-controlled, four-week efficacy and safety evaluation of NASACORT AQ 110 µg qd, followed by six-month open-label safety in children ages 2-5 years with perennial allergic rhinitis.

Objectives:
Primary objective:

- to demonstrate the efficacy of administration of Nasacort AQ 110 µg once daily (qd), compared with placebo in children 2 to 5 years of age with PAR.

Secondary objective:

- to evaluate the systemic effect of Nasacort AQ 110 µg qd on the hypothalamic-pituitary-adrenal (HPA) axis in a subset of children 2 to 5 years of age; to further characterize the steady-state exposure (PK) of Nasacort AQ 110 µg qd in a subset of children 2 to 5 years of age.

Assessor´s comment: *in this section of the assessment report only the PK data will be summarized and evaluated. The efficacy and safety aspects of this study will be addressed in respective sections of this report.*

Pharmacokinetics investigational plan

During the open-label phase of the study, blood samples were collected from each subject who participated in the PK sampling during study visits 5, 6, 7 and 8 (treatment weeks 8±1 week, 14 ±1 week, 21 ±1 week, 28 ± 1 week, respectively). The investigator was instructed to draw blood for two of these four visits between 1 and 4 hours postdose; the remaining two visits were drawn between 4 and 8 hours post-dose. The precise sequence of sample collections with time windows was not specified (i.e., one investigator may have chosen to collect a 4- to 8-hour PK sample on the first visit while another investigator may have chosen to collect a sample during the 1- to 4-hour time window on the first visit). The total of 111 patients were included in the PK analysis.

The PK variables derived from the plasma TAA concentration-time data obtained in subjects included:
• Apparent total body clearance (CL/F) following intranasal administration
• Apparent volume of distribution (V/F)
Based on the population pharmacokinetics (PPK) analyses, using pooled data from studies XRG5029C/3502 and XRG5029C/1000 CL/F and V/F estimates were adjusted by weight.

Nonlinear mixed effects modelling (NONMEM) was used for the plasma concentration-time data to estimate the primary PK parameters of TAA in the paediatric population, including the associated inter-subject variability. Bayesian POSTHOC parameters for individual subjects were also estimated.

Results

Demographic characteristics of the PK population are summarized in Table 6.

Table 6: Demography during the open-label period (pharmacokinetic evaluable population)

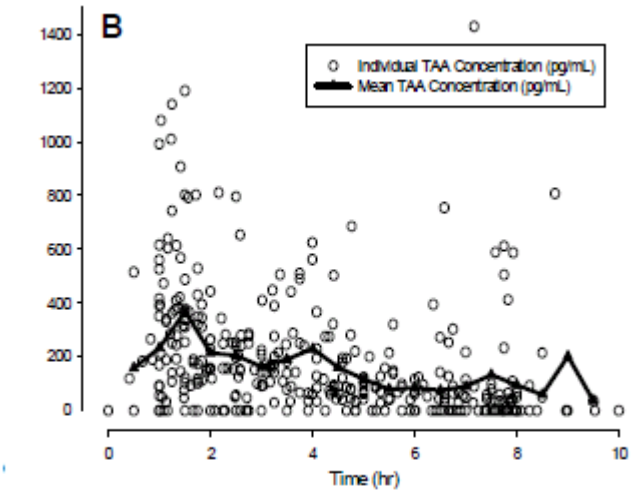
Demographic variable		NASACORT AQ 110 µg qd (N=111)
Age	Mean (y [SD])	3.5 (1.15)
	Median	4
	Range	2 – 5
	2-year-olds [n (%)]	30 (27.0)
	3-year-olds [n (%)]	25 (22.5)
	4-year-olds [n (%)]	27 (24.3)
	5-year-olds [n (%)]	29 (26.1)
Sex	Male [n (%)]	64 (57.7)
	Female [n (%)]	47 (42.3)
Race	White	64 (57.7)
	Black	19 (17.1)
	Other	17 (15.3)
	Multiracial	8 (7.2)
	Asian/Oriental	3 (2.7)
Height	Mean (cm [SD])	102.5 (10.637)[a]
	Median	102.4[a]
	Range	81.0 – 124.0[a]
Weight	Mean (kg [SD])	17.42 (4.162)
	Median	16.4
	Range	10.0 – 33.4
BMI	Mean (kg/m² [SD])	16.53 (2.087)[a]
	Median	16.3[a]
	Range	12.0 – 25.7[a]
BSA	Mean (m² ([SD])	0.70 (0.114)[a]
	Median	0.7[a]
	Range	0.5 – 1.0[a]

[a] Subject 00440033 who did not have height recorded was PK evaluable; thus, N = 110.
BMI = Body mass index
BSA = Body surface area
SD = Standard deviation
y = Years

Assessor´s comment: *the study population seems well balanced in terms of age and sex, less in terms of race. This is however acceptable since the study results provide direct insight into PK of triamcinolone in white population. Furthermore, as will be seen in the population PK model, the race does not seem to have any influence on PK of triamcinolone.*

Mean and individual plasma concentration-time profiles are depicted in Figure 4

Figure 4: Mean and individual triamcinolone acetonide concentration-time profiles (pharmacokinetic evaluable population)



TAA = Triamcinolone acetonide

Assessor´s comment: *the mean plasma concentration-time profile is similar to that observed in the previous study, and the variability, especially during the first time point is significant.*

Population pharmacokinetic analysis

The PPK analyses were performed on the data from pooling TAA plasma concentrations from this study (XRG5029C/3502) and the TAA plasma concentrations obtained from another paediatric PK study (XRG5029C/1000).

Based on the NONMEM analysis, TAA disposition was described by a one compartment model with first order input. Inter-subject variability was described by an exponential error model on the structural PK parameters (CL/F and V/F); the residual variability was a combination of additive and proportional error model. The NONMEM covariate analysis revealed CL/F was correlated with age and weight. V/F was strongly correlated with weight. Race and sex were not significant covariates in the NONMEM analyses. The covariate of age was correlated with weight. Thus, age was chosen in combination with weight in the final model. Incorporation of the covariate of weight resulted in a greater drop in the objective function, compared with weight alone.

According to the final model, CL/F was estimated to be 48.3 L/h (2.87 L/hr/kg) in a typical paediatric subject aged 2 to 5 years and 151 L/h (2.02 L/hr/kg) in a typical adult subject aged 20 to 49 years. Thus, CL/F was strongly correlated with age and weight. V/F was estimated to be 275 L (16.2 L/kg) in a typical paediatric subject 2 to 5 years of age and 456 L/h (6.05 L/kg) in a typical adult subject 20 to 49 years of age. Thus, V/F was strongly correlated with weight.
The PPK parameter estimates CL/F and V/F are summarize in the Table 7.

Table 7: Summary of the individual Bayesian POSTHOC pharmacokinetic parameter estimates, based on the final population pharmacokinetics model.

PK parameter estimate	Normal		Weight adjusted	
	CL/F (L/h)	V/F (L)	CL/F (L/h/kg)	V/F (L/kg)
Mean (SD)	45.6 (16.7)	275 (103)	2.74 (1.11)	16.2 (5.74)
Median	45.1	274	2.69	16.1
Range	5.81 – 90.7	24.3 – 724	0.332 – 5.59	1.43 – 31
%CV	36.6	37.4	40.6	35.3
Geometric mean	41.8	253	2.46	14.9
Total no. of subjects (N)	106	106	106	106

CL/F = Apparent total body clearance (CL/F) following intranasal administration
%CV = Coefficient of variation
PK = Pharmacokinetics
PPK = Population pharmacokinetics
SD = Standard deviation
V/F = Apparent volume of distribution

Based on the results of the two PK trials and population PK modelling, in paediatric subjects with PAR (with or without SAR), as in adults, the PK of TAA following intranasal administration of NASACORT AQ can be described by a one compartment model with first order input. Age and weight are strongly correlated with CL/F; weight is strongly correlated with V/F. Population estimates of clearance and volume of distribution based on data from this study do not appear to be different, compared with the estimates obtained in another paediatric PK study (XRG5029C/1000) conducted by the sponsor. Based on differences in CL/F, a dose of 110 µg qd may be used in paediatric subjects 2 to 5 years of age in order to target exposures similar to those achieved with intranasal administration of NASACORT AQ at a dose of 220 µg qd in adult subjects 18 to 50 years of age.

POH0176: A population pharmacokinetic (PPK) study: a combined analysis of phase I and phase III studies after intranasal administration of an aqueous formulation of triamcinolone acetonide (TAA: Nasacort AQ) in adult and paediatric patients with allergic rhinitis

Objectives:

- The objective of this population pharmacokinetic report was to assess the population PK of TAA in study XRG5029C-1000 (adult and pediatric patients with allergic rhinitis) and study XRG5029C-3502 (pediatric patients with allergic rhinitis).

Study assessments:
The evaluable PK population consisted of 135 subjects (15 adults and 120 children). Among the 15 adult subjects, 10 were male and 5 were female, age ranged from 20 to 49 years, body weight ranged from 49 to 101 kg and BSA ranged from 1.5 to 2.2 m^2. Among the 120 children, age ranged from 2 to 5 years, body weight ranged from 10 to 33.4 kg and BSA ranged from 0.48 to 1.04 m^2. Covariates chosen were age in years (AGE), sex (SEX), race (RACE), body weight (WT), height (HT), body surface area (BSA). When choosing age and weight as covariates, age was normalized by dividing by 25 years (assumed to be typical adult age) and the body weight was normalized by dividing by 70 kg (assumed to be typical adult body weight).
Plasma TAA concentration-time data analysis was performed by nonlinear mixed-effects modelling using the NONMEM program (double precision, version V, level 1.0) with PDx-Pop version 1.1j.

Results:
A total of 1197 observations were included in the PPK database, 821 concentration data points from study XRG5029C-1000 and 376 from study XRG5029C-3502. Based on objective function value, visual inspection of diagnostic plots, one-compartment model was chosen over two-compartment model as the base model. Individual patient pharmacokinetic parameters were calculated by the posterior conditional estimation technique (POSTHOC) of NONMEM. The parameters CL/F and V/F were correlated against demographic variables by performing stepwise regression to select potential significant covariates. A p-value of 0.05 was used in the stepwise regression analysis for entry and retain. The demographic variables examined included age, weight, body surface area, and gender. The final model included age and weight on CL/F and weight on V/F.

Individual PK estimates were obtained by Bayesian estimation using parameter estimates from the final population model.

The predicted (population or individual prediction) vs. observed TAA concentrations were scattered around the line of unity. The weighted residuals did not show any major trend when plotted against predicted concentrations or sampling time, indicating that the model was appropriately unbiased.

Figures 5 and 6 show the correlations between CL/F and age and body weight and V/F and body weight.

Figure 5: Correlation between CL/F (A: weight-unadjusted; B: weight-adjusted) age (top) and body weight (bottom)

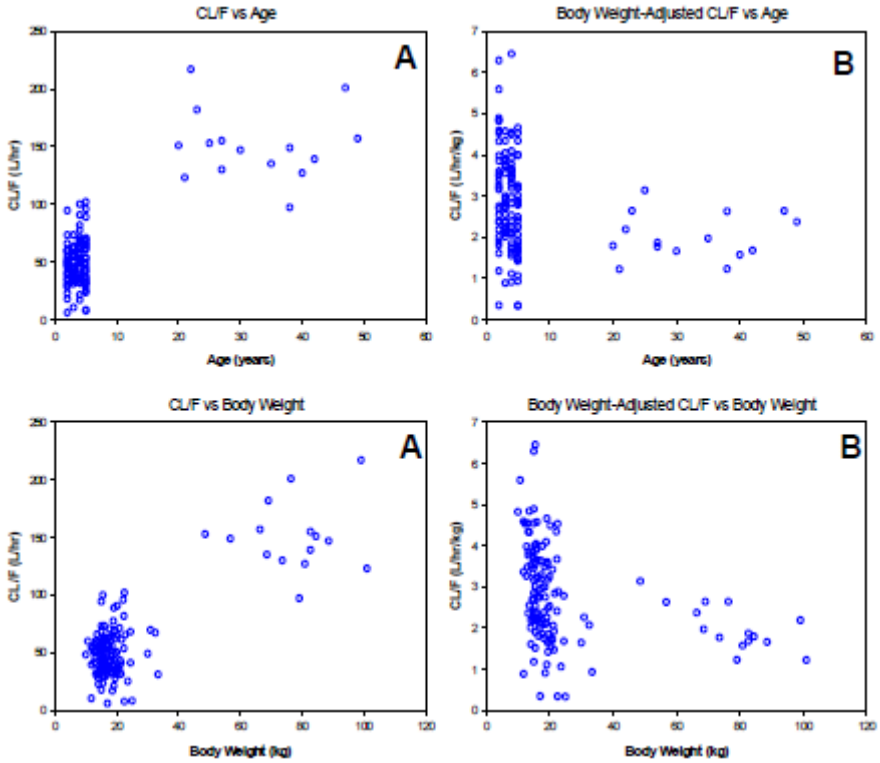
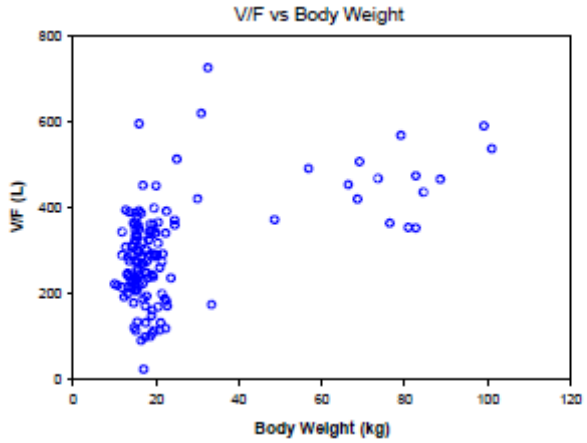


Figure 6: Correlation between post-hoc pharmacokinetic parameter (V/F) and significant covariate (body weight) (final population pharmacokinetic model)



Based on the results of the PPK, the Applicant concludes that in paediatric subjects with allergic rhinitis, as in adults, the pharmacokinetics of TAA following intranasal administration of Nasacort can be described by one-compartment model with first-order input. Age and bodyweight are strongly correlated with CL/F and the bodyweight is strongly correlated with V/F. Based on differences in apparent total body clearance, a dose of 110 mcg daily may be used in paediatric patients aged 2 to 5 years in order to target exposure similar to those achieved after administration of 220 mcg daily to adults.

Assessor´s comment: *based on the results of the PK studies and popPK modelling, it seems that the dose of 110 µg is indeed appropriate in order to reach similar systemic exposure. Nevertheless, before a definite conclusion on the appropriateness of the dose can be made, the MAH should address the following issues:*
Clearance in the youngest age group seems to be markedly lower compared to adults, which might bring up the question of accumulation potential in children age2-5. None of the studies sampled more than cca 10 h post-dose, thus there are no solid data on late concentration-time profile phase of triamcinolone. The MAH should provide additional discussion.

Pharmacodynamics

Study RG5029Y-125: A randomized, double-blind, multicentre, parallel group, multi-dose study of the six-week effect of treatment with once daily used triamcinolone acetonide aqueous (TAA-AQ) nasal spray on Hypothalamic-Pituitary-Adrenal (HPA) function. The study was conducted in paediatric patients between 6 and 12 years of age with at least one-year history of allergic rhinitis and with confirmed perennial and/or seasonal allergy (skin prick test) to allergens presented in her/his environment

Assessor´s comment: *since the study involves children aged 6-12 it is considered supportive only. Therefore, the study will be only briefly summarized in this assessment report.*

Objectives:

The primary objective was to evaluate the impact of TAA-AQ administrated once daily (220 or 440 µg) on the HPA function. The primary assessment of clinical HPA function was based on the response of plasma cortisol levels to a one-hour cosyntropin stimulation test.

The other primary outcome was to establish pharmacokinetic profile. This profile was performed in three centres on patients receiving 440 µg TAA-AQ or matching placebo

Treatments:
The three treatment arms were:
- TAA-AQ nasal spray 220 µg once daily (2 sprays per nostril in the morning)
- TAA-AQ nasal spray 440 µg once daily (4 sprays per nostril in the morning)
- Placebo nasal spray (2 or 4sprays per nostril)

Treatment duration was for 6 weeks.

Outcomes:

The primary pharmacodynamics analysis variable was the change in plasma cortisol levels one-hour after cosyntropin stimulation.
The pharmacokinetic evaluation was based on TAA-AQ plasma levels performed in three centres on patients receiving 440 µg TAA-AQ or matching placebo.

Statistical methods
The primary object of statistical analysis was to compare the effect of two doses of TAA (220 and 440 µg) with that of placebo on HPA function after six weeks of treatment. The primary endpoint was the change in plasma cortisol levels from baseline (pre-treatment) to week 6 at one hour post-stimulation.
The primary analysis was conducted using a one-sided, pair-wise comparison between the TAA-AQ treated groups and the placebo matching group at a 0.05 level of significance. An analysis using the Analysis of variance (ANOVA) method was performed to establish if there are statistically significant differences between groups treated with TAA or placebo. All tests were based on a two-way analysis of variance model with Treatment and Investigator as main effects and no interaction term. The investigator-by-treatment interaction was tested at a 0.15 significance level.

Descriptive statistics were used to summarise safety and pharmacokinetics parameters.

Results:

Baseline data:
At the baseline, the mean age of subjects was 9.5 years, with a range of 6 to 12 years. There were a larger proportion of male (63%) than female (37%) children. The average height and weight were 140 centimetres and 37 kilograms. The majority of the patients were Caucasian (84%). The other races are not specified (16%). No geographic differences were known among the groups.

Results of the PP population analysis for the pharmacodynamics variable:

HPA function was not supressed by the 6 weeks treatment with TAA-AQ at dosage 220 or 440 µg/day. There was no statistically significant difference in the plasma cortisol levels after one-hour cosyntropin stimulation between placebo and either TAA-AQ (220 and 440 µg/day) treated group. The means of cortisol levels before treatment and the changes in levels after treatment are presented in Table 8 as a µg/dl.

Table 8: Plasma cortisol levels one hour post cosyntropin stimulation.

Week 6 Plasma Cortisol Levels
One Hour Post-Cosyntropin Stimulation

Treatment Group	Baseline Mean	Adjusted[a] Mean Change from Baseline (SE)	p-Value[b]
220 mcg	29.68	-0.57 (0.70)	0.6421
440 mcg	29.70	0.56 (0.72)	0.9247
Placebo	29.79	-0.94 (0.75)	

Abstracted from Appendix IV.C, Table 1.
[a] Means (Standard Errors) adjusted for imbalances among treatment groups and investigators.
[b] P-values are one-sided and computed from t-tests for decreasing dose response, based on a two-way analysis of variance model.

There were no statistically significant differences among groups in secondary evaluated parameters (e.g. changes in plasma cortisol levels pre- and 30 minutes post cosyntropin stimulation (pre-treatment versus after 6 weeks treatment) and change in response of the plasma cortisol level to cosyntropin 30 minutes/one hour post stimulation (pre-treatment versus after 6 weeks treatment)). The observed values are presented in Table 9.

Table 9: Plasma cortisol levels cosyntropin stimulation test

TABLE 5
Week 6 Plasma Cortisol Levels
Post-Cosyntropin Stimulation for Secondary Variables

Time Post-Cosyntropin Stimulation	Treatment Group	Baseline Mean	Adjusted[a] Mean Change from Baseline (SE)	p-Value[b]
30 minutes	220 mcg	25.45	0.04 (0.61)	0.6044
	440 mcg	25.73	0.29 (0.63)	0.7044
	Placebo	25.34	-0.19 (0.65)	
Zero hour	220 mcg	13.82	-1.4 (0.93)	0.0673
	440 mcg	14.98	-0.19 (0.96)	0.2645
	Placebo	13.08	0.67 (0.99)	
Zero to one hour	220 mcg	15.86	0.78 (1.11)	0.9304
	440 mcg	14.72	0.75 (1.15)	0.9234
	Placebo	16.71	-1.6 (1.18)	
Zero to 30 minutes	220 mcg	11.63	1.40 (1.00)	0.9365
	440 mcg	10.75	0.49 (1.04)	0.8179
	Placebo	12.26	-0.86 (1.07)	

Abstracted from Appendix IV.C, Table 1.
[a] Means (Standard Errors) adjusted for imbalances among treatment groups and investigators.
[b] P-values are one-sided and computed from t-tests for decreasing dose response, based on a two-way main effects analysis of variance model.

Pharmacokinetics results:
A total of 5 samples of each patient were analysed for pharmacokinetics variables.

Among patients administrated 440 µg/day of TAA-AQ the most had undetectable or very low plasma TAA concentration immediately prior to drug administration (10 out of 12). The remaining two patients had plasma drug concentration unexpectedly high (0.271 and 0.443 ng/ml compared to 0.064 ng/ml). No explanation is available but deviation in dosing is discussed because of the decrease in the concentration in patients' samples during the monitored time period. A summary of mean TAA concentration is shown in Table 10. The observed values are compared to those observed in the adult population. The undetectable or low TAA concentrations prior to drug administration suggest little or no accumulation of drug over the six weeks treatment period of high doses.

The other pharmacokinetics variables measured at the end of treatment period were:
AUC(0-6) mean 3.0751 ng*hr/ml with a range of 0.4715 to 5.7368 ng*hr/ml
Cmax mean 0.8882 ng/ml with a range from 0.214 to 1.580 ng/ml
Tmax mean 0.9583 hr with a range from 0 to 1.5 hr

Table 10: A summary of mean concentrations after the administration of 440 µg TAA to six hours post-dose in paediatric and adult population

TABLE 9
Mean (%CV) Plasma TAA Concentrations Following Aqueous RG 5029Y Administration in Pediatric and Adult Patients with Allergic Rhinitis

	Plasma TAA Concentration (ng/mL)	
Time	Pediatric Male and Female Patients (N=12)	Adult Male Patients (N=21)[@]
0 Hour	0.07 (201)	0
0.5 Hour	0.658 (64.0)	0.518 (49.8)
1 Hour	0.71 (50.8)	0.613 (48.7)
1.5 Hours	0.731 (63.1)	0.653 (44.7)
6 Hours	0.243 (67.2)	0.293 (49.7)

Abstracted from Appendix II.A, Table 7.

[@] Study RG 5029Y-101 in adult males was a single-dose study, whereas the pediatric study was multiple-dose (QD) for 6 weeks with the concentration-time profile constructed from the last day of QD dosing.

Study RG5029Y-315: "A phase III, single centre, randomised, double blind, cross-over, placebo and active comparator (Flonase Nasal Spray) controlled parallel group study evaluating the effect of a two weeks treatment with triamcinolone acetonide aqueous (TAA-AQ) nasal spray 110 µg and 220 µg once daily on short term lower leg growth rate in children between 4 to 10 years of age with allergic rhinitis".

Assessor´s comment: *this study has been conducted in a slightly older population, than that considered in this assessment; nevertheless, the patient population also includes children age 4 and 5, which is relevant for the pharmacodynamics/safety evaluation. The MAH is requested to provide separate analysis for this age group. The study conduct and results will be summarized in this report, but will not be assessed until subpopulation analysis has been provided.*

Objectives:

The primary objective was to assess the suppressive effect of 2-weeks treatment with two different dosage regimens of TAA-AQ nasal spray (220 and 440 µg) as compared to placebo on the short term lower leg growth.

The secondary objectives were:
- To assess the relative effect of TAA-AQ compared to Flonase (fluticasone propionate) on the short term lower leg growth
- To assess the effect of TAA-AQ nasal spray compared to fluticasone propionate (FP) nasal spray and placebo on hypothalamic pituitary adrenal (HPA) axis function
- To compare the adverse events for all treatment periods

Treatments:
The four treatment arms were:
TAA-AQ nasal spray 110 µg (1 spray per nostril) once daily

TAA-AQ nasal spray 220µg (2 sprays per nostril) once daily
FP nasal spray 200 µg (2 sprays per nostril) once daily
Placebo (1 or 2 sprays per nostril) once daily

Treatment duration was for 2 weeks. Each treatment period was followed by a two-week washout period. The last treatment period was followed by a one week follow-up period.

Outcomes:
The primary evaluation was the change from baseline in lower leg growth velocity over the treatment period. The lower leg growth was measured as a distance between the knee and heel of right or left leg of sitting patient using knemometry.

The secondary pharmacodynamics evaluation was to assess the treatment effect on cortisol and creatinine urine levels and the ratio urine cortisol to creatinine as a sensitive marker of HPA axis function.

Statistical methods:
An analysis of covariance model was fitted with patient, treatment and carryover as fixed effects. The growth velocity was estimated in two ways: as the actual growth during the period divided by the length of the treatment period and as the slope obtained by fitting a regression line to the three knemometry values for each patient during the given treatment period.
Statistical comparisons in endpoints between treatment arms and periods were performed. The primary treatment comparisons were performed between the two TAA-AQ dosage regimens and placebo. Secondary comparisons were performed between each TAA-AQ dose treatment and FP treatment, and between FP treatment and placebo.

The same analysis of variance method was used to evaluate the change in overnight cortisol/creatinine ratio from beginning to the end of each treatment period. The cortisol data were found not to be normally distributed, thus, the rank values were analysed using a fixed effects analysis of variance with effects for patient, period, treatment and carryover. Alternatively, the sum of ranks for each treatment group was determined and Friedman's test was applied.

Results:

Baseline data:
The mean age was 7.2 years with a range of 4 to 10 years. A larger proportion of males (71.2 %) compared with females (28.8 %) were randomised. A comparable proportion of black (57.6 %) and Caucasian (42.4 %) were randomised. Based on the Tanner classification, all included subjects were at Stage 1. The mean height was 126.31 cm with a range of 104.13 to 145.03 cm. The mean weight was 29.28 with a range of 16.8 to 50.9 kg.

Pharmacodynamics results:
In the ITT population analysis of the effect of treatments on lower leg growth velocity after two weeks treatment period was performed. The mean growth velocity was 0.51 mm/week during the placebo period, 0.34 and 0.37 mm/week during the 220 and 110 µg TAA-AQ treatment periods, respectively, and 0.38 mm/week during FP treatment period. There was seen a significant treatment effect on growth velocity between the placebo treatment period and 220 µg TAA-AQ treatment period (p=0,036) in the ITT population. The magnitude of the treatment effect was -33.3 % of the growth velocity. This effect was also seen in the population completing all treatment periods (completer population). The magnitude of the treatment effect remained similar (-32.6 %) but the effect was not statistically significant as compared to placebo (p=0.063).

The change in growth velocity during 110 µg TAA-AQ treatment period and FA treatment period as compared to placebo (-27.5 % and 25.5 %, respectively) was assessed not to be statistically significant.
No effect was above the pre-defined clinically significant level of 50 % of growth velocity reduction.

The increase in changes in urine cortisol/creatinine ratio was not statistically significant at the end of treatment with either TAA dose as compared to placebo (p=0.175; 0.217 for 110 and 220 µg, respectively). However, there was observed a significant decrease in cortisol/creatinine ratio at the end of FA treatment period as compared to placebo (-0.359; p=0.002). The statistically significant change at the end of FA treatment was also observed as compared to 220 µg TAA treatment (p=0.037).

Efficacy

Study XRG5029C/3502 (efficacy part): a randomized, double-blind, parallel group, placebo-controlled, four-week efficacy and safety evaluation of Nasacort AQ 110 µg, followed by six-month open-label safety in children ages 2-5 years with perennial allergic rhinitis.

The primary efficacy variable:

- the change from baseline over the double-blind period (overall) in the mean total nasal symptom score (TNSS) – instantaneous (immediately prior to dosing) such that change from baseline overall was equal to the mean TNSS- instantaneous double-blind period overall minus mean TNSS-instantaneous during the baseline period.

The secondary efficacy variables:

- the total nasal symptom score (TNSS) – reflective, which was the change from baseline over the double-blind period in the mean daily TNSS- reflective (previous 24 hours), such that change from baseline was equal to the mean TNSS - reflective double-blind period overall minus mean TNSS - reflective during the baseline period.
- weekly total nasal symptom score – instantaneous, which was the change from baseline over the double-blind period in the mean daily TNSS - instantaneous (immediately prior to dosing) at Weeks 1, 2, 3, and 4, such that change from baseline weekly was equal to the mean TNSS - instantaneous of that week of the double-blind period minus mean TNSS – instantaneous during the baseline period.

Investigational plan:
This was a randomized, double-blind, parallel group, placebo-controlled, multicenter, 4-week efficacy and safety study in paediatric subjects 2 to 5 years of age conducted in the US.
Immediately following the double-blind period, an open-label, 6-month safety segment was conducted at the same sites. Additionally, some sites elected to participate in evaluation of the HPA axis and/or PK.

Relevant to the assessment of the HPA axis, subjects meeting all of the inclusion criteria were considered for enrolment into the study. Specific to the HPA axis assessment, one additional inclusion criterion was required for subjects undergoing the cosyntropin stimulation test (CST). Subjects were required to have a morning (8 AM±1 hour) pre-stimulation serum cortisol level ≥5 µg/dL (138 nmol/L) and 30 minutes post-stimulation serum cortisol level ≥18 µg/dL (496 nmol/L) at baseline.

Daily reflective (previous 24 hours) and instantaneous (immediately prior to dosing) ratings for rhinitis symptoms were performed upon arising in the morning before taking investigational

product. For both the reflective and instantaneous symptom assessments, the symptoms rated daily were: nasal stuffiness, nasal discharge (anterior and/or posterior drainage), sneezing, nasal itching, total eye symptoms of itching, tearing, and/or redness.

The severity of each symptom was scored on a scale of 0 through 3, such that:
• 0 = symptom absent
• 1 = mild (present but not annoying to self)
• 2 = moderate (present and annoying to self but does not interfere with sleep or daily living)
• 3 = severe (interferes with/or unable to carry out activities of daily living or sleep).
Total Nasal Symptom Score (TNSS) was calculated by adding the scores for nasal stuffiness, nasal discharge, sneezing, and nasal itching. The TNSS did not include the score for the total eye symptoms (itching, tearing, and/or redness). The Total Symptom Score (TSS) was calculated by adding the scores for nasal stuffiness, nasal discharge, sneezing, nasal itching, and total eye symptoms of itching, tearing, and/or redness. Thus, the daily TNSS could range from 0 to 12. The daily TSS could range from 0 to 15. Both physician and parent/guardian performed a global evaluation of the investigational product´s efficacy at study visits 4, 6 and 8 based on a scale 0 through 4.
Treatment failure after 2 weeks of treatment was documented in the CRF at the end of the double-blind period. Daily rescue medication use was documented in the daily diary.

Assessor´s comment: *the investigational plan is appropriate. The study has been conducted in US, which might bring up the question of differences in aetiology of allergic rhinitis between US and European patients. However, since Nasacort is intended for the relief of symptoms, and symptoms of allergic rhinitis are similar regardless of the cause, there is no need to extrapolate results on EU population.*

Selection of the doses in the study:
Since systemic exposure determines the risk of systemic adverse effects (eg, adrenal suppression, osteopenia/osteoporosis, growth suppression), the PK of a particular corticosteroid should be characterized at the intended dose(s) in a particular patient population and interpreted in the context of known data from other patient populations for which safety and efficacy have already been established. Therefore, at the time of initiating this current study (XRG5029C/3502), the PK of TAA was investigated and established following intranasal administration of daily doses of 110 µg qd in paediatric subjects 2 to 5 years of age with PAR, compared with 110 µg and 220 µg qd in adult subjects 18 to 50 years of age with PAR. The 110-µg dose was studied in adult subjects 18 to 50 years of age to provide a reference database for interpreting exposure data in paediatric subjects 2 to 5 years of age since data with adults at this dose were not available.
The 110-µg dose was generally safe and well tolerated in both the paediatric and adult subjects. The apparent total body clearance (CL/F) and apparent volume of distribution (V/F) estimates for TAA in 2- to 5-year-old subjects were lower than those in adult subjects. On a body-weight normalized basis, CL/F was similar between paediatric and adult subjects. Inter-subject variability in CL/F was similar between the two groups. The overall exposure to TAA produced at the 110-µg dose in the paediatric subjects 2 to 5 years of age was similar to the overall exposure to TAA produced at the 220-µg dose in the adult subjects 18 to 50 years of age. No significant accumulation of TAA with multiple dosing in either paediatric or adult subjects was apparent.

Statistical methods:
For the primary efficacy analysis the following null hypothesis was tested:

• H0: no treatment difference exists between NASACORT AQ and placebo in the change from baseline (overall) in the mean daily TNSS - instantaneous (immediately prior to dosing);

versus

• H1: a treatment difference does exist between NASACORT AQ and placebo in the change from baseline (overall) in the mean daily TNSS - instantaneous (immediately prior to dosing). In order to test the hypothesis of no difference between both treatment groups, an analysis of covariance (ANCOVA) using SAS Proc Mixed was performed on the ITT population, using the change from baseline as the dependent variable, with treatment and (pooled) site as fixed effects and the corresponding baseline value for the mean daily TNSS - instantaneous as a covariate (ie, primary ANCOVA model): such that change from baseline was equal to the treatment plus the pooled site plus the baseline value.

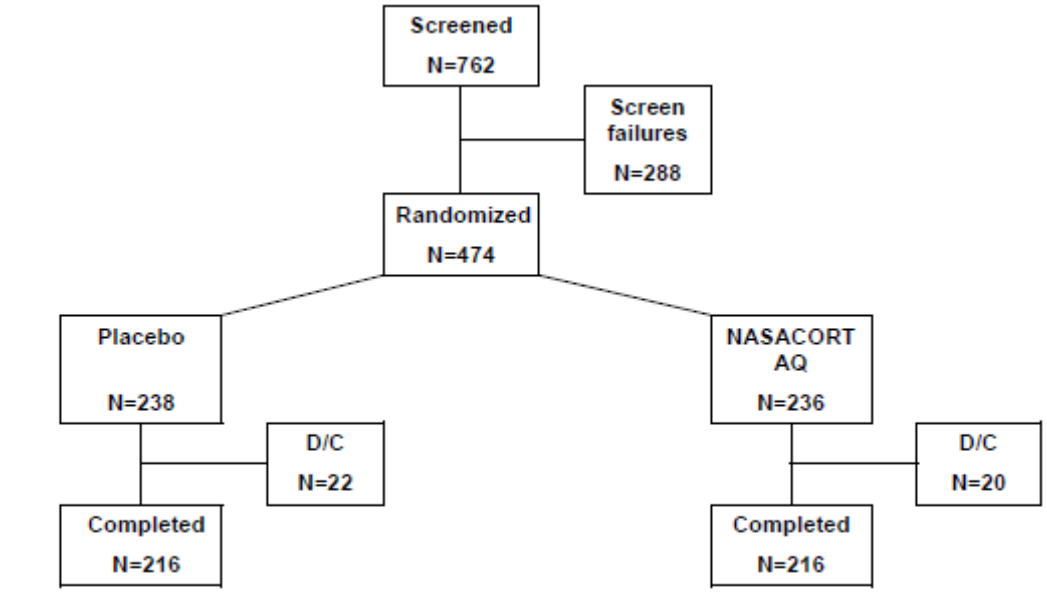
Change from baseline = Treatment + (pooled) Site + Baseline value

Determination of the sample size:
Four hundred (400) subjects were required to achieve a 90% power to reject the null hypothesis of no difference between NASACORT AQ Nasal Spray and placebo for the changes from baseline in instantaneous TNSS when the expected mean difference was no less than 0.65 units, assuming a common SD of 2.0 units. The estimated value of 2.0 units SD used in the calculation was to ensure 200 evaluable subjects per treatment arm (400 subjects) by the end of double-blind period, at least 460 subjects (230 subjects/arm) were to be enrolled in the double-blind period. This assumed a dropout rate of approximately 15%.
Finally, approximately 350 subjects were to be enrolled in the open-label period to achieve approximately 250 subjects by the end of the 6-month open-label period.

Assessor´s comment: *the sample size seems appropriate; nevertheless, it is not clear on what grounds has the margin of 0.65 units been set. The MAH is requested to clarify.*

Disposition of subjects:
The disposition of subject is shown in the flowchart below.

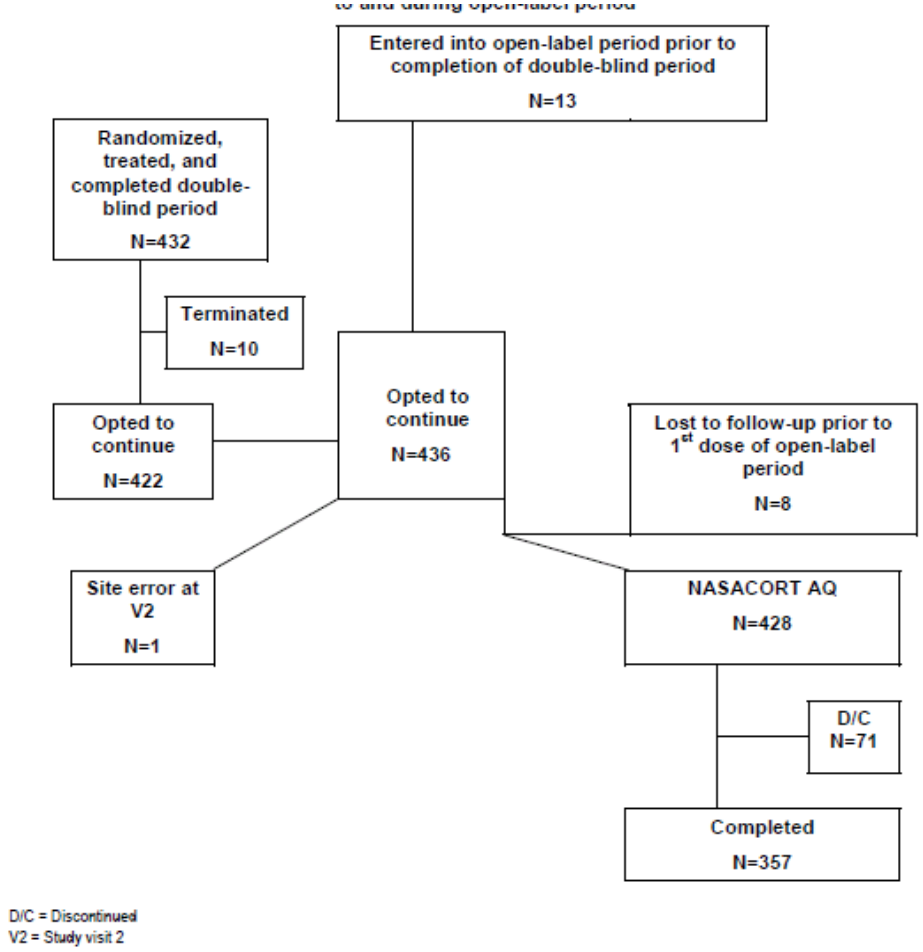
Figure 7: Summary flowchart of subject disposition during double-blind period



D/C = Discontinued
qd = Once daily

Of the 474 randomized subjects, 42 subjects (22 placebo, 20 NASACORT AQ) discontinued the study before the end of the double-blind period. The rates for discontinuation were comparable between the placebo and NASACORT AQ treatment groups. The reasons for discontinuation were as follows: lost to follow-up (7 subjects in the placebo group and 6 in the treatment group), other (3 subjects in the placebo group, 6 in the treatment group), not wishing to continue (6 subjects in the placebo group, 3 subjects in the treatment group), adverse event (3 subjects in the placebo group, 4 subjects in the treatment group), lack of efficacy (3 subjects in the placebo group, 1 subject in the treatment group).
In the open-label period, as subjects completed the double-blind period, continuation into the open-label period was permitted. Of the 432 subjects who completed double-blind period, 422 subjects (97.7%) opted to continue into the open-label period and 10 subjects (2.3%) did not.
The subject disposition during the open-label period is depicted in Figure 8.

Figure 8: Summary flowchart of subject disposition from double-blind period to and during open-label period



D/C = Discontinued
V2 = Study visit 2

Of the 428 subjects who participated in the open-label period, 357 subjects (83.4%) completed the study according to the clinical study protocol and 71 subjects (16.6%) discontinued the study before the end of the open-label period. During the open-label period, there was no subject who withdrew because of lack of efficacy. The reasons for discontinuation were: not wishing to continue (23 subjects), lost to follow-up (17 subjects), adverse event (15 subjects), other (14 subjects), protocol violation (2 subjects).

Data sets analysed:
The evaluable populations for the double-blind and open-label periods are summarized in tables 11 and 12.

Table 11: The study population during the double-blind period

Population type	Placebo (n)	NASACORT AQ 110 µg qd (n)	Total (N)
Safety	238	236	474
ITT	233	231	464
Completer	215	212	427
PP	198	194	392
Cosyntropin evaluable	28	33	61

The 5 populations were defined in Section 6.7.1.2.
ITT = Intent-to-treat population
PP = Per-protocol population

Table 12: The study population during the open-label period

Population type	NASACORT AQ 110 µg qd (N)
Safety	428
ITT	410
Completer	355
PK evaluable	111
Cosyntropin evaluable	49

The 5 populations were defined in Section 6.7.1.2.
ITT = Intent-to-treat population
PK = Pharmacokinetics

Demographic characteristics:
Demographic characteristics of patients enrolled in the double-blind period are summarized in the Table 13.

Table 13: Demography during the double-blind period (ITT population)

Demographic variable		Placebo (n=233)	NASACORT AQ 110 µg qd (n=231)	Overall (N=464)
Age	Mean (y [SD])	3.5 (1.04)	3.6 (1.05)	3.6 (1.05)
	Median	3	4	4
	Range	2 – 5	2 – 5	2 – 5
	2-year-olds [n (%)]	52 (22.3)	43 (18.6)	95 (20.5)
	3-year-olds [n (%)]	67 (28.8)	53 (22.9)	120 (25.9)
	4-year-olds [n (%)]	70 (30.0)	77 (33.3)	147 (31.7)
	5-year-olds [n (%)]	44 (18.9)	58 (25.1)	102 (22.0)
Sex	Male [n (%)]	143 (61.4)	123 (53.2)	266 (57.3)
	Female [n (%)]	90 (38.6)	108 (46.8)	198 (42.7)
Race	White	157 (67.4)	148 (64.1)	305 (65.7)
	Black	29 (12.4)	39 (16.9)	68 (14.7)
	Other	34 (14.6)	27 (11.7)	61 (13.1)
	Multiracial	8 (3.4)	10 (4.3)	18 (3.9)
	Asian/Oriental	5 (2.1)	7 (3.0)	12 (2.6)
Height	Mean (cm [SD])	102.12 (9.272)	103.01 (9.689)[a]	102.61 (9.484)[a]
	Median	102.0	103.7[a]	103.0[a]
	Range	81.0 – 122.0	77.0 – 124.0[a]	77.0 – 124.0[a]
Weight	Mean (kg [SD])	17.31 (3.868)	17.63 (4.116)	17.47 (3.992)
	Median	16.8	17.3	16.8
	Range	8.3 – 33.2	10.0 – 34.5	8.3 – 34.5
BMI	Mean (kg/m² [SD])	16.50 (2.143)	16.49 (2.054)[a]	16.49 (2.097)[a]
	Median	16.4	16.1[a]	16.2[a]
	Range	6.9 – 25.7	12.7 – 24.6[a]	6.9 – 25.7[a]
BSA	Mean (m² ([SD])	0.69 (0.104)	0.70 (0.109)[a]	0.69 (0.106)[a]
	Median	0.7	0.7[a]	0.7[a]
	Range	0.5 – 1.0	0.5 – 1.1[a]	0.5 – 1.1[a]

BMI = Body mass index
BSA = Body surface area
SD = Standard deviation
y = Years

[a] Subject 00440033 did not have height recorded and the reason was unknown; thus, N = 427.

Differences between the ITT and safety populations were not generally observed for any demographic variable. Similarly, differences were not observed for any demographic variable between the ITT and the completer or PP population.

The demography of the open-label population is summarized in the Table 14.

Table 14: Demography during the open-label period (safety population)

Demographic variable		NASACORT AQ 110 µg qd (N=428)
Age	Mean (y [SD])	3.6 (1.05)
	Median	4
	Range	2 – 5
	2-year-olds [n (%)]	85 (19.9)
	3-year-olds [n (%)]	110 (25.7)
	4-year-olds [n (%)]	136 (31.8)
	5-year-olds [n (%)]	97 (22.7)
Sex	Male [n (%)]	246 (57.5)
	Female [n (%)]	182 (42.5)
Race	White	281 (65.7)
	Black	60 (14.0)
	Other	58 (13.6)
	Multiracial	18 (4.2)
	Asian/Oriental	11 (2.6)
Height	Mean (cm [SD])	102.60 (9.444)[a]
	Median	102.8[a]
	Range	77.0 – 124.0[a]
Weight	Mean (kg [SD])	17.49 (4.005)
	Median	16.8
	Range	8.3 – 34.5
BMI	Mean (kg/m² [SD])	16.51 (2.083)[a]
	Median	16.2[a]
	Range	6.9 – 25.7[a]
BSA	Mean (m² ([SD])	0.70 (0.107)[a]
	Median	0.7[a]
	Range	0.5 – 1.1[a]

BMI = Body mass index
BSA = Body surface area
SD = Standard deviation
y = Years
[a] Subject 00440033 did not have height recorded and the reason was unknown; thus, N = 427.

Differences between the safety population and ITT or completer population were not generally observed for any demographic variables. The demographic background variables resembled those of the population during the double-blind period.

Primary efficacy variable results:
Baseline scores for the TNSS - instantaneous were comparable between the 2 treatment groups (7.61 placebo, 7.52 NASACORT AQ; p=0.6187). The adjusted mean change (±SE) from baseline over the double-blind period for the TNSS - instantaneous was –1.92 (±0.157) for the placebo group and –2.28 (±0.157) for the NASACORT AQ treatment group in the ITT population (2- to 5-year-olds). In the ANCOVA, a statistically significant treatment effect was not observed in the primary efficacy variable in the ITT population (p=0.0946). Additional analyses performed

on other populations (PP, completer) were consistent with the analysis performed on ITT population.
Post hoc subgroup analyses were conducted to evaluate the effect of age, sex, race, composite nasal symptom score, and a rescue medication use on the primary efficacy variable. Excluding 2 years subjects from the analysis the significant effect in mean change was observed (difference between groups was 0.63 with p=0.0108).

Secondary efficacy variable results:
In the ITT population the mean change (± SE) in reflective TNSS was -1.87 (± 0,151) for the placebo group and -2.31 (± 0.151) for the TAA AQ treated group. The difference between groups was 0.44 with 95%CI being of (-0.04; +0.84). The statistically significant treatment effect was observed (p=0.0328) but no statistically significant treatment effect was observed in the PP population.

The mean change (± SE) in instantaneous TNSS from baseline was

- -1.38 (± 0.152) for the placebo group versus -1.69 (± 0.156) for the TAA-AQ group during week 1
- -1.93 (± 0.173) for the placebo group and -2.31 (± 0.172) for the TAA-AQ group during week 2
- -2.25 (±0.185) for the placebo group and 2.48 (± 0.184) for the TAA-AQ group during week 3
- -2.43 (± 0.196) for the place group and -2.84 (± 0.196) for the TAA-AQ group during week 4

A statistically significant treatment effect was not observed in any population (ITT, PP, completer).

The mean change (± SE) in reflective TNSS from baseline was:

- -1.33 (± 0.146) for the placebo group versus -1.66 (± 0.146) for the TAA-AQ group during week 1
- -1.92 (± 0.171) for the place group and -2.32 (± 0.170) for the TAA-AQ group during week 2
- -2.18 (±0.178) for the placebo group and -2.55 (± 0.177) for the TAA-AQ group during week 3
- -2.36 (± 0.192) for the place group and -2.89 (± 0.192) for the TAA-AQ group during week 4

A statistically significant treatment effect was observed during week 4 (p=0.0423). The differences during all remaining weeks were not statistically significant.

The mean changes (± SE) in instantaneous TSS from baseline were comparable between the treated groups (-2.27 (± 0.190) for the placebo group and -2.66 (± 0.190) for the TAA-AQ group).

The statistically significant treatment effect was not observed in any population (ITT, PP, completer).

The mean changes (± SE) in reflective TSS from baseline were comparable in the treated groups (-2.24 (± 0.183) for the placebo group and -2.71 (± 0.1183) for the TAA-AQ group).No statistically significant treatment effect was observed in any population.

According to the physician's global evaluation of efficacy more subject's treated with TAA-AQ showed moderate, marked or complete relief of symptoms than subjects treated with placebo did. CMH test with modified RIDIT score demonstrated significant difference between groups (p=0.043). The effect was observed in all populations (PP and completer).

According to the subject's global evaluation of efficacy there was no statistically significant difference between groups treated with either placebo or TAA-AQ in ITT population (p=0.0658). Neither in the other analysed populations (PP, completer), the statistically significant effect was observed.

Post hoc subgroup analyses similar to those conducted for the primary variable were conducted on all data related to secondary variables. Excluding two years old subjects all secondary variables showed statistically significant treatment differences in favour of TAA-AQ treatment. Only one exception was reflective TNSS by week which revealed statistical significance only at weeks 3 and 4.

No statistically significant effect of treatment was observed on using rescue medicine. 60.9 % placebo subjects and 59.7 % TAA-AQ subjects were using rescue medication.

The mean frequency of use of rescue medicine (± SD) was comparable in the TAA-AQ group (5.05 ±0.494) and in the placebo group (5.33 ±0.494) during the double blind period (4 weeks).

Open-label period
According to the physician's global evaluation the efficacy of TAA-AQ treatment was better during the open label period than during the double blind period. The most pronounced effect was observed at the end of week 10 (the open label period was from 5th till 28th week).The mean score (± SD) of efficacy of TAA-AQ was 2.54 (± 0.92) at week 10 and 2.38 (±1.015) at the end of the open label period in the ITT population.

The global evaluation of efficacy by the subjects was consistent with the evaluation by the physicians during the open label period.
The number of subjects using rescue medication increased during the open label period compared to the double blind period (79.0 % in the ITT population), but the frequency of rescue medication use was lower in the open label period than in the double blind period.(14.38 days ± 24,614 (SD) for 24 weeks).

Asessor´s comment: *the results of the study do not unequivocally support the proposed extension of the indication. The primary efficacy variable analysis has not shown statistical significance in comparison to placebo, and neither did the secondary efficacy analysis. Only after excluding the two year-olds did the post hoc analysis show significance. This might suggest that the product should be indicated for use from the age of three. The MAH is thus invited to provide further justification for including the two year olds in the light of the study findings.*

Study RG5029Y-314: a placebo-controlled, double-blind study of the safety and efficacy of Nasacort AQ nasal spray in children with perennial allergic rhinitis

Objectives

- The objective of this study was to compare the safety and efficacy of once daily administration of approximately 110 and 220 µg of Nasacort AQ nasal spray with placebo, in relieving the symptoms of perennial allergic rhinitis in children.

Sample size
The sample size of 100 patients per treatment group was chosen to achieve an overall power of at least 90 % for the two pairwise, two-sided Bonferroni-adjusted comparison of placebo to active treatment. This calculation was based on the analysis of the two-week averaged nasal index score from protocol RG5029Y-312.

Three hundred and nineteen (319) patients were enrolled in the study and 286 patients (89,7 %) completed the 12-week period. The reasons for discontinuation are following: test drug ineffective (6 patients), protocol deviation (7 patients), withdrawn consent (8 patients), adverse clinical experience (6 patients), lost to follow up (4 patients), other (2 patients).
A total of 95 patients completed the study in the placebo arm, 91 patients in the 110 µg arm, and 100 patients in the 220 µg arm.

Assessor´s comment: *the sample size seems adequate. The dropout rate is quite low, and reasons for discontinuation are acceptable.*

Investigational plan
This was a twelve-week randomized, placebo-controlled, double-blind study conducted at 24 centres (2 centres did not enrol any patients). The study consisted of a screening phase, a baseline phase and a twelve-week double-blind treatment phase. There were total of 6 visits (screening, two baseline visits, week 2, week 4, week 8, and final visit at week 12). The patients also obtained the daily symptom diary cards, where the following information were recorded:
Rhinitis symptom score: reflective symptom ratings were performed upon arising (prior to dosing) in the morning and in the evening and represented the patient´s symptoms over the previous approximate 12 hours. The "snap-shot" symptom scoring was performed upon arising (prior to dosing) and represented the patient´s symptoms at the moment of rating. The following symptoms were rated by the reflective and snap-shot" methods: nasal discharge, nasal stuffiness, nasal itching, sneezing, total eye symptoms (itchiness, tearing, redness).
Severity of each symptom was rated according to the following scale:
0=symptom absent
1=mild – present but not annoying to self
2=moderate – present but annoying to self but does not interfere with sleep or daily living
3=severe – interferes with/or unable to carry out activities of daily living or sleep.
The patients also recorded concomitant medication, adverse experiences and the number of sprays of study medication.

Assessor´s comment: *the investigational plan is acceptable. The distribution of patients per centre could not be found in the clinical study report. The MAH is requested to provide it.*

Statistical analysis
For all analyses to assess treatment differences a two-way ANCOVA model was used with treatment and center as main effects and no interaction term. The tests used to compare the 110 and 220 µg doses were two-sided pairwise t-tests with Bonferroni adjustment at the 0.025 level of significance. The variable to be tested was the mean change from baseline in the reflective nasal index over the first four weeks of the double-blind period.
The null hypothesis was that there were no differences among treatments versus the alternative hypothesis that there were differences among treatments.

Results
Demographic characteristics of patients are summarized in the table 15 and the baseline scores of symptom variables in table 16.

Table 15: Demographic characteristics

Treatment Group	N	Sex M% : F%	Race Cauc.%	Other%	Age Mean Years/ (Range)	No. Patients Years of Age 4-8	9-12	Height (cm)	Weight (Kg)
Placebo	100	62 : 38	92	8	9.2 / (4 - 12)	34	66	139	36
110 mcg	105	67 : 33	90	10	8.8 / (4 - 12)	45	60	135	34
220 mcg	114	68 : 32	88	12	9.1 / (4 - 12)	41	73	138	36
Total	319	66 : 34	90	10	9.0 / (4 - 12)	120	199	137	35

Table 16: Summary of mean baseline efficacy scores for symptom variables, all-treated patients

REFLECTIVE, 24 - Hour Score				
	MEAN (S. E.)			
Symptom	Placebo (N = 100)	110 mcg (N = 102)	220 mcg (N = 113)	Total (N = 315)
Nasal Stuffiness	2.39 (0.05)	2.46 (0.04)	2.42 (0.04)	2.42 (0.03)
Nasal Discharge	2.22 (0.06)	2.18 (0.06)	2.11 (0.06)	2.17 (0.03)
Sneezing	1.73 (0.08)	1.63 (0.08)	1.51 (0.07)	1.62 (0.04)
Nasal Index[b]	6.34 (0.13)	6.27 (0.13)	6.04 (0.11)	6.21 (0.07)
Itchy Nose	1.99 (0.06)	1.94 (0.07)	1.85 (0.07)	1.93 (0.04)
Total Eye Symptoms	1.39 (0.09)	1.50 (0.09)	1.36 (0.09)	1.41 (0.05)
SNAP SHOT, AM Score				
Symptom	Placebo (N = 99) [c]	110 mcg (N = 102)	220 mcg (N = 113)	Total (N = 314)
Nasal Stuffiness	2.40 (0.05)	2.35 (0.06)	2.39 (0.05)	2.38 (0.03)
Nasal Discharge	2.04 (0.08)	2.01 (0.08)	1.93 (0.07)	1.99 (0.04)
Sneezing	1.50 (0.09)	1.38 (0.09)	1.29 (0.08)	1.38 (0.05)
Nasal Index[b]	5.93 (0.18)	5.74 (0.18)	5.60 (0.15)	5.75 (0.10)
Itchy Nose	1.82 (0.07)	1.81 (0.08)	1.73 (0.08)	1.78 (0.04)
Total Eye Symptoms	1.40 (0.09)	1.42 (0.09)	1.30 (0.09)	1.37 (0.05)

Abstracted from Appendix IV, Section A, Table A.6.1 and A.6.2

[a] Symptom scores are: 0=absent, 1=mild, 2=moderate, 3=severe.

[b] Nasal Index is sum of Nasal Stuffiness, Nasal Discharge, and Sneezing Scores.

[c] Patient 00027 had no snap shot baseline data

Treatment with Nasacort AQ at doses 110 and 220 µg demonstrated larger reductions from baseline symptoms compared to placebo (24-hour reflective scores) during the first four weeks of treatment (primary endpoint). Patients treated with 110 µg had statistically significant larger mean reductions in nasal stuffiness during week 2, nasal discharge during weeks 2 and 3 and combined weeks 1 through 4, sneezing during weeks 1 and 2 and nasal index during weeks 1 and 2 and combined weeks 1 through 4. Patients treated with 220 µg had statistically significantly larger mean reductions in nasal discharge during weeks 2 and 3 and combined weeks 1 through 4 and nasal index during week 2 and combined weeks 1 through 4. While

mean reductions in all remaining variables in both treatment groups were numerically larger than placebo, the changes were not statistically significant.
For the last 8 weeks of treatment (secondary timepoint) all symptoms had a larger reduction from baseline in the two Nasacort groups compared to placebo. However, these differences were not statistically significant for either Nasacort group. When the symptoms were evaluated by week, statistical significance was achieved at various time points. However, these significant changes were not consistent.
Analysis of both 110 and 220 µg groups for the secondary variables, itchy nose and total eye symptoms, revealed no significant reductions from baseline for the entire study with the exception of itchy nose which was significantly different in the 220 µg group during week 9.
The reductions from baseline snap-shot symptom rating for nasal stuffiness, nasal discharge and nasal index for overall weeks 1-12 for the 220 µg dose were statistically significant when compared to the placebo group. The 110 µg group demonstrated improvement in allergy symptoms; however, this improvement was not statistically significant.
With respect to the onset of action, there was statistically significant reduction in the nasal index score over the 24-hour time period for both dose levels as early as day 6. Reductions in nasal index score remained significant for the 220 µg group through day 10. Although not statistically significant at all daily time points, both the 110 and 220 µg groups demonstrated larger than mean reductions from baseline for nasal index beginning at day1.
Global evaluations by both the patients and physicians indicated numerically that the Nasacort AQ had more favourable responses to treatment than the placebo group. However, only the 110 µg group´s score for the physician´s evaluation was statistically different from the placebo.

The analysis results for the primary allergy symptom variables for reflective scores, mean changes from baseline for nasal index, nasal stuffiness, nasal discharge and sneezing averaged over the first 4 weeks of the double-blind period for the 24-hour timepoint, are presented in table 17.

Table 17: Covariance analysis of mean changes from baseline of primary allergy symptom scores for individual weeks 1-4, and combined double-blind period weeks 1-4 reflective, 24-hour score

All-Treated Patients

			Efficacy Variable							
			Nasal Stuffiness (0 = Absent – 3 = Severe)		**Nasal Discharge** (0 = Absent – 3 = Severe)		**Sneezing** (0 = Absent – 3 = Severe)		**Nasal Index**[a]	
Week of Active Treatment	**Treatment Group**	**N**	**Adj. Mean[a] Change From Baseline (S.E.)**	**P-Value[b] vs. Placebo**	**Adj. Mean[a] Change From Baseline (S.E.)**	**P-Value[b] vs. Placebo**	**Adj. Mean[a] Change From Baseline (S.E.)**	**P-Value[b] vs. Placebo**	**Adj. Mean[b] Change From Baseline (S.E.)**	**P-Value[c] vs. Placebo**
Week 1	110 mcg	102	-0.55 (0.06)	0.066	-0.51 (0.06)	0.147	-0.57 (0.06)	0.004*	-1.63 (0.15)	0.017*
	220 mcg	113	-0.45 (0.05)	0.529	-0.51 (0.06)	0.153	-0.57 (0.06)	0.003*	-1.50 (0.14)	0.070
	Placebo	100	-0.40 (0.06)		-0.39 (0.06)		-0.33 (0.06)		-1.13 (0.15)	
Week 2	110 mcg	101	-0.72 (0.07)	0.013*	-0.65 (0.07)	0.010*	-0.63 (0.06)	0.020*	-2.00 (0.17)	0.005*
	220 mcg	113	-0.67 (0.06)	0.045	-0.63 (0.07)	0.017*	-0.65 (0.06)	0.010*	-1.91 (0.16)	0.011*
	Placebo	100	-0.48 (0.07)		-0.40 (0.07)		-0.42 (0.06)		-1.31 (0.17)	
Week 3	110 mcg	99	-0.72 (0.07)	0.132	-0.73 (0.07)	0.010*	-0.65 (0.07)	0.570	-2.10 (0.18)	0.074
	220 mcg	110	-0.73 (0.07)	0.115	-0.70 (0.07)	0.019*	-0.70 (0.06)	0.234	-2.12 (0.17)	0.054
	Placebo	99	-0.57 (0.07)		-0.47 (0.07)		-0.60 (0.07)		-1.64 (0.18)	
Week 4	110 mcg	96	-0.74 (0.07)	0.155	-0.66 (0.08)	0.189	-0.62 (0.07)	0.519	-2.03 (0.19)	0.201
	220 mcg	110	-0.72 (0.07)	0.211	-0.67 (0.07)	0.153	-0.70 (0.07)	0.157	-2.08 (0.18)	0.135
	Placebo	97	-0.59 (0.07)		-0.52 (0.08)		-0.56 (0.07)		-1.68 (0.19)	
Combined Weeks 1 - 4	110 mcg	102	-0.67 (0.06)	0.037	-0.64 (0.06)	0.015*	-0.62 (0.05)	0.057	-1.93 (0.15)	0.016*
	220 mcg	113	-0.64 (0.05)	0.082	-0.63 (0.06)	0.021*	-0.66 (0.05)	0.013*	-1.91 (0.14)	0.020*
	Placebo	100	-0.50 (0.06)		-0.44 (0.06)		-0.47 (0.05)		-1.42 (0.15)	

Abstracted from Appendix IV, Section A, Table A.7.1.

[a] Nasal Index is the sum of Nasal Stuffiness, Nasal Discharge, and Sneezing.

[b] Means adjusted for baseline and investigators.

[c] P-Values are computed from t-test for a two-way main effects analysis of covariance model with treatment and center as main effects and baseline as the covariate

*: $p < 0.05$ for 2-tailed t-test, Bonferroni adjusted for two comparisons. (adjusted value: $p \leq 0.025$)

The results of the analysis of the nasal symptom variables for the first 12-hour (PM) scores and second 12-hour (AM) scores are presented in tables 18 and 19.

Table 18: Covariance analysis of mean changes from baseline of primary allergy symptom scores for individual weeks 1-4, and combined double-blind period weeks 1-4 reflective, first 12-hour scores (PM)

All-Treated Patients

			Efficacy Variable							
			Nasal Stuffiness (0 = Absent -- 3 = Severe)		Nasal Discharge (0 = Absent -- 3 = Severe)		Sneezing (0 = Absent -- 3 = Severe)		Nasal Index[a]	
Week of Active Treatment	Treatment Group	N	Adj. Mean[a] Change From Baseline (S.E.)	P-Value[b] vs. Placebo	Adj. Mean[a] Change From Baseline (S.E.)	P-Value[b] vs. Placebo	Adj. Mean[a] Change From Baseline (S.E.)	P-Value[b] vs. Placebo	Adj. Mean[b] Change From Baseline (S.E.)	P-Value[c] vs. Placebo
Week 1	110 mcg	102	-0.56 (0.06)	0.197	-0.47 (0.06)	0.335	-0.57 (0.06)	0.004*	-1.59 (0.16)	0.045
	220 mcg	113	-0.49 (0.06)	0.614	-0.49 (0.06)	0.242	-0.58 (0.06)	0.002*	-1.54 (0.15)	0.075
	Placebo	100	-0.45 (0.06)		-0.38 (0.07)		-0.30 (0.07)		-1.14 (0.16)	
Week 2	110 mcg	101	-0.74 (0.07)	0.032	-0.65 (0.07)	0.032	-0.62 (0.07)	0.052	-2.00 (0.18)	0.018*
	220 mcg	113	-0.68 (0.07)	0.102	-0.65 (0.07)	0.030	-0.69 (0.07)	0.007*	-1.99 (0.18)	0.019*
	Placebo	100	-0.51 (0.07)		-0.43 (0.07)		-0.42 (0.07)		-1.38 (0.19)	
Week 3	110 mcg	99	-0.72 (0.07)	0.254	-0.71 (0.07)	0.042	-0.64 (0.07)	0.781	-2.07 (0.19)	0.186
	220 mcg	110	-0.75 (0.07)	0.148	-0.72 (0.07)	0.030	-0.74 (0.07)	0.187	-2.20 (0.18)	0.068
	Placebo	100	-0.60 (0.08)		-0.50 (0.07)		-0.61 (0.07)		-1.71 (0.19)	
Week 4	110 mcg	96	-0.74 (0.08)	0.277	-0.65 (0.08)	0.408	-0.64 (0.07)	0.576	-2.04 (0.20)	0.340
	220 mcg	110	-0.75 (0.07)	0.247	-0.69 (0.07)	0.240	-0.76 (0.07)	0.086	-2.18 (0.19)	0.136
	Placebo	97	-0.62 (0.08)		-0.56 (0.08)		-0.58 (0.08)		-1.77 (0.20)	
Combined Weeks 1 - 4	110 mcg	102	-0.69 (0.06)	0.093	-0.63 (0.06)	0.054	-0.61 (0.06)	0.098	-1.93 (0.16)	0.051
	220 mcg	113	-0.67 (0.06)	0.133	-0.64 (0.06)	0.038	-0.69 (0.06)	0.008*	-1.98 (0.15)	0.026
	Placebo	100	-0.54 (0.06)		-0.46 (0.06)		-0.47 (0.06)		-1.48 (0.16)	

Abstracted from Appendix IV, Section A, Table A.7.1.

[a] Nasal Index is the sum of Nasal Stuffiness, Nasal Discharge, and Sneezing.

[b] Means adjusted for imbalances among baseline and investigators.

[c] P-Values are computed from t-test for a two-way main effects analysis of covariance model with treatment and center as main effects and baseline as the covariate

*: $p < 0.05$ for 2-tailed t-test, Bonferroni adjusted for two comparisons. (adjusted value: $p \leq 0.025$)

Table 19: Covariance analysis of mean changes from baseline of primary allergy symptom scores for individual weeks 1-4, and combined double-blind period weeks 1-4 reflective, second 12-hour scores (AM)

All-Treated Patients

			Efficacy Variable							
			Nasal Stuffiness (0 = Absent -- 3 = Severe)		Nasal Discharge (0 = Absent -- 3 = Severe)		Sneezing (0 = Absent -- 3 = Severe)		Nasal Index[a]	
Week of Active Treatment	Treatment Group	N	Adj. Mean[a] Change From Baseline (S.E.)	P-Value[b] vs. Placebo	Adj. Mean[a] Change From Baseline (S.E.)	P-Value[b] vs. Placebo	Adj. Mean[a] Change From Baseline (S.E.)	P-Value[b] vs. Placebo	Adj. Mean[b] Change From Baseline (S.E.)	P-Value[c] vs. Placebo
Week 1	110 mcg	102	-0.51 (0.06)	0.093	-0.51 (0.07)	0.194	-0.55 (0.06)	0.026	-1.57 (0.15)	0.041
	220 mcg	113	-0.38 (0.06)	0.925	-0.51 (0.06)	0.153	-0.55 (0.06)	0.025*	-1.42 (0.15)	0.158
	Placebo	100	-0.37 (0.06)		-0.38 (0.07)		-0.36 (0.06)		-1.13 (0.15)	
Week 2	110 mcg	101	-0.67 (0.07)	0.009*	-0.63 (0.07)	0.011*	-0.62 (0.07)	0.007*	-1.93 (0.17)	0.002*
	220 mcg	113	-0.63 (0.06)	0.023*	-0.61 (0.07)	0.020*	-0.60 (0.06)	0.011*	-1.81 (0.16)	0.008*
	Placebo	99	-0.43 (0.07)		-0.38 (0.07)		-0.37 (0.07)		-1.18 (0.17)	
Week 3	110 mcg	99	-0.71 (0.07)	0.078	-0.72 (0.07)	0.004*	-0.65 (0.07)	0.399	-2.08 (0.18)	0.032
	220 mcg	110	-0.70 (0.07)	0.106	-0.67 (0.07)	0.013*	-0.66 (0.07)	0.299	-2.03 (0.18)	0.048
	Placebo	99	-0.54 (0.07)		-0.42 (0.07)		-0.56 (0.07)		-1.52 (0.19)	
Week 4	110 mcg	96	-0.72 (0.07)	0.129	-0.66 (0.08)	0.121	-0.59 (0.07)	0.504	-1.96 (0.19)	0.153
	220 mcg	110	-0.68 (0.07)	0.232	-0.65 (0.07)	0.132	-0.62 (0.07)	0.299	-1.94 (0.18)	0.168
	Placebo	97	-0.56 (0.07)		-0.48 (0.08)		-0.52 (0.07)		-1.57 (0.19)	
Combined Weeks 1 - 4	110 mcg	102	-0.65 (0.06)	0.028	-0.63 (0.06)	0.011*	-0.61 (0.06)	0.049	-1.89 (0.15)	0.011*
	220 mcg	113	-0.61 (0.05)	0.077	-0.62 (0.06)	0.018*	-0.62 (0.05)	0.032	-1.82 (0.15)	0.022*
	Placebo	100	-0.47 (0.06)		-0.41 (0.06)		-0.45 (0.06)		-1.34 (0.15)	

Abstracted from Appendix IV, Section A, Table A.7.1.

[a] Nasal Index is the sum of Nasal Stuffiness, Nasal Discharge, and Sneezing.

[b] Means adjusted for imbalances among baseline and investigators.

[c] P-Values are computed from t-test for a two-way main effects analysis of covariance model with treatment and center as main effects and baseline as the covariant

*: $p < 0.05$ for 2-tailed t-test, Bonferroni adjusted for two comparisons. (adjusted value: $p \leq 0.025$)

Table 20: Covariance analysis of mean changes from baseline of primary allergy symptom scores for individual weeks 1-4 and combined double-blind period weeks 1-4 snap shot, AM scores

All-Treated Patients

			Efficacy Variable							
			Nasal Stuffiness (0 = Absent – 3 = Severe)		Nasal Discharge (0 = Absent – 3 = Severe)		Sneezing (0 = Absent – 3 = Severe)		Nasal Index[a]	
Week of Active Treatment	Treatment Group	N	Adj. Mean[a] Change From Baseline (S.E.)	P-Value[b] vs. Placebo	Adj. Mean[a] Change From Baseline (S.E.)	P-Value[b] vs. Placebo	Adj. Mean[a] Change From Baseline (S.E.)	P-Value[b] vs. Placebo	Adj. Mean[b] Change From Baseline (S.E.)	P-Value[c] vs. Placebo
Week 1	110 mcg	102	-0.32 (0.06)	0.990	-0.22 (0.07)	0.930	-0.41 (0.07)	0.232	-0.96 (0.16)	0.640
	220 mcg	113	-0.34 (0.06)	0.881	-0.37 (0.06)	0.135	-0.45 (0.07)	0.095	-1.18 (0.16)	0.151
	Placebo	99	-0.32 (0.06)		-0.23 (0.07)		-0.30 (0.07)		-0.85 (0.16)	
Week 2	110 mcg	101	-0.47 (0.07)	0.293	-0.36 (0.07)	0.335	-0.40 (0.07)	0.332	-1.23 (0.18)	0.244
	220 mcg	113	-0.56 (0.07)	0.045	-0.44 (0.07)	0.069	-0.46 (0.06)	0.095	-1.46 (0.17)	0.035
	Placebo	98	-0.37 (0.07)		-0.26 (0.07)		-0.31 (0.07)		-0.94 (0.18)	
Week 3	110 mcg	99	-0.51 (0.07)	0.509	-0.48 (0.08)	0.041	-0.50 (0.07)	0.396	-1.50 (0.18)	0.155
	220 mcg	110	-0.63 (0.07)	0.056	-0.50 (0.07)	0.025	-0.49 (0.07)	0.445	-1.64 (0.18)	0.047
	Placebo	98	-0.45 (0.07)		-0.26 (0.08)		-0.42 (0.07)		-1.13 (0.19)	
Week 4	110 mcg	96	-0.59 (0.07)	0.278	-0.45 (0.08)	0.155	-0.47 (0.07)	0.954	-1.50 (0.19)	0.299
	220 mcg	110	-0.62 (0.07)	0.151	-0.51 (0.08)	0.042	-0.51 (0.07)	0.631	-1.66 (0.18)	0.101
	Placebo	96	-0.47 (0.08)		-0.28 (0.08)		-0.46 (0.07)		-1.22 (0.20)	
Combined Weeks 1 - 4	110 mcg	102	-0.47 (0.06)	0.408	-0.39 (0.06)	0.144	-0.44 (0.06)	0.387	-1.30 (0.15)	0.221
	220 mcg	113	-0.55 (0.06)	0.071	-0.46 (0.06)	0.019*	-0.48 (0.06)	0.157	-1.50 (0.15)	0.029
	Placebo	99	-0.40 (0.06)		-0.26 (0.06)		-0.37 (0.06)		-1.03 (0.16)	

Abstracted from Appendix IV, Section A, Table A.7.1.

[a] Nasal Index is the sum of Nasal Stuffiness, Nasal Discharge, and Sneezing.

[b] Means adjusted for imbalances among baseline and investigators.

P-Values are computed from t-test for a two-way main effects analysis of covariance model with treatment and center as main effects and baseline as the covariate

*: $p < 0.05$ for 2-tailed t-test, Bonferroni adjusted for two comparisons. (adjusted value: $p \leq 0.025$)

Table 21: Covariance analysis of mean changes from baseline of secondary allergy symptom scores for individual weeks 1-4 and combined double-blind period weeks 1-4 reflective, 24-hour scores

All-Treated Patients

		Efficacy Variable					
		Itchy Nose (0 = Absent – 3 = Severe)			Total Eye Symptoms (0 = Absent – 3 = Severe)		
Week of Active Treatment	Treatment Group	N	Adj. Mean[a] Change From Baseline (S.E.)	P-Value[b] vs. Placebo	N	Adj. Mean[a] Change From Baseline (S.E.)	P-Value[b] vs. Placebo
Week 1	110 mcg	102	-0.55 (0.06)	0.168	102	-0.35 (0.06)	0.379
	220 mcg	113	-0.46 (0.06)	0.737	113	-0.38 (0..06)	0.203
	Placebo	100	-0.44 (0.06)		100	-0.28 (0.06)	
Week 2	110 mcg	101	-0.65 (0.06)	0.140	101	-0.47 (0.06)	0.120
	220 mcg	113	-0.64 (0.06)	0.166	113	-0.43 (0.06)	0.262
	Placebo	100	-0.52 (0.06)		100	-0.34 (0.06)	
Week 3	110 mcg	99	-0.68 (0.07)	0.319	99	-0.45 (0.07)	0.577
	220 mcg	110	-0.75 (0.07)	0.082	110	-0.48 (0.06)	0.357
	Placebo	99	-0.58 (0.07)		99	-0.40 (0.07)	
Week 4	110 mcg	96	-0.76 (0.07)	0.215	96	-0.43 (0.07)	0.780
	220 mcg	110	-0.82 (0.07)	0.057	110	-0.49 (0.07)	0.409
	Placebo	97	-0.63 (0.07)		97	-0.40 (0.07)	
Combined Weeks 1 - 4	110 mcg	102	-066 (0.06)	0.115	102	-0.42 (0.06)	0.379
	220 mcg	113	-0.67 (0.06)	0.088	113	-0.45 (0.06)	0.208
	Placebo	100	-0.53 (0.06)		100	-0.35 (0.06)	

Abstracted from Appendix IV, Section A, Table A.7.1.

[a] Means adjusted for imbalances among baseline and investigators.

[b] P-Values are computed from t-test for a two-way main effects analysis of covariance model with treatment and center as main effects and baseline as the covariate

*: $p < 0.05$ for 2-tailed t-test, Bonferroni adjusted for two comparisons. (adjusted value $p \leq 0.025$)

Analysis of the daily mean changes from baseline comparing the active treatment groups to placebo were done for Days 1 through 14 for each symptom. The results of the analysis of the reflective nasal index for reflective 24-hours are shown in Table 22. Statistically significant reduction from placebo occurred on Days 6 through 10 and on Day 13 for the 220 µg group. Statistically significant reduction from placebo occurred on Days 6 through 8 and Days 12 – 14 fro the 110 µg group. Similar results were obtained for the evaluable population.

The analysis of the daily snapshot symptom failed to demonstrate statistically significant improvement in symptom scores for Days 1 – 14. This was consistent for both all-treated and evaluable populations.

Table 22: Covariance analysis on Days 1 to 14 of the nasal index – reflective 24-hour all-treated patients

Day of Active Treatment	Treatment Group	N	Baseline Mean	Adj. Mean[a] Change From Baseline (S.E.)	P-Value[b] vs. Placebo
Day 1	110 mcg	100	6.29	-1.00 (0.16)	0.641
	220 mcg	109	6.04	-0.91 (0.15)	0.965
	Placebo	99	6.34	-0.90 (0.16)	
Day 2	110 mcg	101	6.27	-1.45 (0.16)	0.038
	220 mcg	112	6.03	-1.31 (0.16)	0.131
	Placebo	100	6.34	-0.97 (0.17)	
Day 3	110 mcg	101	6.28	-1.64 (0.17)	0.087
	220 mcg	112	6.04	-1.49 (0.17)	0.267
	Placebo	99	6.35	-1.22 (0.18)	
Day 4	110 mcg	101	6.28	-1.68 (0.18)	0.052
	220 mcg	110	6.06	-1.54 (0.18)	0.147
	Placebo	99	6.35	-1.17 (0.19)	
Day 5	110 mcg	102	6.27	-1.70 (0.18)	0.114
	220 mcg	112	6.04	-1.62 (0.17)	0.198
	Placebo	98	6.35	-1.30 (0.18)	
Day 6	110 mcg	101	6.28	-1.91 (0.18)	0.013*
	220 mcg	112	6.05	-1.83 (0.17)	0.024*
	Placebo	98	6.34	-1.26 (0.19)	
Day 7	110 mcg	99	6.27	-1.90 (0.18)	0.001*
	220 mcg	112	6.05	-1.78 (0.17)	0.004*
	Placebo	99	6.32	-1.06 (0.18)	
Day 8	110 mcg	101	6.25	-1.98 (0.19)	0.011*
	220 mcg	110	6.03	-1.90 (0.18)	0.021*
	Placebo	97	6.33	-1.29 (0.19)	
Day 9	110 mcg	100	6.27	-1.75 (0.20)	0.214
	220 mcg	109	6.04	-2.06 (0.19)	0.017*
	Placebo	96	6.30	-1.40 (0.20)	
Day 10	110 mcg	99	6.28	-1.86 (0.20)	0.029
	220 mcg	111	6.05	-1.95 (0.19)	0.010*
	Placebo	96	6.31	-1.23 (0.21)	
Day 11	110 mcg	98	6.26	-1.98 (0.20)	0.072
	220 mcg	112	6.03	-1.91 (0.19)	0.106
	Placebo	98	6.30	-1.46 (0.20)	
Day 12	110 mcg	98	6.27	-2.04 (0.19)	0.007*
	220 mcg	113	6.04	-1.85 (0.18)	0.039
	Placebo	99	6.35	-1.30 (0.19)	
Day 13	110 mcg	98	6.27	-2.14 (0.20)	0.001*
	220 mcg	113	4.23	-1.84 (0.19)	0.016*
	Placebo	98	6.35	-1.17 (0.20)	
Day 14	110 mcg	98	6.25	-2.02 (0.20)	0.017*
	220 mcg	110	6.01	-1.84 (0.19)	0.074
	Placebo	97	6.33	-1.35 (0.20)	

Abstracted from Appendix IV, Section A, Table A.9.1.
Nasal Index is the sum of Nasal Stuffiness, Nasal Discharge, and Sneezing.

[a] Means adjusted for imbalances among baseline and investigators.

[b] P-Values are computed from t-test for a two-way main effects analysis of covariance model with treatment and center as main effects and baseline as the covariate

*: $p < 0.05$ for 2-tailed t-test, Bonferroni adjusted for two comparisons. (adjusted value $p \leq 0.025$)

Adjustment of the symptom scores from week 5 to the end of the study was made by replacing the symptom score with the worst possible score at the time when escape medication was taken. The results of the analysis of the scores averaged over weeks 5 through the end of the study on the scores of the unadjusted and adjusted primary symptom scores are given in Table 23. There were no significant differences between the 110 µg or 220 µg treatment groups when compared to placebo.

Table 23: Results of the analysis of covariance on scores adjusted for escape medication reflective scores – overall weeks 5-end, all treated patients

All-Treated Patients

Week of Active Treatment	Treatment Group	N	Nasal Stuffiness (0 = Absent – 3 = Severe) Adj. Mean[a] Change From Baseline (S.E.)	P-Value[b] vs. Placebo	Nasal Discharge (0 = Absent – 3 = Severe) Adj. Mean[a] Change From Baseline (S.E.)	P-Value[b] vs. Placebo	Sneezing (0 = Absent – 3 = Severe) Adj. Mean[a] Change From Baseline (S.E.)	P-Value[b] vs. Placebo	Nasal Index[a] Adj. Mean[b] Change From Baseline (S.E.)	P-Value[c] vs. Placebo
Without Escape Score Adjustment										
24 Hours	110 mcg	96	-0.95 (0.07)	0.072	-0.85 (0.07)	0.058	-0.74 (0.06)	0.526	-2.54 (0.18)	0.103
	220 mcg	110	-0.93 (0.07)	0.086	-0.83 (0.07)	0.077	-0.79 (0.06)	0.263	-2.53 (0.17)	0.095
	Placebo	97	-0.76 (0.07)		-0.66 (0.07)		-0.69 (0.07)		-2.11 (0.18)	
1st 12 Hours (PM)	110 mcg	96	-0.95 (0.07)	0.111	-0.85 (0.07)	0.098	-0.77 (0.07)	0.337	-2.58 (0.19)	0.114
	220 mcg	110	-0.93 (0.07)	0.162	-0.82 (0.07)	0.168	-0.83 (0.06)	0.103	-2.56 (0.18)	0.116
	Placebo	97	-0.79 (0.07)		-0.68 (0.07)		-0.68 (0.07)		-2.15 (0.19)	
2nd 12 Hours (AM)	110 mcg	96	-0.92 (0.07)	0.076	-0.83 (0.07)	0.057	-0.70 (0.07)	0.828	-2.44 (0.19)	0.135
	220 mcg	110	-0.92 (0.07)	0.062	-0.83 (0.07)	0.045	-0.73 (0.06)	0.570	-2.48 (0.18)	0.098
	Placebo	97	-0.74 (0.07)		-0.63 (0.07)		-0.68 (0.07)		-2.05 (0.19)	
With Escape Score Adjustment										
24 Hours	110 mcg	96	-0.86 (0.07)	0.081	-0.75 (0.07)	0.074	-0.60 (0.07)	0.758	-2.21 (0.19)	0.158
	220 mcg	110	-0.87 (0.07	0.064	-0.74 (0.07)	0.080	-0.64 (0.06)	0.474	-2.23 (0.18)	0.127
	Placebo	97	-0.69 (0.07)		-0.57 (0.07)		-0.57 (0.07)		-1.83 (0.19)	
1st 12 Hours (PM)	110 mcg	96	-0.88 (0.07)	0.114	-0.76 (0.07)	0.116	-0.64 (0.07)	0.525	-2.27 (0.20)	0.168
	220 mcg	110	-0.87 (0.07)	0.125	-0.73 (0.07)	0.185	-0.68 (0.07)	0.253	-2.27 (0.19)	0.164
	Placebo	97	-0.71 (0.07)		-0.60 (0.07)		-0.57 (0.07)		-1.89 (0.20)	
2nd 12 Hours (AM)	110 mcg	96	-0.85 (0.07)	0.076	-0.74 (0.07)	0.058	-0.57 (0.07)	0.988	-2.15 (0.19)	0.177
	220 mcg	110	-0.87 (0.07)	0.043	-0.75 (0.07)	0.046	-0.59 (0.06)	0.805	-2.20 (0.18)	0.118
	Placebo	97	-0.67 (0.07)		-0.55 (0.07)		-0.57 (0.07)		-1.79 (0.19)	

Abstracted from Appendix IV, Section A, Table A.7.1. and A.8.1.

[a] Nasal Index is the sum of Nasal Stuffiness, Nasal Discharge, and Sneezing.

[b] Means adjusted for imbalances among baseline and investigators.

[c] P-Values are computed from t-test for a two-way main effects analysis of covariance model with treatment and center as main effects and baseline as the covariate

*: $p < 0.05$ for 2-tailed t-test, Bonferroni adjusted for two comparisons. (adjusted value $p \leq 0.025$)

Analysis of the primary allergy symptoms over the entire 12 week period was performed. The results of the analysis indicate that the both the 110 µg and 220 µg groups demonstrated larger mean reductions from baseline compared to placebo. This reduction numerically favoured the 220 µg group slightly but both groups were very similar. Statistical significance compared to placebo was shown for both groups for nasal discharge and for the 220µg group for nasal index. Statistical significance was not shown for either group for the variables nasal stuffiness or sneezing. Table 24 summarizes the primary nasal symptoms for the combination of weeks 1-4 and weeks 1-12.

Table 24: Covariance analysis of mean changes from baseline of primary allergy symptom scores for overall weeks 1-4 and overall weeks 1-end, reflective 24-hour scores

All-Treated Patients

Week of Active Treatment	Treatment Group	N	Efficacy Variable: Nasal Stuffiness (0 = Absent – 3 = Severe) Adj. Mean[a] Change From Baseline (S.E.)	P-Value[b] vs. Placebo	Nasal Discharge (0 = Absent – 3 = Severe) Adj. Mean[a] Change From Baseline (S.E.)	P-Value[b] vs. Placebo	Sneezing (0 = Absent – 3 = Severe) Adj. Mean[a] Change From Baseline (S.E.)	P-Value[b] vs. Placebo	Nasal Index[a] Adj. Mean[b] Change From Baseline (S.E.)	P-Value[c] vs. Placebo
Overall Weeks 1-4	110 mcg	102	-0.67 (0.06)	0.037	-0.64 (0.06)	0.015*	-0.62 (0.05)	0.057	-1.93 (0.15)	0.016*
	220 mcg	113	-0.64 (0.05)	0.082	-0.63 (0.06)	0.021*	-0.66 (0.05)	0.013*	-1.91 (0.14)	0.020*
	Placebo	100	-0.50 (0.06)		-0.44 (0.06)		-0.47 (0.05)		-1.42 (0.15)	
Overall Weeks 1-End	110 mcg		-0.83 (0.06)	0.054	-0.77 (0.06)	0.019*	-0.69 (0.06)	0.248	-2.30 (0.16)	0.043
	220 mcg		-0.85 (0.06)	0.035	-0.78 (0.06)	0.016*	-0.77 (0.05)	0.035	- 2.37 (0.15)	0.018*
	Placebo		-0.67 (0.06)		-0.57 (0.06)		-0.66 (0.06)		-1.84 (0.16)	

Abstracted from Appendix IV, Section A, Table A.7.1.

[a] Nasal Index is the sum of Nasal Stuffiness, Nasal Discharge, and Sneezing.

[b] Means adjusted for baseline and investigators.

[c] P-Values are computed from t-test for a two-way main effects analysis of covariance model with treatment and center as main effects and baseline as the covariate

*: $p < 0.05$ for 2-tailed t-test, Bonferroni adjusted for two comparisons. (adjusted value $p \leq 0.025$)

For the 110µg group, there was a statistically significant difference in the physician´s evaluation of efficacy when compared to placebo at the last double-blind visit. When the greatly improved and somewhat improved categories were combined, there was a higher percentage of patients and physicians in the 110µg and the 220µg group who rated rhinitis symptoms as greatly improved or somewhat improved compared to the placebo group.

Table 25: Summary of patient´s and physician´s evaluation of efficacy, all-treated population

0 = Greatly Improved -- 4 = Greatly Worsened

Treatment Group	N	Greatly Improved & Somewhat Improved Percent (N)	No Improvement[a] Percent (N)	Adjusted Mean Value (S.E.)	P-Value[b] versus Placebo
Patient's Evaluation					
110 mcg	100	72.0% (72)	28.0% (28)	1.07 (0.08)	0.068
220 mcg	111	73.0% (81)	27.0% (30)	1.14 (0.08)	0.216
Placebo	100	67.0% (67)	33.0% (33)	1.28 (0.08)	
Physician's Evaluation					
110 mcg	100	65.0% (65)	35.0% (35)	1.20 (0.08)	0.024*
220 mcg	111	68.5% (76)	31.5% (35)	1.24 (0.08)	0.055
Placebo	100	53.0% (53)	47.0% (47)	1.45 (0.08)	

Abstracted from Appendix IV, Section A, Tables A.10, A.11, and A.12.

[a] No improvement includes: no change, somewhat worsened, and greatly worsened.

[b] P-Values are computed from t-tests conducted on scores (0=greatly improved,.....,4=greatly worsened. Model was a two-way main effects analysis of variance with treatment and center as main effects and no interaction term..

*: $p < 0.05$ for 2-tailed test

There were no obvious imbalances in demographics or efficacy between the treatment arms for patients that were previously treated with antihistamines/decongestants versus those treated with intranasal steroids.

Assessor´s comment: *the results of this study, similarly to the previous ones, are somewhat inconsistent, which makes the interpretation difficult.*

Based on the results above the MAH concluded that both doses of Nasacort AQ were effective in relieving the symptoms of perennial allergic rhinitis. Statistically significant reductions from baseline in many of the primary efficacy variables were observed during each of the first four weeks and weeks one through four combined. Although all variables were not statistically significant at one particular timepoint, the improvement in allergy symptoms was always greater in the treatment groups when compared to placebo.

Improvement of symptoms was seen as early as day 1 and reached the statistical significance by Day 6. However, the statistical significance was not consistent over the first 14 days.

The inconsistent improvement in allergy symptoms observed in both the weekly and daily efficacy variables was noted in a previous Nasacort AQ adult PAR study (RG5029Y-305 and Nasacort Nasal Inhaler paediatric PAR study WHR5029-106). This trend may be reflective of results from the PAR studies.

Statistical superiority of both Nasacort doses over placebo was shown over the entire 12-week period for nasal discharge. The 220 µg group also demonstrated statistical significance over placebo for nasal index for the 12 weeks treatment period.

Analysis of the snapshot rating the overall 12-week period showed that the 220µg group was statistically superior to placebo for the variables nasal stuffiness, nasal discharge and nasal index. While the 110µg group did not show improvement over placebo, it was not significant.

Responses to global evaluations by both patients and physicians indicated that both Nasacort AQ nasal spray groups had a more favourable response to treatment than the placebo group. For the physicians' global evaluation, the response in the 110µg group was statistically significantly more favourable than in the placebo group.

For the 110 and 220µg Nasacort AQ nasal spray groups, 72% and 73% of the patient´s assessment, respectively, rated the response to treatment as greatly or somewhat improved.

Safety

The safety profile of Nasacort AQ has been well established based on large clinical study data and extensive (>16 years) post-marketing experience. In order to provide an overview of the safety profile of Nasacort-AQ in the paediatric population, the following sources of information were considered:

• Clinical safety data
• Postmarketing safety experience
• Relevant literature review

- **Clinical safety data**

Study XRG5029C-1000: A total of 30 subjects (15 paediatric subjects, 15 adult subjects) received at least one dose of investigational product. Out of 15 paediatric subjects, 3 (20 %) experienced a total of 7 treatment-emergent adverse events (TEAEs) during the study. All 3 paediatric subjects had more than one TEAE. These TEAEs were limited to nasal passage irritation, nasal dryness, pyrexia, abdominal pain, and UTI. All TEAEs were mild in intensity. The duration of all TEAEs did not exceed 1 day, with the exception of the UTI, which was diagnosed on 30 September 2003 and was ongoing at the end of study. One subject had increased thirst and urination, without burning, fever, or difficulty in urination (Investigator's correspondence file). The subject reported these symptoms several hours after the last dose of TAA on Study day 5. Nasal passage irritation (two subjects) and nasal dryness (one subject) were the only TEAEs considered possibly related to investigational product by the investigator.
Of the 15 adult subjects in the study population, 10 (66.7%) experienced a total of 17 TEAEs during the study. A total of 5 subjects experienced 8 TEAEs during Period 1 (110 µg qd x 5 days plus the washout preceeding Period 2) and a total of 7 subjects experienced 9 TEAEs during Period 2 (220 µg qd x 5 days): 2 subjects experienced at least one TEAE during each period. The most frequently reported TEAE was headache, occurring in 4 subjects. One episode of headache was considered moderate in intensity while all other TEAEs were mild. Epistaxis was reported in 2 subjects. Other TEAEs observed in 1 subject each were (in alphabetical order): dizziness, dyspepsia, eye irritation, nasal congestion, nausea, pharyngolaryngeal pain, pollakiuria, and rash.. All TEAEs resolved without intervention or
sequelae. TEAEs considered possibly related to investigational product were: dizziness, epistaxis, headache, nasal congestion, nausea, and pharyngolaryngeal pain.

Study XRG5029C/3502: A total of 428 patients enrolled in the open-label phase during which they received TAA-AQ 110 µg daily. Of the 428 TAA-AQ patients in the safety population, 307 patients (71.7%) experienced a total of 1209 TEAEs during open-label period. The overall prevalence of TEAEs reported by TAA-AQ patients was higher during open label period versus TAA-AQ patients during double-blind period (71.7% versus 50.8%, respectively).
Analysis of TEAEs reported during the 4 weeks of double-blind treatment showed comparable reporting rates for placebo (48.3%) and TAA-AQ (50.8%). The most frequently reported TEAEs with higher frequencies on TAA-AQ were headache, pharyngolaryngeal pain, nasopharyngitis, abdominal pain upper, diarrhoea, asthma, rash, excoriation, and rhinorrhoea. No SAE including death was observed during the double-blind period. Seven (1.5%) patients (3 placebo, 4 TAAAQ) during the double-blind period discontinued due to TEAEs.
During the open-label period of the study, the most frequently reported TEAEs were: pyrexia, cough, nasopharyngitis, upper respiratory tract infection, headache, vomiting, otitis media, rhinorrhoea, ear infection, sinusitis, pharyngolaryngeal pain, asthma, viral infection, nasal congestion, epistaxis, ear pain, streptococcal pharyngitis, rash, upper abdominal pain, influenza, pulmonary congestion, viral gastroenteritis, bronchitis, diarrhoea, and viral upper respiratory tract infection. There were no deaths and 7 patients experienced 8 SAEs that included:

appendicitis, aseptic meningitis, adenoidal hypertrophy, asthma, tonsillar hypertrophy, lymphadenitis, foreign body trauma, or diabetic ketoacidosis. Among 8 SAEs, none of the events were considered to have a causal relationship to TAA-AQ, as evaluated by the investigator.
In long-term studies, upper respiratory tract infections and their symptoms dominate among the reported TEAEs during the open-label period. Fifteen (3.5%) patients on TAA-AQ during the open-label period discontinued due to TEAEs.
The overall safety profile of AEs observed in the 2- to 5-year-old paediatric patients studied was consistent with the known AEs associated with the use of TAA-AQ in 6- to 12-year-old paediatric patients.

Study XRG5029Y-315: A total of 175 AEs were reported during or after the four 2-week treatment periods by 51 (86.4%0 patients. There were 6 patients with at least one AE considered to be possibly or probably related to study drug, 1 (1.8%) patient treated with TAA 110 mcg, 2 (3.6%) treated with TAA 220 mcg, 2 (3.9%) treated with FP nasal spray 200 mcg and 1 (1.8%) treated with placebo. And 4 of these AEs included application site reaction in patients treated with TAA 220 mcg (1), FP nasal spray 200 mcg (2) and placebo (1). Other AEs were, rhinitis in TAA 110 mcg, and hyperkinesia in TAA 220 mcg. Two TEAEs were reported as severe (nasal burning in the TAA 110µg group and hyperactivity in the TAA 220µg group). Fever was the most frequent individual AE reported 4 (7.1%) in the TAA 110µg group, 5 (9.1%) in the TAA 220µg group, and 4 (7.3%) in the placebo group. The next most frequent individual AEs were infection, pharyngitis, increased cough, and headache. The incidence of infection and pharyngitis were also highest during treatment with placebo. There were no SAEs during the active phase of the study.

Study RG5029Y-125: The incidence of AEs was low in all 3 treatment groups. AEs were reported by 34.6% patients who received placebo, by 53.6% patients who received TAA 220 mcg and by 42.3% patients who received TAA 440 mcg. One patient reported severe facial edema and severe eye pain who was in TAA 220 mcg group; all other AEs were mild or moderate in severity. Only 1 AE (epistaxis) was considered to be possibly related to study medication (TAA 440 mcg). No patients discontinued trial due to AEs. There were no deaths, SAEs, or clinically significant changes in physical exam or vital sign results.

Skoner at al 2008: The study results demonstrated that TAA- AQ given for 1 to 2 years had no significant effect on statural growth in children with AR. No adverse events were discussed in the study publication.

Study RG5029Z-314: Safety was evaluated in all patients (319) who were enrolled in the study and the incidence of AEs was comparable between the 3 treatment groups: placebo 72.0%, TAA-AQ 110 µg 71.4% and TAA-AQ 220 µg 66.7%. The most frequently reported AEs (% of placebo/110µg group/220µg group) were: rhinitis (17.0/17.1/12.3), upper respiratory tract infection (14.0/12.4/13.2), headache (17.0/12.4/7.9), increased cough (11.0/12.4/11.4), flu syndrome (15.0/15.2/3.5), and pharyngitis (11.0/11.4/9.6). There were no deaths and one SAE (not related to treatment) of a patient hospitalized with respiratory syncytial virus and severe croup. Six discontinuations (2 in each treatment group) occurred due to AEs. From the placebo group, one patient had chicken pox and the other patient had repeated episodes of epistaxis. From the 110µg group, one patient was given prednisone for poison ivy and the other patient contracted the flu. From the 220µg group, one patient developed croup (SAE) and the other patient was given prednisone for asthma exacerbation.

Assessor´s comment: *although some of the studies have been conducted in mainly older children, it seems that the safety profile across different age groups is similar and in accordance with the well-established safety of triamcinolone.*

Nevertheless, the effect of triamcinolone on HPA axis remains a question in population 2-5 years of age. The pivotal study XRG5029C/3502 has not specifically studied the effect of triamcinolone on growth and HPA axis, and the rest of the data provided involved mainly children age 6 and older. At the moment the effect of triamcinolone on HPA axis and growth remains inconclusive and the MAH is invited to provide the discussion on the possibility of extrapolation of studies Trica_L_04286, XRG5029C/3503 and publication by Skoner et al. on children aged 2-5.

- **Post-marketing experience**

Based upon the available worldwide sales data from the Intercontinental Marketing Services (IMS) Health database for Nasacort-AQ from April 2000 through December 2012, it was ascertained that more than 127 million bottles of Nasacort-AQ have been distributed globally.

A cumulative search of the Sanofi pharmacovigilance database (Application of Worldwide Adverse event Reporting and Evaluation [AWARE]) was performed to identify all spontaneous post-marketing case reports through 29 February 2012 with TAA-AQ as a suspect drug. Since initial approval, a total of 1,396 spontaneous reports involving 2,643 AEs received by Sanofi from worldwide sources have been reported with Nasacort-AQ (98 serious and 1,298 non-serious cases) and all age populations.

Results of the paediatric population (<18 years) revealed 136 AEs (5.1% of all events) occurred in 62 cases. It was noted that five (5) cases with a total of seven (7) AEs were reported in patients younger than 2 years of age. One serious case, was reported by a HCP and involves a pregnancy exposure. However, after further review, this case was found to report Nasacort CFC. The remaining 4 non-serious cases were consumer reports that were not medically confirmed by a HCP and included the following reported AEs: psychomotor hyperactivity, medication error, irritability, initial insomnia, decreased appetite, hypersensitivity, and cerebral ventricle dilatation.

Table 26 lists the most frequently reported AEs by PT ≥ 1.0% according to paediatric age groups. Percentages were calculated as the number of AE reports for a given PT/total AE by PT within the given age group x 100.

Table 26: Most frequently reported adverse events according to paediatric age groups – Nasacort-AQ

	No. (%*) of AEs			
MedDRA PT	2 to <6 years	6 to <12 years	12 to <18 years	Total**
Total adverse events	22 (17.0)	41 (31.8)	66 (51.2)	129
Total cases	13 (22.8)	26 (45.6)	18 (31.6)	57
Epistaxis	2 (9.1)	0 (0.0)	4 (6.1)	6 (4.4)
Headache	0 (0.0)	3 (7.3)	3 (4.5)	6 (4.4)

	No. (%*) of AEs			
MedDRA PT	2 to <6 years	6 to <12 years	12 to <18 years	Total**
Hypersensitivity	0 (0.0)	2 (4.9)	3 (4.5)	6 (4.4)
Irritability	1 (4.5)	1 (2.4)	2 (3.0)	5 (3.7)
Blood cortisol decreased	0 (0.0)	4 (9.8)	0 (0.0)	4 (2.9)
Ocular hyperaemia	3 (13.6)	1 (2.4)	0 (0.0)	4 (2.9)
Pruritus	2 (9.1)	0 (0.0)	2 (3.0)	4 (2.9)
Decreased appetite	0 (0.0)	0 (0.0)	2 (3.0)	3 (2.2)
Drug ineffective	1 (4.5)	1 (2.4)	1 (1.5)	3 (2.2)
Eye pruritus	0 (0.0)	1 (2.4)	2 (3.0)	3 (2.2)
Growth retardation	0 (0.0)	3 (7.3)	0 (0.0)	3 (2.2)
Swelling face	0 (0.0)	1 (2.4)	2 (3.0)	3 (2.2)
Urticaria	0 (0.0)	1 (2.4)	2 (3.0)	3 (2.2)
Angioedema	0 (0.0)	0 (0.0)	2 (3.0)	2 (1.5)
Anxiety	0 (0.0)	0 (0.0)	2 (3.0)	2 (1.5)
Candidiasis	0 (0.0)	0 (0.0)	2 (3.0)	2 (1.5)
Cough	1 (4.5)	1 (2.4)	0 (0.0)	2 (1.5)
Depression	0 (0.0)	2 (4.9)	0 (0.0)	2 (1.5)
Ear discomfort	0 (0.0)	0 (0.0)	2 (3.0)	2 (1.5)
Ear pain	0 (0.0)	0 (0.0)	2 (3.0)	2 (1.5)
Enuresis	0 (0.0)	2 (4.9)	0 (0.0)	2 (1.5)
Eye swelling	2 (9.1)	0 (0.0)	0 (0.0)	2 (1.5)
Fatigue	0 (0.0)	0 (0.0)	2 (3.0)	2 (1.5)
Hypothyroidism	0 (0.0)	0 (0.0)	2 (3.0)	2 (1.5)
Lacrimation increased	0 (0.0)	1 (2.4)	1 (1.5)	2 (1.5)
Laryngeal oedema	0 (0.0)	0 (0.0)	2 (3.0)	2 (1.5)
Lethargy	0 (0.0)	0 (0.0)	2 (3.0)	2 (1.5)
Lip swelling	0 (0.0)	0 (0.0)	2 (3.0)	2 (1.5)
Malaise	0 (0.0)	0 (0.0)	2 (3.0)	2 (1.5)
Mood swings	0 (0.0)	0 (0.0)	2 (3.0)	2 (1.5)
Nasal discomfort	0 (0.0)	0 (0.0)	2 (3.0)	2 (1.5)
Off label use	1 (4.5)	1 (2.4)	0 (0.0)	2 (1.5)
Periorbital oedema	0 (0.0)	0 (0.0)	2 (3.0)	2 (1.5)
Pharyngitis	0 (0.0)	0 (0.0)	2 (3.0)	2 (1.5)
Psychomotor hyperactivity	0 (0.0)	1 (2.4)	0 (0.0)	2 (1.5)
Rash	0 (0.0)	1 (2.4)	1 (1.5)	2 (1.5)
Rash erythematous	2 (9.1)	0 (0.0)	0 (0.0)	2 (1.5)
Rash macular	0 (0.0)	0 (0.0)	2 (3.0)	2 (1.5)
Somnolence	0 (0.0)	2 (4.9)	0 (0.0)	2 (1.5)
Stridor	0 (0.0)	0 (0.0)	2 (3.0)	2 (1.5)
Toothache	0 (0.0)	2 (4.9)	0 (0.0)	2 (1.5)
Viral infection	0 (0.0)	2 (4.9)	0 (0.0)	2 (1.5)

*Note: Frequency of AEs by PT included ≥ 1.0% within any age group. Percentages were calculated as the number of AE reports for a given PT/total AE by PT within the given age group x 100.

**Note: This tables excludes the <2 age group. Total percentages for the PT presentation included the <2 age group with the denominator of 136 events in the calculation (5 cases with 7 AEs).

There were no cases with a fatal outcome. A summary of SAE reports by paediatric age group is presented below in Table 27. Eleven spontaneous SAE reports involving paediatric patients aged 2 to <18 years old were received by Sanofi pharmacovigilance for the review period.

Table 27: Most frequently reported serious adverse events according to paediatric age groups – Nasacort AQ

	No. (%*) of SAEs			
MedDRA PT	2 to <6 years	6 to <12 years	12 to <18 years	Total
Total serious adverse events	**2 (5.3)**	**5 (13.2)**	**30 (78.9)**	**38**
Total case reports	**2 (18.2)**	**5 (45.4)**	**3 (27.3)**	**11****
Blood cortisol decreased	0 (0.0)	4 (80.0)	0 (0.0)	4 (10.5)
Angioedema	0 (0.0)	0 (0.0)	2 (6.7)	2 (5.3)
Ear discomfort	0 (0.0)	0 (0.0)	2 (6.7)	2 (5.3)
Ear pain	0 (0.0)	0 (0.0)	2 (6.7)	2 (5.3)
Eye pruritus	0 (0.0)	0 (0.0)	2 (6.7)	2 (5.3)
Laryngeal oedema	0 (0.0)	0 (0.0)	2 (6.7)	2 (5.3)
Lip swelling	0 (0.0)	0 (0.0)	2 (6.7)	2 (5.3)
Nasal discomfort	0 (0.0)	0 (0.0)	2 (6.7)	2 (5.3)
Periorbital oedema	0 (0.0)	0 (0.0)	2 (6.7)	2 (5.3)
Pharyngitis	0 (0.0)	0 (0.0)	2 (6.7)	2 (5.3)
Pruritus	0 (0.0)	0 (0.0)	2 (6.7)	2 (5.3)
Rash macular	0 (0.0)	0 (0.0)	2 (6.7)	2 (5.3)
Stridor	0 (0.0)	0 (0.0)	2 (6.7)	2 (5.3)
Swelling face	0 (0.0)	0 (0.0)	2 (6.7)	2 (5.3)
Cleft lip and palate	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)**
Adenoidal hypertrophy	0 (0.0)	1 (20.0)	0 (0.0)	1 (2.6)
Cough	1 (50.0)	0 (0.0)	0 (0.0)	1 (2.6)
Hypersensitivity	0 (0.0)	0 (0.0)	1 (3.3)	1 (2.6)
Nasal oedema	0 (0.0)	0 (0.0)	1 (3.3)	1 (2.6)
Nasal septum perforation	0 (0.0)	0 (0.0)	1 (3.3)	1 (2.6)
Presyncope	1 (50.0)	0 (0.0)	0 (0.0)	1 (2.6)
Rhinitis	0 (0.0)	0 (0.0)	1 (3.3)	1 (2.6)

*Note: Frequency of AEs by PT included ≥ 1.0% within any age group. Percentages were calculated as the number of AE reports for a given PT/total AE by PT within the given age group x 100.

**Note: This tables excludes the <2 age group. The PT of Cleft lip and palate occurred in the age group <2 years and is included in the total count

The search of the Sanofi post-marketing safety database found a total of 6 cases related to HPA axis effects: 4 serious and 1 non-serious health care professional (HCP) cases and 1 non-serious consumer case. Four events of blood cortisol decreased were received from the same physician as a group report, involving 4 paediatric patients over the age of 6 with history of cystic fibrosis and nasal polyps, were found to have a cortisol level of zero after receiving TAA-AQ 220 µg per day for an unspecified period of time. These cases were also confounded by the concomitant use of the corticosteroid fluticasone.

Regarding effects on growth the database search identified a total of 2 non-serious cases, one case was reported by a physician which involves 11 years old male who experienced growth suppression, and the other consumer report involved 8 years old female who experienced slow growth while using TAA-AQ. Neither case provided sufficient information for a full assessment.

Assessor´s comment: *the post-marketing data presented by the MAH confirm the well-established safety profile of triamcinolone. No new adverse event has been identified in the paediatric population.*

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

Although the presented clinical data support the addition of additional paediatric age group to a certain extent, positive benefit/risk cannot yet be fully confirmed. The MAH is requested to address the issues raised in the section VI of this assessment report.

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

List of questions:

Pharmacokinetics

General

1. Previous studies in older patients have shown that after 24 h the plasma concentrations of triamcinolone are below the limit of detection. However, this finding has not been unequivocally confirmed in the age group 2-5, since the clearance has been shown to be lower than in adults. The MAH is requested to perform additional analysis and discussion on the late phase of concentration-time profile (up to 24 h post-dose) in order to confirm the adequacy of the proposed posology.

Study XRG5029/1000

2. For sampling in children, a staggered sparse sampling scheme has been derived, but the reasons for such a scheme (different than the adult scheme) are not entirely clear. The MAH is requested to justify.

3. The MAH has declared that no interim analysis has been performed in this study; however, some data have been analyzed before the study was finished, which seems to be the interim analysis. The MAH is requested to clarify in more details the reasons for performing this analysis and to discuss the possible influence of the analysis on overall study findings.

Pharmacodynamics

Study RG5029Y-315

4. Although the patient population enrolled in this study are slightly older patients than those considered in this assessment, children age 4 and 5 have also been included. Since the findings of this study are also relevant for children aged 2-5, MAH is requested to provide separate analysis of results in patients age 4 and 5, only.

Efficacy

Study XRG5029/3502

5. For the determination of the sample size the MAH has chosen a TNSS expected mean difference from the baseline of no less than 0.65 units. It is not clear on which grounds has this margin been set. The MAH should clarify.

6. Primary efficacy variable analysis has not shown statistical significance in comparison to placebo, and neither did the secondary efficacy analysis. Only after excluding the two-year-olds did the post hoc analysis show significance. This might suggest that the product should be indicated for use from the age of three. The MAH is thus invited to provide further justification for including the two-year olds in the light of the study findings.

Study RG5029Y-314

7. Since this was a multicentric trial, the MAH should provide the distribution of patients across centres.

Safety

General

8. The effect of triamcinolone on HPA axis remains a question in population 2-5 years of age. The pivotal study XRG5029C/3502 has not specifically studied the effect of triamcinolone on growth and HPA axis, and the rest of the data provided involved mainly children age 6 and older. At the moment the effect of triamcinolone on HPA axis and growth remains inconclusive in the youngest age group and MAH is invited to provide the discussion on influence of triamcinolone on HPA axis in children age 2-5, as well as the possibility of extrapolation of studies Trica_L_04286, XRG5029C/3503 and publication by Skoner et al. on children aged 2-5.

Member state comments:

Comments from UK:

The UK therefore strongly endorses the RMS request for further evaluation and discussion of data relevant to the 2 – 5 years age group in i) study XRG5029C/3503, conducted in the 3 – 9 years age group, of growth suppression during long term treatment (298 patients for 52 weeks); and ii) study Trica_L_04286 in the 2 – 12 years age group which investigated HPA axis function as a primary pharmacodynamic objective (140 patients for 6 weeks). Extrapolation from the published study by Skoner (2008) of long term effects on growth (39 patients for 1 – 2 years) may also be informative.

Comments from SE:

In question 6 the Rapporteur questions the age limit proposed as statistically significant results were not obtained for the full population of patients 2-6 years of age. We support this question and would like to add that before taking final decision on an appropriate age limit, we would like to see a detailed presentation of descriptive data. Could the company (or the rapporteur dependent on if these data are available in the company's study report or not) please present subgroup analyses for the primary endpoint (change from baseline in the mean total nasal symptom score (TNSS) – instantaneous) and relevant secondary endpoints split by age group (2-<3, 3-<4, 4-<5 and 5 years of age).

Comments from NL

Benefit-risk

1. We currently consider the benefit-risk negative for children 2-5 years old.
   Furthermore, the studies TRICA_L_04286 and XRG5029C/3503 that have been evaluated during Art. 46 paediatric worksharing procedure UK/W/0047/pdWS/001 need also to be included in the assessment in order to assess the benefit-risk on all available information for the newly applied children group. The Applicant/Rapporteur is requested to provide and discuss the results in the subgroup of children 2-5 years of age.

Efficacy -All studies

2. The use of rescue medication indicates insufficient control of symptoms; the symptom score may need adjustment allowing for the use of any rescue medication especially in case the use of rescue medication differs between treatment arm. A discussion or correction for the use of rescue medication is requested for.

3. For the results, a discussion is missing regarding the clinical relevance of the differences found in the studies. What do the results mean for the patients? The Applicant is requested to provide such a discussion when presenting the results.

Safety

4. We support the request for a subanalysis in the specific age group of 4-5 years old in PD study RG5029Y-315. However, the results of the ACTH stimulation test in the investigated paediatric population (4-10 years) already indicated that triamcinolone influences cortisol. Thus it is expected that the concerns for this vulnerable age group will remain even when the results in the subanalysis would not indicate suppression. Furthermore, the Applicant is requested to discuss which precautions can be further taken besides/instead the current SmPC advise in section 4.2 against the continuous use longer than 3 months in children younger than 12 years.

SmPC

Amendment of wording of sections 4.2 and 4.4 was proposed by UK and NL.

VII. ASSESSMENT OF RESPONSE TO QUESTIONS

Q1: Previous studies in older patients have shown that after 24 h the plasma concentrations of triamcinolone are below the limit of detection. However, this finding has not been unequivocally confirmed in the age group 2-5, since the clearance has been shown to be lower than in adults. The MAH is requested to perform additional analysis and discussion on the late phase of concentration-time profile (up to 24 h post-dose) in order to confirm the adequacy of the proposed posology.

MAH´S response:

Following 110 µg intranasal administration of triamcinolone acetonide once a day for 5 days in patients from 2 to 5 years of age (study XRG5029/1000), no patients had a quantifiable triamcinolone acetonide concentration 10 hours after dose administration on Day 5 (see Table 1).

These data are consistent with the absence of significant accumulation of triamcinolone acetonide with multiple dosing in patients from 2 to 5 years of age receiving 110 µg intranasally once a day as documented in older children and in adults for similar or higher doses. Furthermore, the 2-fold lower clearance documented in patients aged from 2 to 5 years compared to adults was offset by the administration of a 110 µg once daily in order to reach exposures similar to those achieved after administration of 220 µg once daily to adults. For these reasons, the MAH considers that pharmacokinetic findings support the proposed regimen in children from 2 to 5 years of age.

Table 1 - Descriptive statistics of triamcinolone acetonide plasma concentrations in patients from 2 to 5 years of age following 110 µg intranasal administration once a day for 5 days (Study XRG5029/1000)

Time Point	Scheduled Time	N	Mean	SD	CV	Median	Min	Max
Assignment = A								
Day 1	1 hr.post-dose	7	552.86	147.66	26.71	592.0	382.0	762.0
	3 hr.post-dose	7	175.86	62.61	35.60	156.0	101.0	286.0
	5 hr.post-dose	7	70.47	50.67	71.91	69.7	0.0	156.0
	8 hr.post-dose	7	0.00	0.00		0.0	0.0	0.0
Day 5	pre-dose	7	0.00	0.00		0.0	0.0	0.0
	2 hr.post-dose	7	245.00	104.05	42.47	248.0	105.0	379.0
	4 hr.post-dose	7	98.24	24.79	25.23	95.3	55.0	131.0
	6 hr.post-dose	7	51.47	57.82	112.3	32.0	0.0	138.0
Assignment = B								
Day 1	pre-dose	8	0.00	0.00		0.0	0.0	0.0
	2 hr.post-dose	7	142.06	87.15	61.35	146.0	0.0	258.0
	4 hr.post-dose	7	54.14	33.34	61.58	63.1	0.0	105.0
	6 hr.post-dose	7	0.00	0.00		0.0	0.0	0.0
Day 5	1 hr.post-dose	6	429.50	150.29	34.99	437.5	216.0	600.0
	3 hr.post-dose	7	121.43	58.42	48.11	97.2	69.5	240.0
	8 hr.post-dose	7	31.94	59.54	186.4	0.0	0.0	163.0
	10 hr.post-dose	5	0.00	0.00		0.0	0.0	0.0

Assessment of the MAH´s response:
The data presented in Table 1 do not suggest any accumulation. From the PK point of view, the proposed posology once daily is considered acceptable.
Issue resolved.

Study XRG5029/1000

Q2: For sampling in children a staggered sparse sampling scheme has been derived, but the reasons for such a scheme (different than the adult scheme) are not entirely clear. The MAH is requested to justify.

MAH´s response:

Blood volume to be collected in young children is limited (i.e., a total of 32 mL per patient in study XRG5029/1000) and smaller to the authorized blood volume in adults. For this reason, a spare sampling approach was used for children in this study with a total of 8 samples (4 on Day

1 and 4 on Day 5) per patient at predetermined times to an overall “population area-under-the curve”.
A population pharmacokinetic analysis was then developed as stated in the protocol to document the pharmacokinetics of triamcinolone acetonide in patients from 2 to 5 years of age.
This strategy is in full agreement with the one described in section 2.4.1 the note for guidance on clinical investigation of medicinal products in the paediatric (CPMP/ICH/2711/99) (1).

Assessment of the MAH´s response:

Issue resolved.

Q3: The MAH has declared that no interim analysis has been performed in this study; however, some data have been analyzed before the study was finished, which actually seems to be the interim analysis. The MAH is requested to clarify in more details the reasons for performing this analysis and to discuss the possible influence of the analysis on overall study findings.

MAH´s response:

As stated in section 5 of clinical study report of study XRG5029/1000, no formal analysis was performed for this study. However, triamcinolone acetonide plasma concentration-time data from the first 5 paediatric subjects were descriptively examined against the same data obtained in adult subjects to preliminarily assess design assumptions and the appropriateness of the 110 µg dose selection for a subsequent efficacy study. No formal population pharmacokinetic analyses were performed.
This pharmacokinetic study was an open-label, repeat-dose study with all children receiving the same treatment (triamcinolone acetonide) and dosing regimen (110 µg intranasally once a day for 5 days). In addition, the preliminary examination of triamcinolone acetonide plasma concentrations allowed to confirm the appropriateness of the selected dose in children from 2 to 5 years of age and then to limit the risk of over/under exposure in this population without impacting the population pharmacokinetic analysis conducted on the whole data. For these reasons, the MAH considers this examination did not influence the analysis of the primary objectives of this study.

Assessment of the MAH´s response:
Clarification is adequate, the analysis during the study does not seem to have influenced the results.

Issue resolved.

Q4: Although the patient population enrolled in this study are slightly older patients than those considered in this assessment, children age 4 and 5 have also been included. Since the findings of this study are also relevant for children aged 2-5, MAH is requested to provide separate analysis of results in patients age 4 and 5, only.

MAH´s response:

No analysis on these groups of age has been done.
The number of children in this range age is too small to perform subgroup analysis:
• 4 years-old: 4 subjects,
• 5 years-old: 6 subjects,
• 6 years-old: 10 subjects,
• 7 years-old or older: rest of included population

These data on this small number of children do not make any meaningful contribution to the safety or efficacy of Triamcinolone acetonide aqueous solution (TAA-AQ) in children 2-5 years of age.
Individual data on this population show results similar to those observed in the “Intent To Treat (ITT) population”.
Individual data are provided in Appendix 4 A3, Listing 3.7. Patient Data of Clinical Study Report for Study RG5029Y-315.

Assessment of the MAH´s response:
The response is agreed with, a small number of subjects would not significantly contribute to the efficacy analysis.

Issue resolved.

Q5: For the determination of the sample size the MAH has chosen a TNSS expected mean difference from the baseline of no less than 0.65 units. It is not clear on which grounds has this margin been set. The MAH should clarify.

MAH´s response:

The planned sample size was based on the primary efficacy endpoint, the mean change from baseline in daily instantaneous Total Nasal Symptom Score (iTNSS) over the 4-week double blind treatment period.
Four hundred (400) subjects were required to achieve a 90% power to reject the null hypothesis of no difference between TAA-AQ Nasal Spray and placebo for the changes from baseline in iTNSS when the expected mean difference was no less than 0.65 units, assuming a common Standard Deviation (SD) of 2.0 units. The estimated value of 2.0 units SD used in the calculation was obtained from a previous study (RG5029Y-314) on TAA-AQ in 4- to 12-year-old subjects with Perennial Allergic Rhinitis (PAR) where the Total Nasal Symptom Score (TNSS) was the 24-hour reflective value. To ensure 200 evaluable subjects per treatment arm (400 subjects) by the end of double-blind period, at least 460 subjects (230 subjects/arm) were to be enrolled in the double-blind period. This assumed a dropout rate of approximately 15%. Finally, approximately 350 subjects were to be enrolled in the open-label period to achieve approximately 250 subjects by the end of the 6-month open-label period.

Assessment of the MAH´s response:
Based on the MAH´s response and the report of the study RG5029Y-314, it seems that the margin of 0.65 units in TNSS difference has been set based on the results of the study RG5029Y-314.

The issue is not further pursued.

Q6: Primary efficacy variable analysis has not shown statistical significance in comparison to placebo, and neither did the secondary efficacy analysis. Only after excluding the two year-olds did the post hoc analysis show significance. This might suggest that the product should be indicated for use from the age of three. The MAH is thus invited to provide further justification for including the two year olds in the light of the study findings.

MAH´s response:
The clinical efficacy data submitted to support the use of TAA-AQ are listed in Table 2. It is to be noted that the studies mentioned in Table 2 were submitted as part of the initial submission for registration of Nasacort nasal spray and therefore not all of them were submitted again in the frame of this Article 45 Work-sharing procedure, which focusses on the paediatric use.

Following multiple dose administration of TAA-AQ 440 µg once daily in paediatric patients 6 to 12 years of age, plasma drug concentrations, AUC0-∞, Cmax and Tmax were similar to those values observed in adult patients receiving the same dose (XRG5029C/1000). Intranasal administration of TAA-AQ 110 µg once daily in paediatric patients 2 to 5 years of age exhibited similar systemic exposure to that achieved in adult patients 20 to 49 years of age with intranasal administration of TAA-AQ at a dose of 220 µg once daily. Based on the population pharmacokinetic modelling, the apparent clearance and volume of distribution following intranasal administration of TAA-AQ in paediatric patients 2 to 5 years of age were found to be approximately half of that in adults (XRG5029C/1000 and XRG5029/3502).
The efficacy of TAA- AQ, administered once daily for the treatment of allergic rhinitis (AR), is confirmed by 13 studies (Table 2) in adults, adolescents and children as young as 2 years of age that supported the prescription approvals in those populations. Results demonstrated that nasal symptoms improved within the first day of use but that one week of daily use may be needed to obtain maximum benefit. Efficacy assessments for up to one year of use in adults and adolescents and to 6 months of use in children, supported efficacy with TAA-AQ in those with perennial nasal allergies. Adults and adolescents self-titrated the TAA-AQ dose according to label directions (1 or 2 sprays/nostril, 110 or 220 µg/day) as needed in the study that extended to one-year. In clinical practice, TAA- AQ is titrated to the minimum dose needed for control of symptoms.

Table 2 - Listing of the 13 randomized, placebo-controlled, double-blind studies that evaluated the efficacy of TAA-AQ in clinical program

Study number (full name)	Study Type	Subject Age (year)	Treatment dose (µg)	Treatment duration (week) Number of subjects treated
Studies in Adults and Adolescents				
201 (RG5029Y-201)	SAR, Dose response	18-67	TAA-AQ 27, 5, 55, 110, 220 placebo	2/360
301 (RG5029Y-301	SAR-ragweed	20-65	TAA-AQ:220, placebo	2/140
302 (RG5029Y-302)	SAR-ragweed	12-17	TAA-AQ 220, placebo	2/136
304 (RG5029Y-304)	SAR- Mountain cedar	19-74	TAA-AQ 55,220, placebo	2/206
305 (RG5029Y-305)	PAR	11-59	TAA-AQ 220, placebo	4/178
306 (RG5029Y-306)	SAR with possible dose titration after 2 weeks	18-82	TAA-AQ 220/110 placebo Budesonide 400	4/293
307 (RG5029Y-307)	SAR	16-66	TAA-AQ 220, placebo	3/81
308 (RG5029Y-308)	SAR-ragweed, Topical vs systemic	18-67	TAA-AQ 220 oral, 275, placebo	2/297
309 (RG5029Y-309)	SAR-ragweed with dose titration after 1 week	18-79	TAA-AQ 220/110, 220/220, placebo	3/429
313 (RG5029Y-313)	SAR-mountain cedar	18-77	TAA-AQ 220, placebo	2/182
Studies in children 2 through 11				
312 (RG5029Y-312)	SAR-spring grass	6-11	TAA-AQ 110, 220, placebo	2/223
314 (RG5029Y-314)	PAR	4-12	TAA-AQ 110, 220, placebo	12/319
3502 (XRG5029C/3502)	PAR	2-5	TAA-AQ 110, placebo	4/474

SAR: Seasonal Allergic Rhinitis
PAR: Perennial Allergic Rhinitis

In the single pivotal study, XRG5029C/3502, including the population to support the safety and efficacy of TAA-AQ nasal spray in children 2-5 years of age with PAR demographics were similar across treatment groups and study populations (safety, ITT, PP, completer). The mean age was 3.5 and 3.6 years for the placebo and TAA-AQ groups, respectively with the age

distribution fairly equally distributed (21, 26, 32, and 22% of subjects being 2, 3, 4, or 5 years of age).
The efficacy of TAA-AQ nasal spray 110 µg once daily in children 2-5 years of age was demonstrated achieving a statistically significant mean change from baseline over the entire treatment period in reflective total nasal symptom score (rTNSS) compared to placebo and showing a numerical difference in favor of TAA-AQ over placebo in the primary endpoint of mean change from baseline in iTNSS (Table 3).

Table 3 - Efficacy endpoints Study XRG5029/3502

	Nasacort AQ 110 µg OnceDaily (ITT Population)	
	Instantaneous Total Nasal Symptom Score (iTNSS)*	**Reflective Total Nasal Symptom Score (rTNSS)**
Mean Change from baseline Placebo (n=233)	-1.92	-1.87
Mean change from baseline TAA-AQ (n=231)	-2.28	-2.31
Difference from placebo, adjusted mean change from baseline**	-0.36	-0.44
p value	**0.095**	**0.033**

*TNSS was identified as the primary endpoint
**ANCOVA with treatment and pooled site effects and the corresponding baseline values as covariate was used for the change from baseline (i.e. endpoint value-baseline values) with p values based on actual data

A subgroup analysis by age (2, 3, 4, 5 year old strata) did not demonstrate a statistically significant difference in iTNSS for any single age group but when an ad hoc analysis was performed for the primary endpoint on the 3-5 year old subgroup, a statistically significant difference was noted (p = 0.0108) [Study 3502 Study Report]. However, this finding is not enough to support the assumption that TAA-AQ should be indicated for use only from the age of three.
In summary, TAA-AQ, at a dose of 110 µg once daily, as evidenced by demonstrating a statistically significant mean change from baseline in rTNSS, a numerical difference over placebo in favour of a reduction in PAR symptoms for the primary endpoint of mean change from baseline in iTNSS, and other supportive data has been shown to be effective in the treatment of nasal allergic rhinitis symptoms in paediatric subjects 2-5 years of age with PAR.
From a clinical perspective, the data submitted support the indication of TAA-AQ nasal spray for the treatment of PAR and seasonal allergic rhinitis (SAR) for children 2-5 years old from the current indication of adults, adolescents, and children 6-11 years of age. The adequate and well-controlled clinical study performed in children 2-5 years of age demonstrated that the proposed dose of 110 µg of TAA-AQ nasal spray once daily provided a statistically significant improvement in rTNSS compared to placebo in children with PAR with or without seasonal allergic rhinitis SAR.
These results are consistent with the results of study RG5029Y-314 in paediatric patients 4 to 12 years of age with PAR, which used the reflective rating of nasal symptoms for the primary efficacy assessment, and global ratings among the secondary efficacy assessments. Due to the similarity of the pathophysiology of SAR and PAR, and the proven efficacy of TAA-AQ in adults

and older paediatric patients in both PAR and SAR, this efficacy can be extrapolated to SAR.
Supportive efficacy results of studies Trica_L_04286, and XRG5029C/3503 confirm the benefits of TAA-AQ 110 µg/day in paediatric patients 2 to 5 years of age with SAR or PAR.
Moreover, both the reflective TNSS score, while a secondary endpoint in the pivotal trial is typically the preferred primary endpoint for allergic rhinitis trials. Thus, positive findings for the rTNSS endpoint would likely be considered significant findings of efficacy. This is especially true due to the fact that the efficacy endpoints in the this phase 3 trial are based on parent/guardian assessments of the child's symptoms which introduces a level of subjectivity and inconsistency in endpoint analyses not present in studies of adults with SAR or PAR thus making it more difficult to demonstrate statistical efficacy.
It is important to note that any children become symptomatic at an age when they can neither read nor write. Therefore, they have to rely on caregivers when it comes to describing subjective symptoms (2).
The influence of parents or caregivers on reporting patient-related outcomes in young children is an important confounder which may have strong impact on study results (2).
Lower treatment effect has been observed in paediatric allergy trials possibly confounded by caregiver.
In addition, EU Guidance states that on Primary efficacy analyses, it is recommended to score the symptoms at least daily. The patient should report on his status and symptoms over the previous period of 24 hours (Reflective Total Nasal Score) (3).
Similarly, the updated FDA Guidance for applicants states that the Primary endpoint for efficacy should be the Reflective Total Nasal Score (4).
In the allergic rhinitis clinical development program for fluticasone furoate (Veramyst®), which was approved to treat SAR/PAR down to children 2 years of age, efficacy data in children 2 < 6 years of age were not included in analyses of the primary endpoints of the paediatric trials. It was,
in general, supportive of results observed in the older children (5).

Assessment of the MAH´s response:
It is agreed with MAH that the subgroup analysis (i.e. exclusion of the 2-year olds) is not indicative of the lack of efficacy in this age group, but it is perceived rather as an uncertainty, further confirmed by the fact that although the statistical significance for the primary endpoint has not been reached, a favourable trend for the use of TAA-AQ is observed. This is further supported by the fact, that the study was patient-reported, which generally carries a certain degree of inaccuracy, making the result interpretation more difficult. Moreover, it is acknowledged, that the secondary endpoint rTNSS appears to be an important efficacy endpoint from the clinical perspective, taking into account once-daily administration, and may be more descriptive of the long-term efficacy.
In conclusion, the MAH´s response is accepted.

Issue resolved.

Q7: Since this was a multicentre trial, the MAH should provide the distribution of patients across centres.

MAH´s response:

List of distribution of patients across the centres is provided in Table 4 [Clinical Study Report RG5029Y-314 (07-Aug-96)].

Table 4 - List of distribution of patients across centers

Investigators	Center Number (RPR*)	Number of patients
Albert Finn, Jr., MD N. Charleston, SC	US01567	20
Bruce Prenner, MD San Diego, CA	US01535	13
Craig LaaForce, MD Raleigh, NC	US00297	15
Mark H Ellis, MD Orange, CA	US01531	11
Nathan Segal, MD Atlanta, GA	US01340	13
Stanley Galant, MD Orange, CA	US00372	17
William E. Berger, MD Mission Viejo, CA	US01279	15
Eric J. Schenkel, MD Easton, PA	US00845	16
Paul Chervinsky, MD North Darmouth, MA	US00482	17
Kraig Jacobson, MD Eugene, OR	US00607	19
M. Richard Ball, MD Albany, NY	US01572	13

Investigators	Center Number (RPR*)	Number of patients
James Rosen, MD West Hartford, CT	US00016	13
Michael Kraemer,MD Spokane,WA	US00188	17
Kirk Kinberg, MD Lincoln, NE	US01530	17
Peter Boggs, MD Shrevoport, LA	US00186	12
Phillip E. Korenblat, MD St. Louis, MO	US00537	0
Pinkus Goldberg, MD Indianapolis, IN	US01551	19
Anjuli Nayak,MD Normal, IL	US01550	8
Gary Gross, MD Dallas, TX	US00005	13
William Howland III, MD Austin, TX	US00606	16
Barry Zimmerman, MD Toronto, On	CA00138	7
S. John Tkachyk Edmonton, Alta	CA00139	15
Georges Luciuk, MD Richmond, BC	CA00140	0
James Day, MD Kingston, Ont	CA00076	13
Total		319

*RPR: Rhone Poulenc Rorer

Assessment of the MAH´s response:
It seems that the patient distribution is fairly uniform across the centres (with the exception of two centres that did not enrol any patients).

Issue resolved.

Q8: The effect of triamcinolone on HPA axis remains a question in population 2-5 years of age. The pivotal study XRG5029C/3502 has not specifically studied the effect of triamcinolone on growth and HPA axis, and the rest of the data provided involved mainly children age 6 and older. At the moment, the effect of triamcinolone on HPA axis and growth remains inconclusive in the youngest age group and MAH is invited to provide the discussion on influence of triamcinolone on HPA axis in children age 2-5, as well as the possibility of extrapolation of studies Trica_L_04286, XRG5029C/3503 and publication by Skoner et al. on children aged 2-5.

MAH´s response:

Sanofi performed a subanalysis of the 4 clinical studies mentioned above for children 2-5 years old; in addition, a search in Sanofi safety database for postmarketing reports and literature search for articles that report hypothalamic-pituitary-adrenal (HPA) axis inhibition in children of this age group was performed.

Clinical studies
Among the studies presented in the Critical Expert Overview, assessment of paediatric studies in accordance with Article 45 of Paediatric Regulation (EC) No1901/2006, as amended for AAAQ 55 µg nasal spray suspension (Worksharing Procedure Number: CZ/W/10/pdWS/01), 4 studies included study on HPA axis and included subjects 2, 3, or 4 to 5 years old (Table 5).

Table 5 - Clinical studies evaluating TAA-AQ effect on HPA axis of subjects 2, 3, 4, or 5 years old

Study identification	Adrenal Function Test	Study design	Subject age (year)	Treatment dose (µg)	Treatment duration (week) / N for adrenal function
XRG5029C/3502	Cosyntropin stimulation test	4-week randomized, double-blind, placebo controlled period followed by 6-month open-label period	2 - 5	TAA-AQ: 110 Placebo	26 / 61
Trica_L_04286*	Serum cortisol AUC (0-24 hour)	Randomized, doubleblind, Placebo controlled, parallel group, multicenter	2 - <12	TAA-AQ: 110, 220, placebo	6 / 140
XRG5029C/3503*	24-hour urinary free cortisol levels and the cortisol/creatinine ratio	Randomized, doubleblind, Placebo controlled, parallel group, multicenter	3 - 9	TAA-AQ: 110, placebo	52 / 126
RG5029Y-315**	Overnight urine cortisol/ creatinine ratio	Randomized, double-blind, 4-way crossover, single center	4 - 10	TAA-AQ: 110, 220, placebo Flonase 200	2 / 59

* Studies submitted as part of Article 46 Worksharing procedure of EU Paediatric Regulation that positively ended on May 2013
** Published by Skoner et al. in 2003 (6)

Study XRG5029C/3502

Study XRG5029C/3502 is a randomized, double-blind, parallel group, placebo-controlled, four-week efficacy and safety evaluation of TAA-AQ 110 µg qd, followed by six-month open-label safety study in children aged 2-5 years with perennial allergic rhinitis.

A total of 474 subjects (238 placebo, 236 TAA-AQ) were treated during double-blind period; followed by 428 subjects treated with TAA-AQ during open-label period. Low dose (1 µg) cosyntropin stimulation tests were performed in a subset of patients to assess HPA axis function, at screening baseline, 4 weeks and 6 months. Overall, 61 children were evaluable for effects of 110 µg/day TAA-AQ on HPA axis, which included 28 children treated with placebo and 33 children treated with110 µg/day TAA-AQ during the double-blinded 4 week period, and 49 children treated with 110 µg/day TAA-AQ during the 6-month open label period.

There was no statistically significant difference between the post-stimulation changes in mean cortisol levels at the end of double-blind treatment period versus screening in the placebo and TAA-AQ groups. The comparison of the cortisol levels post-stimulation with cosyntropin at the end of the open label treatment period and screening also did not reveal any statistically significant difference. However, 2 with placebo and 4 with TAA-AQ did not show the prespecified increase in cortisol levels or did not reach the pre-specified level following cosyntropin stimulation at the end of the double-blind period. Therefore, a possible treatment effect on children aged 2-5 cannot be ruled out.

Study Trica_L_04286

Double-blind placebo-controlled study Trica_L_04286 evaluated the effect of a 6-week treatment with TAA-AQ versus placebo on basal HPA axis function as measured by serum cortisol AUC (0- 24 hour) in children ≥2 to <12 years of age with allergic rhinitis, which showed the ratio of TAA-AQ to placebo for change from baseline in serum cortisol AUC (0-24 hr) was 0.966, with the 95% CI being (0.892, 1.045). The geometric mean changes from baseline (ratio) were 0.898 for the TAA-AQ group and 0.938 for the placebo group. No significant difference was detected.

Among the 140 subjects (71 placebo, 69 TAA-AQ) analyzed, 17 in placebo and 21 in TAA-AQ arm were at age ≥2 to <6. Subanalysis of this age group shows the ratio of TAA-AQ to placebo for change from baseline in serum cortisol AUC (0-24 hr) was 0.898, with the 95% CI being(0.790, 1.020). The geometric mean changes from baseline (ratio) were 0.847 for the TAA-AQ group and 0.907 for the placebo group (see Table 6).

Table 6 - Trica_L_04286: Analysis of serum cortisol 24-hour AUC with log-transformation and average of multiple imputed data in subjects 2 to 5 years – Per-protocol population

Project Code / Study Number / Analysis: XRG5029 / TRICAL04286 / CSR

Pharmacodynamic/Efficacy data

Analysis of serum cortisol 24-hour AUC with log-transformation and average of multiple imputed data in subjects 2 to 5 years – Per-protocol population

	Placebo (N=17)	TAA-AQ (N=21)
Baseline (Visit 2)		
Number	17	21
Geometric Mean	184.2	175.5
Mean (SD) in log-scale	5.22 (0.27)	5.17 (0.22)
Median	193.4	179.8
Min : Max	97 : 284	114 : 279
EOT (Visit 6)		
Number	17	21
Geometric Mean	167.1	148.7
Mean (SD) in log-scale	5.12 (0.14)	5.00 (0.27)
Median	169.7	157.3
Min : Max	137 : 213	86 : 225
Change from baseline (ratio)		
Number	17	21
Geometric Mean	0.907	0.847
Mean (SD) in log-scale	-0.098 (0.292)	-0.166 (0.285)
Median	0.824	0.851
Min : Max	0.57 : 1.53	0.49 : 1.45
Treatment ratio of geometric mean vs.placebo and 95% CI[a]		0.898 (0.790, 1.020)

In comparison to placebo, 6 week treatment with TAA-AQ did not appear to have a significant effect on basal HPA axis function as measured by serum cortisol AUC (0-24 hour) in this age group of ≥2 to <6 years old.

Study XRG5029C/3503

Study XRG5029C/3503 is a randomized, multicenter, double-blind, placebo-controlled, parallel group study of the 12 month effect of treatment with once daily triamcinolone acetonide (TAAAQ, NASACORT® AQ Nasal Spray 110 µg) on the growth velocity of children, 3 to 9 years of age, with PAR.

A total of 298 subjects were treated (148 with placebo and 150 with TAA-AQ), of which 293 subjects (147 with placebo, 146 with TAA-AQ) were evaluated for 24-Hour urinary free cortisol and 24-hour urinary free cortisol/creatinine ratio. Of these 293 subjects, 126 (64 with placebo, 62 TAA-AQ) subjects were at age 2 to 5 (<6) years old.

The following tables show change from baseline in 24-Hour urinary free cortisol (Table 7) and in 24-Hour urinary free cortisol/creatinine ratio (Table 8) with placebo or with TAA-AQ treatment.

Table 7 - 24-Hour urinary free cortisol: Descriptive statistics at assessment visits and change fr baseline – Safety population of 2~5 (<6) years old

Project Code / Study Number / Analysis: XRG5029 / UMA03503 / CSR

24-hour urinary free cortisol

Descriptive statistics at assessment visits and change from baseline in children 3 to <6 years old – Safety population

Assessment Visit	Placebo (N=64)		TAA-AQ (N=62)	
	Value µg/24 hours	Change from baseline	Value µg/24 hours	Change from baseline
Baseline (Visit 2)				
Number	63		58	
Mean (SD)	7.13 (4.03)	-	5.54 (3.08)	-
Median	6.20		5.10	
Min : Max	1.3 : 17.6		1.3 : 18.2	
End of treatment (Visit 10 or Early termination)				
Number	48	48	50	47
Mean (SD)	7.05 (5.62)	0.11 (6.32)	5.41 (3.41)	0.03 (4.40)
Median	5.70	-0.60	4.95	-0.10
Min : Max	0.8 : 28.7	-10.9 : 23.8	0.5 : 12.8	-16.5 : 8.3
Follow-up (Visit 11)				
Number	39	39	46	43
Mean (SD)	6.85 (4.39)	-0.28 (5.30)	5.65 (3.40)	0.56 (4.13)
Median	7.10	-1.00	5.45	0.60
Min : Max	0.9 : 22.0	-12.2 : 11.6	0.8 : 13.5	-8.8 : 10.7

Table 8 - 24-Hour urinary free cortisol/creatinine ratio: Descriptive statistics at assessment visits and change from baseline – Safety population of 2~5 (<6) years old

Project Code / Study Number / Analysis: XRG5029 / UMA03503 / CSR

24-Hour urinary free cortisol/creatinine ratio

Descriptive statistics at assessment visits and change from baseline in children 3 to <6 years old – Safety population

Assessment Visit	Placebo (N=64)		TAA-AQ (N=62)	
	Value µg/g Creatinine	Change from baseline	Value µg/g Creatinine	Change from baseline
Baseline (Visit 2)				
Number	63		58	
Mean (SD)	22.40 (10.88)	-	20.47 (12.99)	
Median	21.00		18.00	-
Min : Max	4.0 : 52.0		4.0 : 86.0	
End of treatment (Visit 10 or Early termination)				
Number	48	48	50	47
Mean (SD)	18.80 (16.49)	-3.59 (17.29)	14.90 (8.07)	-5.59 (14.59)
Median	13.50	-6.00	14.00	-3.00
Min : Max	2.0 : 100.0	-39.0 : 61.0	2.5 : 34.0	-70.0 : 17.0
Follow-up (Visit 11)				
Number	39	39	46	43
Mean (SD)	19.42 (12.22)	-3.32 (12.74)	14.99 (10.11)	-3.69 (13.21)
Median	18.00	-1.50	12.00	-3.00
Min : Max	2.5 : 44.0	-31.0 : 18.0	2.0 : 48.0	-30.0 : 29.0

The tables show that at the end of treatment, the mean (SD) changes from baseline in 24-hour urinary free cortisol level were 0.11 (6.32) and 0.03 (4.40) µg/24 hours in the placebo and TAAAQ, respectively. For 24-hour urinary free cortisol/creatinine ratio, the mean (SD) change from baseline was -3.59 (17.29) and -5.59 (14.59) µg/g in the placebo and TAA-AQ, respectively, with P=0.0577. In comparison to placebo, 12 months' treatment with TAA-AQ Nasal Spray 110 µg qd did not appear to have a statistically significant effect on basal HPA axis function as measured by 24-hour urinary free cortisol and 24-hour urinary free cortisol/creatinine ratio in this age group of ≥2 to <6 years old.

Study RG5029Y-315

Study RG5029Y-315, published by Skoner et al. in 2003 (6), is a randomized, single centre, 4-way cross-over, placebo and active controlled paediatric trial with TAA-AQ assessing short-term growth in patients 4 to 10 years of age with allergic rhinitis. One of the secondary objectives was to evaluate the effect of TAA- AQ (110 and 220 µg/day) and fluticasone propionate nasal spray (200 µg/day) on overnight urine cortisol/creatinine ratio compared to placebo. A total of 59 prepubescent patients aged 4 to 10 years were randomized, and 49 of them completed all four treatment periods. Two- week treatment with TAA-AQ 110 or 220 µg once daily did not significantly affect HPA axis function as measured by overnight urine cortisol/creatinine ratio compared to placebo. Conversely, fluticasone propionate 200 µg daily did result in a significantly

reduced overnight urine cortisol/creatinine ratio compared to placebo. Of the 49 subjects who completed all four treatment periods, 10 of the subjects were at age 2-5 years old. The number of subjects in this subgroup is very small and statistical analyses on this very small group of subjects would not be conclusive.
The following table summarized subanalysis of the 4 clinical studies on subjects 2-5 years old for effect of TAA-AQ nasal spray on HPA axis.

Table 9 - Subanalysis of the 4 clinical studies on subjects 2-5 years old for effect of TAA-AQ nasal spray on HPA axis

Study ID Treatment Duration, N	Adrenal Function Test	Subject age (year)	Results of subanalysis
XRG5029C/3502 (4 Wk DB: Placebo N=28, TAA-AQ N=33; 6Mo OL: 49)	Cosyntropin stimulation test	2 - 5	No statistically significant difference between 1) post-stimulation changes in mean cortisol levels at the end of double-blind (DB) period vs. screening in placebo and TAA-AQ groups. 2) cortisol levels post-stimulation at the end of the open label (OL) period and screening. However, HPA axis effect cannot be ruled out due to low responders (2 in placebo, 4 in TAA-AQ group) to stimulation at the end of DB period.
Trica_L_04286 (6Wk DB: Placebo N=17, TAA-AQ N=21)	Serum cortisol AUC (0-24 hour)	2-5 from 2 - 11	The geometric mean changes from baseline (ratio) were 0.847 for the TAA-AQ group and 0.907 for the placebo group; the ratio of TAA-AQ to placebo was 0.898, 95% CI (0.790, 1.020). No significant difference.
XRG5029C/3503 (12Mo DB: Placebe N=64, TAA-AQ N=62)	24-hour urinary free cortisol levels and the cortisol/ creatinine ratio	3-5 from 3 - 9	At the end of treatment, the mean (SD) change from baseline in 24-hour urinary free cortisol/creatinine ratio was -5.59 (14.59) and -3.59 (17.29) µg/g creatinine in the TAA-AQ and placebo groups, respectively with P=0.0577 (TAA-AQ vs placebo).
RG5029Y-315 (2Wk DB, 4-way crossover, N=10)	Overnight urine cortisol/ creatinine ratio	4-5 from 4 - 10	The numbers of subjects in these sub groups are very small and statistical analyses on these very small groups of subjects would not be conclusive.

Abbreviations:
Wk: week; DB: double blind; N: number in the group; Mo: month; OL: open label.

Overall subanalysis of the 4 clinical studies for children 2-5 years old did not find statistically significant effect of TAA-AQ at clinical dose on the HPA function.

Cases reported to Sanofi pharmacovigilance database (AWARE)
Adverse events overview of all cases (solicited and unsolicited) in Sanofi Application of Worldwide Adverse event Reporting and Evaluation (AWARE) safety database cumulative to 30 November 2016 with triamcinolone acetonide regardless of form and route as suspect drug found the following 14 preferred terms (PTs) that may suggest HPA axis inhibition:
- Adrenal insufficiency
- Adrenal suppression
- Adrenocortical insufficiency acute
- Adrenocorticotropic hormone deficiency
- Blood corticotrophin abnormal
- Blood corticotrophin decreased
- Blood cortisol abnormal
- Blood cortisol decreased
- Cortisol free urine decreased
- Hypopituitarism
- Hypothalamic pituitary adrenal axis

- Hypothalamo-pituitary disorder
- Secondary adrenocortical insufficiency
- Steroid withdrawal syndrome

Search of Sanofi AWARE database with the above 14 PTs with no restriction on formulation retrieved 74 cases cumulative to 30 November 2016. Review of the 74 cases found no case with age 2-5 years old with TAA-AQ nasal spray use.
Meanwhile, a search in Sanofi AWARE safety database cumulative to 30 November 2016 with triamcinolone acetonide with formulation and route suggesting nasal spray as suspect drug with age 2 to 5 (less than 6) years old retrieved 80 cases, 6 solicited and 74 unsolicited. Review of the 80 cases found no cases of HPA axis inhibition.

Literature
A cumulative search in Medline (1966-present) and Embase (1974-present) on 11 January 2017 retrieved the following articles that describe the 4 clinical studies discussed above:

One article described study XRG5029C/3502

• Weinstein S. 2009 (7)

Conclusions: Use of TAA-AQ, 110 ug once daily, for up to 6 months offers a favorable efficacy to safety ratio in children aged 2 to 5 years with perennial AR.

Regarding HPA axis effect: There was no significant change from baseline in serum cortisol levels after cosyntropin infusion at study end.

One article described study Trica_L_04286

• Georges G. 2014 (8)

Conclusions: TAA-AQ was safe, well tolerated, and not associated with clinically meaningful suppression of serum cortisol AUC (0-24h) in children aged 2-11 years with AR.

One article described study XRG5029C/3503

• Skoner D.P., 2015 (9)

Conclusions: By using rigorous Food and Drug Administration-recommended design elements, this study detected a small, statistically significant effect of TAA-AQ on the growth velocity (GV) of children with PAR.
Regarding HPA axis effect: no HPA axis suppression was observed

One article described study RG5029Y-315:

• Skoner D.P., 2003 (6)

Conclusions: Neither TAA-AQ nor fluticasone propionate (FP) had a clinically significant effect on lower-leg growth velocity. In contrast to FP, TAA-AQ nasal spray did not significantly affect HPA-axis function when used over a 2-week interval.
No other articles are relevant to TAA-AQ safety on pediatric population aged 2-5 years old.

In a summary, subanalysis of the 4 studies for children 2~5 years old and review of postmarketing data in Sanofi safety database and literature in this age group do not show significant higher risk of HPA axis inhibition in population 2~5 years old.

Assessment of the MAH´s response:
The MAH has presented the analyses of several studies which, among other, investigated the effect of TAA-AQ on HPA axis. Although the dataset is limited compared to the overall population enrolled in the above-mentioned studies, it seems there is no increased risk of HPA suppression in the age group 2-5 years. This is further supported by the pharmacovigilance database search, which revealed no cases of HPA suppression in this age group.
In conclusion, the available data suggest comparable risk of HPA suppression in the youngest age group and older children.

Issue resolved.

Q9 (UK):

The UK therefore strongly endorses the RMS request for further evaluation and discussion of data relevant to the 2 – 5 years age group in i) study XRG5029C/3503, conducted in the 3 – 9 years age group, of growth suppression during long term treatment (298 patients for 52 weeks); and ii) study Trica_L_04286 in the 2 – 12 years age group which investigated HPA axis function as a primary pharmacodynamic objective (140 patients for 6 weeks). Extrapolation from the published study by Skoner (2008) of long term effects on growth (39 patients for 1 – 2 years) may also be informative.

MAH´s response:

Study XRG5029C/3503 as well as study Trica_L_04286 submitted as part of the Article 46 paediatric regulation (procedure number: UK/W/0047/pdWS/001), were evaluated and positively concluded on May 2013.
Subanalysis of study XRG5029C/3503 with children aged 3-5 years old for growth velocity found the LS mean (SE) during the double-blind period was 6.42 (0.210) cm/year in the placebo group (N=60) and 5.90 (0.210) cm/year in the TAA-AQ group (N=60). The difference between treatment arms (LS mean) and 95% CI were -0.51 (-1.10, 0.08) cm/year. The p-value for difference between treatment arms was p=0.0866 (>0.05). The subanalysis results showed that 12 months therapy with TAA-AQ nasal spray at 110 µg once daily did not have statistically significant effect on growth velocity in children aged 3-5 years old.
For subanalysis of study Trica_L_04286 and XRG5029C/3503 for TAA-AQ effect on HPA axis in children 2-5 years old, see section 1.2 and 1.3 respectively in response to question 8. In study Trica_L_04286, 6 week treatment with TAA-AQ did not appear to have a significant effect on basal HPA axis function as measured by serum cortisol AUC (0-24 hour) in this age group of ≥2 to <6 years old. In study XRG5029C/3503, 12 months' treatment with TAA-AQ Nasal Spray 110 µg qd did not appear to have a statistically significant effect on basal HPA axis function as measured by 24-hour urinary free cortisol and 24-hour urinary free cortisol/creatinine ratio in this age group of ≥2 to <6 years old.
Skoner's publication in 2008 presented effect of long term (1 and 2 years) treatment with TAA-AQ nasal spray on growth of children with AR aged 6-14 years old. Thirty-nine (39) children were treated with TAA-AQ for 1 year, and a subset of 30 children completed a second year of treatment. The authors concluded that TAA-AQ titered to control AR symptoms and given for 1 or 2 years had no significant effect on statural growth in children with AR. The MAH believes this lack of long term significant effects on growth is likely to be able to be extrapolated to children aged 2-5 years old for the following reasons:

Clinical study/PK: as response to question 1, following 110 µg intranasal administration of triamcinolone acetonide once a day for 5 days in patients from 2 to 5 years of age (study XRG5029/1000), no patients had a quantifiable triamcinolone acetonide concentration 10 hours after dose administration on Day 5. These data are consistent with the absence of significant accumulation of triamcinolone acetonide with multiple dosing in patients from 2 to 5 years of age receiving 110 µg intranasally once a day as documented in older children and in adults for similar or higher doses.

• Clinical study/PD: subanalysis of study XRG5029C/3503 with children aged ≥3 to <6 years old and ≥6 to <10 years old for growth velocity found the following:

- Children aged ≥3 to <6 years old: the LS mean (SE) during the double-blind period was 6.42 (0.210) cm/year in the placebo group (N=60) and 5.90 (0.210) cm/year in the TAA-AQ group (N=60). The difference between treatment arms (LS mean) and 95% CI were -0.51 (-1.10, 0.08) cm/year. The p-value for difference between treatment arms was p=0.0866 (>0.05). The subanalysis results showed that 12 months therapy with TAA-AQ nasal spray at 110 µg once daily did not have statistically significant effect on growth velocity in children aged ≥3 to <6 years old.
- Children aged ≥6 to <10 years old: the LS mean (SE) during the double-blind period was 5.83 (0.138) cm/year in the placebo group (N=133) and 5.40 (0.135) cm/year in the TAA-AQ group (N=134). The difference between treatment arms (LS mean) and 95% CI were -0.43 (-0.80, -0.05) cm/year. The p-value for difference between treatment arms was p=0.0266 (<0.05). The subanalysis results showed that 12 months therapy with TAA-AQ nasal spray at 110 µg once daily did have statistically significant effect on growth velocity in children aged ≥6 to <10 years old.

The subanalysis showed that younger children ≥3 to <6 years old did not have worse profile of growth velocity effect than older children of ≥6 to <10 years old, if not better.

• Cases reported to Sanofi pharmacovigilance database (AWARE):

A search in Sanofi AWARE safety database cumulative to 30 November 2016 with triamcinolone acetonide with formulation and route suggesting nasal spray as suspect drug with age 2 to 5 (less than 6) years old retrieved 80 cases, 6 solicited and 74 unsolicited. Review of the 80 cases not only found no cases of HPA axis inhibition, but also no cases of growth retardation.

Therefore, the MAH believes the lack of long term significant effects on growth with TAA-AQ tittered to control AR symptoms reported by Skoner in 2008 publication for children 6-14 years old is likely to be able to be extrapolated to children aged 2-5 years old.

Assessment of the MAH´s response:
Regarding the UK comment on the efficacy, please see assessment of the response to Q6.

Regarding the HPA suppression risk, the Rapporteur is of the opinion that the available data, although limited, do not suggest higher risk in the age group 2-5 (see assessment of the response to Q8). However, since there is no long-term safety data in the larger cohort of the youngest age group, the Rapporteur proposes to keep the wording in the SmPC as per MAH´s proposal, i.e. to limit the duration of treatment to 3 months, without the possibility of the cyclic treatment.

Issue resolved.

Q10 (SE):
In question 6 the Rapporteur questions the age limit proposed as statistically significant results were not obtained for the full population of patients 2-6 years of age. We support this question and would like to add that before taking final decision on an appropriate age limit, we would like to see a detailed presentation of descriptive data. Could the company (or the rapporteur dependent on if these data are available in the company's study report or not) please present subgroup analyses for the primary endpoint (change from baseline in the mean total nasal symptom score (TNSS) – instantaneous) and relevant secondary endpoints split by age group (2-<3, 3-<4, 4-<5 and 5 years of age).

MAH´s response:

Sanofi acknowledges the comment and Table 10, Table 11, Table 12, and Table 13 show the descriptive analysis by age group.
The prospective analyses and the subgroup analyses showed clinically meaningful and statistically significant improvements of symptoms with TAA-AQ 110 µg in patients 2 to 5 years of age with PAR.
Particularly, the 24-hour reflective assessments support the efficacy of TAA-AQ 110 µg. The results of the subgroup analyses for the instantaneous assessments, (primary endpoint in this study) in general, support the once a day dosing-regimen.
Moreover, both the reflective TNSS score, while a secondary endpoint in the pivotal trial is typically the preferred primary endpoint for allergic rhinitis trials. Thus, positive findings for the rTNSS endpoint would likely be considered significant findings of efficacy. This is especially true due to the fact that the efficacy endpoints in this phase III trial are based on parent/guardian assessments of the child's symptoms which introduce a level of subjectivity and inconsistency in endpoint analyses not present in studies of adults with SAR or PAR thus making it more difficult to demonstrate statistical efficacy.
It is important to note that any children become symptomatic at an age when they can neither read nor write. Therefore, they have to rely on caregivers when it comes to describing subjective symptoms.
The influence of parents or caregivers on reporting patient-related outcomes in young children is an important confounder which may have strong impact on study results.
Lower treatment effect has been observed in paediatric allergy trials possibly confounded by caregiver assessment.
In addition, EU Guidance states that on Primary efficacy analyses, it is recommended to score the symptoms at least daily. The patient should report on his status and symptoms over the previous period of 24 hours (Reflective Total Nasal Score).
Similarly, the updated FDA Guidance for applicants states that the Primary endpoint for efficacy should be the Reflective Total Nasal Score (4).
In the allergic rhinitis clinical development program for fluticasone furoate (Veramyst®), which was approved to treat SAR/PAR down to children 2 years of age, efficacy data in children 2 < 6 years of age were not included in analyses of the primary endpoints of the pediatric trials. It was, in general, supportive of results observed in the older children.

Table 10 - Total Nasal Symptom Score (TNSS) - Instantaneous - Double-blind period - ITT analysis - Descriptive analysis by age

			N	Mean	Std	Min	Max	Median	Q1	Q3
Treatment group	Age in years									
Placebo	2	Baseline mean symptom score	52	7.40	2.30	1.50	12.00	7.30	6.15	8.90
		On-treatment mean symptom score	52	4.93	2.75	0.80	10.70	5.00	2.35	7.20
		Change from baseline mean symptom score	52	-2.47	2.30	-7.30	2.60	-2.55	-3.80	-0.50
	3	Baseline mean symptom score	67	7.43	2.28	2.00	12.00	7.50	5.80	8.80
		On-treatment mean symptom score	67	5.56	2.65	0.50	11.90	5.70	3.60	7.20
		Change from baseline mean symptom score	67	-1.88	2.18	-7.40	4.30	-1.60	-3.50	-0.50
	4	Baseline mean symptom score	70	7.40	2.23	0.00	12.00	7.40	5.80	9.00
		On-treatment mean symptom score	70	5.60	2.56	0.10	11.80	5.40	3.90	7.40
		Change from baseline mean symptom score	70	-1.80	2.59	-8.60	3.50	-1.25	-3.60	0.00
	5	Baseline mean symptom score	44	8.20	2.10	4.00	12.00	8.30	6.65	9.50
		On-treatment mean symptom score	44	6.53	2.81	0.20	12.00	6.50	4.35	9.00
		Change from baseline mean symptom score	44	-1.67	1.88	-8.10	1.20	-1.45	-2.95	-0.15
Nasacort AQ	2	Baseline mean symptom score	43	7.36	2.03	3.30	12.00	7.30	5.80	8.50
		On-treatment mean symptom score	43	5.51	2.80	0.30	10.90	5.30	3.30	7.30
		Change from baseline mean symptom score	43	-1.85	2.36	-8.20	4.30	-1.60	-3.10	-0.30
	3	Baseline mean symptom score	53	7.44	1.93	3.50	11.50	7.50	6.00	8.50
		On-treatment mean symptom score	53	5.29	2.15	1.50	9.50	5.20	3.50	6.40
		Change from baseline mean symptom score	53	-2.15	2.38	-8.10	3.60	-2.20	-3.70	-0.70
	4	Baseline mean symptom score	77	7.58	2.10	3.50	12.00	7.80	6.00	9.00
		On-treatment mean symptom score	77	5.19	3.16	0.50	12.00	4.80	2.30	7.30
		Change from baseline mean symptom score	77	-2.39	2.82	-11.20	3.30	-2.00	-4.30	-0.40
	5	Baseline mean symptom score	58	7.58	1.88	4.30	11.70	7.30	6.30	9.00
		On-treatment mean symptom score	58	5.19	2.46	0.00	9.20	5.05	3.50	7.00
		Change from baseline mean symptom score	58	-2.39	2.38	-7.70	1.50	-2.15	-3.90	-0.60

Table 11 - Total Nasal Symptom Score (TNSS) - 24 hour reflective - Double-blind period - ITT analysis - Descriptive analysis by age

Treatment group	Age in years		N	Mean	Std	Min	Max	Median	Q1	Q3
Placebo	2	Baseline mean symptom score	52	7.77	2.22	1.80	12.00	8.00	6.40	9.40
		On-treatment mean symptom score	52	5.43	2.60	0.50	10.70	5.65	3.35	7.55
		Change from baseline mean symptom score	52	-2.34	2.20	-7.30	2.30	-2.25	-3.65	-0.35
	3	Baseline mean symptom score	67	7.72	2.14	2.30	12.00	7.80	6.00	9.00
		On-treatment mean symptom score	67	5.89	2.60	1.30	11.90	5.80	4.10	8.00
		Change from baseline mean symptom score	67	-1.83	2.16	-7.00	4.80	-1.70	-3.10	-0.50
	4	Baseline mean symptom score	70	7.73	1.79	4.00	11.80	7.50	6.30	9.00
		On-treatment mean symptom score	70	5.91	2.50	0.90	11.70	5.65	4.20	7.20
		Change from baseline mean symptom score	70	-1.83	2.48	-8.80	4.30	-1.70	-3.60	-0.40
	5	Baseline mean symptom score	44	8.39	2.29	4.00	12.00	8.50	6.40	10.40
		On-treatment mean symptom score	44	6.97	2.74	0.00	12.00	7.25	4.90	9.25
		Change from baseline mean symptom score	44	-1.42	2.08	-8.10	3.10	-1.00	-2.50	-0.05
Nasacort AQ	2	Baseline mean symptom score	43	7.80	2.13	3.50	12.00	8.00	6.30	9.30
		On-treatment mean symptom score	43	5.54	2.58	0.80	11.00	5.10	4.00	6.80
		Change from baseline mean symptom score	43	-2.26	2.36	-8.40	2.70	-2.00	-4.20	-0.50
	3	Baseline mean symptom score	53	8.12	1.85	4.00	12.00	8.30	6.80	9.30
		On-treatment mean symptom score	53	5.78	2.04	2.10	10.00	5.80	4.10	7.20
		Change from baseline mean symptom score	53	-2.34	1.99	-8.10	1.70	-2.50	-3.30	-0.80
	4	Baseline mean symptom score	77	8.08	2.04	3.80	12.00	8.00	6.50	9.50
		On-treatment mean symptom score	77	5.69	3.01	0.20	11.90	6.20	3.00	7.80
		Change from baseline mean symptom score	77	-2.39	2.58	-11.00	2.50	-2.00	-4.20	-0.50
	5	Baseline mean symptom score	58	7.87	1.85	4.50	12.00	7.80	6.50	9.30
		On-treatment mean symptom score	58	5.61	2.36	0.60	9.90	5.55	3.70	7.60
		Change from baseline mean symptom score	58	-2.26	2.35	-8.50	2.10	-2.25	-3.80	-0.50

Table 12 - Total Symptom Score (TSS) - instantaneous - Double-blind period – ITT analysis - Descriptive analysis by age

			N	Mean	Std	Min	Max	Median	Q1	Q3
Treatment group	Age in years									
Placebo	2	Baseline mean symptom score	52	8.60	2.97	1.80	15.00	8.50	6.80	10.50
		On-treatment mean symptom score	52	5.83	3.40	0.90	13.40	5.50	2.70	8.70
		Change from baseline mean symptom score	52	-2.77	2.74	-8.70	4.20	-2.55	-4.25	-0.75
	3	Baseline mean symptom score	67	9.09	2.88	2.30	15.00	8.50	7.30	11.00
		On-treatment mean symptom score	67	6.79	3.21	1.20	14.90	6.60	4.50	8.60
		Change from baseline mean symptom score	67	-2.30	2.49	-9.00	4.70	-2.20	-3.70	-0.80
	4	Baseline mean symptom score	70	8.68	2.75	0.00	15.00	8.90	6.80	10.80
		On-treatment mean symptom score	70	6.61	3.21	0.10	14.80	6.50	4.30	8.60
		Change from baseline mean symptom score	70	-2.07	3.02	-10.30	3.80	-1.40	-4.00	0.00
	5	Baseline mean symptom score	44	9.99	2.78	5.00	15.00	10.00	8.00	12.15
		On-treatment mean symptom score	44	7.83	3.55	0.20	15.00	7.80	5.50	10.75
		Change from baseline mean symptom score	44	-2.16	2.44	-11.10	1.70	-2.20	-3.25	-0.25
Nasacort AQ	2	Baseline mean symptom score	43	8.87	2.66	3.30	15.00	8.80	7.00	10.50
		On-treatment mean symptom score	43	6.65	3.52	0.30	13.60	6.50	3.80	9.10
		Change from baseline mean symptom score	43	-2.22	2.94	-10.20	5.30	-2.10	-4.00	-0.20
	3	Baseline mean symptom score	53	8.73	2.57	3.80	14.30	8.30	7.00	10.50
		On-treatment mean symptom score	53	6.25	2.64	1.60	11.10	6.20	3.90	8.10
		Change from baseline mean symptom score	53	-2.48	2.88	-10.10	4.60	-2.60	-4.20	-0.90
	4	Baseline mean symptom score	77	9.13	2.78	3.50	15.00	9.00	7.00	11.30
		On-treatment mean symptom score	77	6.29	3.97	0.50	14.90	5.90	2.80	8.70
		Change from baseline mean symptom score	77	-2.85	3.35	-13.40	4.30	-2.20	-5.30	-0.40
	5	Baseline mean symptom score	58	8.89	2.33	4.30	14.50	8.65	7.00	10.30
		On-treatment mean symptom score	58	6.17	3.03	0.00	11.70	6.30	3.70	7.90
		Change from baseline mean symptom score	58	-2.72	3.01	-10.10	2.40	-2.55	-4.70	-0.70

Assessment of the MAH´s response:
See assessment of the response to question 6.

Q11 (NL):
We currently consider the benefit-risk negative for children 2-5 years old.
Furthermore, the studies TRICA_L_04286 and XRG5029C/3503 that have been evaluated during Art. 46 paediatric worksharing procedure UK/W/0047/pdWS/001 need also to be included in the assessment in order to assess the benefit-risk on all available information for the newly applied children group. The Applicant/Rapporteur is requested to provide and discuss the results in the subgroup of children 2-5 years of age.

MAH´s response:

1. RISKS

1.1 Effect on HPA axis

Subanalysis of the 4 clinical studies including TRICA_L_04286 and XRG5029C/3503 for

children 2-5 years old did not find significant risk of HPA axis inhibition with therapeutic dose of TAA-AQ nasal spray in this age group, although possible treatment effect on HPA axis cannot be ruled out. No case of HPA axis effect has been reported in Sanofi pharmacovigilance database for 2-5 years old. No literature articles reported HPA axis effect in children 2-5 years old other than the 4 studies. For details of the analysis results, see response to question 8.

1.2 Effect on Growth Velocity

Reduction of growth velocity has been in current SmPC in section 4.4, 4.8 and 5.1 based on study XRG5029C/3503 with subjects aged 3-9. Subanalysis of the study with children aged 3-5 years old found the LS mean (SE) during the double-blind period was 6.42 (0.210) cm/year in the placebo group (N=60) and 5.90 (0.210) cm/year in the TAA-AQ group (N=60). The difference between treatment arms (LS mean) and 95% CI were -0.51 (-1.10, 0.08) cm/year. The p-value for difference between treatment arms was p=0.0866 (>0.05). The subanalysis results showed that 12 months therapy with TAA-AQ nasal spray at 110 µg once daily did not have statistically significant effect on growth velocity in children aged 3-5 years old.

1.3 Adverse Events in Clinical Studies

1.3.1 Treatment-Emergent Adverse Events

In 5 controlled studies (RG5029Y-305 [DB, age<12 years], RG5029Y-312 [age<12 years], RG5029Y-314 [age<12 years], XRG5029C/3502 (DB), and TRICA_L_04286), treatment-emergent adverse events (TEAEs) of subgroup with age 2~<6 years old were compared with 6 to <12 years in pediatric subjects (cut-off: incidence of at least 2% in total TAA-AQ group) (Table 14).

Table 14 - Treatment-emergent adverse events by age subgroups in all controlled studies in pediatric subjects (cut-off: incidence of at least 2% in total triamcinolone acetonide aqueous group)

	2 to <6 years		6 to <12 years	
Preferred term	Placebo (N=264)	TAA-AQ total (N=273)	Placebo (N=212)	TAA-AQ total (N=371)
Number (%) of subjects with TEAEs	127 (48.1%)	139 (50.9%)	87 (41.0%)	160 (43.1%)
Headache	11 (4.2%)	15 (5.5%)	19 (9.0%)	28 (7.5%)
Cough	22 (8.3%)	20 (7.3%)	11 (5.2%)	26 (7.0%)
Nasopharyngitis	10 (3.8%)	12 (4.4%)	12 (5.7%)	22 (5.9%)
Influenza	1 (0.4%)	4 (1.5%)	15 (7.1%)	19 (5.1%)
Pyrexia	24 (9.1%)	20 (7.3%)	6 (2.8%)	18 (4.9%)
Epistaxis	16 (6.1%)	15 (5.5%)	16 (7.5%)	15 (4.0%)
Oropharyngeal pain	10 (3.8%)	13 (4.8%)	8 (3.8%)	13 (3.5%)
Upper respiratory tract infection	3 (1.1%)	6 (2.2%)	11 (5.2%)	12 (3.2%)
Vomiting	8 (3.0%)	9 (3.3%)	5 (2.4%)	9 (2.4%)
Viral infection	2 (0.8%)	3 (1.1%)	2 (0.9%)	8 (2.2%)
Asthma	5 (1.9%)	7 (2.6%)	5 (2.4%)	7 (1.9%)
Sinusitis	6 (2.3%)	6 (2.2%)	10 (4.7%)	7 (1.9%)
Abdominal pain upper	2 (0.8%)	12 (4.4%)	2 (0.9%)	5 (1.3%)
Rash	4 (1.5%)	6 (2.2%)	1 (0.5%)	4 (1.1%)
Diarrhoea	3 (1.1%)	7 (2.6%)	3 (1.4%)	1 (0.3%)
Excoriation	0	6 (2.2%)	2 (0.9%)	0

Adverse events were coded using MedDRA version 14.1.

Presented are TEAEs that occurred in at least 2% of subjects in any TAA-AQ treatment groups.

Note: Subjects are counted only once per preferred term. The numbers within a column may not add to the total number of subjects with at least one TEAE, since a subject may have had more than one TEAE. Preferred terms are sorted by decreasing frequency of TAA-AQ total group in subjects with age of 6 to < 12 years.

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No meaningful differences between treatment groups were observed in the overall percentage of subjects with a TEAE within either pediatric age group (2 to <6 years or 6 years to <12 years). For the TAA-AQ-treated subjects, the incidence of TEAEs (50.9%) was greater in the subjects in the 2 to <6 year old group compared with the 6 to <12 year group (43.1%) (Table 14). The most frequently occurring TEAEs in TAA-AQ-treated subjects who were 2 to <6 years of age were cough, pyrexia, headache, epistaxis, oropharyngeal pain, nasopharyngitis, upper abdominal pain, and vomiting. In this age group, upper respiratory tract infection, upper abdominal pain, diarrhea, and excoriation occurred with a higher frequency in the TAA-AQ group compared with the placebo group.

Among subjects treated with TAA-AQ, the following TEAEs occurred with a higher frequency in the 2 to <6 year age group compared with the 6 to <12 year age group: upper abdominal pain, rash, diarrhea, and excoriation. Influenza and viral infection occurred with a greater incidence in the 6 to <12 year group compared with the 2 to <6 year group.

Comparison between 2 to <6 year and 6 to <12 year age group was also made in long-term safety studies (XRG5029C/3502 [DB+OL] and XRG5029C/3503) in pediatric subjects (cut-off: incidence of at least 5% in total triamcinolone acetonide aqueous group) (Table 15):

Table 15 - Treatment-emergent adverse events by age subgroups in long-term safety studies in pediatric subjects (cut-off: incidence of at least 5% in total triamcinolone acetonide aqueous

	2 to <6 years		6 to <12 years	
Preferred term	**Placebo (N=64)**	**TAA-AQ total (N=488)**	**Placebo (N=84)**	**TAA-AQ total (N=90)**
Number (%) of subjects with TEAEs	48 (75.0%)	369 (75.6%)	66 (78.6%)	73 (81.1%)
Headache	8 (12.5%)	50 (10.2%)	23 (27.4%)	25 (27.8%)
Nasopharyngitis	9 (14.1%)	65 (13.3%)	9 (10.7%)	19 (21.1%)
Pyrexia	20 (31.3%)	116 (23.8%)	18 (21.4%)	17 (18.9%)
Cough	17 (26.6%)	109 (22.3%)	13 (15.5%)	13 (14.4%)
Upper respiratory tract infection	10 (15.6%)	51 (10.5%)	9 (10.7%)	12 (13.3%)
Oropharyngeal pain	7 (10.9%)	41 (8.4%)	11 (13.1%)	11 (12.2%)
Vomiting	3 (4.7%)	44 (9.0%)	5 (6.0%)	11 (12.2%)
Abdominal pain upper	3 (4.7%)	29 (5.9%)	12 (14.3%)	10 (11.1%)
Epistaxis	4 (6.3%)	32 (6.6%)	3 (3.6%)	9 (10.0%)
Sinusitis	9 (14.1%)	30 (6.1%)	2 (2.4%)	9 (10.0%)
Asthma	6 (9.4%)	30 (6.1%)	4 (4.8%)	6 (6.7%)
Ear pain	6 (9.4%)	20 (4.1%)	8 (9.5%)	6 (6.7%)
Influenza	3 (4.7%)	19 (3.9%)	0	6 (6.7%)
Pharyngitis streptococcal	6 (9.4%)	23 (4.7%)	4 (4.8%)	6 (6.7%)
Viral infection	2 (3.1%)	28 (5.7%)	1 (1.2%)	6 (6.7%)
Viral upper respiratory tract infection	5 (7.8%)	12 (2.5%)	5 (6.0%)	6 (6.7%)
Gastroenteritis viral	2 (3.1%)	16 (3.3%)	4 (4.8%)	5 (5.6%)
Nasal congestion	3 (4.7%)	25 (5.1%)	8 (9.5%)	5 (5.6%)
Rash	2 (3.1%)	24 (4.9%)	2 (2.4%)	5 (5.6%)
Rhinorrhoea	7 (10.9%)	36 (7.4%)	2 (2.4%)	3 (3.3%)
Ear infection	6 (9.4%)	33 (6.8%)	1 (1.2%)	2 (2.2%)
Otitis media	5 (7.8%)	33 (6.8%)	4 (4.8%)	1 (1.1%)

Adverse events were coded using MedDRA version 14.1.

Presented are TEAEs that occurred in at least 5% of subjects in TAA-AQ treatment group.

Note: Subjects are counted only once per preferred term. The numbers within a column may not add to the total number of subjects with at least one TEAE, since a subject may have had more than one TEAE. Preferred terms are sorted by decreasing frequency of the TAA-AQ group in subjects with age of 6 to < 12 years.

No meaningful differences between treatment groups were observed in the overall percentage of subjects with a TEAE within either paediatric age group (2 to <6 years and 6 years to <12 years), and no meaningful differences between paediatric age groups were observed in the overall incidence of TEAE (Table 15). In the age group 2 to <6 years, vomiting tended to occur more frequently in the TAA-AQ group compared with the placebo group. Of note, the number of subjects in 2 to <6 years age group who received placebo was much smaller than the number in the TAA-AQ group. For both treatment groups, most TEAEs in the table appear to have less frequency in 2 to <6 years age group than in 6 to <12 years age group (Headache, Nasopharyngitis, Upper respiratory tract infection, Oropharyngeal pain, Vomiting, Abdominal pain upper, Epistaxis, Sinusitis, Ear pain, Influenza, Pharyngitis streptococcal, Viral upper respiratory tract infection, Gastroenteritis viral); for those TEAEs that appear to have higher

frequency in 2 to <6 years age group than in 6 to <12 years age group (Pyrexia, Cough, Rhinorrhoea, Ear infection, Otitis media), they were all lower (not higher) in frequency than placebo of the same age group.
Summary of TEAEs by age: the incidence of TEAEs was generally higher in the paediatric population compared with the adult/adolescent population. Within the paediatric population of the controlled studies, the overall incidence of TEAEs in subjects treated with TAA-AQ was higher in the younger age group (2 to <6 years) compared with the older group (6 to <12 years). Upper abdominal pain, rash, diarrhoea, and excoriation occurred more frequently in the younger age group and influenza and viral infection occurred more frequently in the older age group of the paediatric population. In the long-term safety studies, the overall incidence of TEAEs was similar between the 2 to <6 year olds and the 6 to <12 year olds. Most TEAEs with incidence >5% in TAA-AQ group appeared to be reported less frequently in the younger group (2 to <6 years) compared with older group (6 to <12 years). For those TEAEs that appear to have higher frequency in 2 to <6 years age group than in 6 to <12 years age group, the incidences were all lower (not higher) than placebo of the same age group. Vomiting tended to occur more frequently in the TAA-AQ group compared with the placebo group in the youngest age group.

1.3.2 Treatment-Emergent Serious Adverse Events

In the same 5 controlled studies (RG5029Y-305 [DB, age<12 years], RG5029Y-312 [age<12 years], RG5029Y-314 [age<12 years], XRG5029C/3502 (DB), and TRICA_L_04286), 1 case of Serious Adverse Event (SAE) was reported in placebo group during pretreatment period, and no SAE from TAA-AQ group in subjects aged 2-<6.
In the long-term safety studies (XRG5029C/3502 [DB+OL] and XRG5029C/3503) with subjects aged 2-<6 (Placebo N=64, TAA-AQ N=488), 9 cases of Treatment-Emergent SAE were reported from TAA-AQ group. None of the SAEs was related to TAA-AQ treatment; 8 patients recovered and 1 patient (with SAE of diabetic ketoacidosis) recovered with sequelae.

1.3.3 Death
There were no deaths reported in any clinical study during the TAA-AQ clinical development program.

Assessment of the MAH´s response:
Available pharmacovigilance and safety data from several clinical studies do not seem to indicate higher safety risk in the youngest patient population. The most important adverse event is the influence on HPA axis, and the presented data, although limited do not suggest significantly higher risk in patients 2 to 5 years old. Furthermore, the MAH has proposed restrictions in the SmPC on the length of use of the product, which should further contribute to the minimisation of the occurrence of HPA suppression in the youngest age group.

Issue resolved.

Q12 (NL): For the results, a discussion is missing regarding the clinical relevance of the differences found in the studies. What do the results mean for the patients? The Applicant is requested to provide such a discussion when presenting the results.

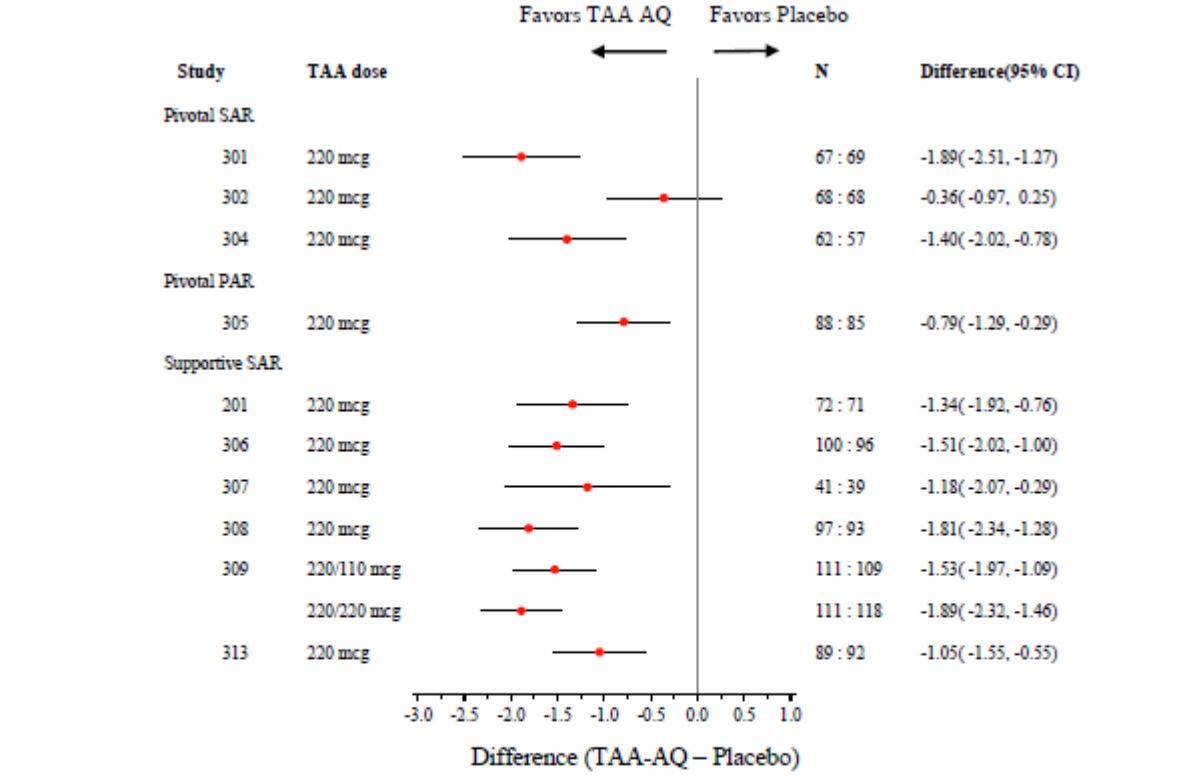
MAH´s response:

Figure 1 and Figure 2 present the differences between TAA-AQ and placebo across each study for the primary analysis of Nasal Index NI or TNSS based upon reflective scoring, in forest plots. The pediatric age group includes children aged 2 through 11 while adolescents are grouped with adults. Pivotal and supportive studies are grouped based upon type of allergic rhinitis (SAR and PAR) included in each study.

Studies in Adults and Adolescents:

In Figure 1, for adults and adolescents, TAA-AQ 220 µg significantly improved the Nasal Index (NI: sum of nasal stuffiness, nasal discharge, and sneezing scores, ranging from 0-9). NI in the pivotal SAR and PAR studies with the exception of Study 302 which demonstrated a numerical improvement with TAA-AQ. Findings across the supportive SAR studies were consistent with the pivotal findings. Separate analyses of the nasal symptom components in the NI also found significant differences from placebo for most components in each study. In study 309 that examined down titration from 220 to 110 µg after one week of treatment, TAA-AQ was also significantly different from placebo. Supporting analyses conducted for separate time periods (Days 1 to 4 or Days 1 to 13, depending upon the study design) and by week (Weeks 1 to 4) also supported the primary findings with efficacy observed within one day. Pooled efficacy analyses supported the primary findings. Additionally, subgroup analyses by age, gender and race supported the primary findings.

Figure 1: treatment difference (TAA-AQ-Placebo) in change from baseline in 24-hour reflective for nasal index of adult and adolescent studies



N: Numbers of subjects in placebo vs. TAA-AQ groups.
CI: confidence interval.
*Nasal index is the sum of nasal stuffiness, nasal discharge, and sneezing scores and ranges from 0 to 9.
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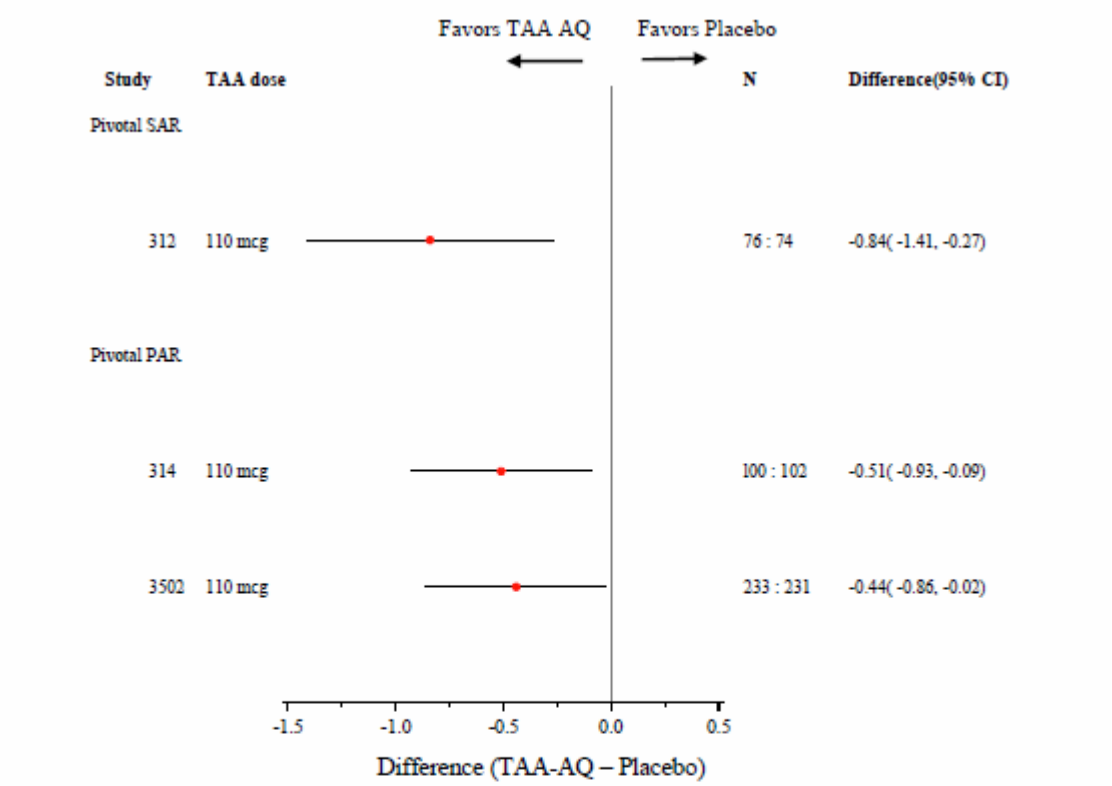
OUT=REPORT/OUTPUT/NASAL_INDEX_forest_adult_i.rtf (18JUN2013 - 19:57)

As stated in the response to question 6, not all the studies were submitted again in the frame of this Article 45 worksharing procedure, since this procedure focuses on paediatric population, but of course, were part of the initial submission for registration of Nasacort nasal spray Studies 305, 306, 307, 308, 309, 313 and 201 are not included in the article 45 file.

Studies in Children 2 through 11

In Figure 2, for the treatment of SAR and PAR in children aged 6 through 11, TAA-AQ 110 µg significantly improved the NI score compared to placebo. For the treatment of PAR, with or without symptoms of SAR, in children aged 2 through 5, TAA-AQ 110 µg significantly improved the TNSS and some of the nasal symptoms, such as sneezing and nasal itching over the 4-week treatment period.
As in adults, separate analyses of symptom components were consistent with the overall analysis. Supporting analyses conducted for separate time periods (Days 1 to 4) and by week (Weeks 1 to 4) also supported the primary findings.

Figure 2: Treatment difference (TAA-AQ-Pacwbo) in change from baseline in 24-hour reflective for nasal index/TNSS of studies in children



N: Numbers of subjects in placebo vs. TAA-AQ groups.
CI: confidence interval.
*Nasal index for studies 312, 314; TNSS for study 3502. Nasal index is the sum of nasal stuffiness, nasal discharge, and sneezing scores and ranges from 0 to 9; TNSS is the sum of nasal stuffiness, nasal discharge, sneezing, and nasal itching scores and ranges from 0 to 12.
PGM=DEVOPS/XRG5029/OTCNDA/ISE2012/REPORT/PGM/NASAL_INDEX_forest_ped.sas
OUT=REPORT/OUTPUT/NASAL_INDEX_forest_ped_i.rtf (18JUN2013 - 20:03)

In global evaluation of efficacy by subjects and investigators, both adult and paediatric subjects assigned to TAA-AQ reported significantly more improvement than placebo. Other secondary endpoints also supported the overall effectiveness of TAA-AQ in treating AR. Subgroup analyses of the primary endpoint were consistent with the overall findings.

TAA-AQ nasal spray effectively treats all four nasal symptoms of allergic rhinitis, including nasal congestion, the symptom that sufferers find most bothersome. The efficacy and safety of the product has been characterized in multiple clinical studies in adults and children, as well as with market experience for over 20 years.

For children, there is also a clear need for a more effective AR remedy and TAA-AQ would address this need.
A multicentre study conducted in the Italy, as part of the European Community Respiratory Health Survey (ECRHS), reported a rhinitis prevalence of 18.5 % among children, with an increase of more than 50 % over the previous decades. Bronchial asthma prevalence has increased, as well, as reported by "The International Study of Allergy and Asthma in Childhood" (ISFAC). Rhinitis and asthma affect both the quality of life in relation to health (as measured by Health-Related Quality Of Life (HRQOL) and the cost of treatment. Several studies show that rhinitis has negative effects on the activities of the patient's everyday life at home, school and work. Nasal corticosteroids are the mainstay of therapy for both non-allergic and allergic rhinitis. With potent but local anti-inflammatory effects, they are efficacious in treating most rhinitis syndromes regardless of etiology. By decreasing inflammation, nasal corticosteroids decrease mucosal edema and vascular leak improving the symptoms of rhinorrhoea and nasal congestion. They also decrease the number of histamine containing mast cells in the nasal mucosa, thus decreasing nasal pruritus and sneezing.

Assessment of MAH´s response:
In the opinion of the Rapporteur, the MAH has provided acceptable explanation of the studies´ results in the context of the quality of life rhinitis patients.

Issue resolved.

Q14 (NL): We support the request for a subanalysis in the specific age group of 4-5 years old in PD study RG5029Y-315. However, the results of the ACTH stimulation test in the investigated paediatric population (4-10 years) already indicated that triamcinolone influences cortisol.
Thus, it is expected that the concerns for this vulnerable age group will remain even when the results in the subanalysis would not indicate suppression. Furthermore, the Applicant is requested to discuss which precautions can be further taken besides/instead the current SmPC advise in section 4.2 against the continuous use longer than 3 months in children younger than 12 years.

MAH´s response:

Study RG5029Y-315 is a randomized, single center, 4-way cross-over, placebo and active controlled pediatric trial with TAA-AQ assessing short-term growth in patients 4 to 10 years of age with allergic rhinitis. One of the secondary objectives was to evaluate the effect of TAA- AQ (110 and 220 µg/day) and fluticasone propionate nasal spray (200 µg/day) on overnight urine cortisol/creatinine ratio compared to placebo. A total of 59 prepubescent patients aged 4 to 10 years were randomized, and 49 of them completed all four treatment periods. Two-week treatment with TAA-AQ 110 or 220 µg once daily did not significantly affect HPA axis function as measured by overnight urine cortisol/creatinine ratio compared to placebo. Conversely, fluticasone propionate 200 µg daily did result in a significantly reduced overnight urine cortisol/creatinine ratio compared to placebo. Of the 49 subjects who completed all four treatment periods, 10 of the subjects were at age 2-5 years old. The number of subjects in this subgroup is very small and statistical analyses on this very small group of subjects would not be conclusive.
ACTH stimulation test on the other hand, was carried out in study XRG5029C/3502, a randomized, double-blind, parallel group, placebo-controlled, four-week efficacy and safety evaluation of TAA-AQ 110 µg qd, followed by six-month open-label safety study in children ages 2-5 years with perennial allergic rhinitis. ACTH (cosyntropin) stimulation test in this study showed no statistically significant difference between the post-stimulation changes in mean cortisol levels at the end of double-blind treatment period versus screening in the placebo and TAA-AQ groups. The comparison of the cortisol levels post-stimulation with cosyntropin at the

end of the open label treatment period and screening also did not reveal any statistically significant difference. Some patients (2 with placebo and 4 with TAA-AQ) did not show the prespecified increase in cortisol levels or did not reach the pre-specified level following cosyntropin stimulation at the end of the double-blind period, so a possible treatment effect on children aged 2-5 cannot be ruled out. The MAH considers that the proposed Product Information correctly addresses the precautions to be taken in this 2 to 5 years old age group. Indeed, in the proposed Product Information:
• Reduction in growth velocity is already mentioned under warnings and precautions
• A treatment longer than 3 months is not recommended for children under 12

In addition, it is to be noted that the product will be under physician prescription/supervision in this age group as it is already for the children from 6 to 18 years old. Furthermore, no cases of HPA suppression have been reported in this age group and no product accumulation is seen from PK data.
Therefore, the MAH considers that the proposed Product Information reflects the available data and no additional amendments are needed.

Assessment of the MAH´s response:
The Rapporteur finds the proposed measures acceptable.

Issue resolved.

Comments proposing further amendment of the SmPC have been received from SE and NL upon updated AR was circulated.

VIII. FINAL RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

From a clinical perspective, the data submitted, although limited, support the indication of TAA-AQ nasal spray for the treatment of PAR and SAR for children aged over 2 years from the current indication of adults, adolescents, and children 6-11 years of age. Adequate clinical study performed in children 2-5 years of age demonstrated that the proposed dose of 110 µg of NAQ nasal spray once daily provided a statistically significant improvement in reflective total nasal symptom score (rTNSS) compared to placebo in children with PAR with or without SAR.
These results are consistent with the results of study RG5029Y-314 in paediatric patients 4 to 12 years of age with PAR, which used the reflective rating of nasal symptoms for the primary efficacy assessment, and global ratings among the secondary efficacy assessments. Due to the similarity of the pathophysiology of SAR and PAR, and the proven efficacy of TAA-AQ in adults and older paediatric patients in both PAR and SAR, this efficacy can be extrapolated to SAR.
Supportive efficacy results of studies Trica_L_04286, and XRG5029C/3503 confirm the benefits of TAA-AQ 110 µg/day in paediatric patients 2 to 5 years of age with SAR or PAR.
Moreover, both the reflective TNSS score, while a secondary endpoint in the pivotal trial is typically the preferred primary endpoint for allergic rhinitis trials. Thus, positive findings for the rTNSS endpoint would likely be considered significant findings of efficacy.
Given its well documented efficacy and greater than 20 years of approved use in children 6-11 years of age with a satisfactory safety profile, the clinical benefit in the 2-5 years age population is positive.

- **Recommendation**

Based on the clinical information submitted by the applicant, an update to paediatric information is approvable.

Changes in the SmPC

The proposed additions are marked in **bold,** proposed deletions in ~~strikethrough~~**.**

4.1 Therapeutic indications

NASACORT is indicated for the treatment of symptoms of seasonal and perennial allergic rhinitis **in adults and children 2 years of age and over.**

4.2 Posology and method of administration

Adults
~~*Patients aged 12 years and over:*~~ The recommended starting dose is 220 micrograms as 2 sprays in each nostril once daily. Once symptoms are controlled patients can be maintained on 110 micrograms (1 spray in each nostril once daily).

Paediatric population
Children aged 12 years and over
The recommended starting dose is 220 micrograms as 2 sprays in each nostril once daily. Once symptoms are controlled patients can be maintained on 110 micrograms (1 spray in each nostril once daily).

Children aged 6 to 12 years
~~*Paediatric patients aged 6 to 12 years:*~~ The recommended dose is 110 micrograms as 1 spray in each nostril once daily. In patients with more severe symptoms, a dose of 220 micrograms may be used. But once symptoms are controlled, patients should be maintained on the lowest effective dose (see sections 4.4 and 5.1). ~~Until further evidence is available, continuous use beyond 3 months is not recommended.~~

Children aged 2 to 5 years
The recommended and maximum dose is 110 micrograms as 1 spray in each nostril once daily (see sections 4.4 and 5.1).

~~Until further evidence is available,~~ **C**ontinuous use beyond 3 months in children under 12 years is not recommended.

4.4 Special warnings and precautions for use

Paediatric population
~~As experience with NASACORT in children under 6 years of age is limited, use in this age group is not recommended~~**. NASACORT is not recommended for use in children under 2 years of age.**

Reduction in growth velocity has been reported in children receiving nasal corticosteroids, ***including NASACORT*** *at licensed doses.* ***See section 5.1.***

It is recommended that the height of children receiving ~~prolonged~~ treatment with nasal corticosteroids is regularly monitored. ~~If growth is slowed, t~~ Therapy should be managed ~~reviewed~~ with the aim of reducing the dose of nasal corticosteroid, if possible, to the lowest dose at which effective control of symptoms is maintained.
~~In addition, consideration should be given to referring the patient to a paediatric specialist~~. The long-term effects of reduction in growth velocity associated with nasal corticosteroids, including

the impact on final adult height are unknown. ***In addition, consideration should be given to referring the patient to a paediatric specialist, especially for children under the age of 6 years this is strongly recommended****.*

5.1 Pharmacodynamic properties
In clinical studies performed in adults and children **6 years of age and above** at doses up to 440 µg/day intranasally, **and in children 2 to 5 years of age at 110 µg/day intranasally,** no suppression of the Hypothalamic-Pituitary-Adrenal (HPA) axis has been observed.

5.2 Pharmacokinetic properties

~~Following multiple doses in paediatric patients, plasma drug concentrations, AUC, Cmax and Tmax were similar to those values observed in adult patients.~~

Paediatric population
Following multiple doses intranasal administration of NASACORT, systemic exposures observed in paediatric patients 6 to 12 years of age were similar to those observed in adult patients.

Intranasal administration of NASACORT 110 µg once daily in pediatric patients 2 to 5 years of age exhibited similar systemic exposure to that achieved in adult patients at a dose of 220 µg once daily.

The apparent clearance and volume of distribution in pediatric patients 2 to 5 years of age were found to be approximately half of that in adults.

Paediatric wording in the PL:

Section 1, What Nasacort is and what it is used for:

Nasacort contains a medicine called triamcinolone acetonide. This belongs to a group of medicines called corticosteroids which means it is a type of steroid. It is given as a spray in the nose to treat the nasal symptoms of allergic rhinitis **in adults and children 2 years of age and over**.

Section 2, Children (under **2** ~~6~~ years):

This medicine is not recommended for use in children under **2** ~~6~~ years of age.

Section 3: How much Nasacort to use:

Children (2 to 5 years)
- **The usual dose is 1 spray in each nostril each day**

Do not use Nasacort for more than 3 months in children under 12 years old
An adult should help a young child use this medicine.
~~Children (under 6 years) Check with your doctor or pharmacist before using~~

IX. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Nasacort (Sanofi Aventis)