U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review

CLINICAL STUDY

NDA / Sequence Number:	NDA 202129 / Seq 0054
Drug Name:	Zetonna® (ciclesonide)
Proposed Indication:	Pediatric seasonal and perennial allergic rhinitis
Applicant:	Sunovion
Date(s):	Received: 12-20-2013 PDUFA Due Date: 12-20-2014
Review Priority:	Standard
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Keywords: NDA review, Clinical Studies

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1 EXECUTIVE SUMMARY

Sunovion has submitted results from two phase 3 pediatric studies, SEP060-305 (305) and SEP060-306 (306), evaluating the safety and efficacy of Zetonna Nasal Aerosol (ciclesonide) for the treatment of symptoms associated with seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in patients 6 to 11 years of age. The submitted studies were conducted in response to requirements outlined in the Agency's January 20, 2012 approval letter to the sponsor for Zetonna Nasal Aerosol for the treatment of symptoms associated with SAR and PAR in adults and adolescents 12 years of age and older.

Each study compared placebo (P) to ciclesonide 74 mcg per day (C74), administered as one 37 mcg actuation per nostril, and ciclesonide 37 mcg per day (C37), administered as one 18.5 mcg actuation per nostril. Study 305 addressed SAR and study 306 addressed PAR.

In study 306 for PAR, both tested doses of ciclesonide were superior to placebo for the primary endpoint, change from baseline reflective total nasal score (ΔrTNSS) to week 6. No significant difference was seen between the two doses of ciclesonide.

However, in study 305 for SAR, neither dose tested was superior to placebo for the primary endpoint change from baseline ΔrTNSS to day 15.

2 INTRODUCTION

2.1 Overview

2.1.1 Drug Class and Indication

Ciclesonide is a glucocorticosteroid approved for the treatment of symptoms associated with seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in patients 12 years of age and older.

2.1.2 History of Drug Development

The clinical development program for Zetonna Nasal Aerosol for the treatment of symptoms associated with SAR and PAR in was introduced to the Agency under IND 074674. On January 20, 2012, the Agency approved its use in adults and adolescents 12 years of age and older. The approval letter also communicated a post-marketing requirement that the sponsor evaluate pediatric safety and efficacy in accordance with the the Pediatric Research Equity Act (PREA).

The approval letter waived pediatric study requirements for ages 0 to 2 years because the product would not provide a meaningful benefit over existing therapies and there were not likely to be a substantial number of patients in that age group. However studies among children 6 to 11 years of age were not waived. The Agency required a 2-week phase 3 trial for SAR and a 12 week phase 3 trial for PAR in children 6 to 11 years of age, to be completed with submission of the final reports by December 2013. Also required were a 2-week phase 3 trial for SAR and a 12 week phase 3 trial for PAR in children 2 to 5 years of age to be completed and submitted by May 2016.

The sponsor did communicate with FDA regarding PREA requirements prior to the January 2012 approval of this product for patients 12 years of age or greater. In a teleconference on September 28, 2011, FDA informed the sponsor that dose ranging would be required in the 6 to 11 year old population, with the lowest effective dose in the 6 to 11 year old population applied to the 2 to 5 year old population. In reply, the sponsor proposed testing in the phase 3 studies a 37 mcg dose in addition to the adult 74 mcg dose. Because systemic exposure was higher than the currently marketed ciclesonide formulation (Omnaris®), FDA recommended that Sunovion test doses lower than 37 mcg. (b) (4)

In partial fulfillment of the PREA requirements communicated in the approval letter, the current submission evaluates safety and efficacy of Zetonna (ciclesonide 37 mcg and 74 mcg daily doses) for the treatment of symptoms associated with SAR and PAR among children 6 to 11 years of age, with one double blind, placebo controlled, 2 week study for children with SAR and one double blind, placebo controlled, 12 week study for children with PAR (Table 1).

2.1.3 Current Submission

The current submission provides results from two randomized, double blind, placebo controlled, parallel arm studies evaluating the efficacy of ciclesonide on SAR and PAR (Table 1). Each study enrolled approximately 850 patients and randomized equal numbers of patients to C74, C37, or P. Further discussion of the design and endpoints associated with each study will be discussed in Section 3.2.1 below.

Study 305 began enrolling patients December 1, 2011, and the last patient completed the final visit on March 13, 2013. Study 306 began enrolling patients September 27, 2010, and the last patient completed the final visit on January 2, 2013. Both studies were conducted at multiple sites in the United States.

Table 1. Phase 3 Studies in Current Submission.

Study	**Design**	**Population**	**Endpoints**
SEP060-305 (305)	C37 C74 P Parallel arm DB P to W2	SAR 6 to 11 years old N=849 1:1:1	Primary: Average ΔrTNSS to Day 15 Key Secondary: Average ΔiTNSS to Day 15 ΔPRQLQ at Day 15 Average ΔrTOSS to Day 15
SEP060-306 (306)	C37 C74 P Parallel arm DB P to W12	PAR 6 to 11 years old N=848 1:1:1	Primary: Average ΔrTNSS to W6 Key Secondary: Average ΔiTNSS to W6 ΔPRQLQ at W6

Source: reviewer
iTNSS and rTNSS instantaneous and reflective nasal symptom scores, rTOSS reflective total ocular symptom score, PRQLQ Pediatric Rhinoconjunctivitis Quality of Life Questionnaire

2.2 Data Sources

Data for all three studies was provided by the sponsor and is currently located at:

\\cdsesub1\evsprod\NDA202129\0054\m5\datasets.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data and analysis quality were adequate in this submission. I was able to derive the primary and secondary endpoints for the submitted study. The statistical analyses of my derived endpoints were in agreement with the applicant's analyses.

The Office of Scientific Investigation did not conduct site inspections for this submission.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Two parallel arm, double blind phase 3 studies (Table 1) randomized patients 6 to 11 years of age who had SAR or PAR to C37, C74, or P in a 1:1:1 ratio. SAR study 305 was placebo controlled for 2 weeks and PAR study 306 was placebo controlled for 12 weeks. Treatment was by daily inhalation of nasal aerosol, with one actuation, half the nominal dose, per nostril.

The primary endpoint in both studies was change from baseline reflective nasal symptom score (ΔrTNSS) averaged over all study visits, from initiation of treatment to week 2 (study 305) or week 6 (study 306). Key secondary variables included change from baseline instantaneous nasal symptom score (ΔiTNSS), averaged from initiation of treatment to week 2 (study 305) or week 6 (study 306), the change from baseline Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) calculated at week 2 (study 305) or week 6 (study 306) and, for study 305 only, average change from baseline of the reflective total ocular symptom score (ΔrTOSS) from treatment initiation to week 2.

3.2.2 Statistical Methodologies

Statistical analyses for ΔrTNSS, ΔrTOSS, and ΔiTNSS were conducted on all randomized subjects at an overall two sided 0.05 level of significance using a mixed model repeated measures (MMRM) analysis, with fixed effects treatment, time, age group (6-8 yr, 9-11 yr), baseline, and treatment by time interaction, with individual patients as the random effect, and with an AR(1) covariance structure to describe correlations between times within individuals. In study 305, the unit of time in the analyses was study day, and in study 306, the unit of time was study week.

In study 305, daily values of rTNSS, rTOSS, and iTNSS were calculated as averages of subject-reported morning and evening responses. Baseline values were averaged over the last six days of the single blind placebo run-in period prior to randomization.

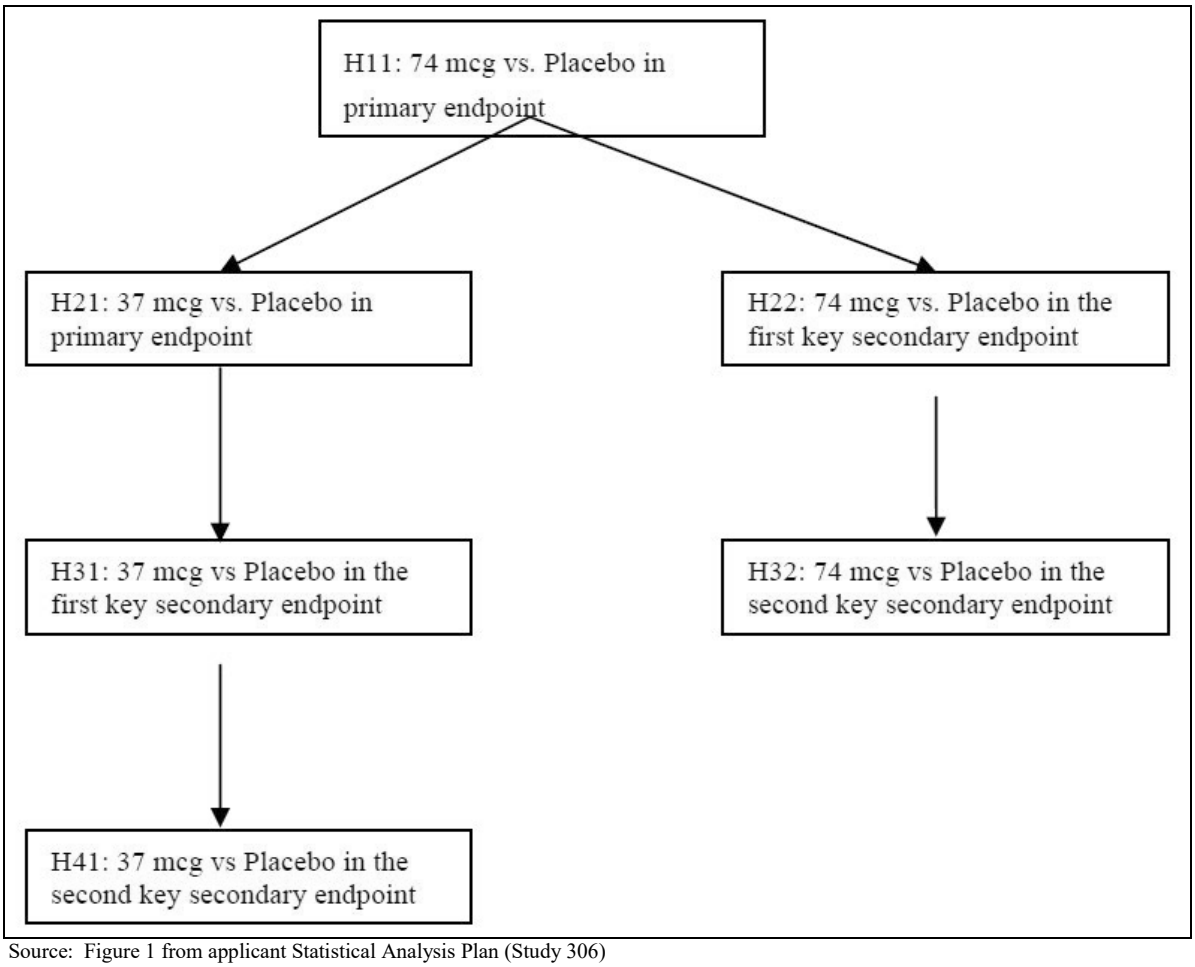
In study 306, values of rTNSS, rTOSS, and iTNSS were calculated for each week as the average of all subject-reported morning and evening responses. As in study 305, baseline values were averaged over the last six days of the single blind placebo run-in period prior to randomization.

Key secondary endpoint ΔPRQLQ was evaluated using analysis of covariance (ANCOVA) with independent factors baseline, age group, and treatment. Missing values of ΔPRQLQ were imputed using last observation carried forward (LOCF).

Primary analyses for both studies were conducted using the intent-to-treat population (ITT) consisting of all randomized patients who received at least one dose of the double blind study medication.

To control overall type 1 error each study used a tree-structured gatekeeping approach (Figure 1), with C74 compared to P at the 0.05 level of significance for the primary endpoint. If the difference was significant, C37 and C74 were compared to P in two parallel branches at the 0.025 level of significance. In the C37 versus P branch, the primary endpoint was tested followed by tests of the secondary endpoints in hierarchical sequence. In the C74 versus P branch, tests of the secondary endpoints were conducted in a hierarchical sequence. For both branches, the testing sequence for key secondary endpoints in each study matched the order presented in Table 1.

Figure 1. Applicant's tree-structured gatekeeping approach to control type 1 error



Source: Figure 1 from applicant Statistical Analysis Plan (Study 306)

Missing efficacy assessments were not imputed for missing days in the MMRM analyses. In both studies, if only a single measurement was available for a particular day (AM or PM), that measurement was used as the average daily score. For PRQLQ, the last post-baseline observation was carried forward for patients who terminated the study early.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

There were no obvious differences between treatments for baseline characteristics in the submitted phase 3 studies (Table 2).

Table 2. Baseline Demographics, N (%)

Study	Variable	Class	P	C37	C74
305	ITT		283 (100)	282 (100)	282 (100)
	Age	6 – 8	132 (47)	132 (47)	131 (47)
		9 – 11	151 (53)	150 (53)	151 (54)
	Sex	F	151 (46)	123 (44)	120 (43)
	Country	USA	283 (100)	282 (100)	282 (100)
	Race	White / Caucasian	209 (74)	220 (78)	226 (80)
		Black or African American	63 (22)	46 (16)	46 (16)
		Asian	5 (2)	7 (3)	3 (1)
		American Indian or Alaska Native	1 (<1)	0 (0)	0 (0)
		Native Hawaiian or Other Pacific Islander	0 (0)	0 (0)	1 (<1)
		Other	0 (0)	1 (<1)	0 (0)
		Multiple	5 (2)	8 (3)	6 (2)
	Ethnicity	Hispanic or Latino	102 (36)	115 (41)	134 (48)
306	ITT		283 (100)	282 (100)	281 (100)
	Age	6 – 8	127 (45)	121 (43)	123 (44)
		9 – 11	156 (55)	161 (57)	158 (56)
	Sex	F	120 (42)	113 (40)	130 (46)
	Country	USA	283 (100)	282 (100)	281 (100)
	Race	White / Caucasian	224 (79)	216 (77)	216 (77)
		Black / African American	37 (13)	43 (15)	39 (14)
		Asian	5 (2)	2 (1)	7 (3)
		American Indian or Alaska Native	0 (0)	2 (1)	1 (<1)
		Native Hawaiian or Other Pacific Islander	0 (0)	0 (0)	1 (<1)
		Other	9 (3)	9 (3)	9 (3)
		Multiple	8 (3)	10 (4)	8 (3)
	Ethnicity	Hispanic or Latino	89 (31)	101 (36)	91 (32)

source: CSR Study 305 Table 10, CSR Study 306 Table 11

Patterns of patient disposition did not contradict efficacy of Zetonna Nasal Aerosol (Table 3). In study 306, patient discontinuation rates were numerically higher among patients randomized to placebo than among patients randomized to ciclesonide.

Table 3. Patient Disposition, n (%)

Study	Disposition Status	Pbo	C37	C74
305	Randomized	284 (100)	282 (100)	283 (100)
	ITT	283 (100)	282 (100)	282 (100)
	Per Protocol	274 (97)	268 (95)	272 (97)
	Discontinue Treatment	14 (5)	13 (5)	9 (3)
	Adverse Event	3 (1)	4 (1)	1 (<1)
	Lack of Efficacy	0 (0)	0 (0)	0 (0)
	Lost to Follow-up	3 (1)	2 (1)	5 (2)
	Withdrawal by Subject	3 (1)	2 (1)	1 (<1)
	Other	5 (2)	5 (2)	2 (1)
306	Randomized	283 (100)	282 (100)	283 (100)
	ITT	283 (100)	282 (100)	281 (99)
	Per Protocol	265 (94)	267 (95)	267 (95)
	Discontinue Treatment	36 (13)	25 (9)	27 (10)
	Adverse Event	4 (1)	3 (1)	6 (2)
	Lack of Efficacy	2 (1)	0 (0)	0 (0)
	Lost to Follow-up	4 (1)	4 (1)	7 (3)
	Withdrawal by Subject	15 (5)	8 (3)	6 (2)
	Other	11 (4)	10 (4)	8 (3)

source: CSR Studies 305 and 306, Table 8

3.2.4 Results and Conclusions

3.2.4.1 Primary Endpoint: ΔrTNSS

Compared to placebo, treatment with ciclesonide improved rTNSS among patients with PAR (study 306) but not among patients with SAR (study 305). In study 306, there was no evidence that the 74 mcg dosage provided more improvement than the 37 mcg dosage. Note that, for the treatment difference, a reduction or negative value indicates improvement.

Table 4. Reflective TNSS Change From Baseline.

Study	Wk	ΔrTNSS (N)			Treatment Difference (P-Value)		
		P	C37	C74	C37-P	C74-P	C74-C37
305 (SAR)	2	-1.63	-1.73	-1.61	-0.10	0.02	0.12
		(283)	(282)	(282)	(0.607)	(0.914)	(0.533)
306 (PAR)	6	-1.51	-2.10	-1.98	-0.59	-0.47	0.12
		(283)	(282)	(281)	(0.001)	(0.011)	(0.523)

Source: reviewer program main mmrm.sas

3.2.4.2 Key Secondary Endpoints

Compared to placebo, ciclesonide did not improve any key secondary variables for SAR patients (Table 5). However, among PAR patients (Study 306), ciclesonide was significantly different from placebo for ΔiTNSS but not for ΔPRQLQ. Similar to the primary endpoint, ΔrTNSS, there was no evidence that improvements associated with the 74 mcg dosage were greater than those provided by the 37 mcg dosage. Again, for treatment differences, a reduction indicates improvement.

Table 5. Change from baseline for Key Secondary Variables

Study	Wk	Var	Treatment (N)			Treatment Difference (P-Value)		
			P	C37	C74	C37-P	C74-P	C74-C37
305 (SAR)	2	ΔiTNSS	-1.32 (283)	-1.48 (282)	-1.35 (282)	-0.16 (0.379)	-0.03 (0.867)	0.13 (0.475)
		ΔrTOSS	-0.84 (283)	-0.69 (282)	-0.79 (282)	0.15 (0.247)	0.06 (0.663)	-0.09 (0.471)
		ΔPRQLQ	-0.41 (278)	-0.43 (279)	-0.51 (279)	-0.02 (0.832)	-0.10 (0.199)	-0.08 (0.284)
306 (PAR)	6	ΔiTNSS	-1.29 (283)	-1.77 (282)	-1.72 (281)	-0.47 (0.006)	-0.43 (0.014)	0.050 (0.782)
		ΔPRQLQ	-0.39 (269)	-0.51 (268)	-0.30 (270)	-0.12 (0.103)	0.09 (0.228)	0.22 (0.005)

Source: reviewer programs main mmrm.sas, main ANCOVA.sas

3.3 Evaluation of Safety

Safety evaluations for this submission will be conducted by the Medical Reviewer, Stacy Chin M.D. and will be provided in her review. An additional review, to evaluate hypothalamic-pituitary axis suppression, will be conducted by the clinical pharmacology reviewer, Timothy Robison.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

To examine the impact of each subgroup on treatment efficacy, subgroup and subgroup by treatment interaction fixed effects were added to the statistical model for the primary endpoint ΔrTNSS. Age was categorized as between 6 and 8 years or between 9 and 11 years. Further investigations were conducted when the nominal significance of the subgroup by treatment interaction was less than 0.05.

4.1 Gender, Race, Age, and Geographic Region

No significant subgroup effects on efficacy were seen in either study for race or age group Analyses of geographic region were not conducted because all study sites were in the United States.

In study 305, a nominally significant treatment by sex interaction was noted (p=0.048), but this interaction was not significant in study 306 (p=0.445). Compared to placebo, in study 305 treatment with either dose of ciclesonide was associated with a numerically detrimental effect in females and a numerically beneficial effect in males (Table 6).

However, the differences in treatment effect between the two sexes were not statistically significant between individual treatments. For example, in Table 6, for the treatment difference for C74-P, the 95% confidence interval for females (-0.11, 1.00) overlaps that for males (-0.81, 0.17).

Cumulative responder analyses in study 305 do not suggest that changes from baseline rTNSS were inordinately driven by outliers in either sex. In particular, among males, the responder curves for C37 and C74 are consistently below that for placebo (Figure 2) and, among females, the responder curves for C37 and C74 are consistently above that for placebo (Figure 1).

Table 6. Reflective TNSS Change From Baseline, by Sex. Study 305

Sex	ΔrTNSS (N)			Treatment Difference (95% CI)	
	P	C37	C74	C37-P	C74-P
F	-1.89 (131)	-1.53 (123)	-1.45 (120)	0.36 (-0.19, 0.91)	0.45 (-0.11, 1.00)
M	-1.41 (152)	-1.88 (159)	-1.73 (162)	-0.47 (-0.96, 0.02)	-0.32 (-0.81, 0.17)

Source: reviewer program main mmrm subgr.sas

Figure 2. Continuous Responder Curves, Change from Baseline rTNSS. Females, Study 305

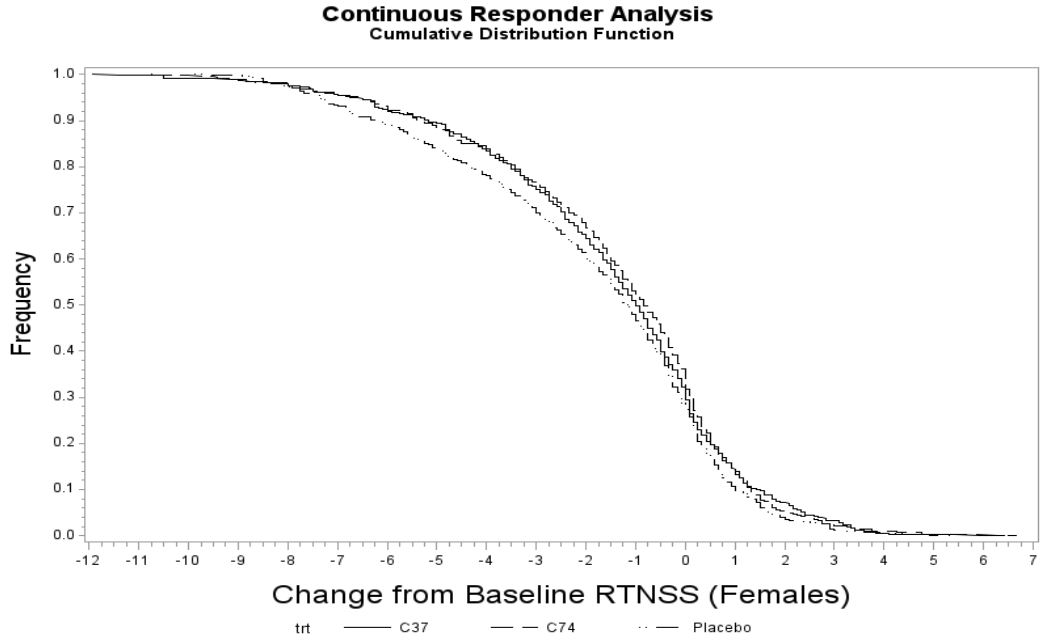


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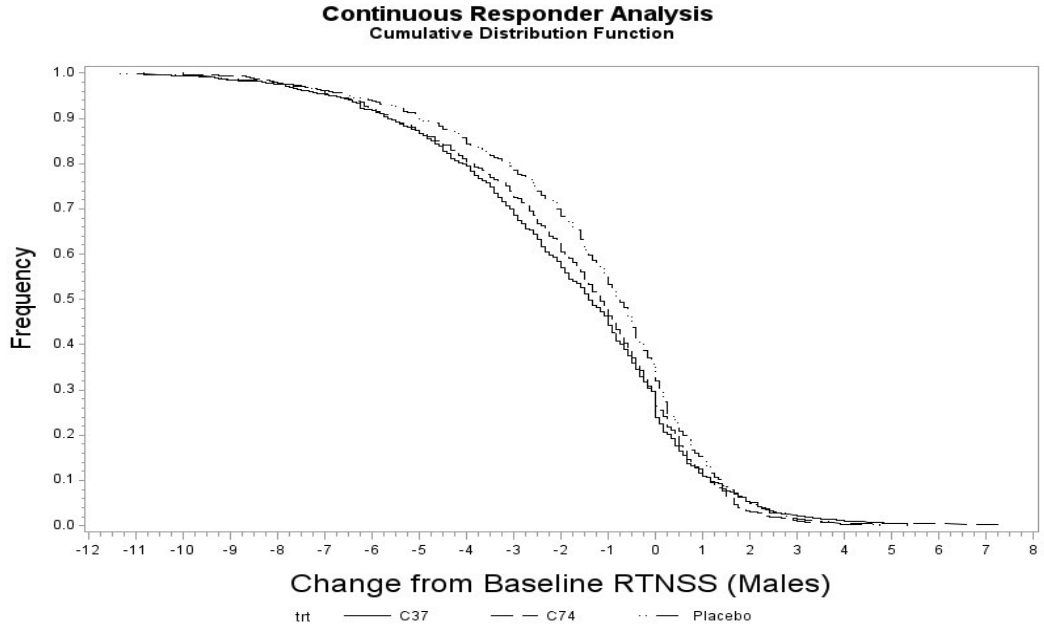
Figure 3. Continuous Responder Curves, Change from Baseline rTNSS. Males, Study 305



Source: reviewer program main mmrm subgr.sas

In study 306 the treatment by sex interaction was not statistically significant (p-value=0.445). Differences between the sexes in treatment effect were much smaller than in study 305, with a numerically larger improvement among males than among females (Table 7).

Table 7. Reflective TNSS Change From Baseline, by Sex. Study 306

Sex	ΔrTNSS (N)			Treatment Difference (95% CI)	
	P	C37	C74	C37-P	C74-P
F	-1.62	-2.14	-1.84	-0.51	-0.22
	(120)	(113)	(130)	(-1.07, 0.04)	(-0.76, 0.32)
M	-1.42	-2.07	-2.10	-0.64	-0.67
	(163)	(169)	(151)	(-1.11, -0.18)	(-1.15, -0.19)

Source: reviewer program main mmrm subgr.sas

4.2 Other Special/Subgroup Populations

No other special subgroups were examined in this review.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical issues

There are no outstanding statistical issues in the current submission.

5.2 Collective evidence

In study 306 for PAR, both doses tested were superior to placebo for the primary endpoint change from baseline ΔrTNSS to week 6. The effect of the lower tested dose, ciclesonide 37 mcg per day, was not significantly different from that of the adult dose, ciclesonide 74 mcg per day.

In study 305 for SAR, however, neither dose tested was superior to placebo for the primary endpoint change from baseline ΔrTNSS to day 15.

5.3 Conclusions and Recommendations

This submission fails to demonstrate statistically significant benefits of Zetonna Nasal Spray for the treatment of symptoms associated with SAR in patients 6 to 11 years of age. In phase 3 study 305 for SAR, neither dose tested was superior to placebo for the primary endpoint change from baseline ΔrTNSS to day 15.

In phase 3 study 306 for PAR both doses tested were superior to placebo for the primary endpoint change from baseline ΔrTNSS to week 6. No significant difference was seen between the two doses of ciclesonide tested.

5.4 Labeling Recommendations

The clinical reviewer may wish to consider whether to (i) consolidate into Section 8.4 descriptions of pediatric studies (b) (4) as recommended by current guidance, and (ii) update the Patient Information, revising the second paragraph of "What is ZETONNA Nasal Aerosol" from "It is not known if ZETONNA Nasal Aerosol is safe and effective in children 11 years of age and younger" to ZETONNA Nasal Aerosol is not approved for use in children 11 years of age and younger."

[1] Paragraph 5, Section III, of "Guidance for Industry and Review Staff. Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling.

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/s/

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09/17/2014

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