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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	22-159
Drug Name:	OraVerse (phentolamine mesylate) injection
Indication(s):	Reversal of soft tissue anesthesia
Applicant:	Septodont Holding SAS
Date(s):	Letter date: May l9, 2015 PDUFA date: March 19, 2016
Review Priority:	Standard
Biometrics Division:	II
Statistical Reviewer:	Yan Zhou, Ph.D.
Concurring Reviewer:	David Petullo, M.S.
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Keywords:	NDA review, clinical studies

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1. EXECUTIVE SUMMARY

OraVerse (phentolamine mesylate) injection was approved in 2009 for the reversal of soft tissue anesthesia and the associated functional deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor in dental patients older than 6 years of age and weighting more than 15 kg. As part of that approval, Septodont Holding SAS was required to conduct a pediatric study. This submission contains the results from that required post-marketing pediatric study.

The efficacy variables evaluated in this study were time to normal function as measured by the pediatric Functional Assessment Battery (pFAB), time to normal lip sensation as measured by standardized lip/tongue palpation procedure and time to normal tongue sensation (for mandibular procedures) as measured by standardized lip/tongue palpation procedure. Results indicated that OraVerse was numerically better than placebo for all three efficacy endpoints with statistical significance noted for time to recovery of normal lip sensation. However, there were no pre-specified primary or secondary efficacy endpoints and no adjustment for multiplicity was planned or performed in the efficacy analyses of these three efficacy variables.

Based on my review, the study was not prospectively designed to demonstrate superiority of OraVerse over sham injection, and as such does not provide substantial evidence of efficacy for the proposed pediatric population. The results from this study should be described in section 8.4 (Pediatric subpopulation) of the product and it should be clearly stated that the efficacy of this product in children below the 6 years of age has not been established.

2. INTRODUCTION

2.1 Overview

OraVerse was approved for the reversal of soft tissue anesthesia in dental patients 6 years of age and older and weighing 15 kg or more. Even though OraVerse was previously studied in children 4 to 5 years old, the Applicant did not collect or provide efficacy data. In the approval letter dated May 9, 2008, a deferred pediatric study was outlined as follows:

> Assessment of efficacy and safety of OraVerse in patients from 2-6 years of age. This study should be a randomized, sham-injection controlled, double-blinded study comparing the times to return of normal sensation and normal function following the injection OraVerse or a sham injection administrated to patients undergoing dental procedures requiring the administration of a local anesthetic agent combined with a vasoconstrictor. Specifically, the following clinical endpoints should be assessed using validated metrics:
>
> a. Time to return of normal sensation of the lip and, where applicable, the tongue
> b. Time to return of normal function for speech, smiling, drinking, eating and not drooling
>
> Safety assessments should include heart rate, blood pressure, oral cavity examinations, assessments for nerve injury, and adverse events.

The study should include a minimum of 100 subjects uniformly distributed by age and evenly distributed by treatment within 1-year age groups.

This submission contains the results from a phase 4 clinical study that was submitted to fulfill the pediatric requirement. Study PHE-11-001 was a multicenter, randomized, double-blind, controlled study to evaluate the safety and efficacy of OraVerse in 150 children aged 2 to 5 years of old. The applicant is proposing the following labeling changes:

- Changes to reflect the results of the post-marketing pediatric study
- (b) (4)
-

2.2 Data Sources

The original submission did not contain any efficacy datasets or related information. However, this information was requested and subsequently submitted by the Applicant. The clinical study report is located at the following location in the CDER electronic document room (EDR):

\\cdsesub\evsprod\NDA022159\0067.

The datasets, define files, and programs are located in EDR at:

\\cdsesub\evsprod\NDA022159\0068.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The electronic datasets and define files submitted by the applicant were of acceptable quality, and were sufficient for validating study results.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study PHE-11-001 was a phase 4, multicenter, randomized, double-blinded, sham injection controlled study in pediatric dental patients 2 to 5 years of age undergoing mandibular and maxillary procedures. The study was conducted in seven sites in United States from February, 2012 until August, 2014. After obtaining informed consent from the parent or legal guardian, eligible pediatric dental patients underwent baseline assessments and received local anesthesia for their dental procedures with lidocaine 2% with 1:100,000 epinephrine. The dental procedure(s) comprising of restoration/fillings were performed in a single quadrant of the mouth. Following the dental procedure, patients who had at least one abnormal pFAB test and/or

numbness of the relevant mouth quadrant were randomized to OraVerse or sham injection in a 2:1 ratio. The randomization was stratified by the location of the dental procedure (maxilla or mandible) and the amount of local anesthetic (1/4, 1/2 or 1 cartridge). Study drug was administered at the same site as the local anesthetic using the same injection technique. There were six periods in the study; 1) screening, 2) anesthetic administration and dental procedure, 3) study drug administration, 4) observation period, 5) telephone follow-up, and 6) in-clinic safety follow-up.

All patients were assessed for safety. Patients 4 and 5 years of age who were trainable in Wong-Baker FACES Pain Rating Scale (W-B PRS) were also assessed for pain. Patients 4 and 5 years of age who were trainable in pFAB and lip and tongue palpation procedures were assessed for efficacy. The observation period for all safety and efficacy assessment was two hours.

The primary objective of the study was to evaluate the safety and tolerability of OraVerse in patients 2 to 5 years of age as measured by the incidence and severity of adverse events, clinically significant changes in vital signs and oral cavity assessments, nerve injury, and analgesics required for intraoral pain. As the secondary objective included evaluating efficacy in trainable patients 4 and 5 years of age, the efficacy variables were time to normal function as measured by the pFAB, time to normal lip sensation as measured by standardized lip/tongue palpation procedure and time to normal tongue sensation (for mandibular procedures) as measured by standardized lip/tongue palpation procedure.

According to the Applicant, the study was powered for detecting adverse events instead of demonstrating the efficacy.

3.2.2 Statistical Methodologies

The statistical analyses of each of the efficacy endpoints were based on the corresponding modified intent-to-treat (mITT) analysis sets which were defined as follows:

- mITT pFAB analysis set included all randomized patients 4 to 5 years of age who were trainable in pFAB, had normal pFAB at baseline prior to administration of local anesthetic, and had at least one abnormal function (smiling, speaking, drinking or drooling) at completion of the dental procedures as rated by the observer

- mITT lip sensation analysis set included all randomized patients 4 to 5 years of age who were trainable in standardized lip palpation procedure, had normal lip sensation at baseline prior to administration of local anesthetic, and had numbness of the relevant lip quadrant at completion of the dental procedures

- mITT tongue sensation analysis set included all randomized patients 4 to 5 years of age who were trainable in standardized tongue palpation procedure, had normal tongue sensation at baseline prior to administration of local anesthetic, and had numbness of the tongue at completion of the dental procedures

Descriptive statistics employing Kaplan-Meier methods were utilized to characterize each of the

efficacy variables. Additionally, inferential statistical methodologies using the stratified log-rank test were employed. The location of the dental procedure (mandibular and maxillary) was used as a stratification factor to compute the stratified log-rank test statistics. Hypothesis testing of efficacy endpoints was conducted using 2-sided significance level of 0.05. There was no adjustment for multiplicity in the analyses of three efficacy variables. As the study was prospectively designed to detect adverse events, the analyses of three efficacy endpoints were only exploratory in nature and not adequately powered to detect statistically significant differences in treatment group comparisons.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The disposition of patients is shown in Table 1. A total of 150 patients were randomized and received study drug. Of the 99 patients randomized to the OraVerse treatment group, 3 patients (3%) did not complete the 2-hour observation period, 6 patients (6%) did not complete the telephone follow-up, and 2 patients (2%) did not complete the in-clinic follow-up appointment. In contrast, of the 51 patients randomized to the sham injection treatment group, all patients completed both the observation period and in clinic safety follow-up, but 1 patient (2%) did not complete the telephone follow-up appointment.

No patients withdrew or were withdrawn from the study prematurely due to safety reasons or concerns. There were no dropouts in the sham treatment group. However, there were five dropouts from the OraVerse treatment group who were documented as withdrawing or being withdrawn prematurely.

The demographic and other background characteristics for all patients are presented in the appendix. Approximately 46% of all patients were girls. The median age was 4 years. The demographic and other background characteristics were comparable between two treatment groups.

The disposition of patients by age is shown in Table 2. The majority of patients (79%) were between 4 and 5 years of old, while there were only 5 patients (3%) aged 2 years of old.

Baseline characteristics of all randomized patients related to the dental procedures and local anesthetic administration are also summarized in Appendix. Topical anesthetics were used on nearly all patients (98%). Both groups were well balanced for injection type, use of supplemental injections, dental procedure and mouth quadrant. A higher proportion of patients in the sham injection group were in the lowest ($\geq$10 kg and <15 kg) weight bracket. More specifically, 12% of patients in the sham group were in the lowest weight category in comparison to only 5% of the patients in the OraVerse group. Approximately 92% of patients in the OraVerse group were in the weight category of greater than 15kg but less than 30 kg, while 82% of patients in the sham injection group were in the same category.

Table 1: Patient disposition in Study PHE-11-001 – Number (%) of Patients

Status		OraVerse® Mandible (N=48)	OraVerse® Maxilla (N=51)	OraVerse® Total (N=99)	Sham Mandible (N=23)	Sham Maxilla (N=28)	Sham Total (N=51)
Randomized Subjects		48 (100.0)	51 (100.0)	99 (100.0)	23 (100.0)	28 (100.0)	51 (100.0)
Subjects who received treatment		48 (100.0)	51 (100.0)	99 (100.0)	23 (100.0)	28 (100.0)	51 (100.0)
Completed assessments							
Treatment:	Yes	48 (100.0)	51 (100.0)	99 (100.0)	23 (100.0)	28 (100.0)	51 (100.0)
	No	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Observation:	Yes	47 (97.9)	49 (96.1)	96 (97.0)	23 (100.0)	28 (100.0)	51 (100.0)
	No	1 (2.1)	2 (3.9)	3 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)
Telephone follow-up:	Yes	45 (93.8)	48 (94.1)	93 (93.9)	23 (100.0)	27 (96.4)	50 (98.0)
	No	3 (6.3)	3 (5.9)	6 (6.1)	0 (0.0)	1 (3.6)	1 (2.0)
In-clinic follow-up visit:	Yes	47 (97.9)	50 (98.0)	97 (98.0)	23 (100.0)	28 (100.0)	51 (100.0)
	No	1 (2.1)	1 (2.0)	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Primary Reason for Early Withdrawal:							
Screen failure Subject		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Significant protocol violation on the part of the Investigator		1 (2.1)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Significant noncompliance on the part of the Subject		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal of consent (refusal of the Subject to continue treatment or observations)		1 (2.1)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse event, Unacceptable toxicity		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Decision by the Investigator to terminate the Subject		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unrelated medical illness or complication		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up		0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other		0 (0.0)	2 (3.9)	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Clinical Study Report Section 14.1.3

Table 2: Patient disposition in Age

Age	OraVerse (N=99) n (%)	Sham (N=51) n (%)	Total (N=150) n (%)
2	2 (2)	3 (6)	5 (3)
3	18 (18)	8 (16)	26 (17)
4	39 (39)	20 (39)	59 (39)
5	40 (40)	20 (39)	60 (40)

Source: Clinical Study Report Table 9-5

There were two baselines established per protocol: (1) assessments done immediately before the administration of local anesthetic; (2) assessments done immediately before the administration of study drug. All mITT patients reported normal lip and/or tongue sensation ratings prior to local anesthetic administration, and numb lip and/or tongue sensation after the dental procedure. Prior to local anesthetic administration, all mITT patients for pFAB reported normal for smiling,

speaking, drinking and absent for drooling. Following the dental procedure, a proportion of patients in both treatment groups reported a variety of combinations of functional deficits in smiling, speaking, drinking and drooling.

3.2.4 Results and Conclusions

3.2.4.1 Time to return of normal function in pFAB

Time to return of normal function was calculated by the number of minutes elapsed from the administration of study drug to the first of two consecutive assessments of the observer rating of smiling, speaking, drinking and drooling as normal or not present. The return to normal function was also considered to occur in the event that all functional tests were rated as normal or not present for the patient's last functional assessment battery and one or more of these tests from the preceding assessment were rated as other than normal. Patients who did not meet these criteria before the end of the 2-hour observation period were censored at the time when the patient completed the last pFAB. None of the individual observer's assessments were missing.

There were 58 patients from the OraVerse treatment group (59%) and 29 patients from the sham injection group (57%) included in the mITT pFAB analysis set. Table 3 shows my results. In the OraVerse group, the median time to normal function was 31 minutes (95% confidence interval: 30 to 44 minutes). In the sham group, the median time to normal function was 45 minutes (95% confidence interval: 31 to 63 minutes). At the end of the observation period, 5 patients (9%) in the OraVerse group and 6 patients (21%) in the sham injection group had not yet recovered normal function and were censored in my analysis.

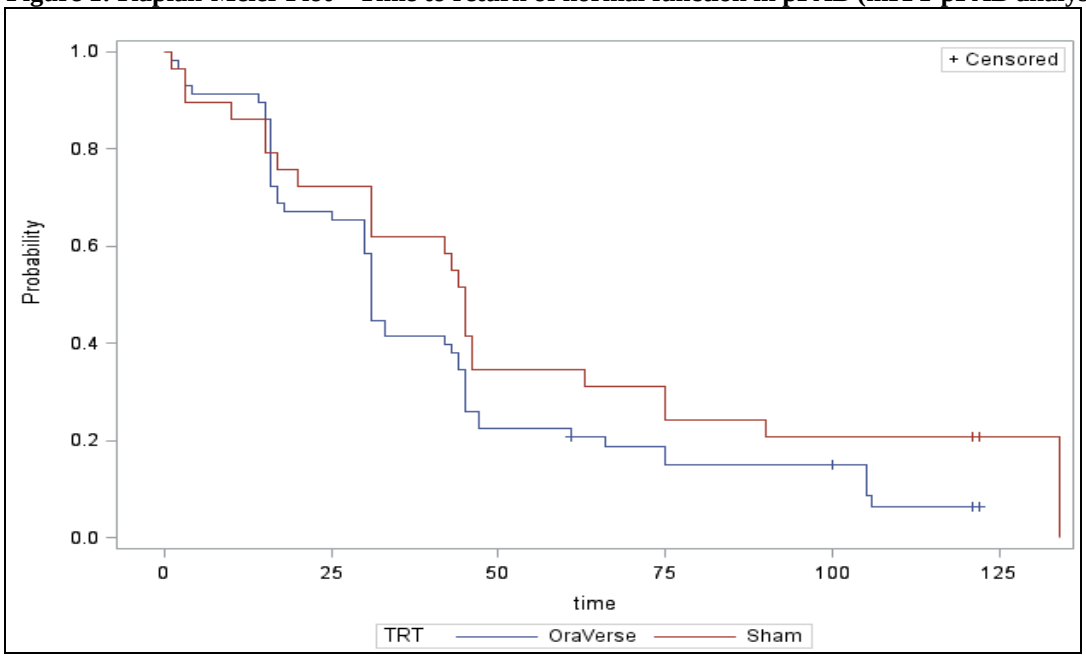
Table 3: Time to return of normal function in pFAB (mITT pFAB analysis set)

	OraVerse (N=58)	**Sham (N=29)**
Time to return of normal function in pFAB: n (%)		
1 to 15 minutes post-administration of study drug	8 (14)	6 (21)
16 to 30 minutes post-administration of study drug	16 (28)	2 (7)
31 to 45 minutes post-administration of study drug	19 (33)	9 (31)
46 to 60 minutes post-administration of study drug	2 (3)	2 (7)
61 to 75 minutes post-administration of study drug	4 (7)	3 (10)
76 to 90 minutes post-administration of study drug	0 (0)	1 (3)
91 to 105 minutes post-administration of study drug	3 (5)	0 (0)
106 to 120 minutes post-administration of study drug	1 (2)	0 (0)
over 121 minutes post-administration of study drug	0 (0)	1 (3)
Not recover normal function at the end of the 2-hour observation period: n (%)	5 (9)	6 (21)
Median time to normal function (minutes)	31	45
95% confidence intervals for median time	(30, 44)	(31, 63)
p-value for log-rank test	0.1365	

Source: Reviewer's analysis

The Kaplan-Meier plot of the time to return of normal function in pFAB is displayed in Figure 1. The stratified log-rank test of the time to return of normal function in pFAB was not significant (p-value =0.1365).

Figure 1: Kaplan-Meier Plot – Time to return of normal function in pFAB (mITT pFAB analysis set)



Source: Reviewer's analyses

3.2.4.2 Time to recovery of normal lip sensation

Time to recovery of normal lip sensation was calculated by the number of minutes elapsed from the administration of study drug to the first of two consecutive reports of normal sensation of the upper or lower lip. The recovery of normal lip sensation was also considered to occur in the event that the lip sensation test was rated normal at the patient's final evaluation and the rating from the preceding assessment was rated other than normal. Patients who did not meet these criteria before the end of the 2-hour observation period were censored at the time when the patient completed the last upper or lower lip sensation rating.

There were 71 patients from the OraVerse treatment group (72%) and 37 patients from the sham injection group (73%) included in the mITT lip sensation analysis set. I replicated the applicant's results for the analyses of time to recovery of normal lip sensation. Table 4 shows my results. In the OraVerse group, the median time to recovery of normal lip sensation was 61 minutes (95% confidence interval: 45 to 62 minutes). In the sham group, the median time to recovery of normal lip sensation was 109 minutes (95% confidence interval: 91 to 123 minutes). At the end of the observation period, 14 patients (20%) in the OraVerse group and 18 patients (49%) in the sham injection group had not yet recovered normal lip sensation and were censored in my analysis.

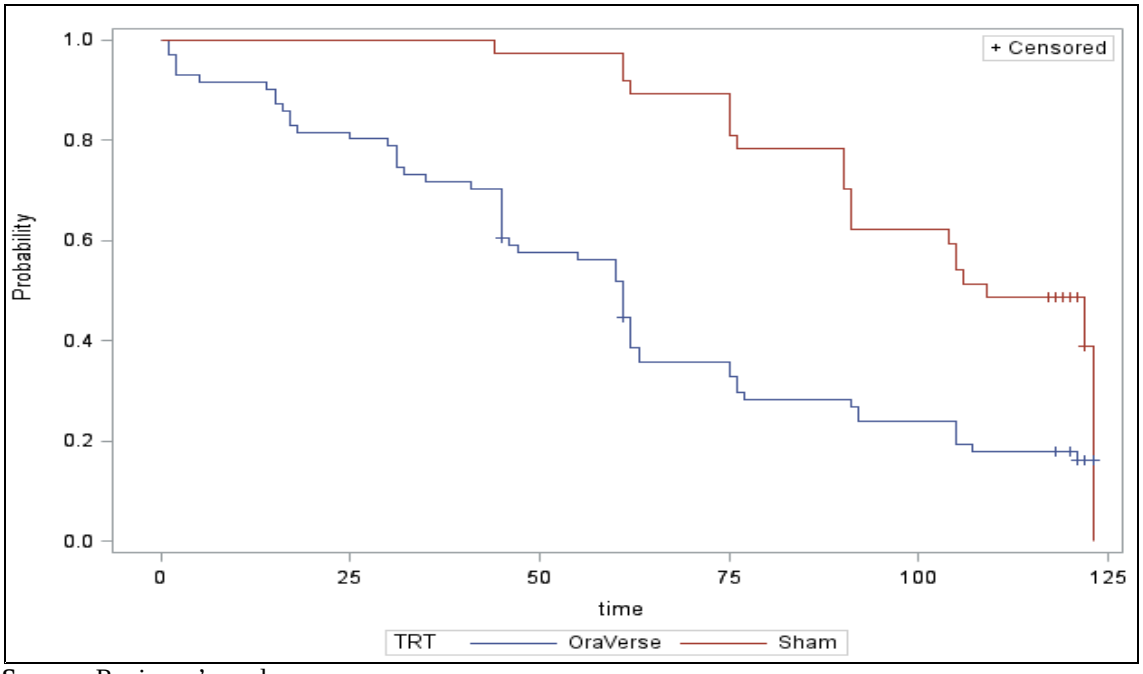
Table 4: Time to recovery of normal lip sensation (mITT lip sensation analysis set)

	OraVerse (N=71)	Sham (N=37)
Time to recovery of normal lip sensation: n (%)		
1 to 15 minutes post-administration of study drug	9 (13)	0 (0)
16 to 30 minutes post-administration of study drug	6 (9)	0 (0)
31 to 45 minutes post-administration of study drug	13 (18)	1 (3)
46 to 60 minutes post-administration of study drug	6 (9)	0 (0)
61 to 75 minutes post-administration of study drug	13 (18)	6 (16)
76 to 90 minutes post-administration of study drug	3 (4)	4 (11)
91 to 105 minutes post-administration of study drug	6 (9)	6 (16)
106 to 120 minutes post-administration of study drug	1 (1)	2 (5)
over 121 minutes post-administration of study drug	1 (1)	2 (5)
Not recover normal lip sensation at the end of the 2-hour observation period: n (%)	14 (20)	18 (49)
Median time to normal sensation (minutes)	61	109
95% confidence intervals for median time	(45, 62)	(91, 123)
p-value for log-rank test	< 0.0001	

Source: Reviewer's analysis

The Kaplan-Meier plot is displayed in Figure 2. The two curves of the time to recovery of normal lip sensation separated well. The stratified log-rank test of the time to recovery of normal lip sensation yielded significant p-value (<0.0001). However, since there were no pre-specified primary or secondary efficacy endpoints, and there was no multiplicity adjustment, the overall type-I error was not controlled, it is difficult to interpret the p-value. Nevertheless, the analyses results were numerically in favor of OraVerse in comparison to sham injection.

Figure 2: Kaplan-Meier Plot – Time to recovery of normal lip sensation (mITT lip sensation analysis set)



Source: Reviewer's analyses

3.2.4.3 Time to recovery of normal tongue sensation (Mandible)

Time to recovery of normal tongue sensation was calculated by the number of minutes elapsed from the administration of study drug to the first of two consecutive reports of normal sensation of the tongue. The recovery of normal tongue sensation was also considered to occur in the event that the tongue sensation test was rated normal at the patient's final evaluation and the rating from the preceding assessment was rated other than normal. Patients who did not meet these criteria before the end of the 2-hour observation period were censored at the time when the patient completed the last tongue sensation rating.

There were 36 patients from the OraVerse treatment group (36%) and 17 patients from the sham injection group (33%) included in the mITT tongue sensation analysis set. I replicated the applicant's results for the analyses of time to recovery of normal tongue sensation. Table 5 shows my results. In the OraVerse group, the median time to recovery of normal tongue sensation was 60 minutes (95% confidence interval: 45 to 76 minutes). In the sham group, the median time to recovery of normal tongue sensation was 91 minutes (the lower limit of the 95% confidence interval was 44 minutes). At the end of the observation period, 10 patients (28%) in the OraVerse group and 5 patients (29%) in the sham injection group had not yet recovered normal tongue sensation and were censored in my analysis.

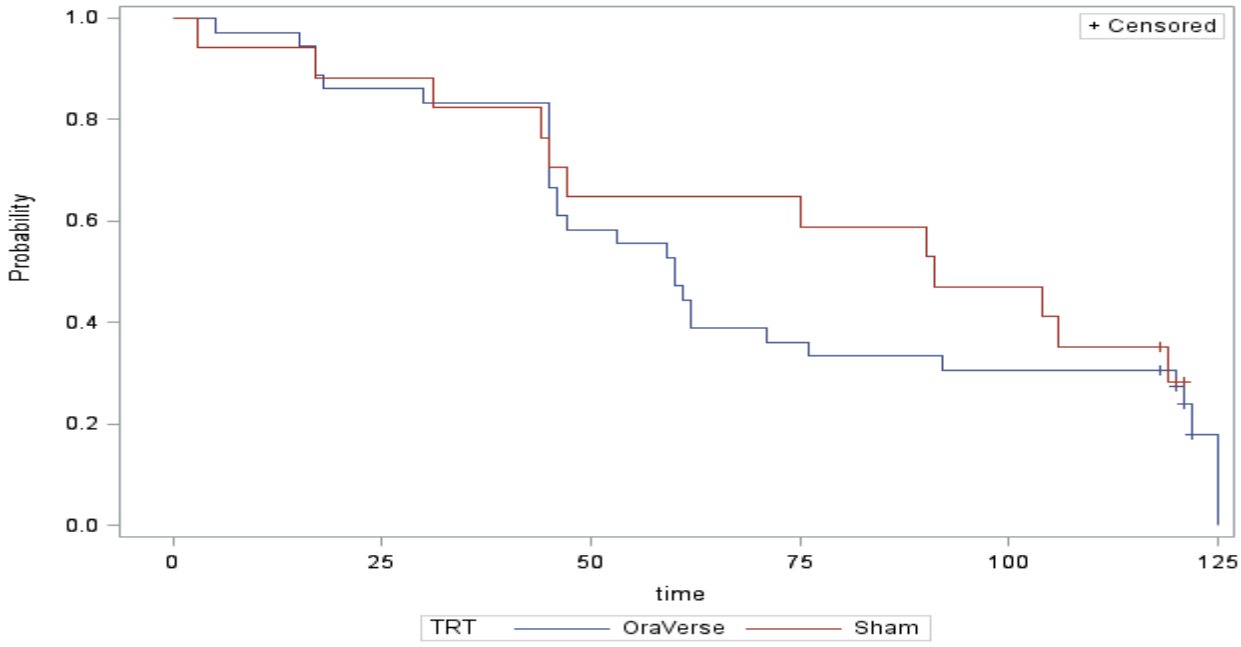
Table 5: Time to recovery of normal tongue sensation (mITT tongue sensation analysis set)

	OraVerse (N=36)	**Sham (N=17)**
Time to recovery of normal tongue sensation: n (%)		
1 to 15 minutes post-administration of study drug	2 (6)	1 (6)
16 to 30 minutes post-administration of study drug	4 (11)	1 (6)
31 to 45 minutes post-administration of study drug	6 (17)	3 (18)
46 to 60 minutes post-administration of study drug	7 (19)	1 (6)
61 to 75 minutes post-administration of study drug	4 (11)	1 (6)
76 to 90 minutes post-administration of study drug	1 (3)	1 (6)
91 to 105 minutes post-administration of study drug	1 (3)	2 (12)
106 to 120 minutes post-administration of study drug	1 (3)	2 (12)
over 121 minutes post-administration of study drug	3 (8)	0 (0)
Not recover normal tongue sensation at the end of the 2-hour observation period: n (%)	10 (28)	5 (29)
Median time to normal sensation (minutes)	60	91
95% confidence intervals for median time	(45, 76)	(44,)
p-value for log-rank test	0.5719	

Source: Reviewer's analysis

The Kaplan-Meier plot is displayed in Figure 3. The stratified log-rank test of the time to recovery of normal tongue sensation was not significant (p-value =0.5719).

Figure 3: Kaplan-Meier Plot – Time to recovery of normal tongue sensation (mITT tongue sensation analysis set)



Source: Reviewer's analyses

3.3 Evaluation of Safety

The evaluation of the safety data was conducted by Dr. Sarah Arnold. The reader is referred to Dr. Arnold's review for detailed information regarding the adverse event profile.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The applicant did not plan any formal subgroup analysis. Subgroup analysis was only conducted for the time to recovery of normal lip sensation based on the location of procedure (maxilla or mandible). The applicant claimed that subgroup analysis by dose/weight was not possible due to the fact that a majority of patients in the OraVerse treatment group (91%) received 1/2 cartridge per their reported weight, and a subgroup analysis of age was accounted as the efficacy analysis and was conducted in the mITT analysis set which, by definition, separated the 4 and 5 year olds in analyses.

Since the tests of the time to return of normal function in pFAB and the time to recovery of normal tongue sensation were not significant, it is not meaningful to conduct subgroup analysis for these two efficacy variables. Moreover, the study was not adequately powered to detect statistically significant differences in treatment group comparisons, and analyses of efficacy endpoints were only exploratory in nature. I only replicated the application's subgroup analysis by the location of procedure for the time to recovery of normal lip sensation.

4.1 Location of procedure

Table 6 presents subgroup analyses results. The results were numerically in favor of OraVerse across subgroups.

Table 6: Reviewer's subgroup analyses

	OraVerse (N=71)	**Sham (N=37)**
Time to recovery of normal lip sensation		
Mandible	**N=36**	**N=21**
Not recover normal lip sensation: n (%)	9 (25)	12 (57)
Median time to normal lip sensation (minutes) 95% confidence intervals for median time	68.5 (45, 92)	123 (91, 123)
Maxilla	**N=35**	**N=16**
Not recover normal lip sensation: n (%)	5 (14)	6 (38)
Median time to normal lip sensation (minutes) 95% confidence intervals for median time	45 (31, 61)	105.5 (75,)

Source: Reviewer's analyses

4.2 Other Special/Subgroup Populations

No other subgroup analyses were performed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Two statistical issues in the applicant's efficacy analyses were identified.

Firstly, the sample size of the study was based on enrolling an adequate number of patients to detect potential adverse events in the OraVerse treatment. The statistical analysis of each of the efficacy endpoints was based on the corresponding modified intention-to-treat analysis set which included the trainable children aged 4 to 5 years of old. The analyses of efficacy endpoints were only exploratory in nature and not adequately powered to detect statistically significant differences in treatment group comparisons.

Secondly, in the absence of an appropriate multiplicity adjustment approach, the overall Type I error was not controlled and it is difficult to interpret the p-values. This may not be a concern when all the tests reached statistical significance favoring the active drug. However, in the analyses of three efficacy variables, only the time to recovery of normal lip sensation had a significant p-value. Without pre-specified primary or secondary efficacy endpoints, it is not adequate to demonstrate the efficacy of OraVerse.

5.2 Collective Evidence

Study PHE-11-001 was conducted to fulfill the pediatric requirement specified in the approval letter of OraVerse. Efficacy was evaluated in a subset of patients 4 to 5 years of age who were trainable for three endpoints: time to normal function as measured by the pFAB, time to normal lip sensation as measured by standardized lip/tongue palpation procedure, and time to normal tongue sensation (for mandibular procedures) as measured by standardized lip/tongue palpation procedure. The results of the three efficacy variables were numerically in favor of OraVerse with statistical significance noted for time to recovery of normal lip sensation. However, there were no pre-specified primary or secondary efficacy endpoints, multiplicity was not considered, and the study was not powered to demonstrate efficacy with respect to these endpoints.

5.3 Conclusions and Recommendations

Based on the information submitted, the Study PHE-11-001 was not prospectively designed to demonstrate superiority of OraVerse over sham injection, and as such does not provide substantial evidence of the efficacy of OraVerse in patients 4 to 5 years of age.

5.4 Labeling Recommendations

According to the draft guidance "Guidance for Industry and Review Staff: Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling" dated February 2013, the information of this failed study should only be described in section 8.4 (Pediatric subpopulation) of the product and it should be clearly stated that the efficacy of this product in children below 6 years of age has not been established.

Appendix

Demographics

Source: Clinical Study Report Section 14.1.6

	OraVerse®			Sham		
Demographic Variable	Mandible N=48	Maxilla N=51	Total N=99	Mandible N=23	Maxilla N=28	Total N=51
Gender						
Female	20 (41.7)	26 (51.0)	46 (46.5)	10 (43.5)	13 (46.4)	23 (45.1)
Male	28 (58.3)	25 (49.0)	53 (53.5)	13 (56.5)	15 (53.6)	28 (54.9)
Ethnicity						
Hispanic or Latino	10 (20.8)	10 (19.6)	20 (20.2)	2 (8.7)	9 (32.1)	11 (21.6)
Not Hispanic or Latino	38 (79.2)	41 (80.4)	79 (79.8)	21 (91.3)	19 (67.9)	40 (78.4)
Race						
White	25 (52.1)	19 (37.3)	44 (44.4)	14 (60.9)	12 (42.9)	26 (51.0)
Black or African American	13 (27.1)	17 (33.3)	30 (30.3)	5 (21.7)	8 (28.6)	13 (25.5)
Asian	1 (2.1)	4 (7.8)	5 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	1 (2.1)	1 (2.0)	2 (2.0)	0 (0.0)	1 (3.6)	1 (2.0)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	1 (2.0)
Other	8 (16.7)	10 (19.6)	18 (18.2)	3 (13.0)	7 (25.0)	10 (19.6)
Age-yrs.						
N	48	51	99	23	28	51
Mean	4.2	4.2	4.2	4.3	3.9	4.1
SD	0.8	0.8	0.8	0.6	1.1	0.9
Median	4.0	4.0	4.0	4.0	4.0	4.0
Range	(2.0, 5.0)	(2.0, 5.0)	(2.0, 5.0)	(3.0, 5.0)	(2.0, 5.0)	(2.0, 5.0)
Grade						
Not applicable	35 (72.9)	35 (68.6)	70 (70.7)	17 (73.9)	19 (67.9)	36 (70.6)
Kindergarten	11 (22.9)	15 (29.4)	26 (26.3)	5 (21.7)	9 (32.1)	14 (27.5)
1	2 (4.2)	1 (2.0)	3 (3.0)	1 (4.3)	0 (0.0)	1 (2.0)
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Height (cm) [1]						
N	48	50	98	23	28	51
Mean	111.4	109.0	110.2	111.0	106.9	108.8
SD	8.4	9.9	9.2	9.5	10.7	10.3
Median	111.5	107.3	109.1	112.0	110.5	111.0
Range	(91.4, 126.0)	(86.0, 135.0)	(86.0, 135.0)	(93.9, 126.5)	(86.4, 122.0)	(86.4, 126.5)
Weight (kg)						
N	48	51	99	23	28	51
Mean	20.3	19.5	19.9	20.5	20.0	20.2
SD	4.2	3.5	3.9	4.8	5.5	5.1
Median	19.3	19.3	19.3	18.5	18.7	18.7
Range	(14.0, 32.0)	(13.7, 30.6)	(13.7, 32.0)	(15.5, 35.8)	(13.0, 35.1)	(13.0, 35.8)

Local Anesthetic Administration and Dental Procedure

Source: Clinical Study Report Section 14.1.14

Site	OraVerse® N=99	Sham N=51	TOTAL N=150
Was topical anesthetic administered			
Yes	96 (97.0)	51 (100.0)	147 (98.0)
No	3 (3.0)	0 (0.0)	3 (2.0)
Was nitrous oxide administered			
Yes	79 (79.8)	41 (80.4)	120 (80.0)
No	20 (20.2)	10 (19.6)	30 (20.0)
Local Anesthetic Quadrant			
Upper	51 (51.5)	28 (54.9)	79 (52.7)
Lower	48 (48.5)	23 (45.1)	71 (47.3)
Left	51 (51.5)	26 (51.0)	77 (51.3)
Right	48 (48.5)	25 (49.0)	73 (48.7)
Cartridge			
Subject >= 10kg and < 15kg (one quarter cartridge)	5 (5.1)	6 (11.8)	11 (7.3)
Subject >= 15kg and < 30kg (half cartridge)	91 (91.9)	42 (82.4)	133 (88.7)
Subject >= 30kg (half cartridge)	0 (0.0)	0 (0.0)	0 (0.0)
Subject >= 30kg (full cartridge)	3 (3.0)	3 (5.9)	6 (4.0)
Injection Type			
Inferior alveolar nerve block	46 (46.5)	22 (43.1)	68 (45.3)
Supraperiosteal injection	53 (53.5)	25 (49.0)	78 (52.0)
Other	8 (8.1)	6 (11.8)	14 (9.3)
Supplemental injections			
Yes	12 (12.1)	8 (15.7)	20 (13.3)
No	87 (87.9)	43 (84.3)	130 (86.7)
Dental Procedure			
Cavity preparation, restoration, and/or filling	96 (97.0)	50 (98.0)	146 (97.3)
Other	3 (3.0)	1 (2.0)	4 (2.7)
Mouth Quadrant			
Upper	51 (51.5)	28 (54.9)	79 (52.7)
Lower	48 (48.5)	23 (45.1)	71 (47.3)
Left	51 (51.5)	26 (51.0)	77 (51.3)
Right	48 (48.5)	25 (49.0)	73 (48.7)

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/s/

YAN ZHOU
01/15/2016

DAVID M PETULLO
01/15/2016
I concur.