CLINICAL REVIEW

Application Type	NDA Supplement
Application Number	22-159 S011
Priority or Standard	Standard
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Division/Office	Division of Anesthesia, Analgesia and Addiction Products
Reviewer Name	Sarah Arnold, M.D., M.P.H.
Review Completion Date	03/17/16
Established Name	Phentolamine Mesylate
(Proposed) Trade Name	OraVerse
Applicant	Septodont Holding SAS
Formulation	injection solution (0.4 mg; 0.235 mg/mL)
Dosing Regimen	intraoral submucosal injection
Proposed Indication	reversal of local anesthesia containing a vasoconstrictor for dental procedures
Intended Population	healthy dental patients 2-5 years of age
Recommendation on Regulatory Action	Approval
Recommended Indication (if applicable)	Unchanged

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Glossary

AC	advisory committee
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PM	phentolamine mesylate
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SEALD	Study Endpoints and Labeling Development
SGE	special government employee
SOC	standard of care
STA	soft tissue anesthesia
STAR	soft tissue anesthesia reversal
TEAE	treatment emergent adverse event

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1 Executive Summary

1.1. Product Introduction

OraVerse (phentolamine mesylate, (PM)) was approved by the Food and Drug Administration in May 2008 for soft tissue anesthesia reversal (STAR) and the associated functional deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor in dental patients. It is currently approved for dental patients 6 years of age and older and weighting 15 kg (33 lbs.) or more. The recommended dose of OraVerse is based on the number of cartridges of local anesthetic with vasoconstrictor administered. The dose of OraVerse administered was in a 1:1 ratio with the dose of the local anesthetic administered, ¼, ½ or whole cartridge. For example, when ¼ cartridge of local anesthetic with vasoconstrictor is used, ¼ cartridge (0.1 mg) of OraVerse is administered [likewise for ½ cartridge (0.2 mg) and 1 cartridge (0.4 mg)]. OraVerse should be administered following the dental procedure using the same location and technique employed for the administration of local anesthetic.

Phentolamine is a short-acting, competitive antagonist at peripheral $alpha_1$ and $alpha_2$ receptors, therefore blocking the actions of the vasoconstrictor contained in the local anesthetic. Through vasodilation, it causes the local anesthetic to dissipate from the affected nerves to the cardiovascular system, which leads to termination of the anesthetic effect. This mechanism accelerates the return of normal sensation and function following restorative and periodontal maintenance procedures.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has not provided the substantial evidence of effectiveness required by 21 CFR 314.126 (a) (b) to support approval for the indication of reversal of soft tissue anesthesia in pediatric patients age 2-5 years. The study was not powered to detect treatment differences in efficacy measures; however, OraVerse was efficacious for inducing recovery of normal lip sensation in 4 to 5 year old pediatric patients as measured by the standardized lip sensation rating. OraVerse was able to reduce the median time to normal function (measured by pFAB) and the median time to normal tongue sensation in 4 to 5 year old pediatric patients, but neither of these measures was statistically significant. Safety and tolerability of OraVerse were assessed in pediatric patients age 2-5 years and were found to be similar to that of adults and older pediatric patients.

Due to recruiting challenges for subjects 2-3 years of age, only 2 subjects age 2 and 18 subjects age 3 were exposed to OraVerse in this study, these subjects were not trainable for efficacy measures. Prior studies did include subjects age 3 and above, as noted in the safety database (Section 8.2, Table 10). The use of this drug product for this indication in the pediatric population meets criteria for extrapolation as described by a working group convened by FDA in 2011 to address the challenges of pediatric drug development (Dunne, 2011). Therefore, we decided to extrapolate the efficacy findings from a prior study conducted in 4-11 year olds down to age 3, in addition to the safety findings in this study. This changes the indication from ≥ age 6 years to ≥ age 3 years, and the weight indication ≥ 15 kg remains the same. This application and rationale for this decision was discussed with the Pediatric Research Committee (PeRC) on February 17, 2016, who concurred with the decision.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The Food and Drug Administration approved OraVerse (phentolamine mesylate, (PM) in May 2008 for soft tissue anesthesia reversal (STAR) and the associated functional deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor in dental patients. It is currently approved for dental patients 6 years of age and older and weighting 15 kg (33 lbs.) or more. The recommended dose of OraVerse is based on the number of cartridges of local anesthetic with vasoconstrictor administered. The dose of OraVerse administered was in a 1:1 ratio with the dose of the local anesthetic administered, ¼, ½ or whole cartridge.

Residual soft tissue anesthesia (STA) (numbness and decreased facial muscle function) in pediatric dental patients leads to accidental injury. One study enrolling 320 patients 2-18 years of age found that 1% of all patients experienced post-operative soft tissue trauma. By age group, trauma frequency was 18% for subjects less than 4 years of age, 16% for subjects 4-7 years of age, 13% for subjects 8-11 years of age, and 7% for subjects 12-18 years of age (College C. et al., 2000). While self-inflicted soft tissue injury is not serious, and is self-limiting, it is of particular concern in this age group (2-5 years) because they may be more vulnerable than adults or older children to injury, such as biting their lip, tongue, or cheek while anesthetized.

This submission is a placebo-controlled study with 99 patients age 2-5 years receiving OraVerse. The study was not powered to detect treatment differences in efficacy measures. OraVerse was efficacious for inducing recovery of normal lip sensation in 4 to 5 year old pediatric patients as measured by the standardized lip sensation rating. OraVerse was able to reduce the median time to normal function (measured by pFAB) and the median time to normal tongue sensation in 4 to 5 year old pediatric patients, but neither of these measures was statistically significant. Therefore, the study did not meet the standard for effectiveness.

Due to study recruitment challenges, fewer subjects age 2-3 were enrolled than initially planned for this study. In addition, the weight range for subjects for this study is 13-35.8 kg. Only 2 subjects age 2 and 18 subjects age 3 were exposed to OraVerse in this study, these subjects were not trainable for efficacy measures. Although 2 of the 3 efficacy measures (pFAB and tongue numbness) in trainable subjects age 4-5 were not statistically significant, median time to recovery of function and sensation was less in the OraVerse group for both measures, and the study was not powered to demonstrate efficacy. Prior studies did include subjects age 3 and above, as noted in the safety database (Section 8.2, Table 10). The use of this drug product for this indication in the pediatric population meets criteria for extrapolation as described by a working group convened by FDA in 2011 to address the challenges of pediatric drug development. Therefore, we decided to extrapolate the efficacy findings from a prior study conducted in 4-11 year olds down to age 3, in addition to the safety findings in this study. This changes the indication from ≥ age 6 years to ≥ age 3 years, and the weight indication ≥ 15 kg remains the same. This application and rationale for this decision was discussed with the Pediatric Research Committee (PeRC) on February 17, 2016, who concurred with the decision.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Soft tissue anesthesia (STA) (numbness and decreased facial muscle function post-procedure) in pediatric dental patients leads to accidental injury. One study enrolling 320 patients 2-18 years of age found that 1% of all patients experienced post-operative soft tissue trauma. By age group, trauma frequency was 18% for subjects less than 4 years of age, 16% for subjects 4-7 years of age, 13% for subjects 8-11 years of age, and 7% for subjects 12-18 years of age (College C. et al., 2000). A more recent study in 264 dental patients 2-14 years of age receiving articaine for restorative procedures reported that soft tissue injury occurred in 14 of the subjects at 3 hours and was found to be highest among children less than 7 years of age (Adewumi A. et al., 2008).	•While self-inflicted soft tissue injury is self-limiting and not serious, it is of particular concern in this age group (2-5 years) because they may be more vulnerable than adults or older children to injury, such as biting their lip, tongue, or cheek while anesthetized.
Current Treatment Options	• No other treatment options are available to reverse soft tissue anesthesia.	OraVerse is the only approved treatment for this indication; therefore, no other treatment meets the medical need of soft tissue anesthesia reversal.
Benefit	• The study was not designed to detect treatment differences in efficacy measures. However, OraVerse was efficacious for inducing recovery of normal lip sensation in 4 to 5 year old pediatric patients as measured by the standardized lip sensation rating. OraVerse was able to reduce the median time to normal function (measured by pFAB) and the median time to normal tongue sensation in 4 to 5 year old pediatric patients, but neither of these measures was statistically significant.	OraVerse did not demonstrate efficacy in 2 of 3 measures in trainable 4-5 year olds, 2-3 year were not considered trainable for the pFAB.

Risk	• Safety and tolerability of OraVerse were assessed in pediatric patients age 2-5 years. Only 2 patients age 2 and 18 patients age 3 were exposed to OraVerse in this study, which is an inadequate safety database for 2-3 year olds. Children who are 2-3 years old do not typically received local anesthesia, they typically receive nitrous oxide when they need dental work. Because so few subjects age 2-3 were studied, the label cannot claim safety and tolerability down to age 2.	Due to recruiting challenges for subjects 2-3 years of age, only 2 subjects age 2 and 18 subjects age 3 were exposed to OraVerse in this study. Prior studies did include subjects age 3 and above, as noted in the safety database (Section 8.2, Table 10). The use of this drug product for this indication in the pediatric population meets criteria for extrapolation as described by a working group convened by FDA in 2011 to address the challenges of pediatric drug development. Therefore, the efficacy findings can be extrapolated down to age 3, in addition to the safety findings in this study. This application and rationale for this decision was discussed with the Pediatric Research Committee (PeRC) on February 17, 2016, who concurred with the decision.
Risk Management	• N/A	N/A

2 Therapeutic Context

2.1. Analysis of Condition

The Food and Drug Administration approved Or averse (phentolamine mesylate, (PM) in May 2008 for soft tissue anesthesia reversal (STAR) and the associated functional deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor in dental patients. It is currently approved for dental patients 6 years of age and older and weighting 15 kg (33 lbs.) or more.

Phentolamine is a short-acting, competitive antagonist at peripheral alpha$_1$ and alpha$_2$ receptors, therefore blocking the actions of the vasoconstrictor contained in the local anesthetic. Through vasodilation, it causes the local anesthetic to dissipate from the affected nerves to the cardiovascular system, which leads to termination of the anesthetic effect. This mechanism accelerates the return of normal sensation and function following restorative and periodontal maintenance procedures.

While residual soft tissue anesthesia (STA) is generally inconvenient for adults and adolescents (numbness and decreased facial muscle function), pediatric dental patients may be more likely to experience accidental injury than adults and will likely benefit from accelerated local anesthesia reversal. One study enrolling 320 patients 2-18 years of age found that 1% of all patients experienced post-operative soft tissue trauma. By age group, trauma frequency was 18% for subjects less than 4 years of age, 16% for subjects 4-7 years of age, 13% for subjects 8-11 years of age, and 7% for subjects 12-18 years of age (College C 2000). A more recent study in 264 dental patients 2-14 years of age receiving articaine for restorative procedures reported that soft tissue injury occurred in 14 of the subjects at 3 hours and was found to be highest among children less than 7 years of age (Adewumi A 2008).

2.2. Analysis of Current Treatment Options

OraVerse is the only approved product indicated for the reversal of soft-tissue anesthesia for dental procedures. Therefore, there are no other treatment options for this indication.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The FDA approved OraVerse on May 9, 2008 for the indication of reversal of soft-tissue

anesthesia for dental procedures for patients age ≥ 6 years. At the time of approval, pediatric study requirements under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) were waived for pediatric patients less than 2 years of age because the necessary studies would be impossible or highly impracticable due to the small number of patients in this age range who present for dental procedures requiring the use of a local anesthetic with a vasoconstrictor. The Agency required a deferred pediatric post marketing commitment to study patients 2-6 years of age in the approval letter, which required the following clinical endpoints to be assessed using validated metrics:

1. Time to return of normal sensation of the lips and, where applicable, the tongue
2. Time to return of normal function for speech, smiling, drinking, eating and not drooling

The final study report was to be due by May 2011. Novalar Pharmaceuticals, Inc., the former owner of NDA 22-159, requested a review of the draft protocol for the phase 4 study in December 2008. Novalar received the Agency's review comments dated April 27, 2010, which were incorporated and the protocol was finalized for submission to IND 65,095 on November 1, 2011. Novalar then requested an extension to submit the final study report dated September 30, 2010 by May 2012 rather than May 2011.

Septodont Holding SAS acquired OraVerse on March 18, 2011 and filed several extension requests to obtain adequate enrollment for the study. The most recent request deferred the final study to February 2015. Study PHE-11-001 began in February 2012, was completed August 22, 2014, and is the only study submitted for review in this supplement.

OraVerse was launched in the United States in February 2009. As of the most recent annual report (May 8, 2015-September 9, 2015), (b) (4) units containing 10 cartridges each were distributed in the United States, (b) (4) units outside of the United States, resulting in a total of (b) (4) units distributed. This is an increase from the prior reporting period ((b) (4) units).

3.2. Summary of Presubmission/Submission Regulatory Activity

A brief regulatory history of OraVerse is as follows:

- IND 65095 was opened on June 20, 2002, with the submission by Novalar Pharmaceuticals, Inc. that included the protocol for NOVA 02-01 (now OraVerse).

An End-of-Phase 2 meeting was held on October 30, 2003. Key clinical issues discussed were as follows:

- Resolution of the effects of the local anesthetics at the lip is a reasonable efficacy endpoint.
- Sites selected for assessment of local anesthetic reversal should be those for which reversal provides some benefit.

- Evidence of the clinical benefits for reversing local anesthetic effects following dental procedures should be provided, such as improved patient satisfaction, reduction in injury such as tongue or lip biting. The benefits should be quantifiable.
- The following would need to be addressed for FDA to consider a general indication for reversal of local anesthetics containing a vasoconstrictor:
    - The mechanism for reversal has not been fully elucidated such that demonstration of efficacy with a few members of a drug class can be extrapolated to the entire class.
    - A demonstration that phentolamine exerts its effect by reversing vasoconstriction caused by vasoconstrictors co-administered with local anesthetics.
    - The full range of concentrations of available vasoconstrictors, as well as the full range of local anesthetics needs to be evaluated.
    - A claim may need to be limited to those local anesthetics/vasoconstrictors studied.
- Concerns about limitations of NOVA 03-001, a Phase 2 study, as a pivotal trial were discussed. Children ages 10-17 were included in the phase 2 study, NOVA 03-001, and were proposed for inclusion in the phase 3 study, NOVA 03-002. The Sponsor proposed that inclusion of children ages 10-17, as described, would satisfy the requirements for the study of OraVerse in the pediatric population of that age group, and allow the indication section of the prescribing information to include "children aged 10 and older, and adults." The Division stated that the label would reflect the populations studied, but potential off-label use will be a consideration in the overall benefit/risk analysis for the drug.
- Apparently 100 children with an adequate age distribution should provide a sufficient safety database; although, adequacy of the database size would depend in part upon clinical findings, dosing, and demographic considerations.
- The Sponsor stated it would be difficult to collect efficacy data in the younger population versus just safety data. The Division stated it might be acceptable to look primarily at safety data in children, but that if the sponsor wished to do so, they would need to provide adequate justification or evidence that it would be appropriate to extrapolate efficacy from older children and adults. The Sponsor questioned if a pediatric study could be a post marketing commitment. The Division stated that this should be addressed at the time of the NDA filing.

Before the NDA filing meeting, the Division met twice with the Sponsor regarding a proposed Special Protocol Assessment (SPA). The key concerns were the following:

- The primary endpoint, duration of numbness, must be linked within the trials to other endpoints that assess the clinical meaningfulness of the drug effect.
- The secondary endpoints themselves may not need to achieve statistically significant

differences among treatment groups, but should clearly demonstrate changes in the desired direction among the groups. These endpoints might not be a basis for a labeling claim without replication and clear validation.

- Evidence of an earlier return of function as well as an earlier return of the perception of return of ability to function with the drug would be sufficient to demonstrate clinical relevance of lip palpation assessment of numbness.
- The primary surrogate endpoint should be return to sensation of facial soft tissue. Other observed outcomes (eating, drinking, smiling, drooling, speaking, etc.) are secondary and would be supportive.
- Assessment of tongue numbness may have clinical relevance in terms of speech and swallowing capabilities; it also assesses STAR in another soft tissue; therefore, its assessment as a secondary endpoint should be performed on patients undergoing mandibular blocks.
- Testing for tongue numbness should be standardized to the degree done for lip testing.

A pre-NDA meeting was held on December 8, 2006. A summary of relevant agreements reached between the Sponsor and the Division is as follows:

- The Division agreed that the population studied, the local anesthetics and vasoconstrictors administered, the types of blocks used and the dental procedures performed, were adequate to support the indication of reversal of soft tissue anesthesia and the associated functional deficits resulting from an intraoral injection of a local anesthetic containing a vasoconstrictor.
- Justification for granting a partial pediatric waiver request pursuant to the Pediatric Research Equity Act (PREA) for pediatrics 0-2 years of age should be included in the NDA submission.

The NDA submission included a Request for Partial Pediatric Waiver for the following two groups:

1. Newborns (birth to 1 month of age): The Sponsor cited literature, which indicated that the first tooth erupts between 4 and 13 months of age, and argued that there is minimal, if any, need for administration of a local anesthetic containing a vasoconstrictor prior to a dental procedure. The Sponsor also indicated that the limited availability of patients in this age group would preclude the conduct of a meaningful clinical trial.
2. Infants (1 month to 2 years of age): The Sponsor again cited literature, which indicated that the first teeth have just begun to erupt in this age group, and, therefore, there is minimal, if any, need for administration of a local anesthetic containing a vasoconstrictor prior to a dental procedure. It was also stated that children receive their first dental evaluation within the first year of life, and that for those infants with teeth up to age 2 years old, dental visits are “wellness visits” where no dental procedure

> is performed. Thus, there is limited need for this drug in this age group and, at best, a limited availability of patients in this age group for the conduct of a meaningful clinical trial.

The Sponsor provided the above adequate justification for not evaluating pediatric patients ages 0-2 years old, and provided safety data for the pediatric population ages 3-18 years of age in the original NDA submission.

Assessments of efficacy in pediatric patients 12-17 years of age were also made in the two pivotal trials, and the Sponsor demonstrated a clinical benefit to the markedly diminished duration of anesthesia in this population. As it is likely that:

- The return to normal sensation in patients 3-5 years old may be accelerated to the same degree as adults and older children.
- The safety profile does not differ substantially in this age group than in the others, and
- A safety benefit may be had in the reduction of self-inflicted injuries,

It was recommended that the Sponsor commit to the following:

1. Develop and, if necessary, validate a technique for assessing return of sensation in pediatric patients 3-5 years of age following soft tissue anesthesia.
2. Conduct clinical trial(s) designed to demonstrate whether a significant and substantial reduction in the return of normal soft tissue sensation occurs in pediatric patients ages 3-5 years old following the administration of OraVerse compared to a sham injection. One trial may be sufficient in light of the data already obtained in this population provided the means of assessing return of normal sensation are valid for the entire age group.

The post-approval regulatory activity for OraVerse is summarized in section 3.1

3.3. Foreign Regulatory Actions and Marketing History

Novalar Pharmaceuticals, Inc. submitted foreign marketing applications for OraVerse in July 2010. OraVerse has been approved in the following European countries: France, Germany, Italy, Spain, and the United Kingdom, but is currently only being marketed in Germany. Novalar Pharmaceuticals chose Sanofi-Aventis Deutschland as the distributor for OraVerse in Germany. OraVerse launched in Germany in early 2011. OraVerse was approved in Canada in February 2014. Due to the transfer of this NDA from Novalar Pharmaceuticals, Inc. to Septodont Holding SAS, the European foreign marketing applications now belong to Septodont Holding SAS. No new foreign applications were submitted as of the last annual report period, May 9, 2014-May 8, 2015.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The sites selected for inspection were the three sites with the most enrollees, which accounts for two-thirds of all enrolled subjects. No concerns of data integrity, or safety or efficacy were noted at the time of consultation. The sites chosen were:

Site #4: Elliot Hersh, University of Pennsylvania School of Dental Medicine, Philadelphia, PA- 30 subjects

Site #5: Brent Lin, University of California School of Dentistry, San Francisco, CA- 30 subjects

Site #6 Adam Marberger, Jean Brown Research, Salt Lake City, UT- 30 subjects

At all three inspected sites, no significant GCP deficiencies were observed. A Form FDA483 was issued at one of the three sites (Site #5) for minor deficiencies unlikely to be significant to the study outcome. At all three sites, study conduct appeared adequate, including IRB/sponsor oversight of study conduct. All audited NDA data were verifiable against source records and case report forms (CRFs). The data from the three study sites appear reliable as reported in the NDA.

4.2. Product Quality

As of the annual report submitted September 9, 2015, no changes were made to the manufacturers, method of manufacturing and packaging, and specification of drug substance or drug product. Drug substance and drug product specification and the associated test methods are provided in the annual report. No changes were made to the container closure or stability protocol of the drug substance manufacturers or the list of approved drug product manufacturers. Expiration dating of the drug product was changed from (b) (4) month to 30-month during the last PADER period, July 2, 2014. This was due to an unexpected Out of Specification result that occurred at the previous (b) (4) month shelf life on degradation product, (b) (4) The product otherwise met all specifications.

4.3. Clinical Microbiology

OraVerse is not a therapeutic antimicrobial; therefore, no clinical microbiological data is required.

4.4. Nonclinical Pharmacology/Toxicology

The following information is from the package insert. No new toxicology studies have been conducted since approval.

> Carcinogenicity studies with OraVerse have not been conducted. Phentolamine was not mutagenic in the in-vitro bacterial reverse mutation (Ames) assay. In the in-vitro chromosomal aberration study in Chinese hamster ovary cells, numerical aberrations were slightly increased after a 4-hour exposure to phentolamine without metabolic activation and structural aberrations were slightly increased after a 4-hour exposure to phentolamine with metabolic activation only at the highest concentrations tested, but neither numerical nor structural aberrations were increased after a 20-hour exposure without metabolic activation. Phentolamine was not clastogenic in two in-vivo mouse micronucleus assays. At doses up to (b) (4) 143 times human therapeutic exposure levels at the Cmax), (b) (4) no adverse effects on male fertility (b) (4).

4.5. Clinical Pharmacology

No new clinical pharmacology studies were conducted since approval. The information for this section is from the package insert.

4.5.1. Mechanism of Action

The mechanism by which OraVerse accelerates reversal of soft-tissue anesthesia and the associated functional deficits is not fully understood. Phentolamine mesylate, the active ingredient in OraVerse, produces an alpha-adrenergic block of relatively short duration resulting in vasodilatation when applied to vascular smooth muscle. In an animal model, OraVerse increased local blood flow in submucosal tissue of the dog when given after an intraoral injection of lidocaine with 1:100,000 epinephrine.

4.5.2. Pharmacodynamics

See “Mechanism of Action” section above.

4.5.3. Pharmacokinetics

Following OraVerse administration, phentolamine is 100% available from the submucosal injection site and peak concentrations are achieved 10-20 minutes after injection. Phentolamine systemic exposure increased linearly after 0.8 mg compared to 0.4 mg OraVerse intraoral submucosal injection. The terminal elimination half-life of phentolamine in the blood

was approximately 2-3 hours. Following OraVerse administration, the phentolamine Cmax was higher (approximately 3.5-fold) in children who weighed between 15 and 30 kg (33 and 66 lbs.) than in children who weighed more than 30 kg. However, phentolamine AUC was similar between the two groups. It is recommended that in children weighing 15-30 kg, the maximum dose of OraVerse should be limited to ½ cartridge (0.2 mg) (see Dosage and Administration section). The pharmacokinetics of OraVerse in adults and in children who weighed more than 30 kg (66 lbs.) are similar after intraoral submucosal injection. (b) (4)

[redacted]

4.6. Devices and Companion Diagnostic Issues

No device or companion diagnostic is included in this supplement.

4.7. Consumer Study Reviews

Dentists administer OraVerse. Therefore, no self-selection or human factors studies were evaluated.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

5.2. Table 1 Clinical Trial Submission for this NDA Supplement

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
PHE-11-001	Phase IV multicenter randomized double blind placebo controlled	OraVerse or placebo by submucosal injection	Safety: SAE incidence, vital signs, oral cavity assessments, pain (WB scale) Efficacy: pFAB, lip and tongue sensation	one treatment post procedure, follow up on days 2-4 post procedure	150	children 2-5 years of age, > 10 kg requiring restorative dental procedure	(7) U.S. Centers

5.3. Review Strategy

One trial, PHE-11-001, was submitted for review for this NDA supplement. PHE-11-001 was reviewed for drug safety, confirming the Applicant's safety analyses in 2-5 year old children,

using JReview and JMP. A statistician confirmed the Applicant's efficacy analyses of primary data. The following sections of the CRT are considered "not applicable." This is a single, multi-center trial submitted as a post-marketing requirement to study the effects of OraVerse in the 2-5 year age group. The reasons for excluding the following sections are noted under each of the following section headings in the CRT.

4.3 Clinical Microbiology
4.6 Devices and Companion Diagnostic Issues
4.7 Consumer Study Reviews
7. Integrated Review of Safety
9. Advisory Committee Meeting and Other External Consultations
11. Risk Evaluation and Mitigation Strategies (REMS)
12. Post Marketing Requirements

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Protocol: PHE-11-001, A Phase 4, Multicenter, Randomized, Double-Blinded, Controlled Study of OraVerse for Safety and Efficacy in Pediatric Dental Patients Undergoing Mandibular and Maxillary Procedure

6.1.1. Study Design

Overview and Objective

The following is summarized from the clinical study report. A thorough review of the original protocol identified four minor amendments, which were also noted in the study report. These are further described in the review in the "protocol amendments" section.

Phase 4, Multicenter, Randomized, Double-blinded, Controlled Study of OraVerse for Safety and Efficacy in Pediatric Dental Patients Undergoing Mandibular and Maxillary Procedures.

This study was conducted as a phase 4 commitment to evaluate the safety and efficacy of OraVerse in approximately 150 children 2 to 5 years of age. OraVerse or sham injection was administered at the completion of a dental procedure requiring local anesthesia with lidocaine 2% with 1:100,000 epinephrine. The dental procedure(s) comprised of restoration/fillings, and were performed in a single quadrant of the mouth. The primary objective was safety and tolerability of OraVerse as measured by adverse events, vital signs, oral cavity assessments, nerve injury, and use of analgesics for intraoral pain. The secondary objective was to evaluate, in trainable subjects 4 and 5 years of age, the safety and tolerability of OraVerse as measured by the incidence, severity and duration of intraoral pain and assessed by the Wong-Baker pain

rating scale (W-B PRS) and to determine if OraVerse accelerated the time to normal function and sensation as measured by the pFAB and standardized lip and tongue sensation ratings. The study was not powered to detect treatment differences in efficacy measures.

Trial Design:

As noted in the study report, this Phase 4 study was designed as a multicenter, randomized, double-blinded, controlled study to evaluate the safety and efficacy of OraVerse administered as a submucosal injection following completion of a restorative procedure requiring local anesthesia with lidocaine 2% with 1:100,000 epinephrine in dental patients 2 to 5 years of age.

Key Inclusion/Exclusion Criteria:

An eligible subject met all the following criteria:

- Male or female, 2 to 5 years of age
- Sufficiently healthy as determined by the investigator to receive routine dental care
- Required a restorative procedure in a single quadrant of the mouth
- Required local anesthesia with lidocaine 2% with 1:100,000 epinephrine administered by submucosal injection
- For subjects undergoing mandibular procedures, required an inferior alveolar nerve block for the restorative procedure
- Dental procedure(s) completed within 60 minutes of injection of local anesthetic
- For subjects 4 and 5 years of age, could be trained in standardized lip/tongue palpation procedure and pFAB
- Subjections who were trainable in standardized lip/tongue palpation procedure and pFAB had either:
  - Normal pFAB at baseline prior to administration of local anesthetic and
  - At least one abnormal pFAB function (smiling, speaking, drinking or drooling) at the completion of the dental procedure

  OR
  - Normal lip sensation at baseline prior to administration of local anesthetic and
  - Numbness of the relevant lip quadrant at completion of the dental procedure
- Subjects gave written or verbal assent, as capable and appropriate, and parent(s) or legal guardian(s) give written informed consent

A subject was ineligible for the study if he/she met any of the following criteria:

- Weight less than 10 kg
- Weight less than 15 kg if 4 or 5 years of age
- History or presence of any condition that contraindicates routine dental care or use of local anesthetic

- Required more than ¼ cartridge of local anesthetic if weight was ≥ 10 kg and < 15 kg, more than ½ cartridge of local anesthetic if weight was ≥ 15 kg and < 30 kg, or more than 1 cartridge of local anesthetic if weight was ≥ 30 kg, excluding supplemental injections
- Allergy or intolerance to lidocaine, epinephrine, sulfites, phentolamine, nitrous oxide or topical benzocaine
- Has used any investigational drug and/or participated in any clinical study within 30 days of study drug administration
- Has participated in this study or any previous study of phentolamine mesylate for reversal of local soft tissue anesthesia (STA)
- Any use of commercial OraVerse within 30 days of study drug administration
- Use of opioid or opioid-like analgesics within 24 hours prior to administration of local anesthetic
- Required the use of local anesthetic other than lidocaine 2% with 1: 100 000 epinephrine to perform the scheduled dental procedure
- Required the use of general anesthesia or sedatives except for nitrous oxide to perform the scheduled dental procedure
- Any condition which in the opinion of the Investigator increased the risk to the subject of participating in this study or decreased the likelihood of compliance with the protocol

Dose Selection:

Three doses of OraVerse were evaluated in this study: 0.1 mg, 0.2 mg, and 0.4 mg phentolamine mesylate. The administered dose was dependent on the weight of the subject and the volume of the local anesthetic administered. The dose of OraVerse administered was in a 1:1 ratio with the dose of the local anesthetic administered, ¼, ½ or whole cartridge.

As described in the study report, the mg/kg dose of phentolamine administered in the pediatric Phase 2 study NOVA 05-PEDS and the approved labeling of OraVerse were considered in the selection of doses for the current study. In study NOVA 05-PEDS, pediatric subjects 4 to 11 years of age received ½ cartridge of local anesthetic and OraVerse if weighing 15 to < 30 kg, and either ½ or full cartridge if weighting ≥ 30 kg. The prescribing information for OraVerse recommends a maximum of a ½ cartridge (0.2 mg) of OraVerse for pediatric subjects weighing between 15 and ≤ 30 kg. OraVerse is currently not recommended for use in children less than 6 years of age or weighing less than 15 kg (33 lbs.). The study population in this Phase 4 study consisted of pediatric dental patients 2 to 5 years of age. It was expected that subjects 2 or 3 years of age may weigh less than 15 kg. In order to ensure the maximum dose administered to pediatric dental patients is not exceeded during the study, subjects weighting between 10 and < 15 kg received ¼ cartridge of OraVerse and subjects less than 10 kg were excluded from the study. Subjects weighing between 15 and ≤ 30 kg and subjects weighing >30 kg received the doses administered in the pediatric Phase 2 study NOVA 05-PEDS. The doses in mg/kg for this study fall within the range administered in the pediatric Phase 2 study NOVA 05-PEDS and deemed safe.

Assignment to Treatment:

After obtaining informed consent from parent or legal guardian, pediatric dental patients scheduled to undergo a restorative procedure were screened for eligibility, assigned a screening number, underwent baseline assessments and training, and then received local anesthesia for their dental procedure.

Authorized study staff using an Interactive Voice Response System (IVRS) performed randomization. Following completion of the dental procedure and confirmation of study eligibility criteria were met, subject who met all eligibility criteria were randomized to receive OraVerse or Sham Injection in a 2:1 allocation ratio. Randomization was stratified by location of the dental procedure (mandible or maxilla) and number of local anesthetic cartridges used (¼, ½ or 1). Randomization confirmation was retained in the study site's source documents. A ratio of maxillary and mandibular procedures per study site and across the study was ensured through IVRS. Randomized subjects were assigned a unique subject number. This number was used to identify all study subjects and was recorded on all CRFs.

Following the dental procedure subjects who had at least one abnormal pediatric functional assessment battery (pFAB) test and/ or numbness of the relevant mouth quadrant were randomized to OraVerse or sham injection in a 2:1 allocation ratio, and stratified according to location of the dental procedure (maxilla or mandible) and amount of local anesthetic (¼, ½ or 1 cartridge). A sham injection was selected as the control for the Phase 4 study to minimize bias of assessments of safety for OraVerse and the second injection, and to mimic the current standard of care, i.e. no injections other than a local anesthetic. This type of control was effectively use in the Phase 3 studies NOVA 04-100 and NOVA 04-200 and the pediatric Phase 2 study NOVA 05-PEDS.

Blinding:

As described in the study report, the investigator administering the anesthetic and study drug (OraVerse or sham) was not blinded to the treatment; however, the subject was blinded to the study treatment received. The following measures were taken to maintain this blind:

- A visual barrier was placed, or a distractive technique was used, to obstruct the subject's view of the preparation and administration of study drug.
- The same Investigator who injected the local anesthetic also administered the study drug. This Investigator did not perform subsequent assessments during the observation period. A blinded observer was responsible for making safety and efficacy assessments.
- The Investigator performing the injection returned study drug cartridges to the study kit and sealed the kit with a tamper-evident label prior to removing the visual barrier from the subject and study personnel involved in subsequent assessments.
- Study personnel who were involved in assessments following the preparation and administration of study drug were not present in the room at the time of the preparation

and administration of study drug but were informed about the site(s) of administration and the site of the procedure.
- Adverse events were monitored and recorded by blinded study personnel.

Study drug was administered at the same site as the local anesthetic using the same injection technique. The investigator who administered local anesthetic and study drug may have been the same or different from the dentist who completed the dental procedure. Precautions were taken to maintain the study blind as described above. Study drug was administered by the Investigator or Sub-investigator according to each study site's delegation of responsibilities. Study drug accountability records were used to monitor treatment compliance.

Concurrent Medications:

As described in the study report, eligibility criteria prohibited the use of an opioid or opioid-like analgesic within 24 hours before administration of local anesthetic. Other investigational agents were prohibited within 30 days of study participation.

Concomitant medications, including any analgesics taken for intraoral pain, medications previously prescribed, and medications required to treat an adverse event, were to be recorded within 24 hours of local anesthetic administration, during the dental procedure, at the time of study drug administration, during the observation period inclusive of the follow-up appointment.

Benzocaine (20%) topical gel was permitted to provide local anesthesia of mucosal surfaces within 30 seconds prior to the injection of the local anesthetic. It has a short duration of approximately 15 minutes, and per the manufacturer's package insert has virtually no systemic absorption.

Subject withdrawal:

Subjects could be removed from the study if one of more of the following events occurred:
- Screen failure
- Significant protocol violation on the part of the investigator
- Significant noncompliance on the part of the subject
- Withdrawal of consent (refusal of the subject to continue treatment or observations)
- Adverse event, unacceptable toxicity
- Decision by the investigator that termination was in the subject's best medical interest
- Unrelated medical illness or complication
- Lost to follow-up

There were no discontinuations for safety reasons that required prompt reporting to regulatory authorities and the applicable IRB(s).

Subjects who decided to withdraw from the study or were withdrawn from the study by the investigator for non-safety reasons were termed "drop-outs." Subjects who were withdrawn by

the investigator because of an acceptable adverse event (AE) were termed a "withdrawal." No subjects were replaced.

Table 2 Schedule of Events (Applicant's Table)

Assessment	Period 1	Period 2	Period 3	Period 4	Period 5	Period 6
	Screening Day -14 to Day 1	**Anesthetic/ Dental Procedure** Day 1	**Study Drug Adminis-tration** Day 1	**Obser-vation** Day 1	**Telephone Follow-Up** Day 1	**In-clinic Safety Follow-up** Day 2 or 3
Informed Consent /Assent and Assign Scn. #	X					
Medical/Dental History/Concurrent Illness	x[a]	X[d]				
Demographics (including height and weight)	X					
Training: W-BPRS, pFAB, lip and tongue palpation procedure in subjects age 4 and 5	X[b]					
BP and pulse (supine or sitting)		X[e]	x[i, j]	X[l]		
Confirm interim eligibility	X[c]					
Apply Topical Anesthetic, if needed		X[e]				
Administer Local Anesthetic and record type of injection and time it is completed		X				
Dental Procedure and record stop time		X				
Randomize to Study Drug - record time and assign Subject ID #			X			
Place Visual Barrier for Blinding			X[i]			
Administer Study Drug and record time administration is completed			X			
Remove Visual Barrier				X		
Discontinue nitrous oxide (if given) and administer oxygen for 5 minutes			X			
pFAB – subjects age 4 and 5 years	X[b]	X[e]	X[g, j]	X[l]		
Lip and tongue palpation - subjects age 4 and 5	x[b]	x[e]	x[g, j]	X[l]		
Confirm final eligibility			X[h]			
W-B PRS of local anesthetic injection		X[f]				
W-B PRS of study drug injection			X[j]			
W-B-PRS of side of dental procedure			X[g]	X[l]		
General Oral Cavity Assessment		X[e]	X[g, j]	X[l]		X
Specific Oral Cavity Assessments (Injection/Procedure Sites)		x[f]		x[l]		X
Concomitant Medications	X[k]	X	X	X[l]	X	X

Adverse Events			X	X	X	X
Schedule Day 1 telephone safety follow-up				X		
Schedule in-clinic safety follow-up				X		
Discharge subject (record time)				X		X

CodingLegendforAssessmentTimePoints:
a) Update during Evaluation on Day 1 if different from day of Initial Screening of Selection Criteria
b) Performed on Day 1
c) Normal lip sensation, no opioid or opioid-like analgesics within 24 hours
d) Update concurrent illness record, if necessary
e) Prior to administration of local anesthetic
f) After administration of local anesthetic
g) Prior to randomization to OraVerse or sham
h) In subjects 4 and 5 years of age who are trainable in pFAB and standardized lip/tongue palpation procedures, at least one abnormal pFAB test OR numbness of the lip on the side of the dental procedure at completion of dental procedure. For mand bular procedures, use of inferior alveolar nerve block to perform the procedure. For all subjects, dental procedure was completed within 60 minutes of administration of local anesthetic, amount of local anesthetic was consistent with weight; no opioid or opioid-l ke analgesics, sedatives except nitrous oxide), or local anesthetic other than lidocaine 2%/epinephrine was administered during dental procedure
i) Prior to preparation and administration of study drug
j) Immediately after administration of study drug
k) Record concomitant medications taken within 24 hours of local anesthetic administration
l) **Post Study Drug:**
All subjects were assessed for safety and efficacy during a 2-hour observation period. Subjects 4 and 5 years of age who are not trainable in W-B PRS did not perform these pain assessments.
Safety assessments were performed at the time points specified below with an acceptable variation of ± 5 minutes unless specified otherwise.
W-BPRS for pain in the mouth on the side of the procedure every 30 minutes post study drug for two hours (all subjects); and prior to analgesics, as needed
Bloodpressureandpulse in supine or sitting position at 15, 30, 60 and 120 minutes and prior to discharge
Specificoralcavityassessments of the injection and procedure site(s) at 15, 30, 60, 120 minutes, and prior to discharge
Generaloralcavityassessment prior to discharge
Adverse Events: Recorded any adverse events from time of study drug administration throughout the observation period. In addition, queried the subject every 30 minutes for adverse events during the observation period, at discharge and at telephone and in-clinic follow-ups
ConcomitantMedications: Medications taken during the observation period, including any analgesics taken for intraoral pain, medications previously prescr bed (subject's parents/legal guardian supplied the medications), and medications required to treat an adverse event
Efficacy Assessments in subjects 4 and 5 years of age
Efficacyassessments were performed at the time points specified below with a variation of ± 5 minutes pFAB: every 15 minutes for 2 hours after study drug administration Standardizedlip/tonguepalpationprocedure: every 15 minutes for 2 hours after study drug administration
(Source: Study Report, page 30)

Study Endpoints

The primary objective for this clinical trial was to determine the safety and tolerability of OraVerse in subjects 2-5 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. Further discussion on these objective parameters can be found in Section 8.

The secondary objective was to establish the safety and tolerability of OraVerse in trainable subjects 4 and 5 years of age, as measured subjectively by the incidence, severity, and duration of intraoral pain assessed by the Wong-Baker Pain Rating scale (W-BPRS).

The efficacy of OraVerse was evaluated in subjects 4 and 5 years of age, who were trainable in

pFAB and standardized lip/tongue palpation procedures, based on the following parameters:

- Time to normal function as measured by the pediatric Functional Assessment Battery
- Time to normal lip sensation as measured by standardized lip/tongue palpation procedure
- For mandibular procedures, time to normal tongue sensation as measured by standardized lip/tongue palpation procedure

The sensation ratings were performed prior to local anesthetic administration, after the dental procedure, after study drug administration, and every 15 minutes for 2 hours after study drug administration.

The pFAB was used to assess 4 functions: smiling, speaking, drinking, and drooling. Observer ratings were reported using the following criteria:

Table 3 Pediatric Functional Assessment Battery (pFAB)

Function	Rating	Definition
Smiling, Speaking, Drinking	Normal	Normal for each function was defined as "same as" or "equivalent" to performance of test at baseline.
	Abnormal	Abnormal for each function was defined as "not normal" or "different" from baseline.
Drooling	Present	Presence of drooling was to be interpreted as "abnormal."
	Absent	Absence of drooling was to be interpreted as "normal."

The pFAB was performed prior to local anesthetic administration, after the dental procedure, after study drug administration, and every 15 minutes for 2 hours after study drug administration.

Lip palpation consists of soft tapping of the upper and lower lip with the subject's index or middle finger. For subjects undergoing mandibular procedures, tongue palpation consists of tapping of the tongue at the side of the dental procedure. Subjects rated the status of their soft- tissue anesthesia as normal, tingling, or numb. Subjects were trained in the technique and were included in the efficacy assessment only if they were able to successfully perform the test.

Statistical Analysis Plan

The safety and tolerability of OraVerse, as described in the study report, was assessed based on the safety analysis data set defined as:

- All randomized subjects administered study drug
- For the W-B PRS: all randomized subjects 4 and 5 years of age who were trainable in the completion of the W-B PRS and administered study drug.

Subjects were grouped in the safety analysis set according to which study drug was actually administered. Descriptive statistics were used to characterize the safety and tolerability profile of OraVerse in comparison to the sham injection. Because the sample size of the study was not based on enrolling an adequate number of subjects to detect specific potential adverse events in the OraVerse treatment, formal inferential statistical methodologies were not appropriate given the study design and number of primary safety endpoints.

The statistical analysis of each of the secondary endpoints is based on the corresponding modified Intent-to-Treat (mITT) analysis sets which were grouped according to their randomized study drug assignment, irrespective of which treatment was actually administered (if any). The mITT analysis sets were defined as follows:

- mITT pFAB analysis set included all randomized subjects 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 procedure as rated by the observer
- mITT Lip Sensation analysis set included all randomized subjects 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 procedure
- mITT Tongue sensation analysis set included all randomized subjects 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 the completion of the dental procedure

Descriptive statistics employing Kaplan-Meier methods were utilized to characterize time to normal sensation of the lip and tongue for each treatment group. Additionally, inferential statistical methodologies using the stratified log-rank test were employed. These additional inferential statistical methods were collected to identify potential trends within these efficacy endpoints. Hypothesis testing was conducted using 2-sided significance level of 0.05.

The primary objective of the study was the safety and tolerability of OraVerse in 2 to 5 year old subjects undergoing a maxillary or mandibular dental procedure. Thus, the sample size justification for this study was based on the probability of detecting potential adverse events that might occur during this study in the OraVerse treatment group. If 100 subjects were enrolled in the OraVerse arm of the study, there would be a 95% confidence level of observing

at least one occurrence of a specific adverse event given the true proportion of subjects that would develop this adverse event in the population is 3% (Louis, T.A., 1981).

Protocol Amendments

There were four (4) amendments to the study protocol described in the study report as follows:

1. One single site-specific amendment (Amendment 1 December 13, 2011) was implemented at site 3 (Indiana University School of Dentistry) that allowed the in-clinic follow up appointment to be completed on day 4 in addition to day 2 or 3. This was the only protocol amendment implemented across the clinical sites to allow this site to enroll subjects on Fridays, and complete the in-clinic follow-up appointment on Monday when the clinic reopened.

2. Originally, fifteen (15) two year olds and fifteen (15) three year olds were to be enrolled in the study for a total of 30 two and three year old subjects. However, additional 3 year olds were to be enrolled to account for the lack of eligible 2 year old subjects across all clinical sites; a cumulative total of 31 two and three year olds, 59 four year olds, and 60 five year olds were enrolled. This amendment did not affect the results of the study. The clinical review of the original study protocol (IND65095) notes the majority of 2-3 year old patients who require a restorative dental procedure tend to undergo systemic anesthesia with nitrous oxide, rather than local anesthetic with vasoconstrictor, and hence, less likely to need reversal, and the 2-3 year olds were not considered trainable for the pFAB or WBPRS.

3. The lip and tongue sensation ratings were rated as normal, tingling, and numb; however, section 1.4.3 of the protocol specified the lip/tongue palpation would be rated as normal or abnormal. This amendment did not impact the results of the study because the simplification of terminology for lip and tongue sensation ratings was done purposely because 4-5 year olds are unlikely to understand the nuances between “numb” and “tingling.”

4. Many eligible subjects required restorations in more than one mouth quadrant. In order to minimize the number of dental visits and anesthetic injections in eligible pediatric patients, clinical sites were permitted to randomize subjects requiring restorations in more than one quadrant during the study so long as all other inclusion and exclusion criteria were met (e.g only a single injection of local anesthetic was administered per protocol, dental procedures were completed within 60 minutes of local anesthetic administration). In these instances, a single quadrant was selected and used for all baseline and efficacy assessments. According to the sponsor, this change was not expected to affect the integrity of data collection. This amendment did not affect the

results of the study because all other criteria were met and the same quadrant was used for all baseline and efficacy assessments.

Data Quality and Integrity: Sponsor's Assurance

Protocol deviations identified by the site personnel or the study monitor were documented on a Protocol Deviation Form. If details of a deviation report would be a source of unblinding the unblinded investigator issued a preliminary deviation report, but withheld such information in a sealed envelope until after all queries and changes to study data were finalized and no further changes could be made.

Novocol or its authorized designee was responsible for data processing. All data were entered into a study database for analysis and reporting. The database was created by (b) (4) . Independent double entry of each CRF was performed with each record of the dual entry databases being compared to identify discrepancies. The paper CRF was used to verify and correct any discrepancies.

Twenty percent (20%) of data from randomly selected CRFs and one hundred percent (100%) of data related to primary endpoints and adverse events were verified manually against the paper CRFs. Range, value and logical edit checks were performed on both continuous metrics (vital signs, age, height, weight) using minimum, maximum, average, standard deviation and range, and discrete metrics (gender, race, ethnicity) using counts and proportions to verify data integrity.

Data Clarification Forms (DCF) were reviewed and resolved by study personnel and the study monitor and approved by the Investigator to confirm any data that was illegible, mistyped, or missing. A final quality audit was performed before final database lock.

After the database was formally locked, the randomization schedule was released from the IVRS/randomization vendor to the data management vendor and biostatistician. At this point, the study was unblinded with respect to the treatment assignment of each subject and data analysis commenced.

Routine site-monitoring visits were conducted by the study monitor to ensure the welfare and safety of study subjects, the accuracy and integrity of the data collected, and compliance with the protocol, GCP, and regulatory requirements. Comprehensive (100%) data monitoring and source data verification was conducted at each clinical site.

Quality assurance audits were conducted at two (2) of the seven (7) clinical sites that participated in the study. Selected sites included those with highest enrolment, and/or a high percentage of noncompliance as identified through study monitoring reports. A random

sample of critical data was audited at the selected sites.

The Office of Scientific Investigations (OSI) was consulted to inspect three sites that enrolled the majority of subjects. The results of these inspections are discussed in section 4.1.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant has provided attestation that the studies were conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with the ICH Guidelines for Good Clinical Practice (GCP).

Financial Disclosure

The Applicant has attested to the fact that they have not entered into any financial arrangements with their clinical Investigators whereby the value of compensation to the Investigator could be affected by the outcome of the study as defined in 21 CFR §54.2(a). The Applicant also certified that no Investigator had a proprietary interest in NV-101 or a significant equity in the Applicant as defined in 21 CFR §54.2(b), and that no Investigator was the recipient of significant payments of other sorts as defined in 21 CFR §54.2(f).

Patient Disposition

Seven clinical sites in the US enrolled subjects. 183 were screened and 33 did not meet initial screening or final inclusion/exclusion criteria and were not randomized into the study.

As noted in the study report, 150 subjects were randomized and received study drug. Of the 99 subjects randomized to the OraVerse treatment group, 3 subjects (3%) did not complete the 2-hour observation period, 6 subjects (6.1%) did not complete the telephone follow-up, and 2 subjects (2%) did not complete the in-clinic follow-up appointment. In contrast, of the 51 subjects randomized to the sham injection treatment group, all subjects completed both the observation period and in-clinic safety follow-up; but 1 subject (2%) did not complete the telephone follow-up appointment.

According to the Applicant, no subjects 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 (5) “dropouts” from the OraVerse treatment group who were documented as withdrawing or being withdrawn prematurely.

Protocol Violations/Deviations

The study report described a total of eleven (11) major deviations across all seven clinical sites. Six (6) subjects had major deviations occur during the informed consent process (102, 224, 410, 528, 530, 701); however, these deviations did not affect the safety of the subjects or integrity of study data.

A total of four (4) subjects had major deviations with respect to the inclusion and/or exclusion criteria (103, 203, 209, and 622). Three (3) of these subjects (2 in the OraVerse treatment group, and 1 in the sham injection group) were undergoing mandibular procedures, but were not given an Inferior Alveolar Nerve Block (IANB) during the administration of the dental anesthetic. The fourth subject was in the OraVerse treatment group, and reported "tingling" rather than "numbness" of the relevant lip quadrant after the dental procedure.

After database lock, it was discovered that an allergy to dental anesthetic was documented in the CRF of subject 111, randomized to the OraVerse treatment group. This allergy and apparent deviation from exclusion criteria (allergy or intolerance to lidocaine, epinephrine, sulfites, phentolamine, nitrous oxide, or topical benzocaine) was not documented as a deviation, but the investigator verified, in the selection of non-selection criteria, that the subject was eligible for the study.

One (1) subject had a major deviation occur during study procedures (302). This subject was in the sham injection treatment group, and the sham injection was mistakenly administered by penetrating the tissue with the needle. All Case Report Forms (CRFs) were reviewed and all information above provided by the Sponsor was verified.

Table 4. Demographics Table

Demographic Variable	OraVerse® Mandible N=48	OraVerse® Maxilla N=51	OraVerse® Total N=99	Sham Mandible N=23	Sham Maxilla N=28	Sham 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)

The demographics table (Source: sponsor submission) above shows an even distribution of gender and ethnicity by percentage in OraVerse and sham treatment arms. Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)
Two baseline characteristics have been 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 subjects 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 subjects for pFAB reported normal for smiling, speaking and drinking, and absent for drooling. Following the dental procedure, a proportion of subjects in both treatment groups reported a variety and/or combination of functional deficits in smiling, speaking, drinking, and drooling.

The OraVerse and sham injection groups were well balanced with respect to baseline vital signs. A summary of mean baseline vital signs is presented below.

Table 5. Mean Baseline Vital Signs-Sponsor's submission

Vial Sign	Treatment Allocation OraVerse	Sham
Systolic (mmHg)		
Prior to local anesthetic	95.0	95.6
Prior to study drug	98.9	96.9
Diastolic (mmHg)		
Prior to local anesthetic	59.4	59.9
Prior to study drug	62.2	61.3
Pulse (beats/min)		
Prior to local anesthetic	93.1	91.8
Prior to study drug	93.7	90.8

The first Wong-Baker pain rating scale (W-B PRS) was completed after local anesthetic administration and prior to study drug; both treatment groups were comparable.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Patient treatment compliance was not an issue for this study, because the study treatment was administered by dentists.

Concomitant medications, including any analgesics taken for intraoral pain, medications previously prescribed, and medications required to treat an adverse event, were to be recorded within 24 hours of local anesthetic administration, during the dental procedure, at the time of study drug administration, and during the observation period inclusive of the follow-up appointment.

No subjects required opioid analgesics, adequate pain control was achieved with non-opioid analgesics. Within the 2-hour observation period, 7.8% of the sham group reported analgesic use; 13.7% of subjects in this group reported use of analgesics from the time of discharge to the in-clinic follow-up visit. In contrast, 4% of the OraVerse group reported analgesic use during the observation period, and 9.1% of the group reported analgesic use after discharge to the time of the in-clinic follow-up visit.

Efficacy Results – Primary Endpoint

The clinical data used in this review were derived from trials conducted by the Applicant. As per the approval letter, dated May 9, 2008, delineates post-marketing requirements, including clinical endpoint assessments using validated metrics include:

- Time to return of normal sensation of the lip and where applicable, the tongue
- Time to return of normal function for speech, smiling, drinking, eating and not drooling

However, the protocol and study report submission describe the above as secondary endpoints exploratory in nature and this study was not powered to detect a statistically significant treatment difference. Both protocol and study report submission further note that the primary endpoint of the study was safety and tolerability of OraVerse as measured by adverse events, vital signs, oral cavity assessments, nerve injury, and analgesics for intraoral pain, which are addressed in section 8 of this review. The clinical endpoints from the approval letter noted above are assessed in this section. Further detail of efficacy assessment can be found in the statistician's review.

Efficacy variables were evaluated in trainable subjects 4 and 5 years of age and include the following:

- 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
- For mandibular procedures, time to normal tongue sensation as measured by standardized lip/tongue palpation procedure

Table 6. Study Disposition By Age

Age	OraVerse (%)	Sham (%)	Total (%)
	N=99	N=51	N=150
2	2 (2.0)	3 (5.9)	5 (3.3)
3	18 (18.2)	8 (15.7)	26 (17.3)
4	39 (39.4)	20 (39.2)	59 (39.3)
5	40 (40.4)	20 (39.2)	60 (40.0)

The Kaplan-Meier method was used to determine the median and the associated 95% confidence interval for the time to recovery of normal function measured by FAB, recovery of normal lip sensation and recovery of normal tongue sensation. The log-rank test was used to test for treatment group stratified by the location of the dental procedure, no multiplicity adjustment was performed.

Time to Normal Function measured by pFAB

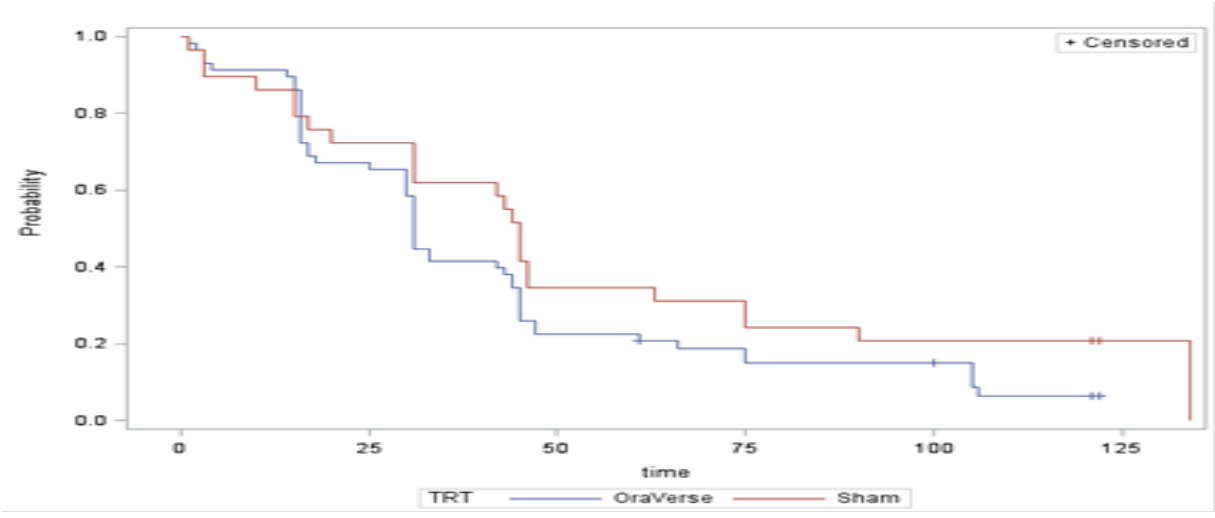
The mITT pFAB analysis set includes all randomized subjects 4 to 5 years of age who were trainable in pFAB, have normal pFAB at baseline prior to administration of local anesthetic, and have at least one abnormal function (smiling, speaking, drinking, or drooling) at completion of the dental procedure as rated by the observed.

Table 7. Modified Intention To Treat Subgroup pFAB Analysis (Statistical Reviewer Analysis)

	OraVerse	Sham	p-value for log-rank test
mITT analysis set (N)	58	29	--------
Not recover function at the end of the 2-hr period: n (%)	5 (9)	6 (21)	--------
Median time to normal function pFAB in minutes (95% CI)	31 (30,44)	45 (31,63)	0.1365

The applicant's results for median time to normal function were 31.0 minutes (95% CI 30.0, 42.0) for the OraVerse group and 45.0 minutes (95% CI 31.0, 63.0), with p-value for Log-rank test was 0.1365, which is not statistically significant. The following is the Kaplan-Meier plot:

Figure 1. Time to Normal Function Measured by pFAB (Statistical Reviewer Analysis)



Time to Recovery of Normal Lip Sensation

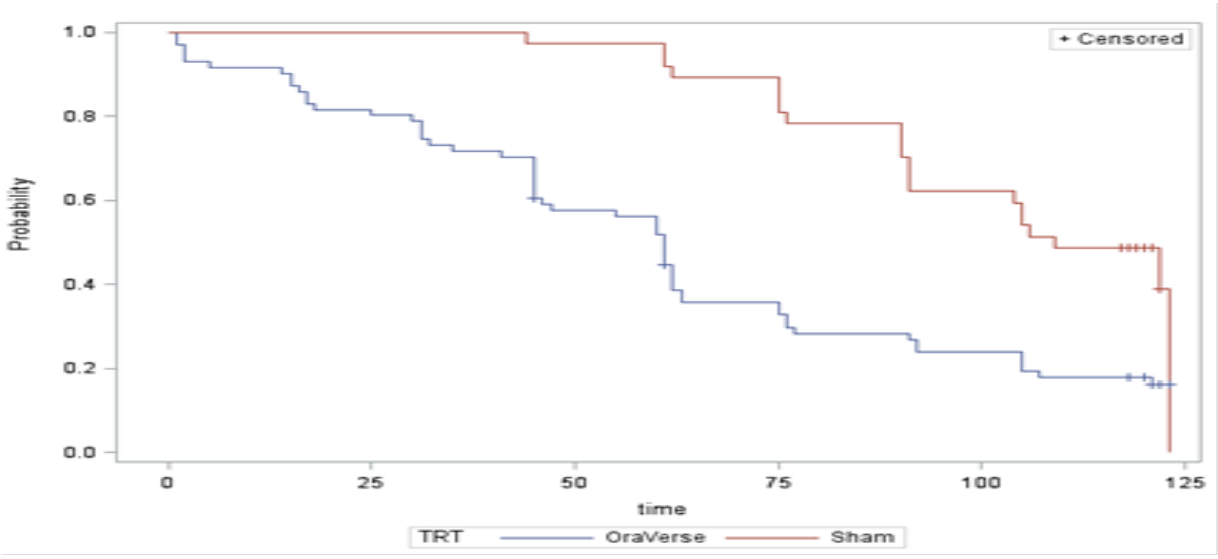
The mITT Lip Sensation analysis set includes all randomized subjects 4 to 5 years of age who were trainable in standardized lip palpation procedure, have normal tongue sensation at baseline prior to administration of local anesthetic, and have numbness of the relevant lip quadrant at completion of the dental procedure.

Table 8. Modified Intention To Treat Lip Sensation Subgroup Analysis (Statistical Reviewer's Analysis)

	OraVerse	Sham	p-value for log-rank test
mITT analysis set (N)	71	37	----------
Not recover normal lip sensation at the end of the 2-hr observation period: n (%)	14 (20)	18 (49)	----------
Median time to normal lip sensation in minutes (95% Confidence Interval)	61 (45,62)	109 (91,123)	< 0.0001

The applicant's results for median time to normal function were 61.0 minutes (95% CI 45.0, 62.0) for the OraVerse group and 109.0 minutes (95% CI 91.0, 123.0), with p-value for Log-rank test of < 0.0001, which is statistically significant. The following is the Kaplan-Meier plot:

Figure 2. Time to Recovery of Normal Sensation of Lip mITT Analysis (Statistical Reviewer Analysis)



Time to Recovery of Normal Tongue Sensation

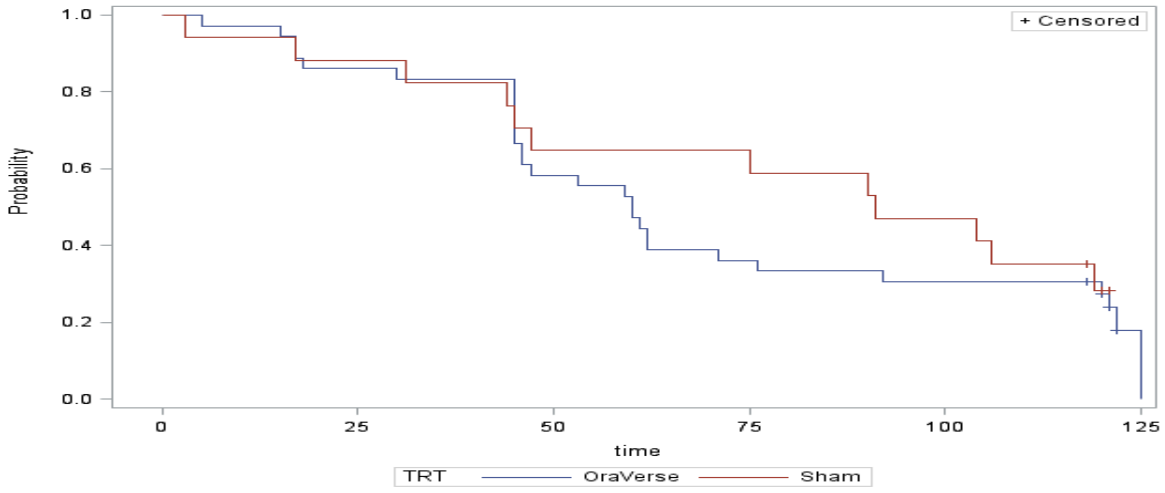
The mITT Tongue Sensation analysis set includes all randomized subjects 4 to 5 years of age who were trainable in standardized tongue palpation procedure, have normal tongue sensation at baseline prior to administration of local anesthetic, and have numbness of tongue at completion of the dental procedure.

Table 9. Modified Intention To Treat Tongue Sensation Subgroup (Statistical Reviewer Analysis)

	OraVerse	Sham	p-value for log-rank test
mITT analysis set (N)	36	17	----------
Not recover normal tongue sensation at the end of the 2-hr observation period: n (%)	10 (28)	5 (29)	----------
Median time to normal sensation in minutes (95% Confidence Interval)	60 (45,76)	91 (44,138)	0.5719

The applicant's results for median time to normal function were 60.0 minutes (95% CI 45.0, 76.0) for the OraVerse group and 91.0 minutes (95% CI 44,138), with p-value for Log-rank test of 0.5719, which is not statistically significant. The following is the Kaplan-Meier plot:

Figure 3. Time to Recovery of Normal Tongue Sensation Analysis



Overall Summary

This study was not designed or powered to demonstrate efficacy. The analysis of these endpoints was based on the corresponding modified ITT dataset. Two variables failed to achieve significance, although time to normal recovery was decreased in the OraVerse group for both of these variables. These endpoints were considered secondary endpoints according to the protocol and study report. The primary endpoint of the study was safety and tolerability of OraVerse as measured by adverse events, vital signs, oral cavity assessments, nerve injury, and analgesics for intraoral pain, which are addressed in section 8 of this review.

Data Quality and Integrity – Reviewers' Assessment

Case report forms were reviewed and revealed no issues with quality or integrity. OSI findings are discussed in section 4.1.

Efficacy Results – Secondary and other relevant endpoints

The secondary endpoints were reviewed in the section above. The study was not designed or powered to demonstrate efficacy.

Dose/Dose Response

OraVerse is injected at the tissue site where the local anesthetic was injected to achieve the desired effect. The phentolamine concentrations at the local sites were not analyzed; therefore, no exposure-response relationship for this product is available.

Durability of Response

According to the label, following OraVerse administration, phentolamine is 100% available from the submucosal injection site and peak concentrations are achieved 10-20 minutes after injection. The terminal elimination half-life of phentolamine in the blood was approximately 2-3 hours.

Persistence of Effect

This section is not applicable to this review because it is a single-dose regimen to reverse the effects of soft tissue anesthesia.

Additional Analyses Conducted on the Individual Trial

No further efficacy analyses were conducted for this study.

6.1.3. Study Conclusions

Due to recruiting challenges for subjects 2-3 years of age, only 2 subjects age 2 and 18 subjects age 3 were exposed to OraVerse in this study, these subjects were not trainable for efficacy measures. Although 2 of the 3 efficacy measures (pFAB and tongue numbness) in trainable subjects age 4-5 were not statistically significant, median time to recovery of function and sensation was less in the OraVerse group for both measures, and the study was not powered to demonstrate efficacy. Prior studies did include subjects age 3 and above, as noted in the safety database (Section 8.2, Table 10). The use of this drug product for this indication in the pediatric population meets criteria for extrapolation as described by a working group convened by FDA in 2011 to address the challenges of pediatric drug development (Dunne, 2011). The criteria for extrapolation are further described in section 10, figure 6. Therefore, we decided to extrapolate the efficacy findings from a prior study conducted in 4-11 year olds down to age 3, in addition to the safety findings in this study. This changes the indication from ≥ age 6 years to ≥ age 3 years, and the weight indication ≥ 15 kg remains the same. This application and rationale for this decision was discussed with the Pediatric Research Committee (PeRC) on February 17, 2016, who concurred with the decision.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Study PHE-11-001 is the only clinical trial submitted for this supplement. Therefore, there is no integrated summary of efficacy. See statistical review for more detailed efficacy analysis.

8 Review of Safety

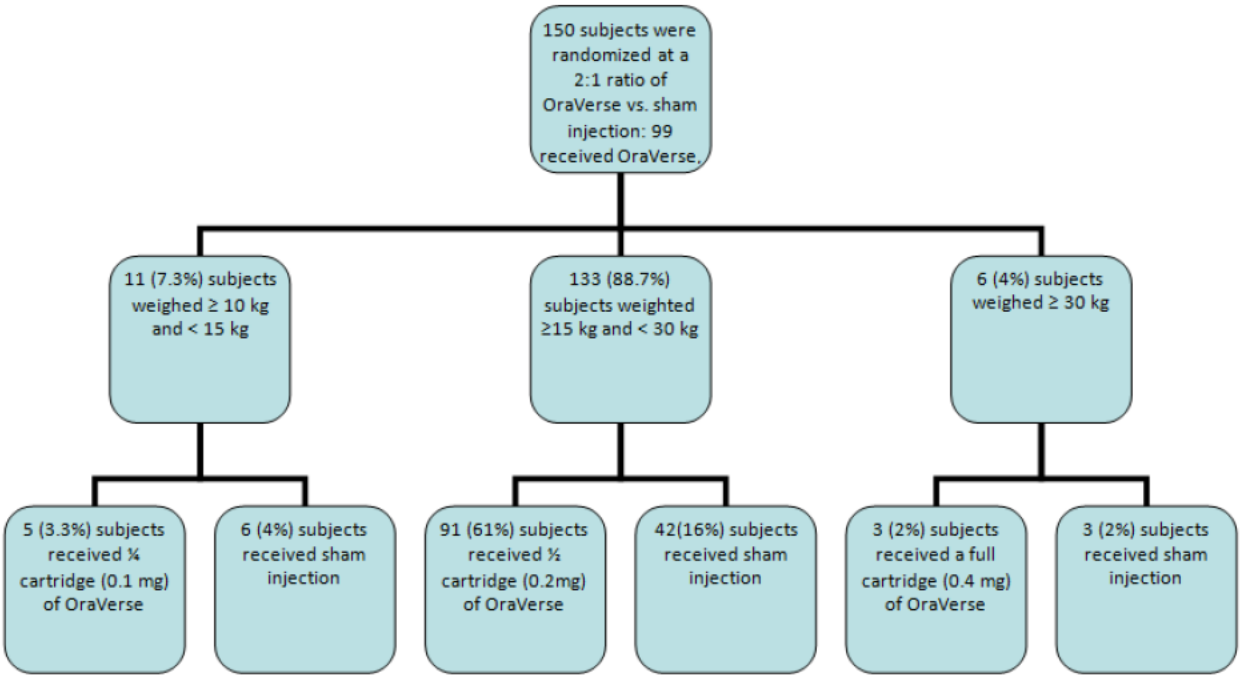
8.1. Safety Review Approach

OraVerse is approved for the reversal of soft tissue anesthesia reversal in adults and children ≥ 6 years old. The primary objective of the single study submitted for review was to determine safety and tolerability of OraVerse in subjects 2-5 years of age. This was 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. The safety review will focus on these parameters specific to this target population. No key safety review issues were identified *a priori*, and there were no clinical holds for safety during this study.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

150 subjects were randomized at a 2:1 ratio of OraVerse versus sham injection: 99 subjects received OraVerse, 51 received sham injections. Exposure to OraVerse and sham injections based on weight and dosage are as follows:



The number of subjects that received each dose of OraVerse is summarized below:

Treatment Group	OraVerse Dose (Subject Weight)			Total
	¼ Cartridge (0.1 mg) (≥ 10 kg but < 15 kg)	½ Cartridge (0.2 mg) (≥ 15 kg but < 30kg)	Full Cartridge (0.4 mg) (≥ 30 kg)	
OraVerse	5	91	3	99
Sham Injection	6	42	3	51
Total	11	133	6	150

OraVerse has been studied previously in pediatric populations. Table 10 lists the studies and phase of drug development.

Table 10. Pediatric Safety Database for OraVerse

Study	Design	OraVerse (dose)	Sham
Phase 4, Randomized Controlled Studies			
PHE-11-001 (age 2-5)	Multi-center, double-blind	N=99 (0.1 mg, 0.2 mg, 0.4mg)	N=51
Phase 2, Randomized Controlled Studies			
Nova-05-PEDS (age 4-11, ≥ 15 kg)	Multi-center blinded	N= 96 (0.2 mg, 0.4 mg)	N=56
Clinical Pharmacology			
NOVA-05-PEDS-PK (age 3-17)	Phase I, open-label	N=19 (0.2 mg, 0.4 mg)	N=0

8.2.2. Relevant characteristics of the safety population:

Procedures are differentiated between maxilla and mandible throughout the study because procedures in the mandible require an inferior alveolar nerve block and local anesthesia for mandible procedures affect the sensation of the tongue, whereas maxilla procedures do not. Table 11 (below) shows the distribution of subjects by age, study drug dosage, procedure, and site. The percentage of subjects undergoing mandibular and maxillary procedures were evenly distributed by treatment arm, as were percentage of subjects age 4-5 years old. In prior communications, the applicant noted significant challenges recruiting subjects age 2-3 years old, due to lack of dental procedures in this age group in which local anesthesia with a vasoconstrictor would be used. The Division agreed to allow the study to proceed with fewer 2-3 year olds than originally planned.

Medical histories of the subjects revealed the most common medical problems were asthma, skin disorders, and allergies (see Table 17). These conditions did not affect the study results because the systemic effects of OraVerse were transient and the subjects were asymptomatic.

Table 11. Pre-Defined Stratification Factors

	Result	OraVerse® N=99	Sham N=51	TOTAL N=150
Age	2	2 (2.0)	3 (5.9)	5 (3.3)
	3	18 (18.2)	8 (15.7)	26 (17.3)
	4	39 (39.4)	20 (39.2)	59 (39.3)
	5	40 (40.4)	20 (39.2)	60 (40.0)
Cartridge	1/4	5 (5.1)	6 (11.8)	11 (7.3)
	1/2	91 (91.9)	42 (82.4)	133 (88.7)
	1	3 (3.0)	3 (5.9)	6 (4.0)
Procedure	Mandibular	48 (48.5)	23 (45.1)	71 (47.3)
	Maxillary	51 (51.5)	28 (54.9)	79 (52.7)
Site	1	8 (8.1)	5 (9.8)	13 (8.7)
	2	16 (16.2)	8 (15.7)	24 (16.0)
	3	13 (13.1)	7 (13.7)	20 (13.3)
	4	20 (20.2)	10 (19.6)	30 (20.0)
	5	20 (20.2)	10 (19.6)	30 (20.0)
	6	20 (20.2)	10 (19.6)	30 (20.0)
	7	2 (2.0)	1 (2.0)	3 (2.0)
	TOTAL	99 (100.0)	51 (100.0)	150 (100.0)

8.2.3. Adequacy of the safety database:

The size of the safety is adequate for children age 4 years and above, weighing ≥ 15 kg, who received ½ cartridge of OraVerse. The size of the safety database is not adequate for lower age, weight, or dose. Only 2 subjects in the 2-year age group and 18 subjects in the 3-year age group were exposed to OraVerse. Only 5 subjects received ¼ cartridge of OraVerse (0.1 mg), and weighed 10-15 kg.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

No issues regarding data integrity or submission were discovered.

8.3.2. Categorization of Adverse Events

As described in the study report, there were a total of 48 subjects who reported 58 adverse events over the duration of the study: 32 subjects (32.3%) in the OraVerse group reported 36 adverse events, and 16 subjects (31.4%) in the sham group reported 22 adverse events. There were no AEs that lead to death, no serious adverse events, or discontinuations due to adverse events. According to the Applicant, the majority of adverse events in both treatment groups

were classified as either mild or moderate. The sham group had one (1) severe adverse event reported.

Nineteen (19) of the 32 subjects (59%) in the OraVerse group reporting AEs, and 8 of the 16 subjects (50%) in the sham group reporting AEs had AEs related to their study drug. The related AEs observed in the OraVerse group were mild (15.2%) or moderate (4%); whereas the related AEs in the sham group were, in a similar proportion to the OraVerse group, classified as mild (15.7%).

Also noted in the study report, the most frequently reported treatment-related event in the OraVerse group was oral pain in 10 subjects (10.1%); in comparison only 2 subjects (3.9%) in the sham group reported oral pain as a treatment-related event. Otherwise, there are no other apparent significant differences in the frequencies AEs reported between treatment groups.

Subjects randomized to OraVerse reported 6 (6.1%) moderate AEs and 26 (26.3%) mild AEs. In contrast, subjects randomized to a sham injection reported 1 (2%) significant AE, 2 (3.9%) moderate AEs, and 15 (29.4%) mild AEs. In the OraVerse group, moderate AEs were reported in 4 subjects (4%) for oral pain, and 1 subject (1%) for increased diastolic blood pressure.

Table 12. Incidence of Treatment Emergent Adverse Events- Adapted from submission table

	OraVerse (%)			Sham (%)		
	Mandible N=48	Maxilla N=51	Total N=99	Mandible N=23	Maxilla N=28	Total N=51
Number of Subjects with AE	15 (31.3)	17 (33.3)	32 (32.3)	7 (30.4)	9 (32.1)	16 (31.4)
Number of AEs	16 (33.3)	20 (39.2)	36 (36.3)	13 (56.5)	9 (32.1)	22 (43.1)

The most common adverse events were oral pain and toothache, as noted in Table 13 below.

Table 13 Incidence of Treatment Emergent Adverse Events 2% or greater (total) by Preferred Term- Adapted from Applicant submission

AE ≥ 2% by Preferred Term	OraVerse (%)			Sham (%)		
	Mandible N=48	Maxilla N=51	Total N=99	Mandible N=23	Maxilla N=28	Total N=51
Apthous stomatitis	----------	----------	----------	----------	1 (3.6)	1 (2.0)
Hypoesthesia oral	----------	----------	----------	----------	2 (7.1)	2 (3.9)
Lip haemorrhage	----------	----------	----------	1 (4.3)	----------	1 (2.0)
Lip oedema	----------	----------	----------	1(4.3)	----------	1(2.0)
Lip swelling	----------	1 (2.0)	1(1.0)	----------	1 (3.6)	1 (2.0)
Lip ulceration	----------	----------	----------	1(4.3)	----------	1 (2.0)
Mouth ulceration	1(2.1)	1(2.0)	2(2.0)	1(4.3)	----------	1(2.0)
Oral mucosa erosion	----------	----------	----------	1(4.3)	----------	1(2.0)
Oral mucosa discoloration	----------	----------	----------	1(4.3)	----------	1(2.0)
Oral pain	7(14.6)	8(15.7)	15(15.2)	3(13.0)	4(14.3)	7(13.7)
Tooth ache	----------	2(3.9)	2(2.0)	----------	----------	----------
Mouth injury	1(2.1)	----------	1(1.0)	1(4.3)	----------	1(2.0)
Skin abrasion	----------	----------	----------	----------	1(3.6)	1(2.0)
Tongue injury	2 (4.2)	----------	2(2.0)	----------	----------	----------

8.3.3. Routine Clinical Tests

The study did not include clinical laboratory monitoring. Due to the acute use of OraVerse and limited systemic exposure at even the highest doses in previous studies, as well as the safety profile for Regitine, no laboratory evaluations were required of the applicant and none were performed. The T_{max} of OraVerse is 10-20 min, with a terminal elimination half-life of 2-3 hours. Since OraVerse affects vital signs, such as heart rate and blood pressure, these parameters were monitored rather than laboratory tests. Study-specific safety assessments are addressed in section 8.5.1.

8.4. Safety Results

8.4.1. Deaths

No deaths occurred during this study.

8.4.2. Serious Adverse Events

No serious adverse events occurred during this study.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

No adverse events led to discontinuation of the study or subjects to drop out.

8.4.4. Significant Adverse Events

The narrative provided by the Applicant for the single subject in the sham treatment group who experienced a severe adverse event, classified as unrelated to the study drug, is provided below:

> Subject 211, a 5-year-old black female weighing 24kg was treated with one-half cartridge of local anesthetic at 12:42 via supraperiosteal injection in the upper left quadrant after application of topical anesthetic. Nitrous oxide and supplemental injections of local anesthetic administered per protocol. The subject underwent a cavity preparation/restoration procedure. The subject was randomized to sham injection at 13:03, which was completed by 13:11. The subject presented with no concurrent illnesses at baseline and a medical history, which included allergy to penicillin and amoxicillin, eczema and precocious puberty. The onset of the severe adverse event "pain intraoral" (investigator term) was recorded at 13:20. At 13:36, 200 mg of Ibuprofen was administered to treat the event, which resolved at 14:05.

According to the investigator, the adverse event was not serious, and was determined to be unrelated to the study. Although the event did not cause the subject to be withdrawn from the study, the pFAB and specific oral cavity assessments at 30 minutes post dose were not completed. These were successfully completed at the 60-minute time point with normal pFAB ratings/function and a normal specific oral cavity assessment at both the procedure and injection site.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Of the reported treatment-emergent adverse events (TEAE), oral pain was reported in the OraVerse group with higher frequency (10.1%) than the sham group (3.9%). Therefore, OraVerse is associated with increased incidence of oral pain.

Table 14. Summary of Treatment Emergent Adverse Events (from Study Report)

	OraVerse®			Sham		
	Mandible N=48	Maxilla N=51	Total N=99	Mandible N=23	Maxilla N=28	Total N=51
Number of adverse events	8	13	21	4	5	9
Subjects with adverse events	7 (14.6)	12 (23.5)	19 (19.2)	3 (13.0)	5 (17.9)	8 (15.7)
Subjects with adverse events that lead to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with severe adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with moderate adverse events	3 (6.3)	1 (2.0)	4 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with mild adverse events	4 (8.3)	11 (21.6)	15 (15.2)	3 (13.0)	5 (17.9)	8 (15.7)
Subjects discontinued due to adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

8.4.6. Laboratory Findings

Not applicable.

8.4.7. Vital Signs

The following protocol-specified criteria denote reportable changes in vital signs:

1. Decrease in systolic blood pressure of >20 mmHg on two consecutive measurements after administration of study drug relative to baseline systolic blood pressure.
2. Decrease in diastolic blood pressure of >20 mmHg on two consecutive measurements after administration of study drug relative to baseline diastolic blood pressure.
3. Increase in pulse of 20 bpm two consecutive measurements after administration of study drug relative to baseline pulse.

The OraVerse group had a higher baseline SBP (98.9 mmHg compared to 96.9 mmHg) prior to study drug administration. Both treatment groups had a decrease in SBP after study drug administration and at 15 minutes post-dose. At 30 and 60 minutes the mean SBP's of each treatment group followed opposite trends: the OraVerse group's mean SBP increased from 97.1 to 98.1 mmHg then decreased to 95.7, while the sham group's mean SBP decreased from 95.7 to 95.4 mmHg then increased to 96.1 mmHg. Aside from the immediate drop in mean SBP after study drug administration (OraVerse or sham), the trend between treatment groups was comparable.

Both treatment groups had an increase in DBP immediately after administration of study drug, followed by a continuous drop in the OraVerse group. The sham treatment group, however, had a decrease in DBP 15 minutes after sham injection, and a slight increase at 30 minutes before displaying a mirrored drop comparable to the OraVerse group.

The OraVerse treatment group's baseline mean heart rate was higher, and remained higher for the duration of the observation period. Both treatment groups had a slight increase post-study drug administration.

A comparison of the vitals relative to baseline data prior to anesthetic administration (Section 14.3.17 in the submission) reveals there was a > 20 mmHg decrease in systolic blood pressure in 2 OraVerse subjects (2%) and 3 sham subjects (5.9%). The same analysis of systolic blood pressures relative to the baseline measurements before study drug administration (Section 14.3.18) showed that the same number and proportion of sham subjects (3 subjects or 5.9%) had a >20 mmHg drop in SBP; but the number of OraVerse subjects with this drop increased to 12 subjects (12.1%).

An analysis of diastolic blood pressure drops of >20 mmHg shows an increase in the number of OraVerse subjects from 2 subjects (2%) relative to DBP measurements prior to anesthetic administration to 7 subjects (7.1%) relative to DBP measurements prior to study drug administration. In contrast, the sham group has a slight decrease in the number of subjects with this substantial decrease in DBP; more specifically, there were 2 subjects (3.9%) relative to baseline DBP prior to anesthetic, and only subject (2%) relative to baseline DBP measured prior to drug administration.

When assessing for an increase in pulse of > 20 bpm both treatment groups had the same number of subjects with this substantial increase regardless of the baseline comparison: 10 OraVerse subjects (10.1%) and 3 sham subjects (5.9%).

When comparing the changes from the different baselines, the OraVerse treatment group had more subjects meeting one or more of the above criteria (substantial decrease in the SBP or DBP, or substantial increase in pulse) relative to measurements prior to study drug administration: 24 OraVerse subjects (24.2%) meeting 1 or more criteria compared to 7 sham subjects (13.7%). In contrast, relative to the measurements prior to local anesthetic administration the groups were comparable with 11 subjects (11.1%) in the OraVerse group meeting one or more criteria and 6 subjects (11.8%) from the sham group. Most importantly, all subjects were asymptomatic and the noted symptoms were short-lived and resolved without treatment. The active ingredient in OraVerse, phentolamine mesylate, produces an alpha-adrenergic block of relatively short duration resulting in vasodilation when applied to smooth muscle. Therefore, the OraVerse group having more subjects with transient decreased blood pressure and increased heart rate after study drug administration is an expected outcome. The applicant noted the transience and resolution of noted symptoms, and subjects required no treatment. These effects are further described in the OraVerse package insert in section 5, “warnings and precautions.”

8.4.8. Electrocardiograms (ECGs)

Not Applicable.

8.4.9. QT

Not Applicable.

8.4.10. Immunogenicity

Not Applicable.

8.5. Analysis of Submission-Specific Safety Issues

Not Applicable

8.5.1. Study-Specific Safety Assessments

Wong-Baker Pain Rating Scale

The W-B PRS was used to evaluate the incidence, severity, and duration of intraoral pain in 4 and 5 year old trainable subjects. The scale uses pictures of facial expressions that correspond with descriptions and numerical ratings. An example of the scale is below.

Figure 4 Wong-Baker Pain Rating Scale

Source: www.wongbakerfaces.org, the scale was adjusted in this trial to 1 decimal place, 10=1.0, 8=0.8, etc.

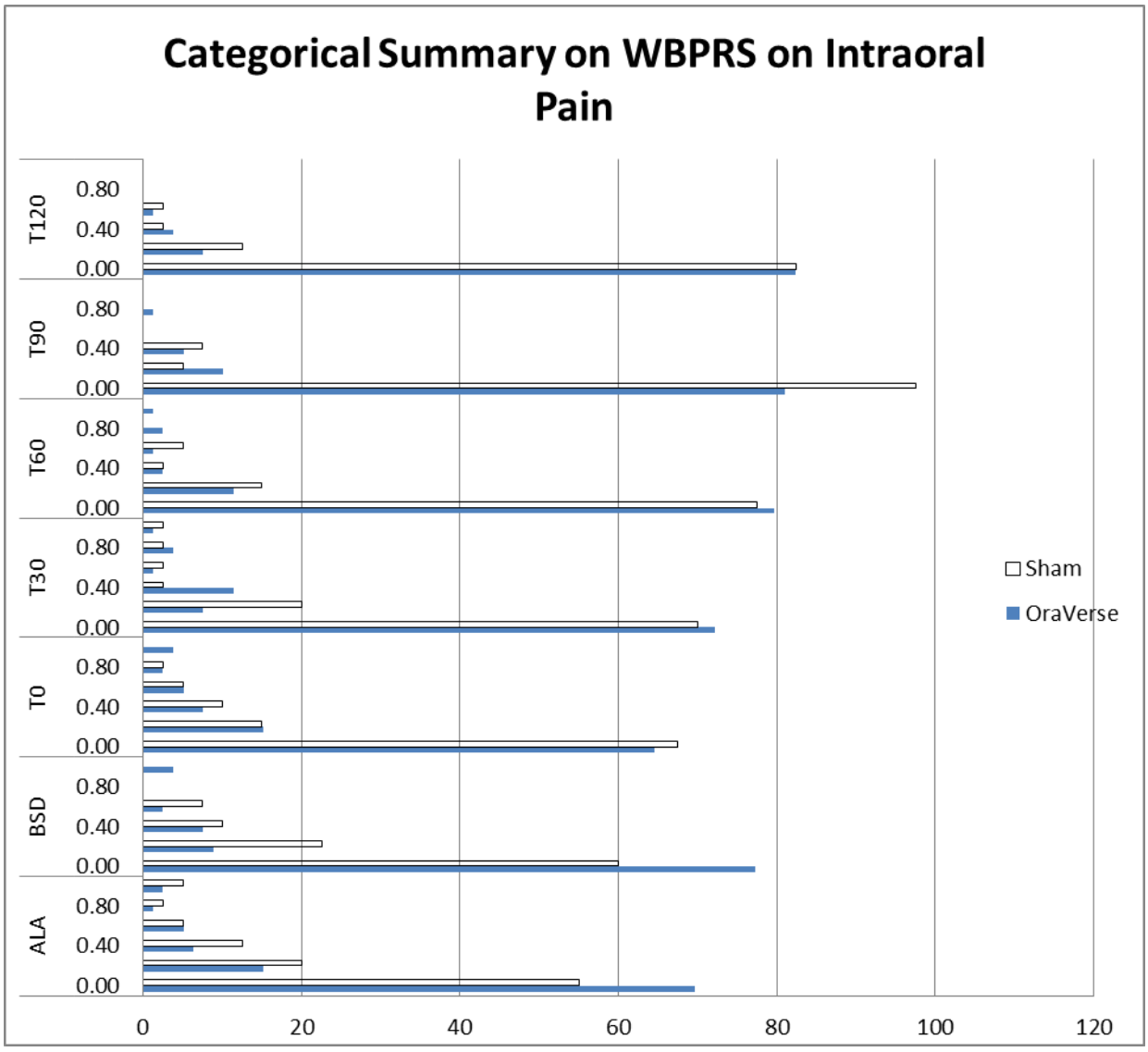
A total of 79 subjects (79.8%) in the OraVerse group, and 40 subjects (78.4%) in the sham group were included in mITT analyses. The sham group had a slightly higher mean W-B PRS score (1.0) than the OraVerse group (0.6) after local anesthetic administration; however, after administration of study drug the mean score reported by the OraVerse group peaks (0.8) while the sham group's mean score decreases (0.6). For the remaining time points, the mean W-B PRS scores for both groups are comparable.

In the categorical summary of the W-B PRS scores for each time point, the individual group trends show that the sham group has 22 subjects (55%) report experiencing no intraoral pain. Prior to study drug administration, after study drug administration (sham injection) and every time point thereafter the number of subjects reporting no intraoral pain continuously increases. In contrast, the OraVerse group begins with 55 subjects (69.6%) reporting no intraoral pain; prior to study drug administration this increases to 61 subjects (77.2%). After study drug administration the number of subjects, experiencing absence of intraoral pain decreases to 51 subjects (64.6%) which continuously increases thereafter. It should be noted that the OraVerse group begins with a higher proportion of subjects reporting no intraoral pain after local anesthetic (69.6% versus 55% in the sham group); and still, immediately after study drug administration, when the number of subjects in the OraVerse group without intraoral pain decreases, both groups have a similar proportion of subjects (64.6% in the OraVerse group, and 67.5% in the sham group) reporting no intraoral pain.

When assessing the treatment group differences in the duration of intraoral pain the OraVerse and sham group had a comparable proportion of subjects beginning immediately after study drug administration through to the 120-minute post-dose time point reporting an absence of intraoral pain. At this final time point 65 (82.3%) OraVerse subjects and 33 (82.5%) sham subjects report no intraoral pain. Similarly, when assessing the severity of W-B PRS scores, OraVerse and sham group have a comparable proportion of subjects reporting no pain (64.6% versus 67.5%), mild pain (hurts a little bit, 15.2% versus 15%), moderate pain (hurts little more 7.6% versus 10%, hurts even more – 5.1% versus 5%), and severe pain (hurts whole lot 2.5% for both groups). The OraVerse group has 3 subjects (3.8%) reporting the most severe pain (hurts worst) in comparison to the sham group with no subjects (0%) indicating intraoral pain of this severity; this observation though is likely not indicative of the study drug since the same proportion of subjects in the OraVerse group reported this severe pain prior to study drug administration.

The proportion of subjects in the OraVerse and sham groups experiencing each level of severity reported during the two-hour observation period is comparable: 30.4% of OraVerse subjects and 30% of sham subjects reported no pain; 22.8% of OraVerse subjects and 22.5% of sham subjects reported mild pain; 31.7% of OraVerse subjects and 32.5% of sham subjects reported moderate pain; and 7.6% of OraVerse subjects and 7.5% of sham subjects reported severe pain.

Figure 5. Categorical Summary on WBPRS



Source: Table 14.3.6 from submission
LEGEND: **Y-AXIS**: WB-PRS= Wong-Baker Pain Scale, Description of numerical ratings: No hurt=0, Hurts Little Bit = 0.2, Hurts Little More= 0.4, Hurts Even More = 0.6, Hurts Whole Lot = 0.8, Hurts Worst = 1.0. Time Points: ALA = after local anesthetic, BSD = before study drug administration, T0 = immediately after study drug administration, T30 = 30 minutes after study drug, T60 = 60 minutes after study drug, T90 = 90 minutes after study drug, T120 = 120 minutes after study drug. X-Axis = Number of subjects in each study arm; OraVerse N=79, Sham N=40. **X-AXIS**: Percentage of subjects in each group.

Oral Cavity Assessments

General oral cavity assessments (GOCA) were completed prior to local anesthetic and study drug administration (baselines), then immediately after study drug is administered, prior to discharge and at the in-clinic follow-up appointment. Specific oral cavity assessments (SOCA) were completed immediately following injection of the local anesthetic, at 15, 30, 60, 120-minutes post-dose study drug administration, prior to discharge, and at the in-clinic safety follow-up appointment. Overall, the OraVerse and sham treatment groups were similar in the proportion of reported clinically significant oral cavity assessments across all time points. There were no reports of nerve injury.

Table 15. Proportion of Clinically Significant Oral Cavity Assessments Across All Time Points

Time Point	Treatment Allocation	
	OraVerse N=99	Sham N=51
15 minutes post-drug administration	1 (1.0)	1 (2.0)
30 minutes post-drug administration	1 (1.0)	1 (2.0)
60 minutes post-drug administration	3 (3.0)	2 (3.9)
120 minutes post-drug administration	4 (4.0)	2 (3.9)
Prior to Discharge	4 (4.0)	2 (3.9)
In-Clinic Follow-Up	3 (3.0)	1 (2.0)

Use of Analgesics for Oral Pain

The sham group reported a slightly higher incidence of analgesic use. Within the 2-hour observation period 7.8% of the sham group reported analgesic use; 13.7% of subjects in this group reported use of analgesics from the time of discharge to the in-clinic follow-up visit. In contrast, 4% of the OraVerse group reported analgesic use during the observation period, and 9.1% of the group reported analgesic use after discharge to the time of the in-clinic follow-up visit. No subjects reported use of opioid analgesics.

8.6. Specific Safety Studies/Clinical Trials

No other safety concerns were identified, no further studies were performed.

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

Not applicable.

8.7.2. Human Reproduction and Pregnancy

Not applicable, this is a pediatric study satisfying a PREA postmarketing requirement.

8.7.3. Pediatrics and Assessment of Effects on Growth

No effects on pediatric growth were assessed for this study.

8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

According to the last patient adverse drug event report (PADER) covering the same period, there was one (1) initial non-expedited adverse drug event (ADE) report, no follow-up non-expedited report, and no initial expedited reports. The ADE preferred term, "swelling of face" reported in the non-expedited report is non-serious and expected. An x-ray revealed no abnormalities, and the cause was most likely due to mechanical trauma of the needle tip into a vein, venule, or capillary bed. A literature search revealed no new safety concerns for OraVerse or phentolamine mesylate. No other indications are being pursued for OraVerse and no other Divisions are reviewing this sNDA.

8.8.2. Expectations on Safety in the Postmarket Setting

OraVerse is administered by dentists with prerequisite training to perform submucosal injections in all populations discussed. There are no further safety concerns other than those previously discussed in this review.

8.9. Additional Safety Issues From Other Disciplines

Not Applicable.

8.10. Integrated Assessment of Safety

A total of 48 of the 150 subjects (32%) reported 58 adverse events. There were no deaths or other serious adverse events and no subject discontinued due to an adverse event. All but one (1) adverse event was rated as mild or moderate. The single severe adverse event of intraoral pain was experienced by a subject randomized to the sham injection. The majority of the AEs (27/48, 56%) were deemed related to study drug treatment; a slightly higher proportion of OraVerse subjects reported treatment-related AEs (19/32, 59%) in comparison to the sham subjects (8/16, 50%). Of the reported treatment-related events, oral pain was reported in the

OraVerse group with a slightly higher frequency (10.1%) than the sham group (3.9%). These results reveal that OraVerse is associated with increased incidence of oral pain.

Clinically significant changes in the vital signs, as defined per protocol, were observed in both treatment groups, but the frequencies between both groups varied depending on the baseline values used. The OraVerse group had a higher frequency of subjects (12 subjects, 12.1%) reporting a decrease of > 20 mmHg in systolic blood pressure relative to measurements of prior to study drug; three (3) subjects in the sham group (5.9%) of subjects reported this clinically significant change in systolic blood pressure. A slightly higher proportion of subjects in the OraVerse treatment group (7 subjects, 7.1%) also reported a decrease of > 20 mmHg in diastolic blood pressure relative to measurements prior to study drug; relative to this baseline, only 1 subject (2%) in the sham group reported this significant change. Lastly, an increase in heart rate of > 20 bpm was observed in 10 OraVerse subjects (10.1%) and 3 sham subjects (5.9%) regardless of baseline comparison. Overall, in assessing the number of subjects experiencing one of more of the clinically significant changes in vitals mentioned above, the proportion of subjects in each treatment group was comparable (11.1% in the OraVerse group, 11.8% in the sham group) relative to baseline prior to local anesthetic administration; but relative to the baseline prior to study drug administration the OraVerse group had a higher incidence of subjects (24 subjects, 24.2%) in comparison to the sham group (7 subjects, 13.7%) with one or more clinically significant changes in vitals. There is some evidence in this study for an effect of OraVerse treatment on blood pressure (decrease in systolic and diastolic blood pressure); however, all subjects were asymptomatic and the noted symptoms resolved quickly without treatment.

The incidence of subjects in both treatment groups experiencing intraoral pain (as measured by the W-B PRS) is comparable at all time points post study drug administration, including immediately after study drug administration. The mean W-B PRS scores for the sham group continuously decreases over time, but peaks in the OraVerse group (0.8) after study drug administration before decreasing in a comparable fashion to the sham group. The OraVerse group had 3 subjects (3.8%) reporting the most severe pain (hurts worst); in comparison, the sham group had no such reports. However, the observation is likely not indicative of the study drug since the sample proportion of subjects in the OraVerse group reported this pain severity prior to study drug administration. Thus, the duration and severity of intraoral pain measured by the W-B PRS was comparable between the two treatment groups. These data suggest that OraVerse was not associated with more severe oral pain than the sham.

Results of the oral cavity assessments, both a broad evaluation of the mouth (GOCA) and specific to procedure and injection site (SOCA), showed minor abnormalities. The proportion of subjects in each treatment group with clinically significant abnormalities were similar across all time points. The incidence of subjects in both treatment groups experiencing intraoral pain (as measured by the W-B PRS) is comparable at all time points post study drug

administration, including immediately after study drug administration.

Lastly, there were no reports of nerve injury in both treatment groups, and the frequency of subjects with analgesic use during the 2-hour observation period and within 48 hours of discharge was higher in the sham group. This data reveals that treatment with OraVerse is not associated with an increased use of analgesics for intraoral pain or nerve injury.

Overall, these data demonstrate that injections of a quarter, half or full cartridge of OraVerse (0.1, 0.2 and 0.4 mg of phentolamine mesylate), when administered by local injection following maxillary or mandibular soft tissue anesthesia, were well tolerated and safe for children 2-5 years of age in this study.

9 Advisory Committee Meeting and Other External Consultations

This section is not applicable to this sNDA review, as there are no issues to be addressed by an advisory committee (AC).

10 Labeling Recommendations

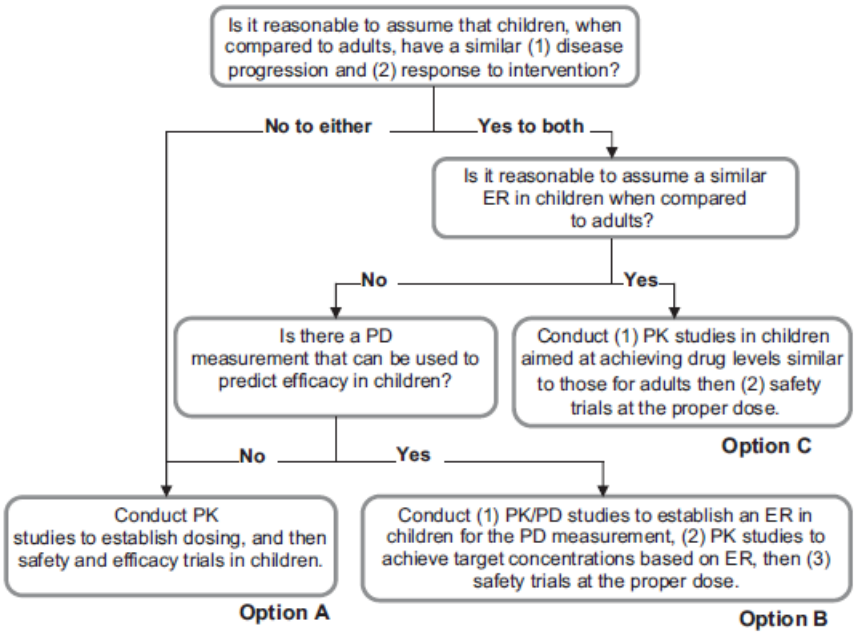
10.1. Prescribing Information

Reviewer Comment: The Sponsor submitted the following proposed labeling change in section 2.2 Dosing in Special Populations:

"In pediatric patients weighing ≥ (b) (4) kg and < (b) (4) kg, the maximum dose of OraVerse recommended is (b) (4)

Due to study recruitment challenges, fewer subjects age 2-3 were enrolled than initially planned for this study. Also, the weight range for subjects for this study is 13-35.8 kg. Therefore, the proposed labeling needs to change to reflect the demographics of the patients actually studied. Although this study was not designed or powered to demonstrate efficacy, the use of this drug product for this indication in the pediatric population for OraVerse fulfills the criteria for extrapolation described in Figure 6. Therefore, efficacy is extrapolated down to age 3 and 15 kg. This application was presented to PeRC on February 17, 2016, and they concurred with extrapolation down to age 3 and 15 kg.

Figure 6. Decision Tree for Pediatric Clinical Trials



Source: Dunne, J. e. (2011). Extrapolation of Adult Data and Other Data in Pediatric Drug-Development Programs. Pediatrics, 2010-4387.
Pediatric study decision tree. This algorithm can be applied to systemically active drugs administered through the oral, intravenous, subcutaneous, or other routes. When applicable, the pediatric dose and dosage regimen can be estimated from adult and pediatric pharmacokinetic data. The algorithm does not apply to locally active drugs, such as drugs administered topically, intranasally, or through oral inhalation. For such drugs, pharmacokinetic data are relevant for the estimation of systemic exposure in relation to safety but are not helpful for the estimation of appropriate effective pediatric doses, because the relevant biospace is local to the skin, nasal passages, or lung and not the blood. Consequently, for locally active products, the correct dose must be estimated clinically and then tested for each age group. ER indicates exposure response; PD, pharmacodynamic; PK, pharmacokinetic.

10.2. Patient Labeling

Not Applicable

10.3. Non-Prescription Labeling

Not Applicable

11 Risk Evaluation and Mitigation Strategies (REMS)

This section is not applicable to this sNDA submission.

12 Postmarketing Requirements and Commitments

- The Sponsor conducted this study in compliance with PREA.
- The conduct of the study revealed that adequate enrollment of 2-3 year olds for dental procedures involving the use of a local anesthetic with vasoconstrictor was not feasible.
- No further studies are warranted at this time because efficacy can be extrapolated down to age 3 and there is adequate evidence of safety in the current established database.
- Final assessment regarding whether this PMR (conducting a pediatric study in patients 2-5 years of age) will be considered fulfilled or if the applicant will be released from this PMR is under discussion.

13 Appendices

13.1. References

Adewumi A, H. M. (2008). The incidence of adverse reactions following 4% septocaine (articaine) in children. *Pediatric Dentistry*, 424-8.

College C, F. R. (2000). Bilateral versus unilateral mandibular block anesthesia in a pediatric population. *Pediatric Dentistry*, 453-57.

Dunne, J. e. (2011). Extrapolation of Adult Data and Other Data in Pediatric Drug-Development Programs. . *Pediatrics*, 2010-4387.

13.2. Financial Disclosure

The Applicant has attested to the fact that they have not entered into any financial arrangements with their clinical Investigators whereby the value of compensation to the Investigator could be affected by the outcome of the study as defined in 21 CFR §54.2(a). The Applicant also certified that no Investigator had a proprietary interest in OraVerse or a significant equity in the Applicant as defined in 21 CFR §54.2(b), and that no Investigator was the recipient of significant payments of other sorts as defined in 21 CFR §54.2(f).

Covered Clinical Study (Name and/or Number): PHE-11-001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: yes		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.6. Selected Tables from Submission

Table 16. Medical/Dental History-Safety Analysis Set

	OraVerse®			Sham		
	Mandible (N=48)	Maxilla (N=51)	Total (N=99)	Mandible (N=23)	Maxilla (N=28)	Total (N=51)
Medical conditions/diagnoses						
None	23 (47.9)	17 (33.3)	40 (40.4)	11 (47.8)	15 (53.6)	26 (51.0)
Yes	25 (52.1)	34 (66.7)	59 (59.6)	12 (52.2)	13 (46.4)	25 (49.0)
Heart Murmur	1 (2.1)	0 (0.0)	1 (1.0)	0 (0.0)	1 (3.6)	1 (2.0)
Rheumatic Fever	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mitral Valve Prolapse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Angina	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Heart Failure (CHF)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Heart Attack (MI)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Arrhythmias	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypotension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stroke (CVA)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asthma	8 (16.7)	11 (21.6)	19 (19.2)	2 (8.7)	4 (14.3)	6 (11.8)
COPD	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Emphysema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Glaucoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Alcoholism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Drug Abuse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rheumatoid Arthritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Osteoarthritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric Illness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Liver Disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Kidney Disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sinus Problems	0 (0.0)	2 (3.9)	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ulcer Disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
HIV/AIDS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Venereal Disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tuberculosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bleeding Disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Back Problems	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neck Problems	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Jaw Problems	1 (2.1)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin Problems	5 (10.4)	2 (3.9)	7 (7.1)	2 (8.7)	3 (10.7)	5 (9.8)
Frequent/Severe Headaches	0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Epilepsy/Seizure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)	1 (2.0)
Hypothyroidism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperthyroidism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Type 1 Diabetes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	OraVerse®			Sham		
	Mandible (N=48)	Maxilla (N=51)	Total (N=99)	Mandible (N=23)	Maxilla (N=28)	Total (N=51)
Type 2 Diabetes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anemia	1 (2.1)	2 (3.9)	3 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leukemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other (Medical Conditions)	19 (39.6)	28 (54.9)	47 (47.5)	11 (47.8)	9 (32.1)	20 (39.2)
Surgical history						
None	44 (91.7)	43 (84.3)	87 (87.9)	18 (78.3)	23 (82.1)	41 (80.4)
Yes	4 (8.3)	8 (15.7)	12 (12.1)	5 (21.7)	5 (17.9)	10 (19.6)
Cardiac Bypass	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Heart Valve Replacement	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pacemaker	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Joint Prosthesis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Maxillofacial Surgery	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Appendectomy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cancer Surgery	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other (Surgical History)	4 (8.3)	8 (15.7)	12 (12.1)	5 (21.7)	5 (17.9)	10 (19.6)
Allergy history						
None	43 (89.6)	46 (90.2)	89 (89.9)	18 (78.3)	23 (82.1)	41 (80.4)
Yes	5 (10.4)	5 (9.8)	10 (10.1)	5 (21.7)	5 (17.9)	10 (19.6)
Antibiotics	0 (0.0)	1 (2.0)	1 (1.0)	3 (13.0)	2 (7.1)	5 (9.8)
Dental Anesthetics	1 (2.1)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other (Allergy History)	4 (8.3)	5 (9.8)	9 (9.1)	4 (17.4)	5 (17.9)	9 (17.6)

Table 17. Incidence of Treatment-Emergent Adverse Events (All Causalities)

System Organ Class Preferred Term	OraVerse® Mandible (N=48)	OraVerse® Maxilla (N=51)	OraVerse® Total (N=99)	Sham Mandible (N=23)	Sham Maxilla (N=28)	Sham Total (N=51)
Number of Subjects with adverse events	15 (31.3)	17 (33.3)	32 (32.3)	7 (30.4)	9 (32.1)	16 (31.4)
Number of Adverse Events	16	20	36	13	9	22
GASTROINTESTINAL DISORDERS	10 (20.8)	12 (23.5)	22 (22.2)	7 (30.4)	8 (28.6)	15 (29.4)
APHTHOUS STOMATITIS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)	1 (2.0)
DIARRHOEA	1 (2.1)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
HYPOAESTHESIA ORAL	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.1)	2 (3.9)
LIP HAEMORRHAGE	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	1 (2.0)
LIP OEDEMA	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	1 (2.0)
LIP PAIN	0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
LIP SWELLING	0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)	1 (3.6)	1 (2.0)
LIP ULCERATION	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	1 (2.0)
MOUTH SWELLING	1 (2.1)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
MOUTH ULCERATION	1 (2.1)	1 (2.0)	2 (2.0)	1 (4.3)	0 (0.0)	1 (2.0)
NAUSEA	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	1 (2.0)
ORAL MUCOSA EROSION	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	1 (2.0)
ORAL MUCOSAL DISCOLOURATION	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	1 (2.0)
ORAL PAIN	7 (14.6)	8 (15.7)	15 (15.2)	3 (13.0)	4 (14.3)	7 (13.7)
TOOTHACHE	0 (0.0)	2 (3.9)	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0 (0.0)	2 (3.9)	2 (2.0)	1 (4.3)	0 (0.0)	1 (2.0)
INJECTION SITE HAEMATOMA	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	1 (2.0)
INJECTION SITE PAPULE	0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
PYREXIA	0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
INFECTIONS AND INFESTATIONS	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	1 (2.0)
UPPER RESPIRATORY TRACT INFECTION	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	1 (2.0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	4 (8.3)	1 (2.0)	5 (5.1)	1 (4.3)	1 (3.6)	2 (3.9)
LIP INJURY	1 (2.1)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
MOUTH INJURY	1 (2.1)	0 (0.0)	1 (1.0)	1 (4.3)	0 (0.0)	1 (2.0)
PROCEDURAL PAIN	0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
SKIN ABRASION	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)	1 (2.0)
TONGUE INJURY	2 (4.2)	0 (0.0)	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
INVESTIGATIONS	1 (2.1)	2 (3.9)	3 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)
BLOOD PRESSURE DIASTOLIC INCREASED	1 (2.1)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
BLOOD PRESSURE INCREASED	0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
BODY TEMPERATURE INCREASED	0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
HEART RATE INCREASED	0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (2.1)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
PAIN IN JAW	1 (2.1)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
EPISTAXIS	0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)

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/s/

SARAH J ARNOLD
03/17/2016
Clinical Review

RIGOBERTO A ROCA
03/17/2016