PRODUCT REGISTRY REPORT

Compound(s): OraVerse® / Phentolamine mesylate

Non-interventional post-authorization study on effectiveness of reversal of local anaesthesia and on the occurrence of local reactions and cardiovascular adverse events in patients treated with OraVerse® versus patients not treated with OraVerse® (control group) in Germany (ORAPAES)

Registry number: PHENLL06495

Registry name: ORAPAES

Registry initiation date [date first patient in (FPI)]: 18-Jun-2013

Registry completion date [last patient out (LPO)]: 31-Dec-2014

Registry design: A national multi-center non-interventional comparative cohort study to describe the effectiveness and safety in patients treated with OraVerse® compared with those not treated with OraVerse® in routine clinical practice irrespective of the patients' age and the concentrations of local anesthetics used.

Report date: 30-Jun-2015

This registry was performed in compliance with the guidelines for Good Epidemiology Practice. This report has been prepared based on the publication 'Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) – Guidelines for reporting observational studies – Ann Intern Med. 2007'[1,2].

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SYNOPSIS

Title of the registry:	Non-interventional post-authorization study on effectiveness of reversal of local anaesthesia and on the occurrence of local reactions and cardiovascular adverse events in patients treated with OraVerse® versus patients not treated with OraVerse® (control group) in Germany (registry number: PHENLL06495).
Design:	A national multi-center non-interventional comparative cohort study to describe the effectiveness and safety in patients treated with OraVerse® compared with those not treated with OraVerse® in routine clinical practice irrespective of the patients' age and the concentrations of local anesthetics used in accordance with the Summary of Product Characteristics (SmPC).
Objectives:	Primary objectives: The primary objectives concerned the effectiveness of reversal of local anesthesia in routine clinical practice by comparing patients treated with OraVerse® with those not treated with OraVerse® after local anesthetic procedures in routine clinical practice in terms of: Time to recovery of normal sensation in the lip/tongue. Time to recovery of normal function (eating, drinking and speaking). Secondary objectives: To compare the frequency of local reactions among patients treated with OraVerse® versus patients not treated with OraVerse® after local anesthetic procedures in routine clinical practice. To compare the frequency of acute cardiovascular events among patients treated with OraVerse® versus patients not treated with OraVerse® after local anesthetic procedures in routine clinical practice.
Treatment:	In this observational study, after routine dental procedure patients were either treated with OraVerse® or not (control group) under the sole responsibility of the treating dentists. OraVerse® is intended to be used at doses ranging from 200 to 800 micrograms in adults administered by intraoral submucosal injection. The OraVerse® cartridge must be used in an appropriate CE certified syringe system that permits aspiration. OraVerse® is indicated in patients at least 6 years old and weighing at least 15 kg. It is contraindicated in patients that are hypersensitive to the active substance or to any of the excipients.
Scientific committee and members:	Sponsor: Sanofi-Aventis Deutschland GmbH Director Medical & Scientific Affairs: [redacted] Project Leader: [redacted] Study Management: [redacted] Pharmacovigilance: [redacted] Statistician: [redacted] Epidemiologist: [redacted]

	Non-interventional Study Management: [redacted] Expert: [redacted] CRO: [redacted]
Publications (reference):	Study data were not published so far.
Introduction - **Background/rationale:**	Phentolamine mesylate, a pharmaceutical product marketed since the 1950s, is a competitive non-selective α1- and α2-adrenergic receptor blocker of relatively short duration. When applied to vascular smooth muscle, it produces an alpha-adrenergic block resulting in vasodilatation. The first indication for phentolamine mesylate was for the control of hypertensive emergencies, most notably due to pheochromocytoma, where it is administered by intravenous or intramuscular injection at doses from 3 to 5 mg. The vasodilatation properties of phentolamine led to its development as OraVerse® for reversal of anesthesia in lip and tongue and associated functional deficits, resulting from intraoral submucosal injection of local anesthetic containing a catecholamine vasoconstrictor following a routine dental procedure. Local reactions such as post-procedural pain (6%) and injection site pain (5.3%) were identified risks with OraVerse® during the clinical trials; other common adverse drug reactions include headache, tachycardia, bradycardia, increased blood pressure/hypertension, and oral pain. The majority of adverse reactions were mild and resolved within 24 hours. The effectiveness of OraVerse® was evaluated in double-blind, randomized, multicenter, controlled studies in patients undergoing dental restorative or periodontal maintenance procedures. In a phase II study OraVerse® was well tolerated and reduced the median duration of soft tissue anesthesia in the lip from 155 to 70 min ($p < 0.0001$).[3] Similar results have been gained in a pediatric phase II study including children of age 6 to 11 years.[4] In a phase III study setting, patients in the control groups received a sham injection. OraVerse® reduced the median time to recovery of normal sensation in the lower lip by 85 minutes (55%) and in the upper lip by 83 minutes (62%) compared to control ($p<0.0001$). There was also a significant reduction ($p<0.0001$) in the time to return to normal oral function (speaking, smiling, drinking and lack of drooling) in the OraVerse® group compared to control. The median time to normal lip sensation in patients 6 to 11 years of age was reduced by 75 minutes (56%) compared to control ($p<0.0001$). No overall differences in safety or effectiveness were observed between adult and pediatric patients.[5] An overview of the acceleration of recovery by OraVerse® in dental treatment is provided by Hersh and Lindemeyer 2010.[6] For the pharmacokinetics of OraVerse® after intravenous and intraoral injection for reversal of local anesthesia see Moore et al 2008.[7] Before administering OraVerse®, the majority of patients included in the clinical studies were treated with local anesthetic and a vasoconstrictor (e.g., epinephrine) at 1:100,000 concentration. Limited data have been submitted to support the effectiveness of OraVerse® when a local anesthetic with a vasoconstrictor at lower concentration is administered. <u>Rationale</u> In order to increase evidence of the overall effectiveness as well as overall safety in patients treated with OraVerse® in routine clinical practice whatever the

	concentrations of local anesthetics used, the study was designed to describe the effectiveness of reversal of local anesthesia and the frequency of local reactions and cardiovascular events associated with the use of OraVerse® in Germany. As OraVerse® is used by dentists in dental interventions and is not reimbursed, it is not recorded in any national databases/registers in the countries where it is used. So, the collection of information on a patient's profile, characteristics of dental intervention and acute clinical outcomes was to be made by dentists at the time of the dental procedures and the follow-up was to be organized from dentists' offices. A comparative design of the study was chosen to compare effectiveness of reversal of local anesthesia and the occurrence of local reactions and cardiovascular adverse events (AEs) in both treatment groups.
Methodology:	<u>Site and patient selection</u> It was originally planned to recruit 672 patients either treated or treated not with OraVerse® after routine dental procedure in 5 universities and 10 private practices including pediatric dental practices from all over Germany. Study sites were selected randomly from the list of centers interested in using OraVerse®. Patients that met all inclusion criteria but none of the exclusion criteria were included in the study consecutively by participating dentists in order to limit selection bias. Eligible for inclusion were patients that - received local anesthesia by intraoral submucosal injection of a local anesthetic containing epinephrine (adrenalin) (dilution 1:100,000 or 1:200,000), following a routine dental procedure such as teeth cleaning, calculus removal, scaling and planing, cavity filling, or crowning. - were at least 6 years old and weighed at least 15 kg. - accepted administration of OraVerse®. - signed an informed consent form. Patients that were allergic (hypersensitive) to OraVerse® or any other ingredient of the pharmaceutical (e.g., as indicated by a local reaction emerging after injection of OraVerse®) were to be excluded. The analysis set included patients that met the inclusion/exclusion criteria and consisted of the OraVerse® group and the control group (A and B): - OraVerse® group: A cohort of patients treated with OraVerse® under normal conditions of use and followed up to 24 hours after injection of anesthesia. - Control group A: A cohort of patients that were proposed OraVerse® but were not treated with OraVerse® and followed up to 24 hours after injection of anesthetic(s). - Control group B: there could be a selection bias introduced by the dentist as the decision to administer OraVerse® made by the dentist was not random and maybe related to the patient cardiovascular risk profile; thus it was expected that untreated patients will be different to treated patients in terms of risk of occurrence of cardiovascular events, complexity and duration of the dental procedure, and medical history and concomitant drugs. For these reasons, control group B was only to be considered as a backup control group if the recruitment rate would have been too low; i.e., if after 6 months the control group A encompassed less than 50 patients. These patients would have been also followed up to 24 hours after injection of anesthetic(s). <u>Data collection</u> On the day of dental procedure (day 1), data were collected on a structured questionnaire at the dental practice by study personnel prior to dental procedure,

	after local anesthesia, and, for the OraVerse® group, upon administration of OraVerse®. On the day after dental procedure (day 2), further data were collected on a structured questionnaire by study personnel during a phone interview of the patient or at the study site. In case a patient was not reachable for follow-up, the closest relative and / or the patient's regular physician – written consent was provided by the patient - were to be contacted in order to obtain follow-up information. Data were reported using a paper CRF. Safety data collection All AEs were to be managed and reported in compliance with all applicable regulations. Dentists had to report all AEs, irrespective of whether serious or not. All adverse drug reactions (ADRs) related to the Company's products (e.g., Ultracaine), observed between the signature of the informed consent form and the end of the study as defined by the protocol for that patient, were to be recorded immediately on the corresponding page(s) of the CRF and to be reported to Sanofi Pharmacovigilance. Data management, review, validation Participating dentists were obliged to respond to any requests arising in the course of the computational analyses by confirming or modifying the data in question. Any requests were listed in the Data Validation Plan (DVP) and were additionally appended along with the replies to the CRFs to be kept by the Company. Plausibility checks were performed as defined in the DVP. Implausible data remaining after database lock due to unanswered queries were corrected if the correct data were definite (such as correction of the year '3015' to '2015') or otherwise excluded from the analysis. Corrections/exclusions were made to analysis data but not to raw data and were described adequately in the documentation of the analysis data and in the analysis tables/listings. Generally, missing data were not replaced. Quality control of data and quality assurance activities were done as defined in advance. On-site quality control was performed at 20% of active sites/patients chosen randomly[8,9,10] - to ensure the existence of patients and compliance with ethical principles (including signed patient informed consent forms, ICFs) - to identify any issues (including systematic ones) as early as possible for appropriate setting of action plans and corrective actions - to ensure the validity of the data. Issues arising during a quality control on-site visit were discussed with the study team/dentist. For each visit the documentation was performed using a structured questionnaire. Sample size calculation The sample size of 672 patients was calculated based on the primary objective, i.e., the effectiveness outcome. Under exponential assumption, to detect a reduction of the median time to recovery by at least 20% (corresponding to a hazard ratio of 1.25 for OraVerse® group vs. control group), a total of 631 events were required with a power of 80% and a two-sided significance level of 0.05. As all patients were expected to recover within the study period, a number of 316 patients per treatment group were required. By taking into account for a 6% loss to follow up rate, totally 672 patients, i.e., 336 in either treatment group, were needed. The study period was originally planned to last from the second quarter 2013 (first patient documented) until 12 months after enrollment of the first patient. However, the distribution of

	patients over the OraVerse® and the control group was not as expected 1:1 but 2:1 instead, causing a loss of statistical power. In order to keep the power at the 80% level, the sample size was increased as per amendment by extending the study period until at least 750 patients (500 in the OraVerse® group and 250 in the control group) were included. Statistical considerations Data management and statistical analyses were done with SAS, version 9.2. All collected and derived data were analyzed descriptively and exploratory. Suitable 95%-Confidence intervals (CIs) were provided for estimated parameters. Descriptive statistics were sample statistics for continuous data, including the total number of patients, mean, standard deviation, median, minimum, maximum, quartiles, and appropriate other percentiles. For categorical data absolute and adjusted relative frequencies were presented. All statistics were provided by treatment group (OraVerse® or control) and by the total population. Information in text fields not subjected to analyses was listed. Listings are per treatment group and contain the center number, the patient number, as well as the baseline variables sex, age, and the other stratification factors. The following variables and evaluation criteria were recorded: Disposition of: - Patients planned (OraVerse® group and control group). - Patients that gave informed consent. - Patients that fulfilled in-/exclusion criteria before dental procedure. - Patients that fulfilled in-/exclusion criteria after dental procedure. - Patients realized in each treatment group and included in the analysis set. - Patients realized in each treatment group and completed treatment. - Reasons for dental treatment not completed as planned. - Violations of in-/exclusion criteria. - Reasons for rejecting OraVerse®. Demographic variables: - Age. - Sex. - Height. - Weight. - Body mass index (BMI), as calculated from a patient's weight and height. Medical history and concomitant medications: - Pain prior to dental procedure. - Analgesics taken prior to dental procedure, coded as per World Health Organization Drug Dictionary (WHO-DD) preferred terms. - Anticoagulation drug therapy (as per WHO-DD preferred terms). - Concomitant diseases, coded by the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC), version 18.0 and Preferred Term (PT). Anesthesia and dental procedure: - Focal tooth/teeth that were anesthetized for intervention – coded according to Fédération Dentaire Internationale (FDI) notation. - Number of teeth anesthetized for intervention. - Sensibility before anesthesia. - Method to measure sensibility. - Indication(s) for anesthesia. - Time of first and last injection. - Number of anesthetic re-injections.

	- Type(s) of anesthetic injection(s). - Region(s) of injection(s). - Number of regions where anesthetic was injected. - Anesthetic products used (free text entry) - as per WHO-DD drug name. - Total dose of anesthetic injected. - Number of vials of anesthetic injected. - Maximum adrenalin concentration of anesthetic used for first injection and for each up to 2 re-injections separately, and totally; the latter served as the stratification factor 'adrenalin concentration' in stratified analyses. - Location of test of anesthesia onset for first injection, and for each of up to 2 re-injections separately. - Patient's description of anesthetic effect; maximum effect of first injection and for each of up to 2 re-injections separately. - Duration of dental intervention. Extent of study treatment exposure: - Patient received OraVerse®. - Time between last anesthetic injection and injection of OraVerse®. - Type(s) of OraVerse® injection(s). - Region(s) of OraVerse® injection(s). - Number of regions where OraVerse® was injected. - Dose of OraVerse® administered. Primary variables: effectiveness variables: - Patient-reported time between last anesthetic injection with known time and recovery of normal sensation in the lip/tongue. - Patient-reported time between last anesthetic injection with known time and recovery of normal function (eating, drinking and speaking). Secondary variables (safety variables): - Any local reaction directly after dental procedure but before planned injection of OraVerse®. - Local reactions after injection of OraVerse®: - Hemorrhage. - Hematoma. - Facial swelling. - Redness. - Any local reaction on day 2: - Hemorrhage. - Hematoma. - Facial swelling. - Post-procedural pain in the oral region: - Pain during OraVerse® injection. - Pain (any) on day 1. - Pain localized in injection region on day 1. - Pain localized at focal tooth on day 1. - Intensity of worst pain on day 1 on Numeric rating scale-11 (NRS-11) ranging from 0 (no pain) to 10 (worst pain conceivable). - Pain (any) on day 2 - Pain on day 2 localized at injection region. - Pain on day 2 localized at focal tooth. - Intensity of worst pain on day 2 on NRS-11 pain scale. - Any analgesic taken after dental procedure (as per WHO-DD preferred terms). - Cardiovascular events: Cardiovascular events were to be reported as such and as AE, in addition, any of

	the following observations were made during the dental procedure: The systolic blood pressure changed by at least 20 mmHg, the diastolic blood pressure changed by at least 10 mmHg, or the heart rate changed by at least 10 beats per minute. This instruction was communicated to all participating dentists and the relevant Ethic Committee by an information letter. - Any cardiovascular event on day 1, if 'yes': hypotension, hypertension, bradycardia, tachycardia, arrhythmia. - Any cardiovascular event leading to healthcare consultation on day 2, if 'yes': hypotension, hypertension, bradycardia, tachycardia, arrhythmia, other. - Cardiovascular event leading to healthcare consultation on day 2: time of occurrence after last anesthetic injection. - Cardiovascular event leading to healthcare consultation on day 2: intensity perceived by patient. - Cardiovascular event leading to healthcare consultation on day 2: recurrent event - Cardiovascular event leading to healthcare consultation on day 2: patient received medical treatment. - Cardiovascular event leading to healthcare consultation on day 2, any medication/therapy (as per WHO-DD, version 2014-June-1, preferred terms) applied. AEs: The observation period for AEs/ADRs was defined as the 48-hour period following injection of OraVerse®. Any AEs/ADRs developing within this period were listed and analyzed. Any further AEs/ADRs documented were to be listed only. AEs/ADRs were coded using MedDRA, version 18.0. Vital signs: - Systolic blood pressure on day 1 before/after dental procedure and day 2. - Diastolic blood pressure on day 1 before/after dental procedure and day 2. - Pulse rate on day 1 before/after dental procedure and day 2. Statistical analyses: Primary (effectiveness) and secondary (safety) variables were each subjected to analysis of the total population as well as to stratified analysis upon appropriate subgrouping. Subgroups that encompassed less than 100 patients were to be considered only in case of particular interest. Analyses of primary (effectiveness) variables For each treatment group and the total population the estimated median time to recovery of normal sensation and normal function and corresponding 95%-CIs were calculated with the Kaplan-Meier method and corresponding curves were displayed. Survival curves were compared by stratified log-rank-tests. In Cox models, the hazard ratio (HR) of outcome of interest was estimated. Analyses of secondary (safety) variables Logistic regression models were implemented to estimate odds ratios (OR) to compare treatment groups and subgroups thereof in terms of frequencies of local reactions, post-procedural pain, cardiovascular events, and cardiovascular events leading to healthcare consultation, and hence, to estimate relationships among variables. As a general rule, models were calculated only in case of at least 10 events. To deal with potential issues of overfitting or linear separation, Firth's penalized maximum likelihood estimation, a method for parameter shrinkage during model fitting, was used for all models.

	Post-procedural pain events with a scale value greater than 0 on the NRS-11 scale were summarized by sample statistics (median, minimum, maximum, and quartiles) and compared between treatment groups by Mann-Whitney U test. All other variables of local reaction, post-procedural pain and cardiovascular events defined above were analyzed descriptively. Analyses of AEs and ADRs included - Calculations of - Frequencies of patients documented with AEs/ADRs. - Incidences of AEs/ADRs, defined as the number of patients with at least 1 AE/ADR divided by the total number of patients in the analysis set. - Frequencies of events ('per event' analyses). These tables include only any AEs/ADRs that were rated as 'diagnosis'. Matching AEs/ADRs that were rated as 'symptom' were not counted in per-event analysis (see also Section 2.2.2). - Per-patient listings of - AEs/ADRs that occurred during the observation period. - AEs/ADRs that occurred outside the observation period. - AEs/ADRs of patients not included in the analysis set. Vital sign variables were analyzed descriptively for day 1 before, and after dental procedure, for day 2, and for differences of data obtained at these time points.
RESULTS	
Participants (actual):	It was originally planned to recruit 672 patients either treated or not treated with OraVerse® after routine dental procedure in 5 universities and 10 private dental practices including pediatric practices from all over Germany. Owing to a discernible imbalance in favor of the OraVerse® group it was decided to increase the total number of patients to at least 750 as per amendment. In order to achieve enrollment of that greater number of patients, the study period was extended accordingly. The registry lasted from June 18th 2013 (dental procedure of first patient) to December 31th 2014 (last documentation of last patient)). Totally, by 11 private practices and 2 university centers (at the same medical university) 873 patients were included, i.e., provided informed consent. Due to organizational circumstances it was not possible to recruit more universities. Totally 857 patients (98.2%) fulfilled the in-/exclusion criteria before dental procedure, after excluding 3 patients due to findings during quality control (no possibility to match source data with study documentation data). Totally, 856 patients (98.1%) fulfilled the in-/exclusion criteria after dental procedure, that is, they showed no local reactions after dental procedure, and hence were included in the analysis set (OraVerse® group: 549 patients, control group: 307 patients), as shown in post-text Table 1-1. Details on the 17 patients excluded from analyses are provided in Listing 6.4-8. Although of no relevance for any analysis, out of the 856 patients participating, 819 patients (93.8%) completed the dental procedure as planned, of whom 525 patients belonged to the OraVerse® group and 294 patients belonged the control group. For 5 of the patients that did not complete, reasons were provided in Listing 1-1). The differentiation between control groups A and B became obsolete, since the control group included sufficient patients. Control group B was not required. 9 out of 307 were recruited to the control group although the application of OraVerse® was not indicated. These patients would have been belonged to control group B. On day 2, further data on the 856 patients included in the analysis set were collected on a structured questionnaire by getting through to 791 patients by phone

on the day following the dental procedure (92.4%) (OraVerse® group: 514 patients, control group: 277 patients), whereas this was not accomplished for 65 patients. Most of the latter patients or their parents were instead reached later as summarized in post-text Table 1-4 and as detailed per-patient in Listing 1-3. However, 'day 2' was actually not in any case as intended the day after dental procedure, since at least in some cases the patient could temporarily not be reached due to a weekend or holidays.

Participant characteristics and primary analyses:

Basic patient characteristics

The 856 patients included in the analysis set differed only marginally between treatment groups in terms of sample statistics calculated: On average, study participants were 40.5 ± 18.0 years old, with the youngest patient being 6, and the oldest patient being 92 years old (OraVerse® group: 41.2 ± 16.8 years, control group: 39.2 ± 20.0 years). Of note, 60.3% of patients in either treatment group were female (8 values missing). The mean BMI – as calculated from patients' body weight and height - was 24.1 kg/m^2 in either treatment group (Table 1, post-text Table 2.1-1).

Table 1: Demographics (analysis set)

Variable	Total N=856	OraVerse® N=549	Control N=307
Age, years	n=856	n=549	n=307
Mean ± SD	40.5 ± 18.0	41.2 ± 16.8	39.2 ± 20.0
Median (Range)	43.0 (6 – 92)	43.0 (6 – 80)	41.0 (6 – 92)
Age, categories	n=856	n=549	n=307
6-11 years	68 (7.9)	30 (5.5)	38 (12.4)
12-17 years	52 (6.1)	27 (4.9)	25 (8.1)
18-64 years	663 (77.5)	452 (82.3)	211 (68.7)
≥65 years	73 (8.5)	40 (7.3)	33 (10.7)
Sex, n (%)	n=848, 8 values missing	n=546, 3 values missing	n=302, 5 values missing
Female	511 (60.3)	329 (60.3)	182 (60.3)
Male	337 (39.7)	217 (39.7)	120 (39.7)
BMI, kg/m^2	n=854, 2 values missing	n=547, 2 values missing	n=307
Mean ± SD	24.1 ± 4.7	24.1 ± 4.4	24.1 ± 5.1
Median (Range)	23.7 (12.4 – 41.7)	23.7 (12.8 – 40.8)	23.9 (12.4 – 41.7)

SD = Standard deviation

BMI = Body mass index

Note: Relative frequencies are calculated as adjusted relative frequencies

Data source: Post-text Table 2.1-1.

Medical history of patients and anesthesia

Most patients (89%) were not in pain prior to dental procedure (OraVerse® group: 90.5%, control group: 86.3%), as shown in post-text Table 2.2-1. Correspondingly, only 4.3% took analgesics before (OraVerse® group: 3.6%, control group: 5.6%), mostly ibuprofen, which was taken by 2.1% of all patients (post-text Table 2.2-2).

Similarly, the proportion of patients that took anticoagulants was 3.2% (OraVerse® group: 2.4%, control group: 4.6%), mostly, i.e., taken by 2.3% of patients, acetylsalicylic acid (post-text Table 2.2-3).

A total of 23.0% of patients were affected by at least 1 concomitant disease. The most frequent diseases were vascular disorders, endocrine disorders, as well as metabolism and nutrition disorders, affecting 9.7%, 6.7%, and 2.2% of patients, respectively (post-text Tables 2.2-4 and 2.2-5).

In most patients a single tooth was treated (overall: 58.9%, OraVerse® group: 58.7%, control group: 59.3%). For considerably less patients, i.e., 25% in each treatment group, 2 teeth were treated. However, in 1 patient of the OraVerse® group 9 teeth were treated (post-text Table 2.2-6). By far the most prevalent indication for anesthesia was the preparation of cavities for placement of fillings and crowns (overall: 76.1%, OraVerse® group: 77.8%, control group: 73.0%), followed by calculus removal (overall: 12.7%, OraVerse® group: 10.0%, control group: 17.6%), and root planing (overall: 10.4%, OraVerse® group: 10.2%, control group: 10.7%). Some patients received 2 or more treatments (Table 2, post-text Table 2.2-8).

Table 2: Indications for anesthesia (analysis set)

Indication*, n (%)	Total N=856	OraVerse® N=549	Control N=307
Preparation of cavities for placement of fillings or crowns	651 (76.1)	427 (77.8)	224 (73.0)
Calculus removal	109 (12.7)	55 (10.0)	54 (17.6)
Root planing	89 (10.4)	56 (10.2)	33 (10.7)
Cleaning	82 (9.6)	46 (8.4)	36 (11.7)
Endodontic treatment	73 (8.5)	38 (6.9)	35 (11.4)
Restorative, prosthetic preparation	13 (1.5)	9 (1.6)	4 (1.3)
Periodontal treatment	2 (0.2)	2 (0.4)	0 (0)

** Multiple indications per patient possible.*

Data source: Post-text Table 2.2-8.

Sensibility testing before anesthesia yielded a positive result in 80.1% of patients in each treatment group. It was tested by using coolant spray in 71.1% of cases, but not tested for 10% of cases in either treatment group (post-text Table 2.2-7). The majority of patients received a single anesthetic injection only (OraVerse® group: 92.3%, control group: 87.0%), as shown in post-text Table 2.3-1. Anesthetics were injected in either treatment group in more than 70% of patients by infiltration and in about 30% of cases by means of conduction (multiple answers per patient were possible), with similar results for first injections and up to 2 re-injections. Additional injection by other types occurred much less frequently; the most prevalent were intraligamentous injection or direct injection into the root canal, which applied to 1.3% and 0.1% of cases, respectively (post-text Table 2.3-2). Most patients were anesthetized in a single region (OraVerse® group: 88.5%, control group: 87.0%). Only 1 patient of each treatment group received anesthetic injections in 4 regions,

corresponding to overall 0.2% of patients. The prevailing regions of injection were the right and left maxilla (36.7% and 32.5% of all patients, respectively), whereas right and left mandibula were treated in 22.0 and 21.7% of patients, respectively. Both maxilla and mandibula together were affected independently of treatment groups in 9.8% of all patients. Likewise, there were no substantial differences among first anesthetic injection and possible re-injections observed (post-text Table 2.3-3). Prevalent anesthetics were Ultracain D-S, Ubistesin, and Artinesol (66.7%, 20.6%, and 12.6% of patients, respectively); any other anesthetic was received by ≤0.2% of patients. Again, no substantial differences among treatment groups as well as among first and any further injection were found (post-text Table 2.3-4).

The anesthetic doses were also comparable in treatment groups, with a mean of 1.7 ± 0.8 mL and 1.6 ± 0.9 mL taken in the OraVerse® group and the control group, respectively, and a range from 0.3 to 5.1 mL in each group (Table 3, post-text Table 2.3-5). The average amount of anesthetic injected was higher for the first injection than for re-injections (post-text Table 2.3-5). The maximum adrenalin concentration for most patients received over all injections was 1:200,000 (OraVerse® group: 63.8%, control group: 55.0%), whereas a maximum adrenalin concentration of 1:100,000 applied to 36.1% and 44.0% of patients in the OraVerse® group and the control group, respectively. For 0.5% of patients the maximal adrenalin concentration was 1:400,000. The concentration of re-injections, i.e., the concentration of first reinjections and second reinjections, respectively, tended to be higher than the concentration of first injections (post-text Table 2.3-6).

Table 3: Dose and number of vials of anesthesia (analysis set)

Anesthetic: total dose injected, mL	**Total N=856**	**OraVerse® N=549**	**Control N=307**
n	856	549	307
Mean ± SD	1.7 ± 0.8	1.7 ± 0.8	1.6 ± 0.9
Median (Range)	1.7 (0.3 – 5.1)	1.7 (0.3 – 5.1)	1.7 (0.3 – 5.1)
Anesthetic: number of vials, n (%)	N=854, 2 values missing	N=547, 2 values missing	N=307
0.5	164 (19.2)	86 (15.7)	78 (25.4)
1.0	527 (61.7)	357 (65.3)	170 (55.4)
1.5	30 (3.5)	17 (3.1)	13 (4.2)
2.0	122 (14.3)	83 (15.2)	39 (12.7)
2.5	5 (0.6)	2 (0.4)	3 (1.0)
3.0	6 (0.7)	2 (0.4)	4 (1.3)

SD = Standard deviation

Note: Relative frequencies are calculated as adjusted relative frequencies.

Data source: Post-text Table 2.3-5.

The onset of anesthesia was tested in the mucosa for 44.0% of patients, whereas it was less frequently tested on a tooth (36.5%), or both (19.6%). Again, no substantial differences between treatment groups or between the first injection and re-injections were found. This was also the case for patients' assessment of anesthetic effects. On average, the anesthetic effect over all injections was assessed as 'complete' by 90.9%, as 'sufficient' by 9.0%, and as 'insufficient' by 0.1% of patients. No patient

reported the anesthetic effect as 'none' (post-text Table 2.3-7).

The mean duration of the dental intervention was 31.8 ± 23.9 minutes (median: 25.0 minutes). Again, treatment groups were comparable (post-text Table 2.4-1).

Use of OraVerse®

OraVerse® was in 70.5% of cases injected by infiltration, and in 34.6% of cases by conduction (post-text Table 3.1-2). On average, OraVerse® was administered 37.8 ± 23.1 minutes after the last anesthetic injection. At the shortest, OraVerse® was administered immediately, and the longest interval was 195 minutes (Table 4, post-text Table 3.1-1). The volume of OraVerse® most frequently injected was 400 µg (69.4% of patients in the OraVerse® group), whereas 200 and 800 µg were injected with similar frequencies (Table 4, post-text Table 3.1-4).

Table 4: Use of OraVerse® (analysis set)

Variable	OraVerse® (N=549)
Time between last anesthetic injection and OraVerse® injection, min	
n	548, 1 value missing
Mean ± SD	37.8 ± 23.1
Median (Range)	33.0 (0 – 195)
OraVerse® dose, n (%)	
200 µg	93 (16.9)
400 µg	381 (69.4)
800 µg	75 (13.7)

SD = Standard deviation

Data source: Post-text Tables 3.1-1 and 3.1-4.

As expected, the distributions of regions of injection of OraVerse® in the corresponding treatment group on the one hand and the regions of injection of the anesthetic in the total population on the other hand were similar. Accordingly, 88.5% of patients in the OraVerse® group received an injection in a single region only, and the remaining 11.3% received it in 2 regions. Likewise, maxilla and mandibula were affected in 46.3% and 44.8% of patients, respectively. Only 8.7% of patients were injected OraVerse® in both regions (post-text Table 3.1-3, compare with regions of anesthetic injection shown in Table 2.3-3). However, in 5 patients a mismatch of anesthetic injection regions with OraVerse® injection regions was documented (Listing 3.1-1).

Time to recovery: OraVerse® vs. control group

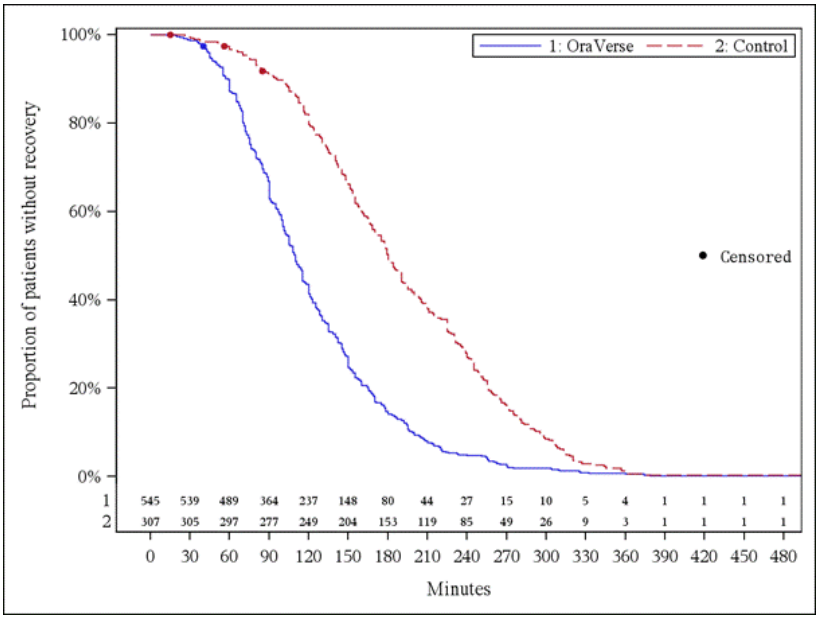
The time to recovery of normal sensation in the lip/tongue was faster in the OraVerse® group than in the control group ($p<0.001$, global Cox model Wald test), with a median time to recovery of 110 minutes and 180 minutes, respectively ($p<0.001$, Log-rank test) as shown in post-text Tables 4.1-1.2, 4.1-2.1, Figure 1, and post-text Figure 4.1-1.1. Patients in the OraVerse® group had, at any given time point, a 2.77-fold higher chance of recovery to normal sensation than patients in the control group, as expressed by a hazard ratio of 2.77 (95%-CI: 2.35 – 3.26) in the global Cox model analysis (post-text Table 4.1-1.2).

Although the time to recovery was shorter in younger patients than in older patients (post-text Table 4.1-2.2, post-text Figure 4.1-2), a Cox model analysis did neither reveal an age-dependent difference between treatment groups regarding the recovery of normal sensation (p=0.370, Wald test) nor a treatment-region-dependent (maxilla or mandibula) difference between treatment groups regarding the recovery of normal sensation (p=0.114, Wald test) (post-text Table 4.1-1.1).

However, the data might indicate an influence of the anesthetic's maximum adrenalin concentration on the treatment effect on time to recovery of normal sensation (p=0.030, Cox model Wald test, post-text Table 4.1-1.1). Specifically, OraVerse® was observed to reduce the recovery time in patients that received anesthetics with an adrenalin concentration 1:200,000 (HR=3.19; 95%-CI: 2.58 – 3.95) slightly more pronounced when compared to control than in patients that received a maximum adrenalin concentration of 1:100,000 (HR=2.25; 95%-CI: 1.75 – 2.89) (post-text Table 4.1-1.2 and post-text Figure 4.1-4, for median times to recovery see post-text Table 4.1-2.4). Patients that received anesthetics with maximum adrenalin concentration 1:400,000 were less than 100, and were thus not presented in the analysis results.

As expected, very similar results regarding the time to recovery of normal function (eating, drinking and speaking) were obtained. Globally, the observed median time to recovery of normal function in the OraVerse® group was 111 minutes, as compared to 190 minutes in the control group. Correspondingly, in the Cox model analysis, a comparison of OraVerse® group vs. control group yielded a HR=2.94 (95%-CI: 2.49 – 3.47) (p<0.001, Wald test), as shown in post-text Tables 4.2-1.1 – 4.2-2.4, Figure 2, and post-text Figures 4.2-1 to 4.2-4).

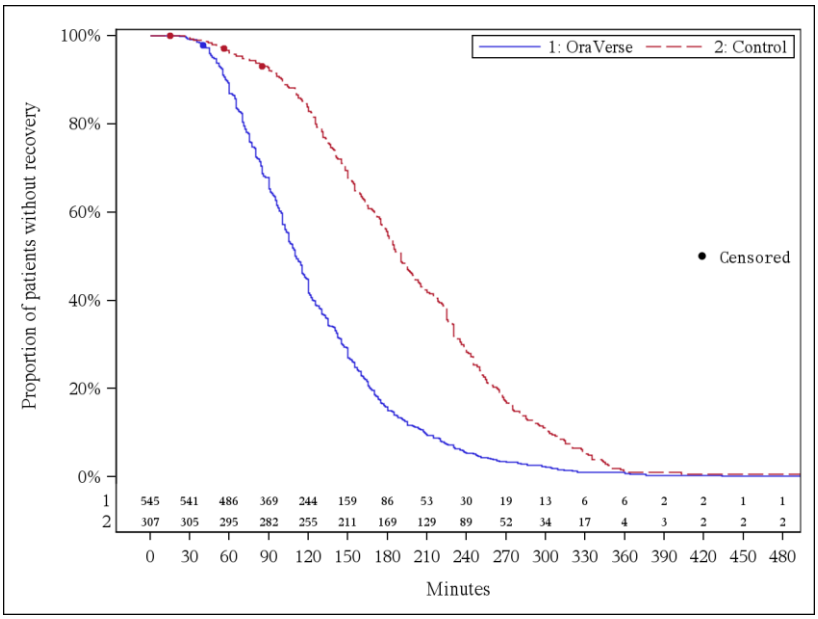
Figure 1: Time to recovery of normal sensation in the lip/tongue (analysis set)



The number of subjects at risk is shown at the bottom.

Note: From the OraVerse® group 4 patients were excluded from this analysis due to missing time of last anesthetic injection.

Data source: Post-text Figure 4.1-1.

	Figure 2: Time to recovery of normal function (eating, drinking, speaking) in the lip/tongue (analysis set)  *The number of subjects at risk is shown at the bottom.* *Note: From the OraVerse® group 4 patients were excluded from this analysis due to missing time of last anesthetic injection.* *Data source: Post-text Figure 4.2-1.*
Other analyses:	<u>Local reactions immediately after dental treatment and after administrating OraVerse®</u> One patient was documented to have had a local reaction emerging immediately after the dental procedure and was hence not included in the analysis (Table 1-1). Additionally, upon injection of OraVerse®, 1 patient (0.2% of the OraVerse® group) was affected from redness reported on day 1 (post-text Table 5.1-3). On day 2, totally 8 patients (0.9% of the total population, 2 values missing) were affected by local reactions (all with facial swelling). Of these patients, 6 belonged to the OraVerse® group (1.1% of this group), 1 of whom was of the age class 6-11 years, 4 patients belonged to the age class 18-64 years, and 1 patient was ≥65 years old; for 3 of these 6 patients the maximal adrenalin concentration of the anesthetics was 1:100,000 and for 3 patients it was 1:200,000. The remaining 2 patients with facial swelling belonged to the control group (0.7% of this group, 2 missing values); both were 18-64 years old; for each of whom the maximum adrenalin concentration was 1:100,000 and 1:200,000, respectively. These data are shown along with 95%-CIs per treatment group and overall in post-text Tables 5.1-2.1 to 5.1-2.3. As the number of patients with local reactions on day 2 was less than 10, no logistic regression was done, in compliance with the statistical analysis plan (SAP). <u>Post-procedural pain</u> Post-procedural pain in the oral region on day 1 was perceived by 12 patients (1.4% of the total population). To the OraVerse® group belonged 8 patients (1.5% of this group, all belonged to the age class 18-64 years); 6 of them perceived the pain in the injection region and 5 at a focal tooth. Their corresponding maximum adrenalin concentrations were 1:100,000 (6 patients) or 1:200,000 (2 patients). Of the 4

control group patients that perceived post-procedural pain (1.3% of this group), 1 perceived it at the injection region, and all at a focal tooth. Of these 4 patients, 2 belonged to the age class 18-64 years, 1 to the age class 65+ years, and 1 to the age class 12-17 years. The maximum adrenalin concentration of the anesthetic for these control group patients was either 1:100,000 (1 patient) or 1:200,000 (3 patients). These data, again along with 95%-CIs per treatment group and overall are provided in post-text Tables 5.2-2.1 to 5.2-2.3. Occurrence of post-procedural pain on day 1 was neither found to depend on whether OraVerse® was given, nor on a patient's age class nor the anesthetic's maximum adrenalin concentration when considering p=0.05 (logistic regression model, Wald test) as a threshold. However, care should be taken when interpreting this result as the case numbers of patients was quite low (Table 5, post-text Tables 5.2-1.1 and 5.2-1.2).

Post-procedural pain on day 2 was perceived by 77 patients (9.0% of the total population, 2 missing values), of whom 53 belonged to the OraVerse® group (9.7% of this group); 19 of those patients perceived the pain in the injection region and 37 perceived it at a focal tooth. Most of these patients (n=51) belonged to the age class 18-64 years and 2 patients were 65 years or older. Corresponding maximum adrenalin concentrations were either 1:100,000 (35 patients) or 1:200,000 (18 patients). Of the 24 control group patients with post-procedural pain (7.9% of this group), 4 perceived it at the injection region, and 20 at a focal tooth. As for the OraVerse® group, most of them, i.e., 16 of the control group patients, belonged to the age class 18-64 years, 7 were 65 years or older, and 1 belonged to the age class 6-11 years. The maximum adrenalin concentration of the anesthetic(s) received was either 1:100,000 (11 patients) or 1:200,000 (13 patients). These data, again along with 95%-CIs per treatment group and overall are provided in post-text Tables 5.3-2.1 to 5.2-2.3. As shown by logistic regression analysis, occurrence of post-procedural pain on day 2 depended on a patient's age class (p=0.041, Wald test).

Table 5: Post-procedural pain: Logistic regression model (analysis set)

Effect	DF	p* | type 3 effect	
		Day 1	Day 2
Treatment group	1	0.930	0.662
Age class	3	0.829	0.041
Maximum adrenalin concentration	1	0.134	0.002
Interaction between treatment group and maximum adrenalin concentration	1	not calculated	0.025

** Wald test*

DF = degrees of freedom

Analysis was based on 856 observations and 12 events for day 1 and on 854 observations and 77 events for day 2.

Note: Maximum adrenalin concentrations 1:200,000 and 1:400,000 were pooled as there are too few observations with maximum adrenalin concentration 1:400,000.

Data source: Post-text Tables 5.2-1.1 and 5.3.1-1.

However, no effect of treatment group (OraVerse® vs. control) on the occurrence of pain on day 2 was found: The logistic regression model analysis indicates that the effect of OraVerse® on the occurrence of pain on day 2 was dependent on the maximum adrenalin concentration (p=0.025, Wald test). However, an effect of

OraVerse® alone was not apparent, neither for patients with adrenalin concentration 1:100,000 (p=0.108, Wald test) nor for patients with adrenalin concentration ≤1:200,000 (p=0.198, Wald test) (Table 5, post-text Tables 5.3-1.1 and 5.3-1.2).

Intensities of the worst post-procedural pain perceived, as assessed by patients on a NRS-11 scale, were comparable in both treatment groups and on day 1 and day 2, with median values ranging from 3.0 to 4.0, and with absolute values ranging from 1.0 to 10.0 (post-text Table 5.4-1). Only 4.1% of patients (n=17) were documented to have taken analgesics after dental procedure (3.8% of patients in the OraVerse® group, 5.0% of patients of the control group). However, only for 414 of 856 patients it was reported whether analgesics were taken or not. Most frequently, ibuprofen was taken (11 patients) (post-text Table 5.4-2). Analgesics taken along with dosages are detailed in post-text Listing 5.4-1. During injection of OraVerse®, most patients (99.6% of the 549 subjects in this group) did not perceive pain (3 values missing), as shown in post-text Table 5.4-3.

Cardiovascular events

Cardiovascular events on day 1 were reported for 15 patients (1.8%, no missing values), mostly of the OraVerse® group (n=13, 2.4%), whereas only 0.7% of patients (n=2) of the control group were affected (95%-CIs: 1.3 – 4.0, and 0.1 – 2.3, respectively). Indeed, the logistic regression analysis suggested a group difference with p=0.044. Hypertension were 10 of the 15 cardiovascular events on day 1 reported (Table 6, post-text Tables 5.5-1.2 and 5.5-2.1).

Table 6: Cardiovascular events on day 1 (analysis set)

Cardio-vascular event	Total N=856 n (%), [95%-CI]	OraVerse® N=549 n (%), [95%-CI]	Control N=307 n (%), [95%-CI]
Any	15 (1.8) [1.0; 2.9]	13 (2.4) [1.3; 4.0]	2 (0.7) [0.1; 2.3]
Hypotension	2 (0.2) [0.0; 0.8]	2 (0.4) [0.0; 1.3]	0 (0.0) [0.0; 1.2]
Hyperten-sion	10 (1.2) [0.6; 2.1]	9 (1.6) [0.8; 3.1]	1 (0.3) [0.0; 1.8]
Bradycardia	5 (0.6) [0.2; 1.4]	5 (0.9) [0.3; 2.1]	0 (0.0) [0.0; 1.2]
Tachycardia	1 (0.1) [0.0; 0.6]	0 (0.0) [0.0; 0.7]	1 (0.3) [0.0; 1.8]
Arrhythmia	0 (0.0) [0.0; 0.4]	0 (0.0) [0.0; 0.7]	0 (0.0) [0.0; 1.2]
Unknown	0 (0.0) [0.0; 0.4]	0 (0.0) [0.0; 0.7]	0 (0.0) [0.0; 1.2]

Multiple cardiovascular events per patient were possible.

Data source: Post-text Table 5.5-2.1.

The occurrence of cardiovascular events on day 1 appeared to be moreover related to age class, as suggested by the logistic regression analysis (p=0.004, Wald test, post-text Table 5.5-1.1), although the size of the effect seemed to be small and not systematic. Specifically, cardiovascular events on day 1 affected foremost the age class 12-17 years (OraVerse® group: n=2, 7.4%; control group: n=2, 8.0%), and slightly less frequently the age class 6-11 years (OraVerse® group: n=2, 6.7%;

	control group: no cases), and the age class 18-64 years (OraVerse® group: n=9, 2.0%; control group: no cases). None of the patients of age 65 or older experienced cardiovascular events on day 1. However, it needs to be taken into consideration that the 95%-CI for the age class 12-17 years is quite broad (0.9-24.3%), resulting in reduced expressiveness of the high percentage of cardiovascular events in this age class. No dependency of cardiovascular events on injected anesthetics' maximum adrenalin concentration was found (post-text Tables 5.5-1.2 to 5.5-2.2). Only 1 cardiovascular event leading to healthcare consultation was recorded on day 2 (bradycardia in the control group) (post-text Tables 5.6-1.1 to 5.6-2.1 and post-text Listing 5.6-1). Vital signs The vital signs assessed (systolic and diastolic blood pressure, and pulse rate) did not change substantially during the dental procedure on day 1. On day 2, only 1 case (in the control group) was documented (post-text Table 7.1-1). Adverse events All AEs occurring in the OraVerse® group were assessed to be causally related with OraVerse® by the Company, i.e. were assessed to be ADRs and affected 8.4% of patients (n=46 patients) in this group. In the control group less patients, i.e., 2.0% of patients (n=6) were affected (post-text Table 6.1-1). No patients were affected by serious adverse events (SAEs) or serious adverse drug effects (SADRs) (post-text Table 6.1-2). Among the patients with reported AEs/ADRs were 61.5% female (similar to the portion of females in the analysis set), with similar results for both treatment groups. Most patients (82.7%, n=43) with reported AEs were between 18 and 64 years old, again with similar results for both treatment groups. In the bottom section of post-text Table 6.1-2, the number of patients with at least 1 AE/ADR unlisted/not unlisted regarding the OraVerse® core safety information (CSI) is shown. Note that a patient might have had both listed and unlisted AEs/ADRs and thus may appear more than once in the table. In the OraVerse® group, there were 3 patients (6.5% of cases) affected by at least 1 AE/ADR not listed in the CSI ('unlisted: yes'), whereas 35 patients had at least 1 AE/ADR that was already listed in the CSI (76.1% of cases). AEs/ADRs that were unlisted were 'disturbance in attention' (1 patient), 'fatigue' (2 patients), 'lip swelling' (1 patient), and 'oropharyngeal pain' (1 patient) (Listing 6.4-3). Additionally, 11 patients had at least 1 AE/ADR for which the term 'unlisted regarding CSI' was either not applicable or missing (post-text Table 6.1-2). These were AEs/ADRs with the preferred terms 'application site hypoesthesia', 'hypoesthesia', 'drug ineffective', and 'therapeutic response decreased' (Listing 6.4-5), all indicating a lack of drug effect. As moreover shown in post-text Table 6.1-2, most patients with AEs/ADRs in the OraVerse® group were affected from events corresponding to MedDRA SOC 'general disorders and administration site conditions' (27 patients), 'vascular disorders' (11 patients), and 'gastrointestinal disorders' (9 patients). Similarly, patients in the control group were most frequently affected by 'general disorders and administration site conditions' (5 patients), followed by 'cardiac disorders' and 'nervous system disorders' (2 patients each). Corresponding indices of AEs/ADRs with 95%-CIs are shown in post-text Table 6.2-1. The AEs/ADRs with the highest incidences in terms of PTs in the OraVerse® group were 'injection site pain' (13 patients, corresponding to 2.4% of patients), 'hypertension' (9 patients, 1.6%), and 'drug ineffective' (6 patients, 1.1%). In the

control group, all AEs but 'pain' (2 patients, 0.7%) corresponded to PTs that each occurred only once (post-text Table 6.2-2).

Numbers of AEs/ADRs documented were 64 for the OraVerse® group and 11 for the control group, respectively. For the OraVerse® group a minority of AEs/ADRs (7.8%, n=5) corresponded to MedDRA PTs that were unlisted in the OraVerse® CSI and the term 'unlisted regarding CSI' was not applicable for 20.3% of events (n=13). In both treatment groups, the distribution of the numbers of AEs/ADRs over sex and age classes compared well to the results regarding the numbers of patients affected by AEs/ADRs described above (post-text Table 6.3-1, compare post-text Table 6.1-2).

Corresponding to the results gained from the analysis of the frequencies of patients with AEs/ADRs (post-text Table 6.1-2) the prevalent MedDRA SOCs were 'general disorders and administration site conditions', with the most frequent PTs being 'injection site pain' in the OraVerse® group (13 AEs/ADRs) and 'pain' in the control group (2 AEs), followed by 'vascular disorders', with the most frequent PTs being 'hypertension' (9 AEs/ADRs in the OraVerse® group and 1 AE in the control group), as shown in Table 7 and post-text Table 6.3-2.

Table 7: Frequencies of AEs/ADRs based on events (analysis set)

MedDRA SOC	Total N=856 n (%)	OraVerse® N=549 n (%)	Control N=307 n (%)
All events*	75 (100)	64 (100)	11 (100)
General disorders and administration site conditions	37 (49.3)	31 (48.4)	6 (54.5)
Vascular disorders	12 (16.0)	11 (17.2)	1 (9.1)
Gastrointestinal disorders	9 (12.0)	9 (14.1)	0 (0.0)
Cardiac disorders	7 (9.3)	5 (7.8)	2 (18.2)
Nervous system disorders	5 (6.7)	3 (4.7)	2 (18.2)
Investigations	3 (4.0)	3 (4.7)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	1 (1.3)	1 (1.6)	0 (0.0)
Skin and subcutaneous tissue disorders	1 (1.3)	1 (1.6)	0 (0.0)

** Used as denominator for calculation of percentages.*

All terms used according to MedDRA version 18.0.

Data source: Post-text Table 6.3-2.

Reported outcomes of AEs/ADRs in the OraVerse® group were 'unknown' (41 events), 'recovered/resolved' (15 events), and 'not applicable' (8 events, e.g., for AE 'drug ineffective'). In the control group, the frequencies of reported outcomes were either 'unknown' (10 events) or 'recovered/resolved' (1 event), as shown in post-text Table 6.3-3.

As post-text Table 6.3-5 shows, most AEs/ADRs that occurred in the OraVerse® group corresponded to PTs previously listed (unlisted: 'no') in the CSI. For the prevalent MedDRA SOC, 'general disorders and administration site conditions', 18 events belonged to PTs (28.1% of all AEs/ADRs in the OraVerse® group) that were

	previously listed, but 2 events (3.1%) did not so, and 11 events corresponded to PTs (17.2%), for which the term 'unlisted regarding CSI was 'not applicable/missing' (post-text Table 6.3-5 However, as 'drug ineffective' is no ADR as such, no coding regarding 'unlisted regarding CSI' was performed for this report. For the OraVerse® group, all AEs that were either unlisted, not unlisted, or not coded regarding 'unlisted regarding CSI' are shown per patient along with the Company's assessment of a causal relationship with any drug taken in Listings 6.4-3, 6.4-4, and 6.4-5, respectively. Correspondingly, all AEs recorded in the control group are shown in Listing 6.4-6. No AEs/ADRs were observed to beginning outside the applicable 48-hour observation period reported (Listing 6.4-7). Regarding the patients not included in the analysis set, 2 AEs/ADRs ('hematoma' and 'off label use') were reported in one patient and 1 AE/ADR was reported in another patient ('hypertension').
Discussions:	The rationale of this non-interventional study was to evaluate the overall effectiveness of reversal of local anesthesia and overall safety of treatment with OraVerse® in routine clinical practice in Germany. A total of 856 patients were assigned to either of the treatment groups (OraVerse® group or control group) and included in the analysis set (549 patients in the OraVerse® group and 307 patients not treated with OraVerse® in the control group). In order to boost the number of recruited patients in the control group it was decided in the course of the study to extend the study period. Another deviation from the original study plan was the inclusion of only 2 university study centers (both at the same university) instead of 5. This was owing to the study design which did rather not fit the general organizational structure of university dental practices in Germany. Both treatment groups were comparable in terms of patients' demographics recorded: On average, study participants were 40.5 ± 18.0 years old (range: 6 to 92 years). Around 60% of patients were female. Both treatment groups were similar regarding the doses of anesthetic injected, which on average was 1.7 ± 0.8 mL and 1.6 ± 0.9 mL in the OraVerse® group and the control group, respectively, as well as regarding the anesthetic's maximum adrenalin concentration, which was 1:200,000 for most patients (63.8% in the OraVerse® group, 55.0% in the control group). Treatment groups were also found to compare well regarding the anesthetic effect, which was described as 'complete' by 90.9%, as 'sufficient' by 9.0% and as 'insufficient' by only 0.1% of study patients. OraVerse® was injected by infiltration in 70.5% of cases and by conduction in 34.6% of cases, with a minimum of 200 µg and a maximum of 800 µg. A volume of 400 µg was administered 69.4% of patients. The primary effectiveness analysis showed that the median time to recovery of normal sensation in the lip/tongue (normal function: eating, drinking, and speaking) after local anesthesia in several routine dental procedures was by 70 minutes (79 minutes) shorter on average in the OraVerse® group than in the control group ($p<0.001$, Wald test). This is in agreement with previous findings.[3] Correspondingly, patients in the OraVerse® group had, at any given time point, a 2.77-fold (2.94-fold) higher chance of recovery of normal sensation than patients in the control group. Hence, the effectiveness results, as gained by both log-rank-tests and Cox model analysis, strongly suggest that OraVerse®, when applied in routine dental procedures, substantially reduces the time to recovery from local anesthesia in most patients. Of note, the data indicate an influence of the anesthetic's maximum adrenalin concentration on this effect, as OraVerse® was observed to reduce the recovery time in patients that received anesthetics with an adrenalin concentration 1:200,000 slightly more pronounced when compared to control than in patients that received a maximum adrenalin concentration of 1:100,000. Local reactions, the observation of which was a secondary objective, were reported in only a few patients. On the day of dental procedure, 1 patient of the OraVerse®

	group (0.2%) was affected by redness; the day after 6 patients of the OraVerse® group (1.1%) and 2 patients of the control group (0.7%) were reported with facial swelling, but the informative value is rather low due to low number of cases. However, as local reactions are commonly associated with dental procedures it is conceivable that a substantial number of cases were actually not documented by dentists. Nevertheless, the results do not indicate an increased risk for local reactions posed by OraVerse®. Study results, moreover, do not point to a relevantly higher risk of post-procedural pain caused by injection of OraVerse®. The comparison of the occurrence of the cardiovascular events 'hypotension', 'hypertension', 'bradycardia', 'tachycardia', 'arrhythmia' and 'other' between treatment groups was another secondary objective. As described in the 'Methodology' section, cardiovascular events were, to be reported as such and as AE and in addition, any of the following observations were made during the dental procedure: The systolic blood pressure changed by at least 20 mmHg, the diastolic blood pressure changed by at least 10 mmHg, or the heart rate changed by at least 10 beats per minute. Independent of administration of OraVerse®, 10 of overall 16 cardiovascular events were hypertension. On day 1, cardiovascular events were recorded for 2.4% of patients (13 events) treated with OraVerse® and for 0.7% of control group patients (2 events). Hence, such events were observed slightly more frequent in the OraVerse® group, which is in accordance with previous findings[4] and already mentioned in the SmPC. On day 2, only 1 cardiovascular event (bradycardia in the control group) was recorded. The number of patients with AEs documented on AE reporting forms was 46 (8.4%) in the OraVerse® group vs. just 6 patients (2.0%) in the control group. This numerical imbalance in favor of more AEs in the OraVerse® group could be explained by the combined effect of 3 issues: (i) the slightly increased frequency of cardiovascular events in the OraVerse® group, (ii) an underreporting of cases of postprocedural pain as AEs (but not as 'local reaction') in the control group, and (iii) the fact that lack of drug effect inevitably occurs only in the OraVerse® group. The Company assumed all AEs in OraVerse® group to be causally related to OraVerse®. As found in previous studies, most, i.e., 48.4% of AEs/ADRs in the OraVerse® group were 'general disorders and injection site pain', mostly injection site pain. In the same group, 7.8% of reported AEs/ADRs were considered 'unlisted' ('fatigue' for 2 patients, as well as 'disturbance in attention', 'lip swelling', and 'oropharyngeal pain' for 1 patient each). The most often reported outcomes of AEs/ADRs in the OraVerse® group were 'unknown' (41 cases), followed by 'recovered/resolved' (15 cases), and 'not applicable' (8 cases). No deaths or serious AEs/ADRs were reported during the course of the study. Overall, treatment with OraVerse® was safe and well tolerated. This finding, together with the results supporting the effectiveness of OraVerse® in reversal of local anesthesia is in agreement with a previous study supporting a high level of satisfaction of both patients and dentists with using OraVerse® in dental practice.[11] In terms of the interpretation of study data it should be taken into consideration that, due to the non-interventional study design, no formal randomization could be performed in order to equally distribute potential confounding factors across treatment groups; this circumstance might pose a limitation on the comparability of the parallel treatment groups studied. However, it was aimed to overcome this drawback by primarily allocating those patients to the control group that otherwise would have been treated with OraVerse®, if they would have agreed to that treatment. Being a strength of the study, the large number of patients with a variety of medical histories and age classes treated under a broad range of routine dental care conditions is likely to enhance the generalizability of the study outcomes. Hence, the study results increase the understanding of the effectiveness and safety

	of OraVerse® when used in contemporary routine dental procedures at least in Germany.
Conclusions:	The study results show that OraVerse® substantially reduces the time to recovery of both normal sensation in the lip/tongue and normal function (eating, drinking, and speaking) in routine dental practice upon administration of commonly used local anesthetics with several concentrations of adrenalin. Moreover, the study shows that only a minority of patients experiences ADRs and increases evidence of the safety profile of OraVerse® in routine dental procedures. Hence, the study results indicate that the use of OraVerse® in daily routine dental procedures is overall safe and effective.
Date of report:	30-Jun-2015