PRODUCT REGISTRY REPORT

Compound(s): **OraVerse® / Phentolamine Mesylate**

Registry Title: **Actual conditions of use of OraVerse® in patients among resident dentists throughout Germany.**

Registry number: PHENLL07113

Registry name: ORADUS

Registry initiation date [date of first CRF received]: 10-Apr-2014

Registry completion date [date of last CRF received]: 11-Jul-2014

Registry design: This was a retrospective, observational, cross-sectional drug utilisation survey among resident dentists throughout Germany to investigate the conditions of use of OraVerse® after local anesthetic procedures in daily routine clinical practice, and to investigate the use of OraVerse® according to labelling.

Report date: 16-Dec-2014

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'.

TABLE OF CONTENTS

SYNOPSIS

Title of the registry:	Actual conditions of use of OraVerse® in patients among resident dentists throughout Germany (ORADUS) (registry number: PHENLL07113).
Design:	This was a retrospective (retrolective) non-interventional, multicenter drug study in patients that were treated with OraVerse® for reversal of local soft-tissue anesthesia after routine dental treatment.
Objectives:	Primary objective: The primary objective was to investigate the conditions of use of OraVerse® after local anesthetic procedure in daily routine practice. The following parameters were of interest: • Patient age class • Body weight class • Type of dental intervention • Local anesthetic used (product and dose) • Dose of OraVerse® used The primary outcome was the proportion of patients that 'comply'/'not comply' with the conditions of use of OraVerse® according to the specifications in the Summary of Product Characteristics (SmPC). Dental interventions considered routine interventions were specified by the Company after discussion with the clinical expert. Eligible for documentation were all patients treated with OraVerse® by dentists after local anesthetic procedure (with a local anesthetic containing a vasoconstrictor) within the last 3 months before signing the study contract.
Treatment:	In this retrospective survey, dentists reported on patients treated with OraVerse® for reversal of local soft-tissue anesthesia after routine dental treatment within the last 3 months. OraVerse® is intended to be used in adults at doses ranging from 200 to 800 µg 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 being at least 6 years old and weighing at minimum 15 kg. It is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients. The medical application was under the sole responsibility of the dentist.
Scientific committee and members:	Study Management: Dr. Eva-Verena Weidemann, Sanofi-Aventis Deutschland GmbH, Klinische Forschung/Clinical Study Unit Epidemiologist: Marie-Laure Kurzinger, MSc, SANOFI, Global Pharmacovigilance & Epidemiology Director Medical & Scientific Affairs: Prof. Dr. med. W. Dieter Paar, Sanofi Aventis Deutschland GmbH Statistician: Karlheinz Theobald, Sanofi-Aventis Deutschland GmbH, EbM & Health Economics/Biostatistics & Epidemiology Non-interventional Study Management: Martina John, Sanofi-Aventis Deutschland GmbH Pharmacovigilance: Dr. med. Juergen-Hans Schmidt, Sanofi-Aventis Deutschland GmbH Expert: Univ.-Prof. Dr. Dr. med. Monika Daubländer, University of

	Mainz Sponsor: Sanofi-Aventis Deutschland GmbH CRO: Winicker Norimed GmbH Medizinische Forschung
Publications (reference):	Study data were not published so far.
Introduction - Background/rationale:	Phentolamine mesylate, the active ingredient of OraVerse®, 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 (IV) or intramuscular (IM) injection at doses ranging from 3 to 5 mg. The vasodilatation properties of phentolamine led to its development as OraVerse® for the reversal of soft tissue anesthesia (lip and tongue): Prolonged soft-tissue anesthesia is an unwanted side effect of local dental anesthesia, especially in routine, restorative or hygienic dental procedures. The local anesthetic remains in and around the nerves in the lips, cheek and tongue, causing the unwanted side effect of lingering numbness. This numbness can last up to five hours following treatment [1,2]. During this period patients have difficulties with speaking, eating and drinking, preventing patients from returning to their daily activities. Prolonged numbness, especially in children, can result in injury due to accidental biting of the lip and/or tongue [3]. OraVerse® has achieved Marketing Authorization in 2012 in Germany for the reversal of soft tissue anesthesia (lip and tongue) and the associated functional deficits, resulting from an intraoral submucosal injection of a local anesthetic containing a catecholamine vasoconstrictor (such as epinephrine) after routine dental procedure such as teeth cleaning, scaling and planning, cavity filling, and crowns. Randomized, controlled studies proved the efficacy and safety of OraVerse® in this indication. A reduction of the median time for full sensation to return to the lower lips by 85 minutes (55%) and to the upper lips by 83 minutes (62%) - or by more than half the usual time was shown. No overall differences in safety or efficacy of OraVerse® were observed between adult patients and younger patients in clinical studies [4]. 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, as described in the SmPC. This retrospective drug utilization survey was planned as an anonymous analysis of existing data and has been described in the RISK MANAGEMENT PLAN (RMP) of OraVerse®. It was agreed upon the European approval procedure. The rationale for this study was to investigate the conditions of use of OraVerse® (i.e., patient age, type of dental intervention, product and dose of local anesthetic used before, and dose of OraVerse®) in daily routine clinical dental practice, and to investigate the use of OraVerse® according to labeling.
Methodology:	<u>Site and patient selection</u> For this study, the inclusion of data from 526 patients treated by a nationwide number of 100 resident dentists throughout Germany was planned. Participating dentists reported the number of patients treated with OraVerse® during the 3 months preceding contract signing and confirmed to report based on patient charts. In order to achieve the target numbers of patients and study centers, the planned duration of

	this survey was 3 months. Data collection Dentists reported the number of patients (up to 6) treated with OraVerse® on a paper form designated as the 'per-dentist' documentation. Dentists moreover reported on conditions of use of OraVerse® from individual patients on 'per-patient' documentation forms. Completed 'per-patient' documentations and 'per-dentist' documentations were collected at dentists' practices and sent to the Contract Research Organization (CRO) by mail anonymously, i.e., without name or address of the sender. Separately, a facsimile indicating the number of documented patients per dentist, as well as the date, name, signature, and personal seal of the respective dentist was faxed to the Non-interventional Study (NIS) Management of Sanofi-Aventis Deutschland GmbH. Safety data collection Since this was a retrospective drug utilization study based on the analysis of preexisting data, only retrospective detection of safety signals was applicable. In case a safety signal was identified during data analysis, this was to be immediately forwarded to the Pharmacovigilance (PV) department of the company. Data management, review, validation In order to assure the quality of data, duplicate data entry was performed and any inconsistencies were clarified by an independent third person. Due to the design of the study, data collection was completely anonymous as requested by the authorities. Therefore, no backtracking was possible and no data quality control at site level was performed. However, data were subjected to plausibility checks. Cases of implausibility were handled as described in the Data Validation Plan (DVP), and implausible data were corrected or excluded from analysis. Any corrections/exclusions beyond the specifications given in the DVP were done as described in the documentation to the analysis datasets. Generally, raw data were not subjected to any corrections or exclusions. Sample size estimation The planned sample size of evaluable patients was 500. By assuming a non-evaluable rate of 5%, the planned number of patients to be included in the study amounted to 526. With the planned number of 500 evaluable patients, the following statistical precision regarding the estimated proportion of patients that 'not comply' / 'comply' with the doses and indications recommended in the SmPC (see definition below) was possible to reach: Assuming rates of non-compliance / compliance of 3% / 97% or 4% / 96% or 5% / 95%, the corresponding 2-sided 95% confidence intervals (CIs) would have been [1.5%; 4.5%] / [95.5%; 98.5%], or [2.3%; 5.7%] / [94.3%; 97.7%], or [3.1%; 6.9%] / [93.1%; 96.9%]. Summary of statistical methods used Data management and statistical analysis were performed using SAS, version 9.2. All study data were analyzed in an exploratory fashion by means of descriptive statistics. Generally, the sample statistics number of patients, mean, standard deviation, median, min, max, and quartiles were calculated for continuous variables. For categorical data, frequencies and percentages were calculated. Suitable 95%-CIs were provided for estimated parameters. 'Per-patient' analysis results were presented in total and by age class (< 6 years, 6 to < 12 years, 12 to < 18 years, and ≥ 18 years). Analysis was done 'per-dentist' as well as 'per-patient'. Accordingly, the following

variables were analyzed:

Analysis variables 'per-dentist':

- Number of patients treated with OraVerse® within the last 3 months before signing the study contract.
- Number of patients documented, defined as the number of returned valid 'per-patient' documentations, whereby 'valid' is defined by inclusion in the 'per-patient' analysis set (see below). The number may differ from the number indicated to be treated, if patients were excluded from the analysis set.
- Documentation based on patient charts (no/yes).

The 'per-dentist analysis set' included 'per-dentist' documentations that were based on patient charts according to 'per-dentist' documentation form and that were not implausible according to DVP.

Analysis variables 'per-patient':

Inclusion criteria:

- OraVerse® treatment after dental procedure with adrenaline containing local anesthetic.
- OraVerse® treatment within the last 3 months before contract signing.

Conditions of OraVerse® use:

- Patient age [years].
- Patient body weight class (< 15 kg, 15 - 30 kg, > 30 kg, no classification possible).
- Type of dental intervention (cleaning, calculus removal, root planing, preparation of cavities for placement of fillings or crowns, other).
- Local anesthetic – adrenaline concentration (1:200,000; 1:100,000; [categories may have been added depending on data]), derived from local anesthetic product.
- Local anesthetic – product (Ultracain D-S (1:200,000); Ultracain D-S forte (1:100,000); Septanest mit Adrenalin 1:200,000; Septanest mit Adrenalin 1:100,000; Ubistesin 1:200,000; Ubistesin forte 1:100,000; other).
- Local anesthetic - number of cartridges (0.5, 1, 1.5, 2, >2, [categories may have been added if more than 2 cartridges were used]); if more than 1 checkbox was ticked, the numbers were summed up to the total number of cartridges; if the number of cartridges was missing but a volume was given, the number of cartridges was calculated as volume [mL] / 1.7 mL.
- Local anesthetic – volume [mL]; if the volume was missing but the number of cartridges was given, the volume was calculated as the number of cartridges multiplied by 1.7 mL.
- OraVerse® - dose, calculated as number of cartridges injected multiplied by 400 µg; if more than 1 checkbox was ticked, the number of cartridges was summed up to the total number of cartridges.

The 'per-patient' analysis set included all 'per-patient' documentations that fulfilled the criteria according to the DVP and that were based on patient charts according to the 'per-dentist' documentation form.

Compliance analysis: For the analysis of the primary outcome, the proportions of compliance and of non-compliance with the specifications in the SmPC were calculated for all compliance variables separately (i.e., compliance regarding age, dental intervention, local anesthetic used, OraVerse® maximum dose, and OraVerse® dose in relation to anesthetic dose) and overall. Missing values in a variable needed to evaluate a criterion led to rating of that criterion as 'missing'. However, if the body weight was missing and the age was ≥ 12 years, a body weight of > 30 kg was assumed. Percentage values for compliant and non-compliant patients were calculated disregarding patients with missing values.

It is important to note that for this study dental interventions that are described as not

	recommended in the SmPC (i.e., extractions) are considered as non-compliance for this evaluation. This is also true for administered doses of OraVerse® which are lower than recommended in the SmPC. In both cases it is not a contraindication. "Compliance" with the respective specifications provided in the SmPC was defined as follows: • Patient age ≥ 6 years. • Type of dental intervention in accordance with pre-specified interventions (i.e., cleaning, calculus removal, root planing, preparation of cavities for placement of fillings or crowns) or specification of 'other' identified as compliant with SmPC by a medical expert. 'Other' identified as compliant applied to 31 types of interventions reported in this study. • Product of local anesthetic in accordance with pre-specified anesthetics (Ultracain D-S [1:200,000]; Ultracain D-S forte [1:100,000]; Septanest mit Adrenalin 1:200,000; Septanest mit Adrenalin 1:100,000; Ubistesin 1:200,000; Ubistesin forte 1:100,000) or specification of 'other' identified as adrenaline containing local anesthetic. • Dose of OraVerse® used not higher than the maximum dose recommended in the SmPC (200 µg for patients being 6 – 11 years old and with body weight 15 - 30 kg, 400 µg for patients being 6 - 11 years old and with body weight > 30 kg, and 800 µg for patients being ≥ 12 years old and with body weight > 30 kg). • OraVerse® dose in relation to anesthetic dose in accordance with recommendations in the SmPC: Number of local anesthetic cartridges ≤ 2 and number of OraVerse® cartridges equal to number of local anesthetic cartridges OR number of local anesthetic cartridges > 2 and number of OraVerse® cartridges equal to 800 µg (2 cartridges). According to these criteria, compliance was assessed as follows: • Compliance regarding age (no or yes), defined as 'no': respective criterion for compliance not fulfilled and not missing vs. 'yes': respective criterion for compliance fulfilled and not missing. • Compliance regarding dental intervention (no or yes), defined analogously. • Compliance regarding OraVerse® maximum dose (no or yes), defined analogously. • Compliance regarding OraVerse® dose in relation to anesthetic dose (no or yes), defined analogously. • Overall compliance (no or yes), defined as 'no': at least 1 criterion for compliance not fulfilled and not missing vs. 'yes': all criteria for compliance fulfilled and not missing. Proportions of compliance were calculated along with 95% CIs, assuming a cluster sampling design with patients of the same dentist forming a cluster. According to the cluster design, CIs were calculated as modified Clopper-Pearson (exact) CIs, using the SAS procedure SURVEYFREQ. The procedure does not allow the calculation of CIs in the presence of 0% or 100% proportions.

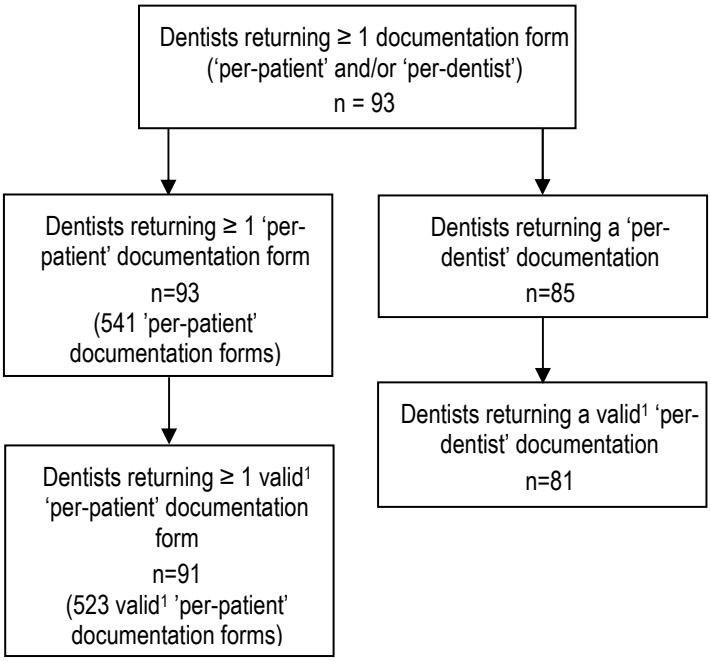
RESULTS	
Participants (actual)	In total, 'per-patient' and 'per-dentist' documentation forms from 93 dentists were received from April to July 2014. All these dentists returned at least one 'per-patient' documentation form amounting to 541 'per-patient' documentation forms. Totally, 18 of these forms were not valid, i.e., did not qualify for inclusion in the analyses sets either because treatment with OraVerse® did not occur within the last 3 months before contract signing (13 counts) or the documentation was not based on patients charts (1 'per-dentist' documentation concerning 5 patients). Two of the 93 dentists who returned a 'per-patient' documentation form returned only invalid 'per-patient' documentation forms. Thus, a total of 523 valid 'per-patient' documentations were received from 91 dentists (Figure 1, post-text Tables 1-1 and 1-2). **Figure 1: Disposition: All dentits/patients**  [1] 'valid' as defined by inclusion into the respective analysis set *Data source: Post-text Table 1-1.* Out of the 93 dentists that returned at least one documentation form, 85 dentists returned a 'per-dentist' documentation form. In 4 of these forms, the number of documented patients was implausible, as the number was higher than the number of patients treated. Thus, 81 'per-dentist' documentation forms were valid (Figure 1, post-text Tables 1-1 and 1-2). No sex of patients was reported.
Participant characteristics and primary analyses:	<u>Basic participant characteristics</u> Regarding the 81 dentists that returned a valid 'per-dentist' documentation ('per-dentist' analysis set), sample statistics were calculated (post-text Table 2-1). The mean number of patients treated per dentist within the last 3 months prior to contract signing was 13.4 ± 10.1, with a minimum of 3 and a maximum of 50 patients (median: 10 patients). The mean number of patients documented per dentist was 5.8 ± 0.6. The number ranged from 3 to 6 patients (median: 6 patients). On average, 62.6 ± 30.5% of treated patients per center were documented, with a minimum of 12% and a maximum of 100% of patients being documented (median: 60.0%).

Table 1: Per-patient analysis set: Demographic characteristics

Variable Statistic/Category	Unit	n
Patient age	**[years]**	
Age class[1]	6 - < 12	7
	12 - < 18	7
	≥ 18	505
	Total	519
Mean ± SD	44.9 ± 15.7	
Median	45	
Minimum	6	
Maximum	97	
Patient body weight	**[kg]**	
Weight class[2]	< 15	-
	15 – 30	6 (1.15%)
	> 30	496 (94.84%)

[1] 4 values missing

[2] 21 values missing

SD = Standard deviation

Data source: Post-text Table 3-1.

Sample statistics regarding the conditions of OraVerse® use were calculated based on the 'per-patient' analysis set. For the 523 patients in the analysis set (corresponding to the number of valid 'per-patient' documentations, post-text Table 1-1), the age was given for 519 patients. The mean age was 44.9 ± 15.7 years, with the youngest patient being 6, and the oldest patient being 97 years old. Most patients (n = 505) were ≥ 18 years of age, whereas the age classes '12 to < 18 years' and '6 to < 12 years' encompassed much less patients, i.e., 7 patients each. In accordance with the inclusion criteria, there was no patient with an age of < 6 years (Table 1, post-text Table 3-1).

As expected from the prevalence of adult patients, most patients' (94.8%) body weight was greater than 30 kg, 1.2% had a body weight ranging from 15 to 30 kg (all belonging to age class '6 to < 12 years'), and for 21 patients' (4.0%) body weight the corresponding dentists indicated either 'no classification possible' or nothing at all (both considered 'missing values') (Table 1, post-text Table 3-1).

Dental interventions

For 68.3% of patients (n = 357, one value missing), OraVerse® was used in the frame of preparations of cavities for placement of fillings or crowns (post-text Table 3-2). This type of dental intervention was prevalent among all age classes. For considerably less patients, OraVerse® was used in the context of root planing (8.4%, n = 44), cleaning (4.6%, n = 24), or calculus removal (3.8%, n = 20). For 118 patients (22.6%), OraVerse® was administered in conjunction with other types of dental

	interventions, the most frequent reported terms being 'PA-Behandlung [*treatment of parodontitis*]' (5.2%, n = 27), 'Wurzelbehandlung [*root treatment*]' (2.1%, n = 11), and 'Endo' (presumably *endodontic treatment*, but the term was not specified in the corresponding CRFs) (1.9%, n = 10). The most frequent 'other' reported term of dental intervention in patients < 18 years old was 'Extraktion Milchzahn [*deciduous tooth extraction*]' (n = 3 out of N = 7 in this age class). However, some patients were subjected to more than one type of dental intervention (post-text Table 3-2). Local anesthetics The most frequently used anesthetic product was Ultracain D-S forte (1:100,000), which was administered to 221 patients (42.3%, N = 523, 4 values missing; post-text Table 3-3). Among 'Product – specification of other' (43 patients injected), only the use of 'Xylonest 3%' (1 case) was considered non-compliant, as this product does not contain adrenaline. However, some patients received more than a single local anesthetic product. If more than one anesthetic product was administered, the adrenaline concentration of these products might have differed. The prevalent adrenaline concentration used was 1:200,000, which was administered to 49.1% of the 523 patients. Almost just as frequently (48.2% of patients) an adrenaline concentration of 1:100,000 was used. Again, 4 values were missing (post-text Table 3-3). The doses of the local anesthetics administered are shown in post-text Table 3-4. Among the N = 505 patients of the age class '≥ 18 years', the 4 patients that were administered an unknown product (post-text Table 3-3) are not listed here. In total, 522 cartridges of local anesthetics corresponding to 887.4 mL were administered. One value was missing, i.e., for one patient neither the number of cartridges nor the volume taken was documented. The mean number of local anesthetic cartridges taken was 1.5 ± 1.3 with a minimum of 0.5 and a maximum of 16 cartridges administered. Most patients (60.4%) were given one cartridge. The latter also holds true for each anesthetic product considered separately, except for 'Septanest mit Adrenalin 1:100,000', of which most frequently two cartridges were given. Please note that in the category 'Number of cartridges by local anesthetic product' of post-text Table 3-4 for patients that took more than one product, only data pertaining to the first product in alphabetical order are shown. The number of cartridges applied corresponded to a mean of 2.5 ± 2.2 mL injected per patient, with a range from 0.5 mL at minimum to 27.2 mL at maximum (value verified with CRF, in which 16 cartridges are documented). The volume patients received most frequently was 1.7 mL (n = 299, 57.2% of patients). Again, this is also the case for each anesthetic product considered separately, except for 'Septanest mit Adrenalin 1:100,000', of which most frequently twice the volume (3.4 mL) was injected (post-text Table 3-4). Use of OraVerse® The doses of OraVerse® administered to 521 patients (2 values missing) are given in post-text Table 3-5. On average, patients received 474 ± 246 µg (median: 400 µg). The minimum dose injected was 200 µg (9.4% of patients), at maximum 3200 µg (1 patient, who received 16 cartridges of local anesthetic) was administered. The dose most frequently received (i.e., by 69.8% of patients) was 400 µg (1 cartridge). Analysis of compliance with SmPC (primary outcome) The primary outcome of this study was the proportion of patients that did 'comply'/ 'not comply' with the specifications in the SmPC (Table 2, post-text Table 4-1). It is important to note that in this study 'non-comply' is defined not only as non-compliant with the specifications but also as non-recommended according the SmPC.

A 100% compliance for the 'per-patient analysis set' was achieved regarding age, whereby the age of 4 patients was not specified. Almost equally high (99.8%) was the compliance regarding the local anesthetic used (95%-CI: [98.9%; 100%]) (again 4 values were missing).

Compliance was relatively lowest with respect to the dose of OraVerse® in relation to the dose of the local anesthetic (77.9%; 95%-CI: [71.9%; 83.1%]) (3 values missing). Compliance regarding this issue ranged from 100% (n = 7) (age class '6 to < 12 years') to 57.1% (n = 4) (age class '12 to < 18 years'; 95%-CI: [18.4%; 90.1%]). As shown in Listing 4-1, in the latter age class, 3 of the 4 patients were non-compliant regarding the dose of OraVerse® in relation to the dose of the local anesthetic, although they were compliant regarding the maximum dose of OraVerse®. However, in case of these 3 patients, as in most other cases of non-compliance regarding the dose relation, the dose of OraVerse® used was lower than recommended in the SmPC.

Compliance regarding the indication (type of dental intervention) and the maximum dose of OraVerse® was 93.9% and 96.9%, respectively. Regarding the indication, of the 7 patients belonging to the age class 6 to < 12 years, 4 patients (57.1%; 95%-CI: [13.3%; 93.5%]) were non-compliant (all were subject to tooth extraction). Two of these 4 patients were additionally non-compliant as they received a dose of OraVerse® exceeding the maximum dose recommended in the SmPC.

Table 2: Proportion of compliance with the SmPC

Variable	Proportion of compliance with SmPC n (%) [95%-CI]			
	Total	Age class 6 - < 12 years	Age class 12 - < 18 years	Age class > 18 years
Age	N=519 519 (100.0) [n. c.]	N=7 7 (100.0) [n. c.]	N=7 7 (100.0) [n. c.]	N=505 505 (100.0) [n. c.]
Indication	N=522 490 (93.9) [90.4; 96.4]	N=7 3 (42.9) [6.5; 86.7]	N=7 6 (85.7) [42.1; 99.6]	N=505 478 (94.7) [91.6; 96.8]
Local anesthetic used	N=519 518 (99.8) [98.9; 100.0]	N=7 7 (100.0) [n. c.]	N=7 7 (100.0) [n. c.]	N=501 500 (99.8) [98.9; 100.0]
OraVerse® maximum dose	N=517 501 (96.9) [93.9; 98.7]	N=7 5 (71.4) [29.0; 96.3]	N=7 7 (100) [n. c.]	N=503 489 (97.2) [94.2; 98.9]
OraVerse® dose/local anesthetic dose	N=520 405 (77.9) [71.9; 83.1]	N=7 7 (100.0) [n. c.]	N=7 4 (57.1) [18.4; 90.1]	N=502 390 (77.7) [71.8; 82.9]
Overall compliance	N=512 377 (73.6) [67.2; 79.4]	N=7 3 (42.9) [6.5; 86.7]	N=7 3 (42.9) [9.9; 81.6]	N=498 371 (74.5) [68.1; 80.2]

n. c. = not calculable (modified Clopper-Pearson CIs of cluster sampling design are not calculable if proportion = 0% or 100%)
Note: No. of missing values are not provided in this table.

	Data source: Post-text Table 4-1. Finally the cumulative analysis of compliance showed that 377 patients overall (73.6%; 95%-CI: [67.2%; 79.4%]) were compliant with each of the specified recommendations, whilst 135 patients (26.4%; 95%-CI: [20.6%; 32.8%]) were non-compliant with at least one of the specified recommendations (missing data in 11 patients). None of the patients was completely incompliant, i.e., incompliant regarding each age, type of dental intervention, product and dose of local anesthetic used, and the dose of OraVerse® administered (Listing 4-1). No safety signals were reported.
Other analyses:	N.A.
Discussions:	In this retrospective, observational, cross-sectional drug utilization survey the conditions of use of OraVerse® in dental routine practice was investigated. In this nationwide study, 523 valid 'per-patient' documentation forms and 81 valid 'per-dentist' documentation forms were received. Within the last 3 months before contract signing, a mean number of 13.4 ± 10.1 patients were treated with OraVerse® per dentist. The mean number of documented patients by dentist - which was *a priori* restricted to 6 patients - was 5.8 ± 0.6. Hence, on average, the number of patients treated with OraVerse® within this period was twice as large. On average, the patients were 44.9 ± 15.7 years old, with a range from 6 years - the minimum age according to inclusion criteria - to 97 years. However, the age class '≥ 18 years' included a substantially greater number of patients (n = 505) than the younger age classes '12 to < 18 years' and '6 to < 12 years' (n = 7 each). Corresponding to the prevalence of adult patients, far more patients fit into the body weight class '> 30 kg' than into the class `15 – 30 kg'. Therefore, the expressiveness of results gained from analyzing the age class '≥ 18 years' or the body weight class `15 - 30 kg' is much higher than in case of the other age classes or the lower body weight class, and no robust comparisons across age or body weight groups can be made. Within this study, OraVerse® was used to reverse the effects of local anesthesia for a broad range of indications, suggesting its wide field of application and the acceptance in dental routine practice. Most frequently, it was applied to reverse the anesthetic effect of Ultracain D-S forte (1:100.000) and in the frame of preparations of cavities for placement of fillings or crowns. The primary outcome of this study was the proportion of compliance of OraVerse® use with the recommendations given in the SmPC. A 100% compliance was observed regarding patients' age (≥ 6 years). Almost equally high (99.8%) was the compliance regarding the product of the local anesthetic used (adrenaline-containing products), followed by the compliance with respect to the maximum dose of OraVerse® (depending on age and body weight) (96.9%), and the type of dental intervention (93.9%). Compliance was relatively lowest (77.9%) regarding the dose of OraVerse® in relation to the dose of the local anesthetic. However, in most of the latter cases of non-compliance, the dose relation of OraVerse® to the anesthetic was actually lower than recommended in the SmPC. Possible reasons might be that i) depending on the duration of the dental intervention the effect of the anesthesia had already substantially dropped and the administered dose may have been adapted, ii) dentists intended to use OraVerse® with caution since it is a quite new product on the market, or iii) dentists might have wanted to limit the overall amount of injected volume. In almost three quarters of cases, OraVerse® was used in complete compliance with

	the recommendations according to the SmPC. But as noted before in this study 'non-compliance' is defined not only as non-compliant with the specifications but also as non-recommended according to the SmPC. The study enlightens the conditions of use of OraVerse® in uninfluenced dentist routine practice particular in adults. Due to the high proportion of adult patients observed the results are particularly applicable to adults. No safety signals were identified.
Conclusions:	The results of the study suggest that OraVerse® is used for a broad range of dental interventions at least in adults and is in compliance with the SmPC regarding patient's age (100%), the maximum dose of OraVerse® (96,9%), and the type of dental inerventions (93,9%). The greatest deviation is underdosing of OraVerse® in relation to the dose of the anesthetic.
Date of report:	16-Dec-2014

APPENDICES

1 APPENDIX I – ADMINISTRATIVE AND LEGAL CONSIDERATIONS

1.1 ETHICAL CONSIDERATIONS

1.1.1 Ethical principles

This registry was conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) including all subsequent amendments.

1.1.2 Laws and regulations

This registry was conducted in compliance with all international guidelines, and national laws and regulations of the country in which the registry was performed, as well as any applicable guidelines.

Each participating country locally ensured that all necessary regulatory submissions (eg, IRB/IEC) were performed in accordance with local regulations including local data protection regulations.

1.2 DATA PROTECTION

Since this was a retrospective drug utilization study based on the analysis of anonymous preexisting data, no patient's personal data and physician's personal data were used.

1.3 RECORD RETENTION

The physician was responsible for the retention of the registry documentation until the end of the registry. In addition, the physician had to comply with specific local regulations and recommendations regarding patient record retention.

1.4 THE COMPANY AUDITS AND INSPECTIONS BY COMPETENT AUTHORITIES (CA)

Not applicable

1.5 CENTRAL LABORATORY

Not applicable.

1.6 OWNERSHIP OF DATA AND USE OF REGISTRY RESULTS

Unless otherwise specified by local laws and regulations, the Company retains ownership of data, results, reports, findings, and discoveries related to the registry. Therefore, the Company reserves the right to use the data from the present registry for any purpose, including to submit them to the Competent Authorities of any country.

The Study Committee, if any involved in the registry, has full access to the final data base allowing for appropriate academic analysis and reporting of the registry results.

1.7 STUDY CONSULTANTS

1.7.1 Scientific Committee and Charter
Not applicable.

1.7.2 National coordination
Not applicable.

1.7.3 Other experts/consultants
Daubländer, Monika, Univ.-Prof. Dr. Dr. med., University of Mainz, Expert

1.8 PARTICIPATING PHYSICIANS
The physicians performed the registry in accordance with the protocol, applicable local regulations and international guidelines.
The participating physicians did not need to inform the patients using an informed consent form (ICF), since this was a retrospective drug utilization study based on the analysis of anonymous preexisting data.
The following numbers of centers per federal state of Germany have enrolled at least one patient:

- 18 centers in Baden-Württemberg
- 29 centers in Bayern
- 6 centers in Berlin
- 5 centers in Hamburg
- 9 centers in Hessen
- 1 center in Mecklenburg-Vorpommern
- 3 centers in Niedersachsen
- 17 centers in Nordrhein-Westfalen
- 5 centers in Rheinland-Pfalz
- 2 centers in Saarland
- 2 centers in Schleswig-Holstein

1.9 STUDY PERSONNEL

1.9.1 Personnel involved in the registry
The Coordinating physician's and Company responsible medical officer's signed approvals of the report are provided in Section 3.8.

This report was prepared by:

- Daubländer, Monika, Univ.-Prof. Dr. Dr. med., University of Mainz, Expert
- John, Martina, Sanofi-Aventis Deutschland GmbH, NIS Management
- Kurzinger, Marie-Laure, MSc, SANOFI, Global Pharmacovigilance & Epidemiology, Epidemiologist

- Paar, W. Dieter, Prof. Dr. med., Sanofi Aventis Deutschland GmbH, Director Medical & Scientific Affairs
- Schmidt, Juergen-Hans, Dr. med., Sanofi-Aventis Deutschland GmbH, Pharmacovigilance
- Theobald, Karlheinz, Sanofi-Aventis Deutschland GmbH, EbM & Health Economics/Biostatistics & Epidemiology, Statistician
- Weidemann, Eva-Verena, Dr., Sanofi-Aventis Deutschland GmbH, Clinical Project Leader, Country Liaison Manager Austria, Study Management

1.9.2 The Company Internal Staff

The Company was responsible for providing adequate resources to ensure the proper conduct of the registry.
The Company was responsible for local submission(s) complying with data protection rules and any other local submission(s) required.

1.9.3 Contract Research Organization (CRO)

Data management, statistical activities, and medical writing were carried out by Winicker Norimed GmbH, Deutschherrnstraße 15-19, D-90429 Nürnberg under the supervision of the company.

2 APPENDIX II – TABLES AND GRAPHS

Table of Contents

1 Disposition

Table 1-1 Disposition

All dentists/patients

Disposition	Count
No. of dentists who returned at least 1 documentation (dentist or patient)	93
No. of dentists who returned a "per-dentist" documentation	85
No. of dentists who returned a valid [1)] "per-dentist" documentation	81
No. of dentists who returned at least 1 "per-patient" documentation	93
No. of dentists who returned at least 1 valid [1)] "per-patient" documentation	91
No. of returned "per-patient" documentations out of 93 dentists	541
No. of valid [1)] "per-patient" documentations out of 91 dentists	523

[1)]"valid" defined by inclusion into the respective analysis set.

Reference: SAP
Program: TAB_1_1_DISPO, 140911 17:32

Table 1-2 Violation of inclusion criteria / reasons for exclusion from analysis set(s)

All dentists/patients

Violation	Count
Dentist documentation: Documentation not based on patient charts	1
Dentist documentation: No. of patients treated with OraVerse® within the last 3 months before contract signing implausible	0
Dentist documentation: No. of documented patients implausible	4
Patient documentation: OraVerse® treatment not after dental procedure with adrenaline containing local anesthetic	0
Patient documentation: OraVerse® treatment not within the last 3 months before contract signing	13

Note that the first 3 lines refer to the number of "per-dentist" documentations with respective violation (out of 85 "per-dentist" documentations), while the latter 2 lines refer to the number of "per-patient" documentations with respective violation (out of 541 "per-patient" documentations). Multiple violations per documentation are possible for both types of documentation.

Note also that the violation "Documentation not based on patient charts" in 1 "per-dentist" documentation (line 1) concerns 5 patients that were also excluded from the per-patient analysis set (in addition to the 13 patients with violation "OraVerse® treatment not within the last 3 months before contract signing" (line 5); 18 exclusions from the per-patient analysis set in total).

Reference: SAP
Program: TAB_1_2_VIOLA, 140911 17:32

2 Extent of OraVerse® use

Table 2-1 Number of patients treated with OraVerse® and documented per dentist

Per-dentist analysis set

Variable **Statistic**	**Result (N=81)**
No. of patients treated [1)]	
n	81
Mean	13.4
SD	10.1
Minimum	3.0
Q1	6.0
Median	10.0
Q3	16.0
Maximum	50.0
No. of patients documented	
n	81
Mean	5.8
SD	0.6
Minimum	3.0
Q1	6.0
Median	6.0
Q3	6.0
Maximum	6.0

Variable Statistic	Result (N=81)
Proportion of patients documented relative to treated [%]	
n	81
Mean	62.6
SD	30.5
Minimum	12.0
Q1	37.5
Median	60.0
Q3	100.0
Maximum	100.0

1) per dentist within the last 3 months before contract signing.

Reference: SAP
Program: TAB_2_1_EXTENDORAVERSE, 140911 17:32

3 Conditions of OraVerse® use

Table 3-1 Conditions of OraVerse® use - patient data

Per-patient analysis set

Variable Statistic/Category	Age missing (N=4)	6 to < 12 years (N=7)	12 to < 18 years (N=7)	>= 18 years (N=505)	Total (N=523)
Patient age [years]					
n	0	7	7	505	519
Mean	-	7.9	15.4	45.9	44.9
SD	-	1.8	1.7	14.9	15.7
Minimum	-	6.0	13.0	18.0	6.0
Q1	-	6.0	14.0	34.0	33.0
Median	-	8.0	16.0	45.0	45.0
Q3	-	9.0	17.0	56.0	55.0
Maximum	-	11.0	17.0	97.0	97.0
Patient body weight class, n (%)					
< 15 kg	-	-	-	-	-
15 - 30 kg	-	6 (85.71)	-	-	6 (1.15)
> 30 kg	3 (75.00)	1 (14.29)	6 (85.71)	486 (96.24)	496 (94.84)
No classification possible	-	-	-	13 (2.57)	13 (2.49)
Missing values	1 (25.00)	-	1 (14.29)	6 (1.19)	8 (1.53)

Reference: SAP
Program: TAB_3_1_CONDITIONORAVERSE, 140911 17:32

Table 3-2 Conditions of OraVerse® use - dental intervention

Per-patient analysis set

Variable Category	Routine intervention[1)]	Age missing (N=4)	6 to < 12 years (N=7)	12 to < 18 years (N=7)	>= 18 years (N=505)	Total (N=523)
Type of dental intervention [2)], n (%)						
Cleaning	yes	-	-	-	24 (4.75)	24 (4.59)
Calculus removal	yes	-	-	-	20 (3.96)	20 (3.82)
Root planing	yes	-	-	-	44 (8.71)	44 (8.41)
Preparation of cavities for placement of fillings or crowns	yes	3 (75.00)	4 (57.14)	5 (71.43)	345 (68.32)	357 (68.26)
Other		-	4 (57.14)	2 (28.57)	112 (22.18)	118 (22.56)
Missing values		1 (25.00)	-	-	-	1 (0.19)
Type of dental intervention - specification of other [2)], n (%)						
DENTITIO DIFFICILIS	yes	-	-	1 (14.29)	-	1 (0.19)
EINSETZEN VON ZE	yes	-	-	-	1 (0.20)	1 (0.19)
ENDO	yes	-	-	-	10 (1.98)	10 (1.91)
ENDO (VITE 46)	yes	-	-	-	1 (0.20)	1 (0.19)
ENDO-REVISION	yes	-	-	-	1 (0.20)	1 (0.19)
ENDODONT. BEHANDLUNG	yes	-	-	-	1 (0.20)	1 (0.19)
EXTRAKTION	no	-	-	-	6 (1.19)	6 (1.15)
EXTRAKTION 7.38 (###) [3)]	no	-	-	-	1 (0.20)	1 (0.19)
EXTRAKTION MILCHZAHN	no	-	2 (28.57)	1 (14.29)	-	3 (0.57)
EXTRAKTION MILCHZAHN (62)	no	-	1 (14.29)	-	-	1 (0.19)
EXTRAKTION UNKOMPLIZIERT	no	-	-	-	1 (0.20)	1 (0.19)
EXTRAKTION WEISHEITSZAHN	no	-	-	-	2 (0.40)	2 (0.38)
EXTRAKTION WURZELREST	no	-	-	-	2 (0.40)	2 (0.38)

Variable Category	Routine intervention[1)]	Age missing (N=4)	6 to < 12 years (N=7)	12 to < 18 years (N=7)	>= 18 years (N=505)	Total (N=523)
EXTRAKTIONEN	no	-	1 (14.29)	-	2 (0.40)	3 (0.57)
FÜLLUNG	yes	-	-	-	4 (0.79)	4 (0.76)
FÜLLUNGEN	yes	-	-	-	3 (0.59)	3 (0.57)
GERÜSTANPROBE	yes	-	-	-	1 (0.20)	1 (0.19)
IMPLANTATFREILEGUNG	no	-	-	-	3 (0.59)	3 (0.57)
IMPLANTATION	no	-	-	-	5 (0.99)	5 (0.96)
KNOCHENAUFBAU	no	-	-	-	1 (0.20)	1 (0.19)
KONS. BEHANDLUNG	yes	-	-	-	3 (0.59)	3 (0.57)
KRONE EINGESETZT	yes	-	-	-	1 (0.20)	1 (0.19)
KRONEN EINGESETZT	yes	-	-	-	2 (0.40)	2 (0.38)
KRONEN ZEMENTIERUNG	yes	-	-	-	2 (0.40)	2 (0.38)
KRONEN-PRÄPARATION	yes	-	-	-	1 (0.20)	1 (0.19)
KRONENABTRENNUNG	yes	-	-	-	1 (0.20)	1 (0.19)
KÜRETTAGE	yes	-	-	-	1 (0.20)	1 (0.19)
OFFENE KÜRETTAGE	no	-	-	-	1 (0.20)	1 (0.19)
PA-BEHANDLUNG	yes	-	-	-	27 (5.35)	27 (5.16)
PA-BEHANDLUNG SYSTEM.	yes	-	-	-	1 (0.20)	1 (0.19)
PA-OP	no	-	-	-	1 (0.20)	1 (0.19)
PROTHETIK + KONS + STIFT	yes	-	-	-	1 (0.20)	1 (0.19)
PRÄPARATION	yes	-	-	-	1 (0.20)	1 (0.19)
VITAL-EXSTIRPATION	yes	-	-	-	2 (0.40)	2 (0.38)
VOLLNARKOSE	NA	-	1 (14.29)	-	-	1 (0.19)
WURZELBEHANDLUNG	yes	-	-	-	11 (2.18)	11 (2.10)
WURZELFÜLLUNG	yes	-	-	-	1 (0.20)	1 (0.19)
WURZELKANALAUFBEREITUNG	yes	-	-	-	1 (0.20)	1 (0.19)

Variable Category	Routine intervention[1)]	Age missing (N=4)	6 to < 12 years (N=7)	12 to < 18 years (N=7)	>= 18 years (N=505)	Total (N=523)
WURZELKANALBEHANDLUNG	yes	-	-	-	5 (0.99)	5 (0.96)
WURZELSPITZENRESEKTION	no	-	-	-	1 (0.20)	1 (0.19)
ZAHNERSATZ EINGLIEDERN	yes	-	-	-	1 (0.20)	1 (0.19)
ZWISCHENSCHRITT BEI KOMBI ZE	yes	-	-	-	1 (0.20)	1 (0.19)

[1)] classification performed by Sanofi after discussion with clinical expert
[2)] multiple answers possible per patient
[3)] input data error; correct: EXTRAKTION Z.38 (3 unreadable symbols)

Reference: SAP
Program: TAB_3_2_CONDITIONORAVERSE, 140911 17:32

Table 3-3 Conditions of OraVerse® use - local anaesthetic product

Per-patient analysis set

Variable Category	Age missing (N=4)	6 to < 12 years (N=7)	12 to < 18 years (N=7)	>= 18 years (N=505)	Total (N=523)
Product [1)], n (%)					
Ultracain D-S (1:200.000)	2 (50.00)	5 (71.43)	4 (57.14)	194 (38.42)	205 (39.20)
Ultracain D-S forte (1:100.000)	1 (25.00)	2 (28.57)	3 (42.86)	215 (42.57)	221 (42.26)
Septanest mit Adrenalin 1:200.000	-	-	-	11 (2.18)	11 (2.10)
Septanest mit Adrenalin 1:100.000	-	-	-	12 (2.38)	12 (2.29)
Ubistesin 1:200.000	1 (25.00)	-	-	22 (4.36)	23 (4.40)
Ubistesin forte 1:100.000	-	-	-	6 (1.19)	6 (1.15)
Other	-	-	-	43 (8.51)	43 (8.22)
Missing values	-	-	-	4 (0.79)	4 (0.76)
Adrenaline concentration, n (%)					
1:100.000	1 (25.00)	2 (28.57)	3 (42.86)	246 (48.71)	252 (48.18)
1:200.000	3 (75.00)	5 (71.43)	4 (57.14)	245 (48.51)	257 (49.14)
1:400.000	-	-	-	6 (1.19)	6 (1.15)
Unknown	-	-	-	4 (0.79)	4 (0.76)
Missing values	-	-	-	4 (0.79)	4 (0.76)
Product - specification of other, n (%)					
ARTINESTOL	-	-	-	1 (0.20)	1 (0.19)
ARTINESTOL 1:100.000	-	-	-	7 (1.39)	7 (1.34)
ARTINESTOL 1:200.000	-	-	-	17 (3.37)	17 (3.25)
SOPIRA	-	-	-	2 (0.40)	2 (0.38)
SOPIRA 1:100.000	-	-	-	7 (1.39)	7 (1.34)

Variable Category	Age missing (N=4)	6 to < 12 years (N=7)	12 to < 18 years (N=7)	>= 18 years (N=505)	Total (N=523)
SOPIRA 1:200.000	-	-	-	2 (0.40)	2 (0.38)
SOPIRA 1:400.000	-	-	-	6 (1.19)	6 (1.15)
XYLONEST 3%	-	-	-	1 (0.20)	1 (0.19)

[1)] multiple answers possible per patient

Reference: SAP
Program: TAB_3_3_CONDITIONORAVERSE, 140911 17:33

Table 3-4 Conditions of OraVerse® use - local anaesthetic dose

Per-patient analysis set

Variable Category/Statistic	Age missing (N=4)	6 to < 12 years (N=7)	12 to < 18 years (N=7)	>= 18 years (N=505)	Total (N=523)
Number of cartridges - in total - continuous					
n	4	7	7	504	522
Mean	1.5	0.7	1.0	1.5	1.5
SD	0.6	0.3	0.0	1.3	1.3
Minimum	1.0	0.5	1.0	0.5	0.5
Q1	1.0	0.5	1.0	1.0	1.0
Median	1.5	0.5	1.0	1.0	1.0
Q3	2.0	1.0	1.0	2.0	2.0
Maximum	2.0	1.0	1.0	16.0	16.0
Number of cartridges - in total - categorical, n (%)					
0.5	-	4 (57.14)	-	37 (7.33)	41 (7.84)
1.0	2 (50.00)	3 (42.86)	7 (100.00)	304 (60.20)	316 (60.42)
1.5	-	-	-	27 (5.35)	27 (5.16)
2.0	2 (50.00)	-	-	81 (16.04)	83 (15.87)
2.5	-	-	-	2 (0.40)	2 (0.38)
3.0	-	-	-	24 (4.75)	24 (4.59)
3.5	-	-	-	1 (0.20)	1 (0.19)
4.0	-	-	-	15 (2.97)	15 (2.87)
5.0	-	-	-	4 (0.79)	4 (0.76)
6.0	-	-	-	4 (0.79)	4 (0.76)
7.0	-	-	-	1 (0.20)	1 (0.19)

Variable Category/Statistic	Age missing (N=4)	6 to < 12 years (N=7)	12 to < 18 years (N=7)	>= 18 years (N=505)	Total (N=523)
9.0	-	-	-	2 (0.40)	2 (0.38)
10.0	-	-	-	1 (0.20)	1 (0.19)
16.0	-	-	-	1 (0.20)	1 (0.19)
Missing values	-	-	-	1 (0.20)	1 (0.19)
Volume [ml] - in total - continuous					
n	4	7	7	504	522
Mean	2.6	1.3	1.7	2.6	2.5
SD	1.0	0.5	0.0	2.2	2.2
Minimum	1.7	0.8	1.7	0.5	0.5
Q1	1.8	0.9	1.7	1.7	1.7
Median	2.6	0.9	1.7	1.7	1.7
Q3	3.4	1.7	1.7	3.4	3.4
Maximum	3.4	2.0	1.7	27.2	27.2
Volume [ml] - in total - categorical n (%)					
0.5	-	-	-	1 (0.20)	1 (0.19)
0.6	-	-	-	1 (0.20)	1 (0.19)
0.7	-	-	-	1 (0.20)	1 (0.19)
0.8	-	1 (14.29)	-	3 (0.59)	4 (0.76)
0.9	-	3 (42.86)	-	24 (4.75)	27 (5.16)
1.0	-	-	-	5 (0.99)	5 (0.96)
1.2	-	-	-	1 (0.20)	1 (0.19)
1.5	-	-	-	6 (1.19)	6 (1.15)
1.6	-	-	-	1 (0.20)	1 (0.19)
1.7	1 (25.00)	2 (28.57)	7 (100.00)	289 (57.23)	299 (57.17)
1.8	1 (25.00)	-	-	2 (0.40)	3 (0.57)

Variable Category/Statistic	Age missing (N=4)	6 to < 12 years (N=7)	12 to < 18 years (N=7)	>= 18 years (N=505)	Total (N=523)
2.0	-	1 (14.29)	-	7 (1.39)	8 (1.53)
2.5	-	-	-	1 (0.20)	1 (0.19)
2.6	-	-	-	25 (4.95)	25 (4.78)
3.0	-	-	-	4 (0.79)	4 (0.76)
3.4	2 (50.00)	-	-	75 (14.85)	77 (14.72)
3.6	-	-	-	2 (0.40)	2 (0.38)
4.0	-	-	-	1 (0.20)	1 (0.19)
4.3	-	-	-	2 (0.40)	2 (0.38)
5.1	-	-	-	24 (4.75)	24 (4.59)
6.0	-	-	-	1 (0.20)	1 (0.19)
6.8	-	-	-	15 (2.97)	15 (2.87)
8.5	-	-	-	4 (0.79)	4 (0.76)
10	-	-	-	4 (0.79)	4 (0.76)
12	-	-	-	1 (0.20)	1 (0.19)
15	-	-	-	2 (0.40)	2 (0.38)
17	-	-	-	1 (0.20)	1 (0.19)
27	-	-	-	1 (0.20)	1 (0.19)
Missing values	-	-	-	1 (0.20)	1 (0.19)

Number of cartridges by local anesthetic product [1)]					
Number of cartridges - Ultracain D-S (1:200.000) (N=204), n (%)					
0.5	-	3 (60.00)	-	25 (12.95)	28 (13.73)
1.0	1 (50.00)	2 (40.00)	4 (100.00)	117 (60.62)	124 (60.78)
1.5	-	-	-	11 (5.70)	11 (5.39)
2.0	1 (50.00)	-	-	30 (15.54)	31 (15.20)

Variable Category/Statistic	Age missing (N=4)	6 to < 12 years (N=7)	12 to < 18 years (N=7)	>= 18 years (N=505)	Total (N=523)
3.0	-	-	-	6 (3.11)	6 (2.94)
4.0	-	-	-	2 (1.04)	2 (0.98)
5.0	-	-	-	1 (0.52)	1 (0.49)
6.0	-	-	-	1 (0.52)	1 (0.49)
Number of cartridges - Ultracain D-S forte (1:100.000) (N=220), n (%)					
0.5	-	1 (50.00)	-	8 (3.74)	9 (4.09)
1.0	-	1 (50.00)	3 (100.00)	133 (62.15)	137 (62.27)
1.5	-	-	-	13 (6.07)	13 (5.91)
2.0	1 (100.00)	-	-	35 (16.36)	36 (16.36)
2.5	-	-	-	2 (0.93)	2 (0.91)
3.0	-	-	-	8 (3.74)	8 (3.64)
3.5	-	-	-	1 (0.47)	1 (0.45)
4.0	-	-	-	7 (3.27)	7 (3.18)
5.0	-	-	-	3 (1.40)	3 (1.36)
6.0	-	-	-	2 (0.93)	2 (0.91)
10.0	-	-	-	1 (0.47)	1 (0.45)
Missing values	-	-	-	1 (0.47)	1 (0.45)
Number of cartridges - Septanest mit Adrenalin 1:200.000 (N=11), n (%)					
1.0	-	-	-	5 (45.45)	5 (45.45)
1.5	-	-	-	1 (9.09)	1 (9.09)
2.0	-	-	-	2 (18.18)	2 (18.18)
3.0	-	-	-	3 (27.27)	3 (27.27)

Variable Category/Statistic	Age missing (N=4)	6 to < 12 years (N=7)	12 to < 18 years (N=7)	>= 18 years (N=505)	Total (N=523)
Number of cartridges - Septanest mit Adrenalin 1:100.000 (N=12), n (%)					
0.5	-	-	-	1 (8.33)	1 (8.33)
1.0	-	-	-	1 (8.33)	1 (8.33)
2.0	-	-	-	5 (41.67)	5 (41.67)
3.0	-	-	-	2 (16.67)	2 (16.67)
4.0	-	-	-	2 (16.67)	2 (16.67)
6.0	-	-	-	1 (8.33)	1 (8.33)
Number of cartridges - Ubistesin 1:200.000 (N=23), n (%)					
0.5	-	-	-	1 (4.55)	1 (4.35)
1.0	1 (100.00)	-	-	14 (63.64)	15 (65.22)
1.5	-	-	-	1 (4.55)	1 (4.35)
2.0	-	-	-	5 (22.73)	5 (21.74)
4.0	-	-	-	1 (4.55)	1 (4.35)
Number of cartridges - Ubistesin forte 1:100.000 (N=6), n (%)					
1.0	-	-	-	3 (50.00)	3 (50.00)
4.0	-	-	-	1 (16.67)	1 (16.67)
9.0	-	-	-	2 (33.33)	2 (33.33)
Number of cartridges - Other (N=43), n (%)					
0.5	-	-	-	2 (4.65)	2 (4.65)
1.0	-	-	-	30 (69.77)	30 (69.77)
1.5	-	-	-	1 (2.33)	1 (2.33)
2.0	-	-	-	4 (9.30)	4 (9.30)
3.0	-	-	-	2 (4.65)	2 (4.65)

Variable Category/Statistic	Age missing (N=4)	6 to < 12 years (N=7)	12 to < 18 years (N=7)	>= 18 years (N=505)	Total (N=523)
4.0	-	-	-	2 (4.65)	2 (4.65)
7.0	-	-	-	1 (2.33)	1 (2.33)
16.0	-	-	-	1 (2.33)	1 (2.33)

Volume [ml] by local anesthetic product [1)]					
Volume [ml] - Ultracain D-S (1:200.000) (N=204), n (%)					
0.5	-	-	-	1 (0.52)	1 (0.49)
0.6	-	-	-	1 (0.52)	1 (0.49)
0.8	-	-	-	1 (0.52)	1 (0.49)
0.9	-	3 (60.00)	-	15 (7.77)	18 (8.82)
1.0	-	-	-	5 (2.59)	5 (2.45)
1.2	-	-	-	1 (0.52)	1 (0.49)
1.5	-	-	-	3 (1.55)	3 (1.47)
1.6	-	-	-	1 (0.52)	1 (0.49)
1.7	1 (50.00)	2 (40.00)	4 (100.00)	110 (56.99)	117 (57.35)
1.8	-	-	-	1 (0.52)	1 (0.49)
2.0	-	-	-	3 (1.55)	3 (1.47)
2.6	-	-	-	11 (5.70)	11 (5.39)
3.0	-	-	-	3 (1.55)	3 (1.47)
3.4	1 (50.00)	-	-	25 (12.95)	26 (12.75)
3.6	-	-	-	2 (1.04)	2 (0.98)
5.1	-	-	-	6 (3.11)	6 (2.94)
6.8	-	-	-	2 (1.04)	2 (0.98)
8.5	-	-	-	1 (0.52)	1 (0.49)
10	-	-	-	1 (0.52)	1 (0.49)

Variable Category/Statistic	Age missing (N=4)	6 to < 12 years (N=7)	12 to < 18 years (N=7)	>= 18 years (N=505)	Total (N=523)
Volume [ml] - Ultracain D-S forte (1:100.000) (N=220), n (%)					
0.7	-	-	-	1 (0.47)	1 (0.45)
0.8	-	1 (50.00)	-	2 (0.93)	3 (1.36)
0.9	-	-	-	5 (2.34)	5 (2.27)
1.5	-	-	-	3 (1.40)	3 (1.36)
1.7	-	-	3 (100.00)	126 (58.88)	129 (58.64)
2.0	-	1 (50.00)	-	4 (1.87)	5 (2.27)
2.5	-	-	-	1 (0.47)	1 (0.45)
2.6	-	-	-	11 (5.14)	11 (5.00)
3.0	-	-	-	1 (0.47)	1 (0.45)
3.4	1 (100.00)	-	-	34 (15.89)	35 (15.91)
4.0	-	-	-	1 (0.47)	1 (0.45)
4.3	-	-	-	2 (0.93)	2 (0.91)
5.1	-	-	-	8 (3.74)	8 (3.64)
6.0	-	-	-	1 (0.47)	1 (0.45)
6.8	-	-	-	7 (3.27)	7 (3.18)
8.5	-	-	-	3 (1.40)	3 (1.36)
10	-	-	-	2 (0.93)	2 (0.91)
17	-	-	-	1 (0.47)	1 (0.45)
Missing values	-	-	-	1 (0.47)	1 (0.45)
Volume [ml] - Septanest mit Adrenalin 1:200.000 (N=11), n (%)					
1.7	-	-	-	5 (45.45)	5 (45.45)
2.6	-	-	-	1 (9.09)	1 (9.09)
3.4	-	-	-	2 (18.18)	2 (18.18)
5.1	-	-	-	3 (27.27)	3 (27.27)

Variable Category/Statistic	Age missing (N=4)	6 to < 12 years (N=7)	12 to < 18 years (N=7)	>= 18 years (N=505)	Total (N=523)
Volume [ml] - Septanest mit Adrenalin 1:100.000 (N=12), n (%)					
0.9	-	-	-	1 (8.33)	1 (8.33)
1.7	-	-	-	1 (8.33)	1 (8.33)
3.4	-	-	-	5 (41.67)	5 (41.67)
5.1	-	-	-	2 (16.67)	2 (16.67)
6.8	-	-	-	2 (16.67)	2 (16.67)
10	-	-	-	1 (8.33)	1 (8.33)
Volume [ml] - Ubistesin 1:200.000 (N=23), n (%)					
0.9	-	-	-	1 (4.55)	1 (4.35)
1.7	-	-	-	14 (63.64)	14 (60.87)
1.8	1 (100.00)	-	-	-	1 (4.35)
2.6	-	-	-	1 (4.55)	1 (4.35)
3.4	-	-	-	5 (22.73)	5 (21.74)
6.8	-	-	-	1 (4.55)	1 (4.35)
Volume [ml] - Ubistesin forte 1:100.000 (N=6), n (%)					
1.7	-	-	-	3 (50.00)	3 (50.00)
6.8	-	-	-	1 (16.67)	1 (16.67)
15	-	-	-	2 (33.33)	2 (33.33)
Volume [ml] - Other (N=43), n (%)					
0.9	-	-	-	2 (4.65)	2 (4.65)
1.7	-	-	-	29 (67.44)	29 (67.44)
1.8	-	-	-	1 (2.33)	1 (2.33)
2.6	-	-	-	1 (2.33)	1 (2.33)
3.4	-	-	-	4 (9.30)	4 (9.30)
5.1	-	-	-	2 (4.65)	2 (4.65)

Variable Category/Statistic	Age missing (N=4)	6 to < 12 years (N=7)	12 to < 18 years (N=7)	>= 18 years (N=505)	Total (N=523)
6.8	-	-	-	2 (4.65)	2 (4.65)
12	-	-	-	1 (2.33)	1 (2.33)
27	-	-	-	1 (2.33)	1 (2.33)

[1)] Cartridges and volumes are counted once per patient for the alphabetically 1st product if more than 1 product was documented.

Reference: SAP
Program: TAB_3_4_CONDITIONORAVERSE, 140911 17:33

Table 3-5 Conditions of OraVerse® use - OraVerse®dose

Per-patient analysis set

Variable Category/Statistic	Age missing (N=4)	6 to < 12 years (N=7)	12 to < 18 years (N=7)	>= 18 years (N=505)	Total (N=523)
Dose [µg] - continuous					
n	4	7	7	503	521
Mean	600.0	285.7	314.3	477.5	473.7
SD	230.9	106.9	106.9	247.0	245.8
Minimum	400.0	200.0	200.0	200.0	200.0
Q1	400.0	200.0	200.0	400.0	400.0
Median	600.0	200.0	400.0	400.0	400.0
Q3	800.0	400.0	400.0	400.0	400.0
Maximum	800.0	400.0	400.0	3200.0	3200.0
Dose [µg] - categorical, n (%)					
200	-	4 (57.14)	3 (42.86)	42 (8.32)	49 (9.37)
400	2 (50.00)	3 (42.86)	4 (57.14)	356 (70.50)	365 (69.79)
600	-	-	-	19 (3.76)	19 (3.63)
800	2 (50.00)	-	-	72 (14.26)	74 (14.15)
1200	-	-	-	10 (1.98)	10 (1.91)
1600	-	-	-	2 (0.40)	2 (0.38)
2000	-	-	-	1 (0.20)	1 (0.19)
3200	-	-	-	1 (0.20)	1 (0.19)
Missing values	-	-	-	2 (0.40)	2 (0.38)

Reference: SAP
Program: TAB_3_5_CONDITIONORAVERSE, 140911 17:34

4 Analysis of primary outcome

Table 4-1 Incidence of compliance and non-compliance with SmPC recommendations

Per-patient analysis set

Incidence of compliance and non-compliance with SmPC recommendations	**compliant**	**n (%) [95% CI]**
Compliant with SmPC regarding indication - age	yes	519 (100) [. - .]
	no	0
	missing	4
Compliant with SmPC regarding indication recommendations - type of dental intervention	yes	490 (93.9) [90.4-96.4]
	no	32 (6.1) [3.6- 9.6]
	missing	1
Compliant with SmPC regarding indication - local anaesthetic used	yes	518 (99.8) [98.9- 100]
	no	1 (0.2) [0.0- 1.1]
	missing	4
In accordance with SmPC dose recommendations - OraVerse® maximum dose	yes	501 (96.9) [93.9-98.7]
	no	16 (3.1) [1.3- 6.1]
	missing	6
In accordance with SmPC dose recommendations - OraVerse® dose in relation to anesthetic dose	yes	405 (77.9) [71.9-83.1]
	no	115 (22.1) [16.9-28.1]
	missing	3
Completely compliant with SmPC recommendations	yes	377 (73.6) [67.2-79.4]
	no	135 (26.4) [20.6-32.8]
	missing	11

Note that the calculation of CIs is not possible for 0% or 100% compliance as the calculation of CIs is based on a cluster sampling design using modified Clopper-Pearson CIs.

Reference: SAP
Program: TAB_4_1_COMPLIANCE, 140911 17:34

AGECLASS=Age missing

Incidence of compliance and non-compliance with SmPC recommendations	compliant	n (%) [95% CI]
Compliant with SmPC regarding indication - age	yes	0
	no	0
	missing	4
Compliant with SmPC regarding indication recommendations - type of dental intervention	yes	3 (100) [. - .]
	no	0
	missing	1
Compliant with SmPC regarding indication - local anaesthetic used	yes	4 (100) [. - .]
	no	0
	missing	0
In accordance with SmPC dose recommendations - OraVerse® maximum dose	yes	0
	no	0
	missing	4
In accordance with SmPC dose recommendations - OraVerse® dose in relation to anesthetic dose	yes	4 (100) [. - .]
	no	0
	missing	0
Completely compliant with SmPC recommendations	yes	0
	no	0
	missing	4

Note that the calculation of CIs is not possible for 0% or 100% compliance as the calculation of CIs is based on a cluster sampling design using modified Clopper-Pearson CIs.

Reference: SAP
Program: TAB_4_1_2_COMPLIANCE, 140911 17:34

AGECLASS=6 to < 12 years

Incidence of compliance and non-compliance with SmPC recommendations	compliant	n (%) [95% CI]
Compliant with SmPC regarding indication - age	yes	7 (100) [. - .]
	no	0
	missing	0
Compliant with SmPC regarding indication recommendations - type of dental intervention	yes	3 (42.9) [6.5-86.7]
	no	4 (57.1) [13.3-93.5]
	missing	0
Compliant with SmPC regarding indication - local anaesthetic used	yes	7 (100) [. - .]
	no	0
	missing	0
In accordance with SmPC dose recommendations - OraVerse® maximum dose	yes	5 (71.4) [29.0-96.3]
	no	2 (28.6) [3.7-71.0]
	missing	0
In accordance with SmPC dose recommendations - OraVerse® dose in relation to anesthetic dose	yes	7 (100) [. - .]
	no	0
	missing	0
Completely compliant with SmPC recommendations	yes	3 (42.9) [6.5-86.7]
	no	4 (57.1) [13.3-93.5]
	missing	0

Note that the calculation of CIs is not possible for 0% or 100% compliance as the calculation of CIs is based on a cluster sampling design using modified Clopper-Pearson CIs.

Reference: SAP
Program: TAB_4_1_2_COMPLIANCE, 140911 17:34

AGECLASS=12 to < 18 years

Incidence of compliance and non-compliance with SmPC recommendations	compliant	n (%) [95% CI]
Compliant with SmPC regarding indication - age	yes	7 (100) [. - .]
	no	0
	missing	0
Compliant with SmPC regarding indication recommendations - type of dental intervention	yes	6 (85.7) [42.1-99.6]
	no	1 (14.3) [0.4-57.9]
	missing	0
Compliant with SmPC regarding indication - local anaesthetic used	yes	7 (100) [. - .]
	no	0
	missing	0
In accordance with SmPC dose recommendations - OraVerse® maximum dose	yes	7 (100) [. - .]
	no	0
	missing	0
In accordance with SmPC dose recommendations - OraVerse® dose in relation to anesthetic dose	yes	4 (57.1) [18.4-90.1]
	no	3 (42.9) [9.9-81.6]
	missing	0
Completely compliant with SmPC recommendations	yes	3 (42.9) [9.9-81.6]
	no	4 (57.1) [18.4-90.1]
	missing	0

Note that the calculation of CIs is not possible for 0% or 100% compliance as the calculation of CIs is based on a cluster sampling design using modified Clopper-Pearson CIs.

Reference: SAP
Program: TAB_4_1_2_COMPLIANCE, 140911 17:34

AGECLASS=>= 18 years

Incidence of compliance and non-compliance with SmPC recommendations	compliant	n (%) [95% CI]
Compliant with SmPC regarding indication - age	yes	505 (100) [. - .]
	no	0
	missing	0
Compliant with SmPC regarding indication recommendations - type of dental intervention	yes	478 (94.7) [91.6-96.8]
	no	27 (5.3) [3.2- 8.4]
	missing	0
Compliant with SmPC regarding indication - local anaesthetic used	yes	500 (99.8) [98.9- 100]
	no	1 (0.2) [0.0- 1.1]
	missing	4
In accordance with SmPC dose recommendations - OraVerse® maximum dose	yes	489 (97.2) [94.2-98.9]
	no	14 (2.8) [1.1- 5.8]
	missing	2
In accordance with SmPC dose recommendations - OraVerse® dose in relation to anesthetic dose	yes	390 (77.7) [71.8-82.9]
	no	112 (22.3) [17.1-28.2]
	missing	3
Completely compliant with SmPC recommendations	yes	371 (74.5) [68.1-80.2]
	no	127 (25.5) [19.8-31.9]
	missing	7

Note that the calculation of CIs is not possible for 0% or 100% compliance as the calculation of CIs is based on a cluster sampling design using modified Clopper-Pearson CIs.

Reference: SAP
Program: TAB_4_1_2_COMPLIANCE, 140911 17:34

Listing 4-1 Patients deviating from SmPC recommendations

Per-patient analysis set

						Local anesthetic			Compliance regarding[1)]				
Dentist	**Patient**	**Weight**	**Age**	**Type of dental intervention**	**Anaesthetic product**	**No. of cartridges**	**Volume [ml]**	**OraVerse® dose [µg]**	**age**	**di**	**la**	**md**	**rel**
2	2	> 30 kg	70	Preparation of cavities for placement of fillings or crowns	Ultracain D-S (1:200.000)	2	3.4	600	yes	yes	yes	yes	no
	3	> 30 kg	30	Calculus removal	Ultracain D-S (1:200.000)	2	3.4	600	yes	yes	yes	yes	no
3	3	15 - 30 kg	6	EXTRAKTION MILCHZAHN	Ultracain D-S (1:200.000)	0.5	0.85	200	yes	no	yes	yes	yes
	4	> 30 kg	13	EXTRAKTION MILCHZAHN	Ultracain D-S (1:200.000)	1	1.7	400	yes	no	yes	yes	yes
	5	> 30 kg	27	EXTRAKTION WEISHEITSZAHN	Ultracain D-S forte (1:100.000)	2	3.4	400	yes	no	yes	yes	no
	6	15 - 30 kg	9	EXTRAKTION MILCHZAHN	Ultracain D-S (1:200.000)	1	1.7	400	yes	no	yes	no	yes
4	1	> 30 kg	42	Calculus removal	Ultracain D-S (1:200.000)	0.5	1.7	400	yes	yes	yes	yes	no
5	6	> 30 kg	45	IMPLANTATFREILEGUNG	Ultracain D-S forte (1:100.000)	1	1.7	400	yes	no	yes	yes	yes
6	3	> 30 kg	35	Preparation of cavities for placement of fillings or crowns	Ultracain D-S forte (1:100.000)	2	3.4	400	yes	yes	yes	yes	no
	4	> 30 kg	52	Calculus removal	Ultracain D-S (1:200.000)	0.5	0.85	400	yes	yes	yes	yes	no

						Local anesthetic			Compliance regarding[1)]				
Dentist	**Patient**	**Weight**	**Age**	**Type of dental intervention**	**Anaesthetic product**	**No. of cartridges**	**Volume [ml]**	**OraVerse® dose [µg]**	**age**	**di**	**la**	**md**	**rel**
7	3	> 30 kg	30	Calculus removal	Ultracain D-S forte (1:100.000)	1	1.7	200	yes	yes	yes	yes	no
	5	> 30 kg	35	Calculus removal	Ultracain D-S forte (1:100.000)	-	-	400	yes	yes	yes	yes	-
9	1	> 30 kg	46	IMPLANTATION	Ultracain D-S forte (1:100.000)	2	3.4	800	yes	no	yes	yes	yes
	2	> 30 kg	82	IMPLANTATION	Ultracain D-S forte (1:100.000)	2	3.4	800	yes	no	yes	yes	yes
	3	> 30 kg	74	Calculus removal	Ultracain D-S forte (1:100.000)	2	3.4	600	yes	no	yes	yes	no
	4	> 30 kg	68	Calculus removal	Ultracain D-S (1:200.000)	2	3.4	400	yes	yes	yes	yes	no
	5	> 30 kg	49	Calculus removal	Ultracain D-S (1:200.000)	1.5	2.55	400	yes	yes	yes	yes	no
	6	> 30 kg	38	Calculus removal	Ultracain D-S forte (1:100.000)	2	3.4	400	yes	yes	yes	yes	no
10	3	> 30 kg	42	PA-OP	Ultracain D-S forte (1:100.000)	2	3.4	400	yes	no	yes	yes	no
	6	> 30 kg	32	WURZELSPITZENRESEKTION	Ultracain D-S forte (1:100.000)	2	3.4	400	yes	no	yes	yes	no
14	3	Klassifizierung nicht möglich	48	Calculus removal	Ultracain D-S (1:200.000)	2	3.4	400	yes	yes	yes	yes	no

						Local anesthetic			Compliance regarding[1)]				
Dentist	**Patient**	**Weight**	**Age**	**Type of dental intervention**	**Anaesthetic product**	**No. of cartridges**	**Volume [ml]**	**OraVerse® dose [µg]**	**age**	**di**	**la**	**md**	**rel**
	6	Klassifizierung nicht möglich	33	Cleaning	Ultracain D-S (1:200.000)	1.5	2.55	400	yes	yes	yes	yes	no
16	4	> 30 kg	51	EXTRAKTION	Ultracain D-S forte (1:100.000)	1	1.7	400	yes	no	yes	yes	yes
	6	> 30 kg	24	Calculus removal		3	5.1	800	yes	yes	-	yes	yes
17	1	> 30 kg	47	PA-BEHANDLUNG	Ubistesin forte 1:100.000	4	6.8	400	yes	yes	yes	yes	no
	6	> 30 kg	49	PA-BEHANDLUNG	Ubistesin forte 1:100.000	9	15.3	400	yes	yes	yes	yes	no
18	3	> 30 kg	27	FÜLLUNG	Septanest mit Adrenalin 1:200.000	2	3.4	600	yes	yes	yes	yes	no
	4	> 30 kg	45	Calculus removal	Septanest mit Adrenalin 1:100.000	6	10.2	1600	yes	yes	yes	no	no
	6	> 30 kg	65	Preparation of cavities for placement of fillings or crowns	Septanest mit Adrenalin 1:200.000	3	5.1	1200	yes	yes	yes	no	no
19	1	> 30 kg	37	Calculus removal	Ultracain D-S (1:200.000)	0.5	1	400	yes	yes	yes	yes	no
	4	> 30 kg	54	Calculus removal	Ultracain D-S (1:200.000)	0.5	1.2	400	yes	yes	yes	yes	no
21	4	> 30 kg	19	EXTRAKTION WEISHEITSZAHN	Septanest mit Adrenalin 1:100.000	2	3.4	400	yes	no	yes	yes	no
22	1	> 30 kg	32	Calculus removal	ARTINESTOL 1:100.000	16	27.2	3200	yes	yes	yes	no	no

						Local anesthetic			Compliance regarding[1)]				
Dentist	**Patient**	**Weight**	**Age**	**Type of dental intervention**	**Anaesthetic product**	**No. of cartridges**	**Volume [ml]**	**OraVerse® dose [µg]**	**age**	**di**	**la**	**md**	**rel**
	2	> 30 kg	59	Calculus removal	ARTINESTOL 1:200.000	2	3.4	400	yes	yes	yes	yes	no
	3	> 30 kg	54	PA-BEHANDLUNG	ARTINESTOL 1:200.000	7	11.9	1200	yes	yes	yes	no	no
	5	> 30 kg	37	Calculus removal	ARTINESTOL 1:100.000	3	5.1	400	yes	yes	yes	yes	no
25	2	> 30 kg	42	Preparation of cavities for placement of fillings or crowns	Ultracain D-S (1:200.000)	1.5	2.55	400	yes	yes	yes	yes	no
27	1	> 30 kg	17	Calculus removal	Ultracain D-S forte (1:100.000)	1	1.7	200	yes	yes	yes	yes	no
	3	> 30 kg	32	Calculus removal	Ultracain D-S (1:200.000)	1.5	2.55	200	yes	yes	yes	yes	no
	5	> 30 kg	53	Root planing	ARTINESTOL 1:200.000	1	1.7	200	yes	yes	yes	yes	no
	6	> 30 kg	28	Calculus removal	ARTINESTOL 1:100.000	1	1.7	200	yes	yes	yes	yes	no
28	2	> 30 kg	48	Calculus removal	ARTINESTOL 1:200.000	1.5	2.55	400	yes	yes	yes	yes	no
	5	> 30 kg	27	WURZELBEHANDLUNG	Ultracain D-S forte (1:100.000)	2	3.4	400	yes	yes	yes	yes	no
29	2	> 30 kg	64	Calculus removal	Ultracain D-S forte (1:100.000)	1.5	2.55	400	yes	yes	yes	yes	no
30	3	> 30 kg	42	Calculus removal	Ultracain D-S forte (1:100.000)	1.5	2.55	400	yes	yes	yes	yes	no

						Local anesthetic			Compliance regarding[1)]				
Dentist	**Patient**	**Weight**	**Age**	**Type of dental intervention**	**Anaesthetic product**	**No. of cartridges**	**Volume [ml]**	**OraVerse® dose [µg]**	**age**	**di**	**la**	**md**	**rel**
	6	> 30 kg	29	Calculus removal	Ultracain D-S forte (1:100.000)	1.5	2.55	400	yes	yes	yes	yes	no
31	3	> 30 kg	27	Calculus removal	Ultracain D-S forte (1:100.000)	1	1.7	-	yes	yes	yes	-	-
32	2	> 30 kg	65	Preparation of cavities for placement of fillings or crowns	Ultracain D-S forte (1:100.000)	0.5	0.7	400	yes	yes	yes	yes	no
	3	> 30 kg	73	Calculus removal	Ultracain D-S (1:200.000)	0.5	0.8	400	yes	yes	yes	yes	no
	6	> 30 kg	97	EXTRAKTION	Ultracain D-S (1:200.000)	1	1.7	400	yes	no	yes	yes	yes
33	1	> 30 kg	53	WURZELBEHANDLUNG	Ultracain D-S forte (1:100.000)	2	3.4	400	yes	yes	yes	yes	no
	2	> 30 kg	63	IMPLANTATFREILEGUNG	Ultracain D-S forte (1:100.000)	3	5.1	600	yes	no	yes	yes	no
	3	> 30 kg	58	Cleaning	Ultracain D-S forte (1:100.000)	1	1.7	200	yes	yes	yes	yes	no
	4	> 30 kg	45	WURZELBEHANDLUNG	Ultracain D-S forte (1:100.000)	2	3.4	400	yes	yes	yes	yes	no
35	2	> 30 kg	87	Cleaning	Ultracain D-S forte (1:100.000)	0.5	0.75	400	yes	yes	yes	yes	no
37	5	Klassifizierung nicht möglich	32	Calculus removal	Ultracain D-S forte (1:100.000)	1.5	2.55	400	yes	yes	yes	yes	no

						Local anesthetic			Compliance regarding[1)]				
Dentist	**Patient**	**Weight**	**Age**	**Type of dental intervention**	**Anaesthetic product**	**No. of cartridges**	**Volume [ml]**	**OraVerse® dose [µg]**	**age**	**di**	**la**	**md**	**rel**
38	1	> 30 kg	64	EXTRAKTION WURZELREST	Ultracain D-S (1:200.000)	1	1.7	400	yes	no	yes	yes	yes
	5	> 30 kg	41	Preparation of cavities for placement of fillings or crowns	SOPIRA 1:400.000	2	3.4	400	yes	yes	yes	yes	no
40	2	> 30 kg	47	Calculus removal	Ultracain D-S forte (1:100.000)	2	3.4	400	yes	yes	yes	yes	no
42	2	> 30 kg	58	EXTRAKTIONEN	Ultracain D-S (1:200.000)	3	5.1	800	yes	no	yes	yes	yes
	3	> 30 kg	35	EXTRAKTIONEN	Ultracain D-S (1:200.000)	2	3.4	800	yes	no	yes	yes	yes
	5	> 30 kg	47	KRONENABTRENNUNG	Ultracain D-S (1:200.000)	1.5	2.55	800	yes	yes	yes	yes	no
43	1	15 - 30 kg	6	EXTRAKTIONEN	Ultracain D-S forte (1:100.000)	1	2	400	yes	no	yes	no	yes
	5	> 30 kg	53	KNOCHENAUFBAU	Ultracain D-S forte (1:100.000)	3.5	6	1200	yes	no	yes	no	no
44	3	> 30 kg	33	PA-BEHANDLUNG		3	5.1	800	yes	yes	-	yes	yes
	4	> 30 kg	46	PA-BEHANDLUNG	Septanest mit Adrenalin 1:100.000	3	5.1	400	yes	yes	yes	yes	no
45	1	> 30 kg	56	Preparation of cavities for placement of fillings or crowns	Ultracain D-S (1:200.000)	2	3	600	yes	yes	yes	yes	no
	2	> 30 kg	23	Calculus removal	Ultracain D-S (1:200.000)	0.5	1	400	yes	yes	yes	yes	no
	3	> 30 kg	74	Calculus removal	Ultracain D-S (1:200.000)	0.5	1	400	yes	yes	yes	yes	no

						Local anesthetic			Compliance regarding[1)]				
Dentist	**Patient**	**Weight**	**Age**	**Type of dental intervention**	**Anaesthetic product**	**No. of cartridges**	**Volume [ml]**	**OraVerse® dose [µg]**	**age**	**di**	**la**	**md**	**rel**
	4	> 30 kg	50	Calculus removal	Ultracain D-S (1:200.000)	0.5	1	400	yes	yes	yes	yes	no
46	4	> 30 kg	34	Calculus removal	Ultracain D-S (1:200.000)	2	3.4	400	yes	yes	yes	yes	no
	6	> 30 kg	-	Calculus removal	Ultracain D-S (1:200.000)	1	1.7	400	-	yes	yes	-	yes
47	2	> 30 kg	48	Calculus removal	Ultracain D-S forte (1:100.000)	2	3.4	400	yes	yes	yes	yes	no
	4	> 30 kg	60	PA-BEHANDLUNG	Ultracain D-S forte (1:100.000)	2	3.4	400	yes	yes	yes	yes	no
	5	> 30 kg	53	Calculus removal	Ultracain D-S forte (1:100.000)	2	3.4	400	yes	yes	yes	yes	no
48	1	> 30 kg	54	Calculus removal	Ubistesin 1:200.000	2	3.4	400	yes	yes	yes	yes	no
	3	> 30 kg	53	Calculus removal	Ultracain D-S (1:200.000)	5	8.5	400	yes	yes	yes	yes	no
50	1	> 30 kg	50	Calculus removal	Ultracain D-S forte (1:100.000)	1	1.7	200	yes	yes	yes	yes	no
	2	> 30 kg	46	Calculus removal	Ultracain D-S forte (1:100.000)	1	1.7	200	yes	yes	yes	yes	no
	3	> 30 kg	47	Calculus removal	Ultracain D-S forte (1:100.000)	1	1.7	200	yes	yes	yes	yes	no
	4	> 30 kg	51	Calculus removal	Ultracain D-S forte (1:100.000)	1	1.7	-	yes	yes	yes	-	-

						Local anesthetic			Compliance regarding[1)]				
Dentist	**Patient**	**Weight**	**Age**	**Type of dental intervention**	**Anaesthetic product**	**No. of cartridges**	**Volume [ml]**	**OraVerse® dose [µg]**	**age**	**di**	**la**	**md**	**rel**
	6	> 30 kg	17	Calculus removal	Ultracain D-S forte (1:100.000)	1	1.7	200	yes	yes	yes	yes	no
52	1	> 30 kg	37	Calculus removal	Ubistesin 1:200.000	2	3.4	600	yes	yes	yes	yes	no
	6	> 30 kg	49	Calculus removal	Ubistesin 1:200.000	2	3.4	600	yes	yes	yes	yes	no
53	1	> 30 kg	-	Calculus removal	Ultracain D-S (1:200.000)	2	3.4	800	-	yes	yes	-	yes
	6	> 30 kg	22	Cleaning	Ultracain D-S (1:200.000)	2	3.4	400	yes	yes	yes	yes	no
56	2	> 30 kg	51	Calculus removal	Ultracain D-S forte (1:100.000)	2	3.4	400	yes	yes	yes	yes	no
57	5	> 30 kg	38	WURZELKANALBEHANDLUNG	Ubistesin 1:200.000	2	3.4	400	yes	yes	yes	yes	no
	6	> 30 kg	-	Calculus removal	Ubistesin 1:200.000	1	1.8	400	-	yes	yes	-	yes
58	2	> 30 kg	35	Calculus removal	Ultracain D-S forte (1:100.000)	1	1.7	200	yes	yes	yes	yes	no
	3	Klassifizierung nicht möglich	63	PA-BEHANDLUNG	Ultracain D-S forte (1:100.000)	2	3.4	600	yes	yes	yes	yes	no
	4	> 30 kg	14	Calculus removal	Ultracain D-S (1:200.000)	1	1.7	200	yes	yes	yes	yes	no
	6	Klassifizierung nicht möglich	77	Preparation of cavities for placement of fillings or crowns	Ultracain D-S forte (1:100.000)	1	1.7	200	yes	yes	yes	yes	no

						Local anesthetic			Compliance regarding[1)]				
Dentist	**Patient**	**Weight**	**Age**	**Type of dental intervention**	**Anaesthetic product**	**No. of cartridges**	**Volume [ml]**	**OraVerse® dose [µg]**	**age**	**di**	**la**	**md**	**rel**
59	3	15 - 30 kg	8	EXTRAKTION MILCHZAHN (62)	Ultracain D-S (1:200.000)	0.5	0.85	200	yes	no	yes	yes	yes
60	1	-	32	PRÄPARATION	SOPIRA	3	5.1	1200	yes	yes	yes	no	no
	2	> 30 kg	22	EXTRAKTION	Ultracain D-S forte (1:100.000)	1.5	2.55	600	yes	no	yes	yes	yes
61	3	> 30 kg	65	IMPLANTATFREILEGUNG	ARTINESTOL 1:100.000	0.5	0.85	400	yes	no	yes	yes	no
63	1	> 30 kg	43	PA-BEHANDLUNG		3	5.1	800	yes	yes	-	yes	yes
67	1	> 30 kg	60	Calculus removal	Ultracain D-S (1:200.000)	2	3.4	400	yes	yes	yes	yes	no
	6	> 30 kg	58	Calculus removal	Ultracain D-S (1:200.000)	2	3.4	400	yes	yes	yes	yes	no
68	1	> 30 kg	28	EXTRAKTION	Ultracain D-S forte (1:100.000)	3	5.1	800	yes	no	yes	yes	yes
	3	-	45	EXTRAKTION	Ultracain D-S forte (1:100.000)	2	3.4	600	yes	no	yes	yes	no
	4	> 30 kg	18	Calculus removal	Ultracain D-S forte (1:100.000)	1.5	2.55	400	yes	yes	yes	yes	no
	5	> 30 kg	65	Preparation of cavities for placement of fillings or crowns	Ultracain D-S (1:200.000)	1	1.7	200	yes	yes	yes	yes	no
	6	> 30 kg	36	Calculus removal	Ultracain D-S forte (1:100.000)	1.5	2.55	400	yes	yes	yes	yes	no
70	1	Klassifizierung nicht möglich	45	IMPLANTATION	Ultracain D-S forte (1:100.000)	1	1.7	400	yes	no	yes	yes	yes

						Local anesthetic			Compliance regarding[1)]				
Dentist	**Patient**	**Weight**	**Age**	**Type of dental intervention**	**Anaesthetic product**	**No. of cartridges**	**Volume [ml]**	**OraVerse® dose [µg]**	**age**	**di**	**la**	**md**	**rel**
71	6	> 30 kg	34	Calculus removal	Ubistesin 1:200.000	1.5	2.55	400	yes	yes	yes	yes	no
75	3	> 30 kg	76	PA-BEHANDLUNG	Ultracain D-S forte (1:100.000)	4	6.8	1200	yes	yes	yes	no	no
	4	> 30 kg	48	Root planing	Ultracain D-S forte (1:100.000)	4	6.8	1200	yes	yes	yes	no	no
	6	> 30 kg	76	Calculus removal	Ultracain D-S forte (1:100.000)	3	5.1	1200	yes	yes	yes	no	no
76	3	> 30 kg	62	ENDO	XYLONEST 3%	1	1.7	400	yes	yes	no	yes	yes
78	2	> 30 kg	37	EXTRAKTION	Ultracain D-S forte (1:100.000)	1	1.7	400	yes	no	yes	yes	yes
	4	> 30 kg	55	Calculus removal	Ultracain D-S (1:200.000)	1.5	2.55	400	yes	yes	yes	yes	no
79	1	> 30 kg	54	Calculus removal	Septanest mit Adrenalin 1:200.000	2	3.4	400	yes	yes	yes	yes	no
	2	> 30 kg	65	Calculus removal	Septanest mit Adrenalin 1:200.000	1.5	2.55	400	yes	yes	yes	yes	no
	3	> 30 kg	54	EXTRAKTION 7.38 (###) [2)]	Septanest mit Adrenalin 1:100.000	2	3.4	400	yes	no	yes	yes	no
	4	> 30 kg	53	Calculus removal	Septanest mit Adrenalin 1:200.000	3	5.1	400	yes	yes	yes	yes	no

						Local anesthetic			Compliance regarding[1)]				
Dentist	**Patient**	**Weight**	**Age**	**Type of dental intervention**	**Anaesthetic product**	**No. of cartridges**	**Volume [ml]**	**OraVerse® dose [µg]**	**age**	**di**	**la**	**md**	**rel**
81	2	> 30 kg	40	Preparation of cavities for placement of fillings or crowns	Ultracain D-S forte (1:100.000)	6	10.2	1600	yes	yes	yes	no	no
	3	> 30 kg	59	Calculus removal	Ultracain D-S forte (1:100.000)	4	6.8	1200	yes	yes	yes	no	no
	5	> 30 kg	19	Calculus removal	Ultracain D-S forte (1:100.000)	5	8.5	1200	yes	yes	yes	no	no
82	1	> 30 kg	58	PA-BEHANDLUNG	Ultracain D-S (1:200.000)	3	5.1	400	yes	yes	yes	yes	no
	3	> 30 kg	61	FÜLLUNGEN	Ultracain D-S (1:200.000)	2	3.4	400	yes	yes	yes	yes	no
	5	> 30 kg	30	WURZELKANALAUFBEREITUNG	Ultracain D-S (1:200.000)	1.5	2.55	400	yes	yes	yes	yes	no
	6	> 30 kg	29	FÜLLUNGEN	Ultracain D-S (1:200.000)	2	3.4	600	yes	yes	yes	yes	no
84	1	> 30 kg	49	Calculus removal		1	1.7	400	yes	yes	-	yes	yes
86	3	> 30 kg	52	Preparation of cavities for placement of fillings or crowns	Ultracain D-S (1:200.000)	1.5	2.55	400	yes	yes	yes	yes	no
87	1	> 30 kg	27	Calculus removal	Ultracain D-S (1:200.000)	1	1.7	200	yes	yes	yes	yes	no
	2	> 30 kg	29	Calculus removal	Ultracain D-S (1:200.000)	1.5	2.55	400	yes	yes	yes	yes	no
	3	> 30 kg	42	Calculus removal	Ultracain D-S (1:200.000)	1	1.7	200	yes	yes	yes	yes	no
	4	> 30 kg	39	Calculus removal	Ultracain D-S (1:200.000)	1	1.7	200	yes	yes	yes	yes	no
	5	> 30 kg	28	Calculus removal	Ultracain D-S (1:200.000)	1	1.7	200	yes	yes	yes	yes	no

						Local anesthetic			Compliance regarding[1)]				
Dentist	**Patient**	**Weight**	**Age**	**Type of dental intervention**	**Anaesthetic product**	**No. of cartridges**	**Volume [ml]**	**OraVerse® dose [µg]**	**age**	**di**	**la**	**md**	**rel**
	6	> 30 kg	45	Calculus removal	Ultracain D-S (1:200.000)	1.5	2.55	400	yes	yes	yes	yes	no
88	1	> 30 kg	46	Calculus removal	Ultracain D-S forte (1:100.000)	2	3.4	400	yes	yes	yes	yes	no
	3	-	-		Ultracain D-S forte (1:100.000)	2	3.4	800	-	-	yes	-	yes
89	1	> 30 kg	18	Calculus removal	Ultracain D-S forte (1:100.000)	2	3.4	400	yes	yes	yes	yes	no
91	1	> 30 kg	49	EXTRAKTION UNKOMPLIZIERT	Ultracain D-S forte (1:100.000)	1	2	400	yes	no	yes	yes	yes
	4	> 30 kg	23	EXTRAKTION WURZELREST	Ultracain D-S forte (1:100.000)	2	4	600	yes	no	yes	yes	no
	5	> 30 kg	48	Preparation of cavities for placement of fillings or crowns	Ultracain D-S forte (1:100.000)	1	2	200	yes	yes	yes	yes	no
	6	> 30 kg	83	Root planing	Ultracain D-S forte (1:100.000)	1.5	3	800	yes	yes	yes	yes	no
92	1	> 30 kg	60	PA-BEHANDLUNG	Ultracain D-S forte (1:100.000)	5	8.5	2000	yes	yes	yes	no	no
93	1	> 30 kg	66	IMPLANTATION	Ultracain D-S forte (1:100.000)	2	3.4	400	yes	no	yes	yes	no

						Local anesthetic			Compliance regarding[1)]				
Dentist	**Patient**	**Weight**	**Age**	**Type of dental intervention**	**Anaesthetic product**	**No. of cartridges**	**Volume [ml]**	**OraVerse® dose [µg]**	**age**	**di**	**la**	**md**	**rel**
	2	> 30 kg	90	PA-BEHANDLUNG	Ultracain D-S forte (1:100.000)	2	3.4	400	yes	yes	yes	yes	no
	3	> 30 kg	70	IMPLANTATION	Ultracain D-S forte (1:100.000)	2	3.4	400	yes	no	yes	yes	no
	4	> 30 kg	50	Calculus removal	Ultracain D-S (1:200.000)	2	3.4	400	yes	yes	yes	yes	no
	5	> 30 kg	44	OFFENE KÜRETTAGE	Ultracain D-S (1:200.000)	3	5.1	800	yes	no	yes	yes	yes
	6	> 30 kg	30	PA-BEHANDLUNG	Ultracain D-S forte (1:100.000)	5	8.5	1200	yes	yes	yes	no	no

1) di: type of dental intervention, la: local anaesthetic used, md: OraVerse® maximum dose, rel: OraVerse® dose in relation to anesthetic dose

2) input data error; correct: EXTRAKTION Z.38 (3 unreadable symbols)

Reference: SAP Program: LIS_4_1_COMPLIANCE, 140911 17:34

3 APPENDIX III – SUPPORTIVE DOCUMENTS

3.1 PROTOCOL

SANOFI

OBSERVATIONAL STUDY PROTOCOL

Actual conditions of use of OraVerse® in patients among resident dentists throughout Germany

Retrospective Drug Utilization survey

STUDY NUMBER: PHENLL07113

STUDY NAME: ORADUS

VERSION DATE 1.0/STATUS: 19 February 2014

The Study is conducted by Sanofi, hereinafter referred also as the "COMPANY".

NAMES AND ADDRESSES OF

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CRO		**NN**

TABLE OF CONTENTS

1. SYNOPSIS

COMPOUND: OraVerse® **STUDY No.: PHENLL07113**

Title	Actual conditions of use of OraVerse® in patients among resident dentists throughout Germany
Location	Germany
Scientific Expert	Prof. Monika Daubländer
Objectives	To investigate the conditions of use of OraVerse® after local anesthetic procedure in daily routine practice. The primary outcome will be the incidence of patients who "comply" / "not comply" with the recommendations in the SmPC regarding the following points: • patient age, • classification of body weight • type of dental intervention, • local anesthetic used (product and dose), • dose of OraVerse® used
Population	• Inclusion Criteria - Patients treated with OraVerse® after treatment with a local anesthetic containing a vasoconstrictor (such as epinephrine) by dentists within the last 3 months before contract signing • Expected number of patients: 526 (500 evaluable) - Sample Size: 500 treated (evaluable) patients assuming a 5% non-evaluable rate. • Expected number of sites: ca. 100 - To gather a nationwide number of resident dentists
Population	• Inclusion Criteria - Patients treated with OraVerse® after local anesthetic procedure by dentists within the last 3 months before contract signing • Expected number of patients: 526 (500 evaluable) - Sample Size: 500 treated (evaluable) patients assuming a 5%

	non-evaluable rate. • Expected number of sites: ca. 100 - To gather a nationwide number of resident dentists
Recruitment modalities	• Retrospective cross-sectional drug utilisation survey among resident dentists throughout Germany • Eligible patients: - All patients normally treated with OraVerse® after local anesthetic procedure by dentists within the last 3 months before contract signing • Participating dentists: - must be practicing dentists working in private practices, - must be dentists performing routine dental interventions using local anesthetic procedure, - must have used OraVerse® in the 3 previous months.

Main evaluation criteria	• **Primary outcomes:** The outcomes of interest will be the conditions of use of treatment. The primary outcomes will be the incidence of patients who "comply" / "not comply" with the recommendations in the SmPC regarding the following points: • patient age, • classification of body weight • type of dental intervention, • local anesthetic used (product and dose), • dose of OraVerse® used
Main data collected	Dentists will be asked - to indicate total number of patients normally treated with OraVerse® within the previous 3 months, - to record retrospective data coming from the charts of eligible patients (latest consecutive administrations of OraVerse® within the last 3 months up to a maximum of 6 patients) including patient age, classification of body weight, type of dental intervention, name and dose of the product for anaesthetic procedure, dose of OraVerse® Information will be obtained anonymously directly from patients files by dentists retrospectively.

Statistical methodology	• Descriptive statistics for all collected and derived data will be provided. For continuous data number of patients, mean, standard deviation, median, min, max, quartiles and appropriate other percentiles will be provided. For categorical data frequencies and percentages will be presented. For estimated parameters suitable 95% confidence intervals will be provided. Statistical power and sample size justification: With a sample size of 500 patients the following statistical precision for the estimated proportion of patients who 'not comply' / 'comply' with the doses and indications recommended in the SPC can be reached: Assuming rates of not adherence / adherence to labelling of 3%/97% or 4%/96% or 5%/95%, the 2-sided 95% confidence intervals will be [1.5%; 4.5%] / [95.5%; 98.5%] or [2.3%; 5.7%] / [94.3%; 97.7%] or [3.1%; 6.9%] / [93.1%; 96.9%]. In general: when the sample size is 500, a two-sided 95.0% confidence interval for a single proportion using the large sample normal approximation will extend 0.015 or 0.017 or 0.019 from the observed proportion for an expected proportion of 0.030 (or 0.97) or 0.04 (or 0.96) or 0.05 (or 0.95).
Timelines	Protocol planned date: February 2014 Database lock planned date: 31 July 2014 Duration of retrospective survey / data collection: planned May – June 2014 Estimated Report date: January 2015

2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event(s)
BPM	Beats per minute
CI	Confidential Interval
CRF	Case Report Form
CRO	Contract Research Organization
GEP	Good Epidemiological Practices
ICF	Informed Consent Form
IEC	Independent Ethics Committee
INN	International Non Proprietary Name
IRB	Institutional Review Board
NA	Not Applicable
NIS	Non Interventional Study
NRS	Numerical Rating Scale
QC	Quality Control
RMP	Risk Management Plan
SAE	Serious Adverse Event(s)
SmPC	Summary of Product Characteristics

3. INTRODUCTION AND RATIONALE

3.1 Background

Phentolamine mesylate, the active ingredient of OraVerse®, 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 (IV) or intramuscular (IM) injection at doses ranging from 3 to 5 mg.

The vasodilatation properties of phentolamine led to its development as OraVerse® for the reversal of soft tissue anaesthesia (lip and tongue): Prolonged soft-tissue anesthesia is an unwanted side effect of local dental anesthesia, especially in routine, restorative or hygienic dental procedures. The local anesthetic remains in and around the nerves in the lips, cheek and tongue, causing the unwanted side effect of lingering numbness. This numbness can last up to five hours following treatment[1,2]. During this period patients have difficulties in speaking, eating and drinking, preventing patients from returning to their daily activities. Prolonged numbness, especially in children, can result in injury due to accidental biting of the lip and/or tongue[3].

OraVerse® has achieved the Marketing Authorisation in 2012 in Germany for the reversal of soft tissue anesthesia (lip and tongue) and the associated functional deficits, resulting from an intraoral submucosal injection of a local anesthetic containing a catecholamine vasoconstrictor (such as epinephrine) after routine dental procedure such as teeth cleaning, scaling and planning, cavity filing, crowns. Randomized, controlled studies[4] proved the efficacy and safety of OraVerse® in this indication. A reduction was shown of the median time for full sensation to return to the lower lips by 85 minutes (55 %) and to the upper lips by 83 minutes (62 %) - or by more than half the usual time[4].

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 will permit aspiration. OraVerse® is indicated in adults and

children 6 years of age and older and weighing at least 15 kg. It is contraindicated in patients who are hypersensitive to the active substance or to any of the excipients.

Local reactions such as post-procedural pain (6%) and injection site pain (5.3%) were identified risk 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 efficacy of OraVerse® was evaluated in double-blinded, randomized, multicentre, controlled studies in patients undergoing dental restorative or periodontal maintenance procedures. The control group consisted of patients receiving a sham injection. OraVerse® reduced the median time to recovery of normal sensation in the lower lip by 85 minutes (55%) compared to control ($p<0.0001$). The median time to recovery of normal lip sensation in the upper lip was reduced by 83 minutes (62%) compared to control ($p<0.0001$). There was 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.

Before administering OraVerse®, the majority of patients included in the clinical studies were treated with local anaesthetic and a vasoconstrictor (eg. epinephrine) at 1:100000 concentration. Limited data have been submitted to support the efficacy of OraVerse® when a local anaesthetic and a vasoconstrictor (eg. epinephrine) at concentration less than 1:100000 is administered.

In clinical studies, paediatric patients between the ages of 3 and 17 years received OraVerse®. The median time to normal lip sensation in patients 6 to 11 years of age was reduced by 75 minutes (56%) compared to control ($p<0.0001$).

In clinical studies of OraVerse®, no overall differences in safety or effectiveness were observed between elderly patients and younger patients.

3.2 Rationale

This retrospective drug utilisation survey is described in the RISK MANAGEMENT PLAN (RMP) of OraVerse® and was requested during the European approval procedure. It is planned to investigate the conditions of use of OraVerse® after local anesthetic procedures in daily routine clinical practice, whatever the concentrations of local anesthetics used is and to investigate the use of OraVerse® according to labelling.

4. STUDY OBJECTIVES

Primary objectives:
To investigate the conditions of use of OraVerse® after local anaesthetic procedure in daily routine. The documentation will include the following points:

- total number of patients treated with OraVerse® within the previous 3 months

latest consecutive administrations of OraVerse® within the last 3 months up to a maximum of 6 patients before contract signing:

- patient age,
- classification of body weight
- type of dental intervention,
- local anesthetic used (product and dose),
- dose of OraVerse® used

5. STUDY DESIGN

5.1 Description of the study design

This drug utilization survey is described in the RISK MANAGEMENT PLAN (RMP) of OraVerse® and was requested during the European approval procedure. It will provide further information about the conditions of use of OraVerse® in routine clinical practice (i.e. patient age, type of dental intervention, local anesthetic used (product and dose) and dose of OraVerse®) used in patients normally treated with OraVerse® after local anesthetic procedure by dentists. It also provides information about use for orofacial procedures other than routine dental procedures, use in children < 6 years or use in patients undergoing complex dental procedures, i.e. for indications different from those described in the SmPC.

The only way to monitor the use of the product will be to collect information directly from dentists. In order to limit intervention bias, a retrospective (retrolective) design will be used to evaluate patients already treated with OraVerse®.

As OraVerse® is planned to be used by dentists in the frame of dental interventions and will not be reimbursed, it will not be recorded in any national databases/registers in the countries where it will be used. So, the collection of

information on patients profile and characteristics of dental intervention will need to be made at dentists' level.

Data documentation will happen after signing the contract:

- In order to limit intervention bias, a retrospective design will be used to collect data of the latest consecutive administrations of OraVerse® within the last 3 months up to a maximum of 6 patients after signing the contract.

5.2 Duration of the study (data documentation)

Duration of retrospective survey / data documentation: planned May – June 2014.

5.3 Evaluation criteria

The Outcome will be

- patient age
- classification of body weight
- type of dental intervention,
- local anesthetic used (product and dose),
- dose of OraVerse® used

6. STUDY POPULATION AND SELECTION OF PATIENTS

6.1 Sample size

Expected number of patients: ca. 526 (500 evaluable)
It is planned to recruit 500 treated (evaluable) patients assuming a 5% non-evaluable rate in Germany.

6.2 Eligibility criteria

6.2.1 Inclusion criteria

- Patients treated with OraVerse® after local anesthetic procedure (with a local anesthetic containing a vasoconstrictor) by dentists within the last 3 months before contract signing

6.3 Modalities of recruitment

6.3.1 Dentist selection

To gather a nationwide number of resident dentists, the expected number of sites is ca. 100 of practicing dentists working in private practices throughout Germany.

6.3.2 Patient selection

Each selected dentist and who will have agreed to participate to the study should have included up to 6 patients who meet inclusion criteria (treatment with OraVerse® within the last 3 months before contract signing).

7. TREATMENTS

The medical application was under the only responsibility of the patient's dentist.
The patients who will be documented in the study have been treated with OraVerse® within the last 3 months before contract signing.

8. STUDY PROCEDURES AND DATA COLLECTION

8.1 Data collected

At the dental office

Inclusion criteria will be collected.

- Information on patient age, classification of body weight, type of dental intervention, local anesthetic used (product and dose), dose of OraVerse® will be collected by the dentist.

8.2 Logistic aspects

Each of the participating dental centres and each of the dentists will be provided by Sanofi a file containing:

- NIS contract
- Protocol of the study
- Overview-page
- Facsimile
- For each documented patient (n=6)
    - CRF
- OraVerse® SmPC

The documents (CRF, overview-page) will be collected at dentist practice level and send in the enclosed envelope by mail to the CRO (Important: without name or address of the sender).
The enclosed Facsimile (containing number of documented patients (max 6), date, name, signature and personal seal of the dentist) will be faxed to NIS Management of Sanofi-Aventis Deutschland GmbH to Mrs Martina John (No: +49 69 305 25730).

9. MANAGEMENT OF DATA

9.1 Data collection, validation and data quality control at company level

Data will be collected using a paper CRF.
Data collection and validation procedures will be detailed in appropriate operational documents (Data Management Plan including a Data Validation Plan).

For quality assurance reasons, a duplicate data entry will be performed to assure the consistency of data.

9.2 Data quality control at site level

Based on the insights in the actual documentation practice gained at dentists' level with two recent studies on OraVerse®, we adjusted the current CRF to a standardized questionnaire with tickboxes for selection wherever possible. As a consequence of the anonymous study design, data quality control at site level can not be performed.

10. SAFETY REPORTING

Since this is a retrospective drug utilization study based on the analysis of preexisting data, only detection of safety signal is applicable. In case a safety signal will be identified during data analysis, this shall be immediately forwarded to Pharmacovigilance.

11. STATISTICAL METHODOLOGY

11.1 Analysis population(s)

- Patients treated with OraVerse® after local anaesthetic procedure by dentists within the last 3 months before contract signing

11.2 Analysis variables

- patient age,
- classification of body weight (< 15 kg, 15-30 kg, > 30 kg, no classification possible)
- type of dental intervention,
- local anesthetic used (product and dose),
- dose of OraVerse®

11.2.1 Primary variables – criteria

The primary outcome will be the incidence of patients who "comply" / "not comply" with the recommendations in the SmPC regarding the following points:

- patient age
  - The extent to which OraVerse® has been used in children < 6 years
- type of dental intervention
  - The extent to which OraVerse® has been used for indications other than recommended in the SmPC
- local anesthetic used (product and dose),
- dose of OraVerse®
  - The extent to which doses of OraVerse® has been used other than recommended in the SmPC (dose of OraVerse® depends on e.g. patient's age, class of body weight and dose of used local anesthetic)

11.3 Statistical methods

Descriptive statistics for all collected and derived data will be provided. For continuous data number of patients, mean, standard deviation, median, min, max, quartiles and appropriate other percentiles will be provided. For categorical data frequencies and percentages will be presented. For estimated parameters suitable 95% confidence intervals will be provided. All statistical analyses are exploratory in nature. All statistical analyses will be described in detail in a separate document (Statistical Analysis Plan (SAP)) prepared before data base closure.

11.4 Determination of sample size

With a sample size of 500 patients the following statistical precision for the estimated proportion of patients who are 'not comply' / 'comply' with the doses and indications recommended in the SPC can be reached: Assuming rates of not adherence / adherence to labelling of 3%/97% or 4%/96% or 5%/95%, the 2-sided 95% confidence intervals will be [1.5%; 4.5%] / [95.5%; 98.5%] or [2.3%; 5.7%] / [94.3%; 97.7%] or [3.1%; 6.9%] / [93.1%; 96.9%].
In general: when the sample size is 500, a two-sided 95.0% confidence interval for a single proportion using the large sample normal approximation will extend 0.015 or 0.017 or 0.019 from the observed proportion for an expected proportion of 0.030 (or 0.97) or 0.04 (or 0.96) or 0.05 (or 0.95).

11.5 Interim analysis

No interim analysis is planned.

12. TASKS AND RESPONSIBILITIES

12.1 Responsibilities of the expert

The expert will be involved in the preparation and approval of the protocol and its amendment(s).

12.2 Responsibilities of the Dentists

The Dentist will collect the data in accordance with this protocol.

It is the Dentist's responsibility to fill in the CRF and to record all data pertinent to the investigation. She/he will ensure that the information reported in the CRF is precise and accurate.

12.3 Responsibilities of Sanofi

Sanofi is responsible for taking all reasonable steps and providing adequate resources to ensure the proper conduct of the study.

13. ETHICAL, REGULATORY AND ADMINISTRATIVE RULES

13.1 Ethical principles

This is an anonymous retrospective retrolective cross-sectional drug utilisation survey. Therefore an assessment by an ethics committee is not necessary.

13.2 Laws and regulations

This study will be conducted in accordance with the guidelines for Good Pharmacoepidemiological Practice[5] and the guidelines for Good Epidemiological Practice[6] and the ENCePP Guide on Methodological Standards[7].

13.3 Data protection

As defined and described in the RISK MANAGEMENT PLAN for Oraverse®, data collection will be completely anonymous. No backtracking will be possible, since the CRFs will be documented and evaluated without any identification attribute (no patient number, no site number). Therefore no informed consent of the patient is necessary.

13.4 Secrecy agreement

All material, information (oral or written) and unpublished documentation provided to the Dentist (or any action carried out by the company on their behalf), including the present protocol and the CRF, are exclusive property of the Company.
These materials or information (both global and partial) cannot be given or disclosed by the Dentist or by any person of her/his group to unauthorized persons without the prior formal written consent of the Company.
The Dentist shall consider as confidential all the information received, acquired or deduced during the study and will take all necessary steps to ensure that there is no break of confidentiality, other than for information to be disclosed by law.

13.5 Record retention

The dentist shall arrange for the retention of study documentation until the end of the study. In addition the dentist will comply with specific local regulations/ recommendations with regards to patient record retention.

It is recommended that the Dentist retains the study documents at least five years (5) after the completion or discontinuation of the study, unless otherwise specified in the Dentist Agreement in line with additional standards and/or local laws.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

13.6 Discontinuation of the study

The Company can decide at any time and for any reason to discontinue the study; the decision will be communicated in writing to the participating Dentist and to the local regulations.
If appropriate, according to local regulations, Ethic Committee(s) (IRB/IEC) and Competent Authorities should be informed.

14. DOCUMENTATION AND USE OF THE STUDY RESULTS

14.1 Ownership and use of data and study results

No use of the data will be possible without the authorization of the Company conducting the study.

14.2 Publications

It is planned to communicate the results of the ORADUS study to the participating dentists.

It is planned to publish the results of the ORADUS study in a peer review journal based on the study report. Possible authors are all those matching the STROBE-initiative[8] requirements and who have been implicated in:

- the design, data collection and analysis or interpretation of the data
- writing the manuscript or who significantly contributed to its review
- finalizing the manuscript.

If necessary a publication committee can be set up upon needs. Its main mission could be:

- to define the overall publication plan including the primary publications reporting new scientific findings/ data from the study
- to review and approve (or abstain) all other publications proposals and drafts manuscripts regarding subsequent publications

15. REFERENCE

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http://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideofMethStandardsinPE.pdf
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3.2 STATISTICAL ANALYSIS PLAN (SAP)

3.2.1 Final Statistical Analysis Plan

Research & Development **Global Medical Affairs**	sanofi aventis Because health matters
Statistical Analysis Plan	

Actual conditions of use of OraVerse® in patients among resident dentists throughout Germany

Study number: PHENLL07113 Study name: ORADUS

STUDY BIOSTATISTICIAN: Karlheinz Theobald (Sanofi) /
Dr. Monika Schwager (Winicker Norimed GmbH)

DATE OF ISSUE: 11-Sept-2014

VERSION/STATUS: Final 1.1

Note: Few errors were corrected and few specifications were added to the definition of compliance as compared to the final Version 1.0 that was finalised before database lock on 09-July-2014. All changes were made in "track change" mode.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
CI	Confidence Interval
DVP	Data Validation Plan
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics

1. OVERVIEW AND INVESTIGATIONAL PLAN

This statistical analysis plan (SAP) provides a comprehensive and detailed description of strategy and statistical technique to be used to realize the analysis of data for the study ORADUS (PHENLL07113). The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data prior to data base lock. All statistical analyses are exploratory in nature.

1.1 Study design

Retrospective cross-sectional drug utilisation survey among resident dentists throughout Germany.

Data are collected by dentists on the total number of patients treated with OraVerse® within the previous 3 months, and on the conditions of use of the latest consecutive administrations of OraVerse® within the last 3 months up to a maximum of 6 patients before contract signing.

Inclusion criteria for documented patients: patients treated with OraVerse® after treatment with a local anesthetic containing a vasoconstrictor (such as epinephrine) by dentists within the last 3 months before contract signing.

Information to be documented on the latest consecutive administrations: patient age, classification of body weight, type of dental intervention, local anesthetic used (product and dose), dose of OraVerse® used.

Information are obtained anonymously directly from patient files retrospectively.

Duration of retrospective survey / data documentation: planned May – June 2014.

1.2 Objectives

1.2.1 Primary objectives

To investigate the conditions of use of OraVerse® after local anesthetic procedure in daily routine practice. The primary outcome will be the incidence of patients who “comply” / “not comply” with the recommendations in the Summary of Product Characteristics (SmPC) regarding the following points:

- patient age
- classification of body weight
- type of dental intervention
- local anesthetic used (product and dose)
- dose of OraVerse® used

1.2.2 Secondary objectives

None.

1.3 Determination of sample size

Expected number of patients: 526 (500 evaluable). Sample Size: 500 treated (evaluable) patients assuming a 5% non-evaluable rate.

Statistical power and sample size justification:

With a sample size of 500 patients the following statistical precision for the estimated proportion of patients who 'not comply' / 'comply' with the doses and indications recommended in the SmPC can be reached: Assuming rates of not adherence / adherence to labelling of 3%/97% or 4%/96% or 5%/95%, the 2-sided 95% confidence intervals (CI) will be [1.5%; 4.5%] / [95.5%; 98.5%] or [2.3%; 5.7%] / [94.3%; 97.7%] or [3.1%; 6.9%] / [93.1%; 96.9%].

In general: when the sample size is 500, a 2-sided 95.0% CI for a single proportion using the large sample normal approximation will extend 0.015 or 0.017 or 0.019 from the observed proportion for an expected proportion of 0.03 (or 0.97) or 0.04 (or 0.96) or 0.05 (or 0.95).

Expected number of sites: ca. 100, to gather a nationwide number of resident dentists.

1.4 Study plan

Retrospective cross-sectional survey.

The dentist completes 1 structured questionnaire (in the following: "per-dentist" documentation) on the total number of patients treated with OraVerse® within the previous 3 months, and up to 6 questionnaires (in the following: "per-patient" documentation) collecting information on the latest consecutive administrations of OraVerse® within the last 3 months before contract signing. Data are collected retrospectively from the charts of eligible patients.

1.5 Modifications from the statistical section of the protocol

Modifications are not planned.

2. STATISTICAL AND ANALYTICAL PROCEDURE

2.1 Analysis variables

Per dentist:

- Number of patients treated with OraVerse® within the last 3 months before contract signing.
- Number of patients documented, defined as the number of returned, valid "per-patient" documentations, where "valid" is defined by inclusion in the per-patient analysis set (see below). The number may differ from the number given in the "per-dentist" documentation if patients were excluded from the analysis set.
- Documentation based on patient charts (no, yes).

Per patient:

Inclusion criteria:

- OraVerse® treatment after dental procedure with adrenaline containing local anesthetic (no, yes).
- OraVerse® treatment within the last 3 months before contract signing (no, yes).

Conditions of OraVerse® use:

- Patient age [years].
- Patient body weight class (<15 kg, 15-30 kg, >30 kg, no classification possible).
- Type of dental intervention (cleaning, calculus removal, root planing, preparation of cavities for placement of fillings or crowns, other).
- Local anesthetic - adrenaline concentration (1:200.000, 1:100.000 [categories may be added depending on data]), derived from local anesthetic product.
- Local anesthetic - product (Ultracain D-S (1:200.000), Ultracain D-S forte (1:100.000), Septanest mit Adrenalin 1:200.000, Septanest mit Adrenalin 1:100.000, Ubistesin 1:200.000, Ubistesin forte 1:100.000, other).
- Local anesthetic - number of cartridges (0.5, 1, 1.5, 2, >2 [categories may be added depending on data >2]). If more than 1 field is marked the numbers will be summed up to the total number of cartridges. If the number of cartridges is missing but a volume is given, the number of cartridges will be calculated as volume [ml] / 1.7ml.
- Local anaesthetic - volume [ml]. If the volume is missing but the number of cartridges is given, the volume will be calculated as number of cartridges * 1.7ml.
- OraVerse® - dose (200 µg, 400 µg, 600 µg, 800 µg [categories may be added depending on the data]), calculated as number of cartridges injected times 400 µg. If more than 1 field is marked, the number of cartridges will be summed up to the total number of cartridges.

2.1.1 Primary variables

The primary outcome is the incidence of patients who “comply” / “not comply” with the recommendations in the SmPC. Criteria for non-compliance are defined as:

- Patient age <6 years.
- Type of dental intervention other than pre-specified interventions (cleaning, calculus removal, root planing, preparation of cavities for placement of fillings or crowns) and specification of "other" not identified as compliant with SmPC.
- Local anesthetic other than pre-specified anesthetics (Ultracain D-S [1:200.000], Ultracain D-S forte [1:100.000], Septanest mit Adrenalin 1:200.000, Septanest mit Adrenalin 1:100.000, Ubistesin 1:200.000, Ubistesin forte 1:100.000) and specification of "other" not identified as adrenaline containing local anaesthetic.
- OraVerse® maximum dose: body weight < 15 kg or (body weight 15 - 30 kg and OraVerse® dose > 200 µg) or (age 6 - 11 years and OraVerse® dose > 400 µg) or (OraVerse® dose > 800 µg).

- OraVerse® dose in relation to anesthetic dose: (OraVerse® number of cartridges not equal to local anaesthetic number of cartridges and number of cartridges ≤ 2) or (OraVerse® number of cartridges not equal to 800 µg and number of cartridges > 2).

Missing values in a variable needed to evaluate a criterion leads to missingness of the criterion. However, if weight class is missing and age ≥12 years, a weight of >30 kg is assumed.

According to these criteria, the following compliance variables are defined:

- Complete compliance (no, yes), defined as "no": at least 1 criterion for non-compliance fulfilled *vs.* "yes": all criteria for non-compliance not fulfilled and not missing.
- Compliant regarding age (no, yes), defined as "no": respective criterion for non-compliance fulfilled *vs.* "yes": respective criterion not fulfilled and not missing.
- Compliant regarding dental intervention (no, yes), defined analogously.
- Compliant regarding OraVerse® maximum dose (no, yes), defined analogously.
- Compliant regarding OraVerse® dose in relation to anesthetic dose (no, yes), defined analogously.

2.1.2 Safety variables

None.

2.2 Analysis population

2.2.1 Analysis sets

The "per-patient analysis set" will include all "per-patient" documentations where the inclusion criteria are fulfilled according to the definition in the data validation plan (DVP)[1] and where the question "documentation based on patient charts" on the corresponding "per-dentist" documentation is not answered "no". All analyses of per-patient variables will be performed with this dataset.

The "per-dentist analysis set" will include all "per-dentist" documentations where the question "documentation based on patient charts" is not answered "no" and the numbers of treated and documented patients are not implausible according to the DVP[2]. All analyses of per-dentist data will be performed with this dataset.

2.2.2 Disposition

[1] See DVP checks CRF_01 to CRF_04.

[2] See DVP checks ZENT_03 and ZENT_04.

The following absolute counts will be tabulated: number of dentists who returned at least 1 documentation, number of dentists who returned a valid "per-dentist" documentation (i.e., that was included in the analysis set), number of dentists who returned at least 1 valid "per-patient" documentation (i.e., that was included in the analysis set), total number of returned "per-patient" documentations, total number of valid "per-patient" documentations.

Violations of the inclusion criteria and reasons for exclusion from the analysis set(s) will be tabulated for both analysis sets by their absolute frequencies.

2.3 Statistical methods

Generally, descriptive statistics for continuous data encompass the number of patients, mean, standard deviation, median, min, max, and quartiles. For categorical data frequencies and percentages (not adjusted) will be presented. All per-patient analyses will be presented in total and by age class (<6 years, 6 to <12 years, 12 to <18 years, ≥ 18 years).

2.3.1 Extent of OraVerse® use

The number of patients treated with OraVerse® per dentist within the last 3 months before contract signing, the number of patients documented per dentist, and the percentage of patients documented relative to the patients treated will be summarized by descriptive statistics. The per-dentist analysis set is used for these analyses.

2.3.2 Conditions of OraVerse® use

All variables on the conditions of use (patient age and body weight, type of dental intervention, local anesthetic adrenaline concentration, product and dose, and OraVerse® dose) will be presented descriptively. The dose of the local anesthetic (number of cartridges and volume) will be presented in total and by anesthetic product. The analyses will be performed using the per-patient analysis set.

2.3.3 Analysis of primary outcome (incidence of compliance and non-compliance with SmPC)

The incidences of compliance and of non-compliance with the recommendations in the SmPC will be calculated for all compliance variables (complete compliance and compliant regarding age, dental intervention, OraVerse® maximum dose, and OraVerse® dose in relation to anesthetic dose).

Incidences will be calculated together with 95% CIs, assuming a cluster sampling design with patients of the same dentist forming a cluster. CIs will be calculated as modified Clopper-Pearson (exact) CIs, using the SAS procedure SURVEYFREQ with the specification:

```
proc surveyfreq data=&dat.;
  tables &compliance. / cl (type = clopperpearson);
  cluster &dentist.;
run;
```

where `&dat.` is the respective dataset, `&compliance.` the respective compliance variable, and `&dentist.` a number assigned to the dentist.

In addition to the analyses, data of non-compliant patients will be listed.

2.3.3.1 Multiplicity issues

Multiplicity issues will not be treated since all analyses of the survey are exploratory.

2.3.4 Analyses of safety data

Not applicable.

2.4 Data handling conventions

2.4.1 Plausibility checks

Plausibility checks will be performed and implausibilities will be treated as defined in the DVP. In addition, the following corrections will be made in the analysis datasets:

- "Other" will be marked if an adequate specification of "other" is given (variables: type of dental intervention, local anesthetic product).
- The inclusion criteria will be marked "yes" if they are considered to be fulfilled according to the definition in the DVP[3].

Further implausibilities identified during the analysis will be treated adequately and corrections/exclusions will be made in the analysis datasets. All corrections/exclusions beyond the definitions in the DVP will be described in the documentation of the analysis datasets. Generally, no corrections or exclusions will be made in the raw datasets.

2.4.2 Missing data

Missing values will not be replaced.

2.4.3 Pooling of centres for statistical analyses

Not applicable as no 'by centre' analysis is planned.

2.4.4 Statistical technical issues

[3] See DVP checks CRF_01 to CRF_04.

No issues.

3. INTERIM ANALYSIS

No interim analysis is planned.

4. SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.2.

5. LIST OF APPENDICES

Appendix name	Title
Appendix A:	Summary of statistical analyses

APPENDIX A: SUMMARY OF STATISTICAL ANALYSES

1. Disposition:

Table No.	Table Title	Analysis Population	Variable(s)	Statistical Analysis / Table
Table 1-1	Disposition		No. of dentists who returned at least 1 documentation, no. of dentists who returned a valid[1)] "per-dentist" documentation, no. of dentists who returned at least 1 valid[1)] "per-patient" documentation, no. of returned "per-patient" documentations, no. of valid[1)] "per-patient" documentations. [1)] "valid" defined by inclusion into the respective analysis set.	Absolute frequencies
Table 1-2	Violation of inclusion criteria / reasons for exclusion from analysis set(s)		Documentation not based on patient charts, no. of patients treated with OraVerse within the last 3 months before contract signing implausible, no. of documented patients implausible, OraVerse treatment not after dental procedure with adrenaline containing local anesthetic, OraVerse treatment not within the last 3 months before contract signing.	Absolute frequencies

2. Extent of OraVerse® use:

Table No.	Table Title	Analysis Population	Variable(s)	Statistical Analysis / Table
Table 2-1	Number of patients treated with OraVerse and documented per dentist.	Per-dentist analysis set	No. of patients treated[1)], no. of patients documented, proportion of patients documented relative to treated [%]. [1)] per dentist within the last 3 months before contract signing.	Sample statistics

3. Conditions of OraVerse® use:

Table No.	Table Title	Analysis Population	Variable(s)	Statistical Analysis / Table / Figure
Table 3-1	Conditions of OraVerse use - patient data	Per-patient analysis set	Patient age [years], patient body weight class.	Sample statistics / frequency table
Table 3-2	Conditions of OraVerse use - dental intervention	Per-patient analysis set	Type of dental intervention.	Frequency table, multiple answers possible. Specifications of "other" included in table or listed separately, depending on data.
Table 3-3	Conditions of OraVerse use - local anaesthetic product	Per-patient analysis set	Adrenaline concentration, product.	Frequency tables. Specifications of "other" included in table or listed separately, depending on data.

Table No.	Table Title	Analysis Population	Variable(s)	Statistical Analysis / Table / Figure
Table 3-4	Conditions of OraVerse use - local anaesthetic dose	Per-patient analysis set	No. of cartridges, volume. Both variables in total (as continuous and categorical variable) and by local anesthetic product (as categorical variable only).	Frequency tables. Specifications of "other" included in table or listed separately, depending on data.
Table 3-5	Conditions of OraVerse use - OraVerse dose	Per-patient analysis set	OraVerse dose (as continuous and categorical variable).	Frequency table. Specifications of "other" included in table or listed separately, depending on data.

4. Analysis of primary outcome (incidence of compliance and non-compliance with SmPC)

Table No.	Table Title	Analysis Population	Variable(s)	Statistical Analysis / Table / Figure
Table 4-1	Incidence of compliance and non-compliance with SmPC	Per-patient analysis set	Complete compliance, compliant regarding age, compliant regarding dental intervention, compliant regarding OraVerse maximum dose, compliant regarding OraVerse dose in relation to anesthetic dose.	Frequency tables including 95% CIs.
Listing 4-1	Patients non-compliant with SmPC	Per-patient analysis set	Patient age, patient body weight class, type of dental intervention, anesthetic product, anesthetic no. of cartridges, anesthetic volume, OraVerse dose, compliance variables.	Listing of per patient data. Include patients with at least 1 compliance variable="no".

3.2.2 Changes from the final Statistical Analysis Plan

Not applicable.

3.3 CASE REPORT FORM (CRF)/ PATIENT QUESTIONNAIRE

Dokumentationsbogen I

Patientenselektion für Dokumentation

OraVerse®-Injektion nach zahnärztlicher Behandlung mit Adrenalin-haltigem Lokalanästhetikum	☐	ja	☐	nein
Patient wurde in den letzten 3 Monaten vor Vertragsunterzeichnung mit OraVerse® behandelt	☐	ja	☐	nein

→ Falls ein Feld mit NEIN beantwortet wird, Patient bitte nicht dokumentieren!

Patientendaten

Alter des Patienten am Tag der Behandlung mit OraVerse® ☐☐ Jahre

Gewicht:
- ☐ < 15 kg
- ☐ 15-30 kg
- ☐ > 30 kg
- ☐ Klassifizierung nicht möglich

Angaben zur zahnärztlichen Behandlung

Art der Behandlung:
- ☐ Zahnreinigung
- ☐ Entfernen von Zahnstein
- ☐ Wurzelglättung
- ☐ Präparation von Kavitäten zum Einsetzen von Füllungen oder Kronen
- ☐ Andere.....(bitte angeben)

Lokalanästhesie

Produkt
- ☐ Ultracain D-S (1:200.000)
- ☐ Ultacain D-S forte (1:100.000)
- ☐ Septanest mit Adrenalin 1:200.000
- ☐ Septanest mit Adrenalin 1:100.000
- ☐ Ubistesin 1:200.000
- ☐ Ubistesin forte 1:100.000
- ☐ Andere.....(bitte angeben)

Gesamtanzahl der Zylinderampullen / Patronen (inklusive evtl. Nachinjektionen)

- ☐ 0,5
- ☐ 1
- ☐ 1,5
- ☐ 2
- ☐ > 2, wenn ja, wieviel .....(Anzahl)

oder:

Gesamtvolumen der Lokalanästhesie (inklusive evtl. Nachinjektionen)

☐☐**,**☐ ml

OraVerse-Injektion

Gesamtanzahl der Zylinderampullen / Patronen

- ☐ 0,5
- ☐ 1
- ☐ 1,5
- ☐ 2
- ☐ > 2 wenn ja, wieviel .....(Anzahl)

Dokumentationsbogen II

Insgesamt habe ich in den 3 Monaten vor Vertragsunterzeichung behandelt:

…….(Anzahl) Patienten mit OraVerse®

Von den oben genannten Patienten habe ich die letzten

…….(Anzahl, max. 6) dokumentiert

Ich habe die Daten auf Basis der mir vorliegenden Dokumentation (Patientenakte) ausgefüllt ☐ ja ☐ nein

3.4 PATIENT INFORMED CONSENT

Not applicable.

3.5 OTHER DOCUMENTS RELEVANT TO THE REGISTRY

Not applicable.

3.6 OTHER REGISTRY INFORMATION

Not applicable.

3.6.1 Safety reporting

Since this was a retrospective drug utilization study based on the analysis of preexisting data, only detection of safety signals was applicable. In case a safety signal was identified during data analysis, this was to be immediately forwarded to the PV department.

3.6.1.1 Adverse events (AE)

Not applicable.

3.6.1.2 Serious adverse events (SAE)

Not applicable.

3.6.1.3 Adverse events of Special Interest (AESI)

Not applicable.

3.7 REGULATORY AUTHORITIES' SUBMISSIONS BY COUNTRY

3.8 REPORT APPROVAL

3.8.1 Coordinating physician's approval

Study report: Principal or coordinating Investigator signature form

Product Code:	*OraVerse® - Phentolamin Mesilate*
Study Code / Name:	*PHENLL07113*
Study Title:	*Actual conditions of use of OraVerse® in patients among resident dentists throughout Germany*
Document Type:	☐ Clinical Study Report ☒ Product Registry Report ☐ Disease Registry Report ☐ Compassionate Use Cohort Study Report
Final draft dated:	16-12-2014

I have read this report and confirm that to the best of my knowledge, it accurately describes the conduct and results of the study.

Investigator University of Mainz Prof. Dr. Dr. med. Monika Daubländer	Daubländer	17/12/14
	Signature	Date:

3.8.2 The Company's approval

Study report or synopsis Sponsor approval form for local/regional Medical Affairs studies

SANOFI

Product Code:	Phentolaminmesilat/ORAVERSE
Study Code / Name:	ORADUS (PHENLL07113)
Study Title:	ORADUS (Actual conditions of use of OraVerse® in patients among resident dentists throughout Germany)
Document Type: (Tick appropriate box)	☐ Clinical Study Report / ☐ Synopsis ☒ Product Registry Report / ☒ Synopsis ☐ Disease Registry Report / ☐ Synopsis ☐ Compassionate Use Cohort Study Report / ☐ Synopsis
Name of Medical Director (i.e. individual responsible for medical oversight of the report)	Dr. M. L. Helmich

THE STUDY REPORT / SYNOPSIS

Final Draft dated 16.12.2014

is APPROVED*.

*Note: to approve the document, the Medical Director should ensure that the local PV responsible has reviewed the document and comments have been incorporated

Sponsor's responsible medical officer:		
☒ Medical Director	W.D. Paar	16.12.14 D. Paar Signature Date:

4 APPENDIX IV - PUBLICATIONS

4.1 REFERENCES

1. Hersh EV, Hermann DG, Lamp CJ, Johnson PD, MacAfee KA. Assessing the duration of mandibular soft tissue anesthesia. J Am Dent Assoc 1995;126(11):1531–36.

2. Malamed SF. Handbook of local anesthesia. 5th edition. St Louis (MO): Mosby Inc; 2004.

3. College C, Feigal R, Wandera A, Strange M. Bilateral versus unilateral mandibular block anesthesia in a pediatric population. Pediatr Dent 2000;22(6):453-57.

4. Hersh EV, Moore PA, Papas AS, Goodson JM, Navalta LA, Rogy S, et al. Reversal of soft-tissue local anesthesia with phentolamine mesylate in adolescents and adults. J Am Dent Assoc. 2008;139(8):1080-93.

4.2 PUBLICATIONS/ABSTRACTS OF THE REGISTRY RESULTS

The results of this non-interventional study have not been published as of date of this report.

4.3 PUBLICATIONS CITED IN THE REFERENCE LIST

Copies of the cited publications will be made available upon request.