RESULT REPORT ACCORDING TO § 42B AMG

Synopsis

(in compliance with ICH E3 guideline)

Name of Company Chemische Fabrik Kreussler & Co. GmbH Rheingaustrasse 87-93, 65203 Wiesbaden Name of Finished Product Dynexan Mundgel® Name of Active Ingredient Lidocaine hydrochloride	Individual Study Table Referring to Module 5 of the CTD not applicable
Title of study:	Multicenter, randomized, split-mouth study to evaluate the acceptance and preference of lidocaine gel compared to injection anesthesia after non surgical periodontal treatment
Protocol amendments/ addendum:	Addendum from 18-Jun-2018 concerning extension of the recruitment period. Due to the delayed recruitment of patients, the duration of the study had to be extended in order to enroll the planned number of patients. The end of the recruitment period was extended from second quarter 2018 to fourth quarter 2018.
Investigators:	5
Study centers:	5
Publication:	planned
Study period:	First patient enrolled: 05-December-2017 Last patient completed: 02-November-2018
Premature withdrawal from study:	Three patients (3.19%) ended the study prematurely (Patient 1-02, *Alleged violation of exclusion criteria*; Patient 3-05, *Patient stayed away*; Patient 4-15, *Revocation of consent*)
Development Phase:	Phase IV

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Objectives:	Primary objective: • Comparison of acceptance and preference of topical lidocaine mouth gel anesthesia vs. injection anesthesia with articaine in patients undergoing subgingival debridement by comparing the proportion of patients after the second periodontal treatment who prefer topical anesthesia with lidocaine gel against the injection anesthesia with articaine to a proportion of 0.5; the patient rated the preferred anesthesia method on a questionnaire by stating if the patient's preference was treatment with anesthetic gel, treatment with anesthetic injection, or no preference Secondary objectives: • Comparative assessment of pain the patients experienced during treatment; a visual analogue scale was used for maximum pain and average pain rating • Evaluate type and number of side effects (incl. after-effects due to study treatment) • Comparison of the handling/application of both methods; the treating physician rated the handling/application on a questionnaire by using German school grades (1-6) • Comparison of the onset of anesthetic effect in both treatment groups; the treating physician rated the onset of the anesthetic effect on a questionnaire by using German school grades (1-6) • Compare the duration of anesthetic effect in both treatment groups; the treating physician rated the duration of the anesthetic effect on a questionnaire by using German school grades (1-6) • Comparison of the patient compliance in both treatment groups; the treating physician rated the patient compliance on a questionnaire by using German school grades (1-6) • Evaluation which of the anesthetic methods the treating physician preferred. The treating physician rated the preferred anesthesia method on a questionnaire by stating if the treating physician's preference was treatment with anesthetic gel, treatment with anesthetic injection, or no preference • Assessment of the number of re-application of the anesthetic gel or the rescue anesthesia injections that were required in every treatment group • Evaluation of the overall patient satisfaction with anesthesia. The patient rated the overall satisfaction on a questionnaire by using German school grades (1-6) • Evaluation of the willingness to pay for lidocaine gel by using a questionnaire • Re-evaluation of preference of topical lidocaine mouth gel anesthesia vs. injection anesthesia with articaine 24 h after end of last treatment. The patient again rated the preferred anesthesia method by stating if his/her preference was treatment with anesthetic gel, treatment with anesthetic injection, or no preference. The preference 24 h after end of last treatment was collected by using the patient diary.

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Endpoints:	Primary endpoint • Comparison of the proportion of patients who preferred gel anesthesia versus the proportion of patients who preferred injection anesthesia. Evaluation of this endpoint was performed after the second treatment session (Visit 2) had been completed and the patient had filled out the questionnaire. Secondary endpoints • Comparison of the patients' maximum and average pain ratings in mm on a VAS (0-100 mm) in the gel anesthesia group versus the patients' maximum and average pain ratings in mm on a VAS (0-100 mm) in the injection anesthesia group • Comparison of type and number of side and after effects in the gel anesthesia group versus type and number of side and after effects in the injection anesthesia group • Comparison of the treating physicians' ratings (German school grades 1-6) concerning the handling/application of both anesthesia methods • Comparison of the treating physicians' ratings (German school grades 1-6) concerning the onset of the anesthetic effect in both treatment groups • Comparison of the treating physicians' ratings (German school grades 1-6) concerning the duration of the anesthetic effect in both treatment groups • Comparison of the treating physicians' ratings (German school grades 1-6) concerning the patient compliance during treatment in both treatment groups • Comparison of the number of treating physicians who preferred gel anesthesia versus the number of treating physicians who preferred injection anesthesia • Comparison of the number of re-applications of the anesthetic gel or the rescue anesthesia injections required in every treatment group • Comparison of the patients' ratings (German school grades 1-6) concerning the overall satisfaction in both treatment groups • Number of patients who were willing to pay extra for the gel anesthesia. If a patient was willing to pay for the gel anesthesia what amount of money would he/she have payed extra? Comparison of the proportion of patients who preferred gel anesthesia versus the proportion of patients who preferred injection anesthesia 24 h after end of last treatment
Methodology:	National, open label, randomized, multicenter, split-mouth study
Number of patients:	Planned: 90 patients Studied: 94 patients

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Diagnosis and main inclusion criteria:	Medical condition or disease to be investigated: • Moderate Periodontitis Principal inclusion criteria: • Patients 18-70 years of age • Signed informed consent had to be available • Willingness and ability to comply with scheduled visits, treatment plan, and other study procedures • Patient systemically healthy except for controlled diabetes and hypertension • Patients with comparable periodontal status of the right and left jaw, with ≥ 3 teeth with pockets ≥ 4 mm and ≤ 7 mm per quadrant • Female patients of childbearing potential had to practice highly effective contraception methods
Test product, dose, mode of administration, batch number(s) & treatment duration:	Test product was Lidocaine hydrochloride (Dynexan Mundgel®). Cylinder vials with 1.7 g gel containing 34 mg lidocaine (1 g gel contained 20 mg lidocaine) were used. For the application of the study drug all study sites were supplied with identical dental cartridge syringes and blunt cannulas. Application of the gel into the periodontal pockets or the sulcus was performed with a blunt cannula according to the summary of product characteristics (SmPC). A total dose of 40 mg lidocaine should not be exceeded. Two treatment sessions at intervals of 48 h-14 days were planned. The duration of each treatment session was about an hour. The first scaling and root planing (SRP) was performed in the right upper and lower jaw. The second SRP was performed in the left upper and lower jaw. Batch numbers used: Dynexan Mundgel®: 5B11105 (4B05104, 6F14103 und 7B20103)

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Reference therapy, dose, mode of administration and batch number(s) & treatment duration:	Reference therapy was Articaine hydrochloride/epinephrine (adrenaline) hydrochloride (Ultracain® DS 1:200,000). Ultracain® DS was selected as comparator drug, being the most commonly used anesthetic drug for infiltration and nerve-block anesthesia in Germany at the time the study protocol was written. Cylinder vials with 1.7 ml solution for injection containing 68 mg articaine and 0.0102 mg epinephrine (1 ml contains 40 mg articaine and 0.006 mg epinephrine) were used. For the application of the comparator drug, the study sites were supplied with identical dental cartridge syringes and needles. Infiltration anesthesia for the upper jaw and infiltration or nerve block anesthesia for the lower jaw with articaine solution for injection according to SmPC could be performed. Adults could be treated with up to 7 mg articaine per kg of body weight per treatment session. Two treatment sessions at intervals of 48 h - 14 days were planned. The duration of each treatment session was about an hour. The first SRP was performed in the right upper and lower jaw. The second SRP was performed in the left upper and lower jaw. Batch numbers used: Ultracain® DS: 6F009A, 6F010A (7F479A)

Criteria for evaluation

Efficacy:

- Evaluation of the primary efficacy endpoint was performed directly after the second treatment session (Visit 2). The patient stated his/her preferred anesthetic drug in the questionnaire provided.

Safety:

- Recording of adverse events (AEs)
- Specific recording of anesthesia induced adverse effects after treatment
- Pulsoximetry measurements

Statistical methods

The order of the two treatments under anesthetic gel and anesthetic injection was randomized. Patients were allocated randomly in blocks to the two treatment groups in the ratio 1:1.
For the proportion of patients p_{Gel} who preferred the anesthetic gel, the following hypotheses were formulated:
H_0: $p_{Gel} = 0.5$
H_1: $p_{Gel} \neq 0.5$
The null hypothesis H_0 was tested using a two-sided binomial test.

SUMMARY OF RESULTS

Patient disposition

In total, five study centers enrolled 94 patients. The mean number of patients per center was 18.80 (±5.93, median 19.00) patients. The number varied between 11 patients and 25 patients per center.

Data of all three visits (Visit 0, Visit 1 and Visit 2) and data recorded at study end were available for 91 patients (96.81% of all patients). Two patients left the study after Visit 0 (enrollment) and one patient after Visit 1.

Three patients (3.19%) ended the study prematurely (Patient 1-02, *Alleged violation of exclusion criteria*; Patient 3-05, *Patient stayed away*; Patient 4-15, *Revocation of consent*).

Concerning patients' suitability at the conclusion of Visit 0, 93 patients met all inclusion criteria and 93 patients did not meet any of the exclusion criteria (n=93). Again, data from Patient 4-15 was missing due to the revocation of consent.

At Visit 1, 92 of 93 patients still met all inclusion criteria whereas one patient (1.08%, Patient 4-15) did not. Additionally, Patient 3-05 did not return to Visit 1, therefore this information is missing for this patient. 92 patients did not meet any of the exclusion criteria (n=92). Data from the two Patients 3-05 and 4-15 were missing.

According to randomization, 47 patients should be treated in the sequence Dynexan Mundgel®/Ultracain® DS and 45 patients in the sequence Ultracain® DS/Dynexan Mundgel®. If performed, the actual order of treatments corresponded to randomization in all patients.

In total, two patients discontinued the study before treatment at Visit 1 (Patient 3-05 and 4-15). In addition, one patient (Patient 1-02) who had been treated with Ultracain® DS at Visit 1 did not receive the second treatment with Dynexan Mundgel® due to premature ending of the study (*Alleged violation of exclusion criteria*).

Exposure to study medication

Extent of exposure was described by the number of used cylinder ampoules without rescue medication and the frequency of rescue medication/re-application that was needed.

Dynexan Mundgel®:

On average, 0.49 (±0.19, median 0.50) cylinder ampoules of Dynexan Mundgel® were used per treatment (minimum, 0.25 ampoules; maximum, 1.00 ampoules). For more than half of the patients (52 patients, 57.14% of patients with data on number of used ampoules) 0.50 cylinder ampoules were recorded. Data of one patient was missing.

Ultracain® DS:

As for Ultracain® DS, a mean number of 1.78 (±0.67, median 2.00) cylinder ampoules were used with a minimum of 0.75 and a maximum of 4.00 ampoules. Most often, the number of used ampoules was 2.00 ampoules (32 patients, 34.78% of patients with data on number of used ampoules).

Efficacy

Given a free choice, immediately after treatment, almost 60% (58.24%, 53 patients) of patients prefer the topical lidocaine mouth gel anesthesia Dynexan Mundgel®. About 20% each preferred injection anesthesia with articaine Ultracain® DS (21.98%, 20 patients) or stated that they had no preference (19.78%, 18 patients). The same was true when patients were asked about their preference 24 hours post treatment. In most patients (57.14%, 52 patients), a preference of Dynexan Mundgel® was recorded. Similar to data documented immediately after treatment, about 20% (20.88%, 19 patients) prefer Ultracain® DS or had no preference (21.98%, 20 patients) when asked 24 hours post treatment.

In total, three patients (3.30 %) who were treated with Dynexan Mundgel® anesthesia needed an additional dose of Ultracain® ("rescue medication").

In the great majority of patients a very good or good satisfaction with Dynexan Mundgel® was recorded (23 patients, 25.27%; 40 patients, 43.96%). Overall satisfaction with Ultracain® DS similarly was assessed as very good or good (32 patients, 35.16%; 39 patients, 42.86%) in most cases.

With regard to comparative assessment of pain the patients experienced during treatment, mean as well as maximum pain of patients treated with Dynexan Mundgel® anesthesia were more pronounced than in patients treated with Ultracain® DS anesthesia (mean VAS pain value: 24.14±20.16 versus 10.36±15.64, maximum VAS pain value: 41.01±29.12 versus 17.40±21.31).

More than 60% of the patients (56 patients) would be willing to pay an additional charge for Dynexan Mundgel®. Most of these patients would pay more than 5€ up to 10€ (27 patients, 29.67%).

The treating physicians rated the handling/application, onset of anesthetic effect, duration of anesthesia, and patients' compliance in terms of behavior of the patient during treatment slightly better for Ultracain® DS than for Dynexan Mundgel®.

None of the dentists chose the German school grades 5 (inadequate) and 6 (insufficient), respectively, to assess handling/application of the anesthetic. As for Dynexan Mundgel®, handling/application was rated with grade 1 "very good" in 32 patients (35.16%), with grade 2 "good" in 33 patients (36.26%), with grade 3 "satisfactory" in 23 patients (25.27%) and for three patients (3.30%) grade of 4 "adequate" was chosen. Regarding Ultracain® DS, dentists most often chose grade 1 "very good" and 2 "good" (43 patients, 47.25%; 44 patients, 48.35%), followed by grade 3 "satisfactory" (4 patients, 4.40%). An assessment of handling/application of Ultracain® DS with grade 4 "adequate" was not documented.

None of the physicians chose the grade 5 to assess onset of action of the anesthetic. With regard to anesthesia with Dynexan Mundgel®, onset of effect was rated with grade 1 "very good" in 26 patients (28.57%), with grade 2 "good" in 42 patients (46.15%), with grade 3 "satisfactory" in 19 patients (20.88%), with grade 4 "adequate" in three patients (3.30%) and the worst grade of 6, meaning an insufficient onset of action, was seen in one patient (1.10%). In patients with Ultracain® DS treatments, dentists most often chose grade 1 "very good" and 2 "good" (55 patients, 60.44%; 31 patients, 34.07%) to assess onset of action, followed by grade 3 "satisfactory" (5 patients, 5.49%). Assessments with grades 4 to 6 were not recorded for onset of effect of Ultracain® DS treatment.

Duration of anesthetic effect with Dynexan Mundgel® was rated by grades 1-3 in the great majority of patients (grade 1, 29 patients, 31.87%; grade 2, 32 patients, 35.16%; grade 3, 23 patients, 25.27%). Grades 4-6 were chosen in four patients (4.40%), two patients (2.20%) and one patient (1.10%). In contrast, duration of anesthetic effect with Ultracain® DS was mostly assessed with grade 1 and 2 (50 patients, 54.95%; 37 patients, 40.66%). A satisfactory duration (grade 3) was documented in four patients (4.40%). Duration of anesthesia of Ultracain® DS was not assessed by grades 4-6.

Most often, patient compliance (behavior of the patient during treatment) with Dynexan Mundgel® was recorded as very good, good or satisfactory (grade 1, 30 patients, 32.97%; grade 2, 29 patients, 31.87%; grade 3, 21 patients, 23.08%). Grades 4-6 were chosen in few patients (7 patients, 7.69%; 1 patient, 1.10%; 3 patients, 3.30%). In almost 70% of the patients (62 patients, 68.13%) with Ultracain® DS anesthesia, compliance was assessed as very good. A good compliance was seen in 23 patients (25.27%), a satisfactory compliance in five patients (5.49%) and an adequate one in one patient (1.10%).

In contrast to the significant patients' preference towards Dynexan Mundgel®, dentists would prefer Dynexan Mundgel® or Ultracain® DS in an equal proportion of patients (33 patients each, 36.26%).

Safety

Lidocaine and articaine have been approved for anesthetic treatment for a long time and have demonstrated efficacy with a favorable safety profile. This was underlined by safety data recorded during this study.

No serious and severe adverse events (AEs) occurred with any anesthesia. Furthermore, no patients discontinued the study due to AEs and no fatal cases were noted during the study.

Of note, all recorded treatment-emergent AEs and adverse drug reactions (ADRs) were non-serious and of mild or moderate nature.

Overall, the safety profile of Dynexan Mundgel® differs positively from the safety profile of Ultracain® DS in type and frequency of AEs. However, both anesthetic treatments were generally safe and no new safety issues were encountered.

92 AEs were noted in 50 patients (53.19%) and 54 ADRs occurred in 34 patients (36.96%).

23.08% of patients receiving Dynexan Mundgel® (30 events in 21 patients) suffered from an AE. This percentage is lower when compared to Ultracain DS® anesthesia with 40.22% of patients (61 events in 37 patients) affected by an AE. The number of ADRs was also lower in patients under Dynexan Mundgel® anesthesia (12 events in 9 patients [9.89%] versus 42 events in 27 patients [29.35%] with Ultracain® DS anesthesia).

No measures regarding the study medication had to be taken, neither during Dynexan Mundgel® anesthesia nor under Ultracain® DS anesthesia.

With regard to further measures concerning patients treated under Dynexan Mundgel® anesthesia, only one patient (1.10% of patients under Dynexan Mundgel® anesthesia) with a subcutaneous emphysema (1 event in Patient 1-06, 3.33% of treatment-emergent AEs during anesthesia with Dynexan Mundgel®) had to be medically treated. Relation of the event to the study drug Dynexan Mundgel® was regarded as being unlikely. None of the events during treatment under Ultracain® DS anesthesia were medically treated.

Concerning the outcome of ADRs with Dynexan Mundgel®, all events were resolved. Similarly, with exception of one event with an unknown outcome (*oral hypoaesthesia)*, all ADRs of Ultracain® DS were resolved in this study.

With regard to vital signs, all pulse oximetry measurements during this study showed normal values of hemoglobin saturation and heart rate under Dynexan Mundgel® and Ultracain® DS anesthesia.

Patients documented intensity of numbness four hours post treatment by patient diary. More than half of the patients with Dynexan Mundgel® (57.14%, 52 patients) anesthesia recorded the absence of numbness in contrast to a substantially lower number of patients with Ultracain® DS anesthesia (10.87%, 10 patients) for whom no numbness was documented.

In the great majority of patients, no adverse effect and/or impairment was noted four hours after treatment (75 patients, 82.42%, Dynexan Mundgel®; 67 patients, 72.83%, Ultracain® DS) or 24 hours post treatment (80 patients, 87.91%, Dynexan Mundgel®; 78 patients, 84.78%, Ultracain® DS).

In conclusion, no SADR or SAE became known from this trial. Other information which affected the drug safety in any way was not reported and no safety actions of any kind were necessary.

CONCLUSIONS

Data obtained from the phase IV DyMZIS-01 study demonstrates that the majority of patients preferred the topical lidocaine mouth gel anesthesia (Dynexan Mundgel®).

About 60% of patients would choose Dynexan Mundgel® when asked immediately (58.24%, 53 patients) or 24 hours post treatment (57.14%, 52 patients), although mean as well as maximum pain of patients under Dynexan Mundgel® anesthesia were more pronounced than in patients receiving Ultracain® DS. In total, three patients (3.30%) under Dynexan Mundgel® anesthesia needed an application of Ultracain® DS. In the great majority of patients of both treatment groups no adverse effect and/or impairment was noted four hours (82.42% versus 72.83%) or 24 hours post treatment (87.91% versus 84.78%).

Patients predominantly assessed their overall satisfaction with Dynexan Mundgel® and Ultracain® DS as very good or good (25.27% versus 35.16%, 43.96% versus 42.86%).

More than 60% of the patients (56 patients) would be willing to pay an additional charge for Dynexan Mundgel®. Most of them were willing to pay more than 5€ up to 10€.

The treating physicians rated the handling/application, onset of anesthetic effect, duration of anesthesia, and patients' compliance in terms of behavior of the patient during treatment slightly more favorable for Ultracain® DS than for Dynexan Mundgel®. In contrast to the clear patients' preference towards Dynexan Mundgel®, dentists would prefer Dynexan Mundgel® or Ultracain® DS in an equal proportion of patients (33 patients each, 36.26%).

With regard to safety, no serious adverse event or adverse drug reaction became known from this trial. The safety profile of Dynexan Mundgel® differs in type and frequency of adverse events from the one of Ultracain® DS. In contrast to nine Dynexan Mundgel® treated patients (9.89%) with ADRs, a higher proportion of patients (27 patients, 29.35%) suffered from ADRs under Ultracain® DS anesthesia. However, both treatments were generally safe and no new safety issues encountered.

Date of report: Version 1.1 – 06 September 2019

APPENDICES:

List of investigators and centers

Prof. Dr. med. dent. Nicole Arweiler
Site No.: 01
Universitätsklinikum Giessen und Marburg GmbH, Standort Marburg
Zentrum für Zahn-, Mund- und Kieferheilkunde
Abteilung für Parodontologie und peri-implantäre Erkrankungen
Georg-Voigt-Str. 3
D-35033 Marburg

Prof. Dr. med. dent. Christof Dörfer (**Coordinating/Principal Investigator**)
Site No.: 02
Universitätsklinikum Schleswig-Holstein, Campus Kiel
Klinik für Zahnerhaltungskunde und Parodontologie
Arnold-Heller-Str. 3
D-24105 Kiel

Prof. Dr. med. dent. Henrik Dommisch
Site No.: 03
Charité - Universitätsmedizin Berlin
Charité Centrum Zahn-, Mund- und Kieferheilkunde CC 3, Parodontologie und Synoptische Zahnmedizin
Aßmannshauser Straße 4-6
D-14197 Berlin

PD Dr. med. dent. Gregor Petersilka
Site No.: 04
Praxis Dr. Gregor Petersilka
Haugerpfarrgasse 7
97070 Würzburg

Site No. 05 (not started)
Dr. med. dent. Ralph Heckel
Site No.: 06
Praxis Dr. Ralph Heckel
Sandacker 2
D-91341 Röttenbach

Flow diagram