1. Title Page

"A randomised, mono-center, placebo-controlled, double-blind, comparative study to evaluate the efficacy and safety of Dynexan® Mundgel in minors with acute painful sites of the mouth."

Author: Dr. Anja Wildner Date: 10.10.2014

Generic name: Dynexan® Mundgel	**Indication:** Acute, painful sites of the mouth mucosa without strong impairment of general condition	
Name of investigational product: Dynexan® Mundgel	**Dose:** Single local application of 0.2 g gel, corresponding to a pea size amount of gel	**Batch number:** 01421
Name of reference product: Placebo gel	**Dose:** Single local application of 0.2 g gel, corresponding to a pea size amount of gel	**Batch number:** 09021
Dose: Single application of 0.2 g gel	**Population:** • Age Group I: 129 minors from 4 years to 8 years (children, who have celebrated their 4th anniversary at the time of enrolment, and who have not celebrated their 9th anniversary at the time of enrolment) • Age Group II: 32 minors from 6 month to 3 years (children from older than 180 days, and who have not celebrated their 4th anniversary at the time of enrolment)	
Study design: Mono-centre, single dose, double-blind, placebo controlled, randomised post approval study to evaluate efficacy and safety of Dynexan® Mundgel in comparison to placebo in minors with acute painful sites of the mouth.		
Protocol number Sponsor: **Protocol number CRO:** **Date of final protocol:** **Date(s) of protocol amendments:**	DMKS-2011 11ct/am29dy V01, 2012-01-25 None	**Clinical study phase:** Phase IV (post approval)

Sponsor: Chemische Fabrik Kreussler & Co. GmbH Rheingaustr. 87-93 65203 Wiesbaden, Germany Tel.: +49-(0) 611-92 71 126 Fax: +49-(0) 611-92 71 111	**CRO:** CardioSec Clinical Research GmbH Peterstr. 5 99084 Erfurt, Germany Tel.: +49-(0) 361-789 19 740 Fax: +49-(0) 361-789 19 744	**Biometrics:** ACOMED Statistik Fockestr. 57 04275 Leipzig, Germany Tel: +49-(0) 341-391 01 95 Fax: +49-(0) 341-391 01 96
Sponsor's responsible medical officer: Dr. Joachim Otto Chemische Fabrik Kreussler & Co. GmbH Rheingaustr. 87-93 65203 Wiesbaden, Germany Tel.: +49-(0) 611-92 71 126 Fax: +49-(0) 611-92 71 111	**Principal Investigator** Dr. Dörte Wolf CardioSec Clinical Research GmbH Peterstr. 5 99084 Erfurt, Germany Tel.: +49-(0) 361-789 19 740 Fax: +49-(0) 361-789 19 744	**Monitoring:** Dr. Winfried Gißke Storkower Str. 113 10407 Berlin, Germany Tel.: +49-(0) 30-467 93 426 Fax: +49-(0) 30-467 93 427
Study initiation date (first subject enrolled): 21.05.2012	**Date of early study termination:** N.A.	**Study completion date** (last subject completed): 14.06.2014

Earlier reports from the same study: N.A.

This study was conducted in compliance with Good Clinical Practice (GCP) including the archiving of essential documents

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Name of the finished product Dynexan® Mundgel		
Name of the active ingredients: lidocaine hydrochloride		

2. Synopsis

Title of the study:	"A randomised, mono-center, placebo-controlled, double-blind, comparative study to evaluate the efficacy and safety of Dynexan® Mundgel in minors with acute painful sites of the mouth."		
Study centre:	1	CardioSec Clinical Research GmbH	Peterstr. 5 99084 Erfurt, Germany
Investigators:	Principal Investigator:	Dr. med. Dörte Wolf	
	Deputy Investigator:	Dr. med. Jörg Kremser	
	Investigators:	Holger Sörgel	
		Dr. med. Carina Schenk	
		Dr. med. Daniele Bencivinni	
Publication (reference):	None		
Study period (years):	**Date of first enrolment:** **Date of last exclusion:**	21.05.2012 14.06.2014	**Clinical phase:** IV (post-approval)
Objectives:	The primary objective is the comparison of pain reduction after local application of Dynexan® Mundgel or placebo on painful sites in the mouth in age group I. **Primary efficacy variable:** Pain reduction from T1 to T2 (application – 10 ± 5 min after application). The main secondary objectives are the evaluation of the safety and local tolerability of Dynexan® Mundgel. **Secondary efficacy variable:** Pain reduction from T1 to T3 (application – 30 ± 10 min after application). Comparison of children's and parent's assessment, whenever both ratings are eligible. Assessment of subject's satisfaction (parent's assessment) as rated on a 5-point verbal rating scale. **Secondary safety variable:** Characterisation of safety and tolerability of the investigational product considering Adverse Events in the study population, descriptive evaluation. Assessment of local tolerability by the investigator (number of subjects with global tolerability ratings of "very good", "good", "moderate", "poor", descriptive evaluation.		
Total number of subjects (planned and analysed):	222 subjects planned to achieve 160 evaluable subjects (age group I: 128 subjects, age group II: 32 subjects) 269 pre-screened subjects by telephone 195 subjects performed screening visit 33 subjects without ICF (not passed inclusion/exclusion criteria) 162 included (age group I: 129 subjects (one re-screening patient included), age group II: 32 subjects) 1 Screening Failure with ICF and CRF (not randomised / treated) 161 randomised / treated subjects 161 analysed subjects 0 Drop-outs		
Study design:	Mono-centre, single dose, double-blind, placebo controlled, randomised post approval study to evaluate efficacy and safety of Dynexan® Mundgel in comparison to placebo in minors with acute painful sites in the mouth.		

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Synopsis (continued)	
Indication studied:	Acute, painful sites of the mouth mucosa without strong impairment of general condition
In- / Exclusion criteria:	**Inclusion criteria** 1. Male and female subjects, from 6 month to 8 years of age at the time of enrolment. 2. Written informed consent of the legal representative. 3. Verbal assent from minors ≥ 4 years, written assent depending on intellectual maturity of the minor. 4. Ability to comply with the requirements of the study. 5. Clinical diagnosis of a painful site/s in the mouth (at least "Face 2 = Hurts little more") on the Wong-Baker FACES pain scale). The painful site has to be large enough to enable recognizing of pain reduction and may not be too large for the amount of gel to be applied. 6. At least 2 of the following signs have to be reported by the legal representative at the screening examination: weeping, crying, grouching, mood swings, changes in behaviour, and increase in body temperature above normal, sleepiness, or sick feeling. Small infants may appear over-sleepy or inactive, be irritable, vomit or feed poorly.
	Exclusion criteria 1. Participation in an investigational trial within 30 days prior to enrolment and for the whole study duration. 2. Any current uncontrolled infection. 3. Inflammatory oral and mucosal disease. 4. Known hypersensitivity to lidocaine or any of the ingredients of Dynexan® Mundgel (benzalkonium chloride, aromatic oil, galactomanan, glycerol, paraffin, saccharin sodium, silicon dioxide, thymol, titanium dioxide, vaseline). 5. Known pronounced allergic disposition. 6. Acute severe systemic disease or poor general health. 7. Severe generalized infection. 8. Acute strong febrile states. 9. Subjects with earache, or other painful situations. 10. Teething subjects with cleft palate. 11. Subjects with known history of instable diseases (diabetes, heart failures, etc.), consuming diseases (cancer), heritage diseases, or liver or renal insufficiency. 12. Any chronic or acute condition including the mucosa and skin, susceptible, in the opinion of the investigator, of interfering with the evaluation of the drug effect. 13. Subject with any of the following: • Known Ehlers-Danlos syndrome • Known Attention Deficit Hyperactivity (ADHD) 14. Systemic intake of pain relievers within 8 hours prior to enrolment and for the whole study duration. 15. Any local acting (mouth cavity) medication, including over the counter products and dietary supplements such as iodine, fluoride, or vitamins, which would interfere with study results, within 8 hours before and during the study course. 16. Subjects who are placed in an institution due to a judicial or official directive.

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Synopsis (continued)	
Test product:	Dynexan® Mundgel (provided by Chemische Fabrik Kreussler & Co GmbH)
Dose:	Single local application of maximum 0.2 g gel or 4 mg lidocaine hydrochloride, corresponding to a pea size amount of gel
Mode of administration:	A thin layer of the respective IMP was applied to the painful site/s
Batch number:	01421
Duration of treatment:	Single application of the test treatment, observation time 24 hours after treatment
Reference therapy:	Placebo gel (provided by Chemische Fabrik Kreussler & Co GmbH)
Dose:	Single local application of maximum 0.2 g gel, corresponding to a pea size amount of gel
Mode of administration:	A thin layer of the respective IMP was applied to the painful site/s
Batch number:	09021
Duration of treatment:	Single application of the placebo treatment, observation time 24 hours after treatment
Criteria for evaluation:	
Efficacy:	Primary • Statistics for pain as self-assessed (T1 –T2) via ordinal Wong-Baker FACES Pain Rating Scale, description of difference between active treatment and placebo by HL-estimate incl. 95%-CI, result of nonparametric test (Mann-Whitneys U-Test) testing null hypothesis of no difference in distributions (assessment by children was used, whenever valid) Secondary • Statistics for pain as self-assessed (T1-T3) via ordinal Wong-Baker FACES Pain Rating Scale, description of difference between active treatment and placebo by HL-estimate incl. 95%-CI, result of nonparametric test (Mann-Whitneys U-Test) testing null hypothesis of no difference in distributions (assessment by children was used, whenever valid) • Statistics for pain as assessed via continuously Wong-Baker FACES Pain Rating Scale by parents, description of difference between parents and children's assessment by mean difference incl. 95%-CI, (exploratory) result of parametric test (t-test) • Subject's satisfaction, response with ratings "very satisfied" / "satisfied" out of 5 possible scores) was described by frequencies and percentages (related to number of patients with information), (exploratory) result of 2 – test and Mantel-Haenszel-test stratified by initial Wong-Baker FACES Pain Rating Scale
Safety:	Secondary • local tolerability assessment by the investigator was described by frequencies and percentages (related to number of patients with information). • Adverse events were coded according to MedDRA and evaluated on preferred term (PT) and system organ class level (SOC) with regard to intensity, drug relationship and seriousness.
Statistical methods:	**Analyse-Populations:** **Full Analysis Set (FAS) or Intention- to-treat Analysis Set (ITT)** The FAS consists of all included subjects of the age group I and II, treated with IMP / comparative compound. **Per-protocol population (PP)** The PP population consists of all subjects who completed the study without major protocol deviations. A detailed list of major protocol violations and criteria for excluding subjects from the PP population was finalized prior to database lock. The age groups I and II were evaluated separately.

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Synopsis (continued)	
	Definite exclusion criteria are: • No evaluable pain assessment by parents • Previous, or parallel treatment with pain relievers • Concomitant medication / treatment which may interfere with a reliable assessment of the IMP • Non-compliance of the minor **Safety population / Safety Set (SAF)** All included subjects were analysed into the safety population. The safety population was the primary analysis set for the safety / tolerability analyses. The decision to eliminate a subject of any of the analysis sets based on review of the data prior to database lock. **Evaluation of the efficacy parameters:** This scale was interpreted by applying a numeric scale with values assigned to each of the six facial expressions. The face 0 that depicts a slight smile was scored 0 points. The remaining faces were scored from 1 to 5 points depending upon the severity of the pain depicted by the face. The numeric notation for the faces on the scale was not displayed to the subjects. The primary efficacy endpoint was the absolute percentage reduction of acute pain from T1 to T2 self-rated by the minor or by the legal representative. The reduction in pain from T1 to T2 was evaluated as follows: Score at T2 – Score at T1. Analysis Method: Mean reduction in pain score from T1 to T2 was compared between Dynexan® Mundgel and placebo arm (age group I, only) by appropriate test. Test Null Hypothesis: H_0:µ1 = µ2 where, µ1: mean reduction in Wong-Baker scale from T1 to T2 in Dynexan® Mundgel group. µ2: mean reduction in Wong-Baker scale from T1 to T2 in placebo arm. As statistical method, Mann Whitney's U-test was used. In addition, it was checked whether prerequisites for application of t-test and ANCOVA (for investigation of covariates like centre effects and baseline pain) are given. In case of positive check, these methods were first choice for analysis of null hypothesis. Details are given in a statistical analysis plan (SAP). If a higher reduction was observed in Dynexan® Mundgel group and the null hypothesis H_0 is rejected on 0.05 level, the efficacy of Dynexan® Mundgel in comparison with placebo was demonstrated. The secondary efficacy endpoint was assessed as follow:

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Synopsis (continued)

Assessment of subject's satisfaction (parent's assessment	The guardian of the minor assessed the satisfaction with treatment at 1 h, and 24 h p.a. on a 5-point verbal rating scale: 1 = Very unsatisfied 2 = Somewhat unsatisfied 3 = Slightly satisfied 4 = Satisfied 5 = Very satisfied Frequencies and percentages (related to number of subjects with information) were given for each subject.
Pain reduction from T1 to T3	see primary objectives
Comparison of pain rating (minors vs. parents)	via descriptive statistics

Analysis of covariates:

Centre, gender, age and baseline pain were investigated in analysis of covariates. If centre and baseline pain were significant covariates, the primary outcome was reported by models (ANCOVA) including these variables.

Missing Values:

Missing values for primary variable were imputed according to LOCF rule (last observation carried forward).

Evaluation of the safety parameters:

All subjects who received the test or reference product were included in the safety analysis (safety set). AEs, PTSS, findings in medical examination / medical history, concomitant medication were coded according to MedDRA.

The absolute and relative frequencies of subjects with at least one AE were determined totally within each treatment arm (verum or placebo) and within each treatment period. Summary tables for AEs were structured by treatment and by body system. Additionally, AEs were summarised by seriousness, maximum intensity, and relationship to treatment, start time, duration and countermeasures taken. PTSS were summarised by intensity.

All data and results were presented in statistical summary tables and individual subject data listings. Continuous variables (e.g. vital signs: pulse rate, respiration rate and body temperature) were summarised using standard descriptive sample statistics (number of observations, arithmetic mean, standard deviation, minimum, median and maximum for quantitative variables). Categorical data (e.g. tolerability) were described using absolute and relative frequencies.

Due to the short treatment duration, the topical administration (associated with a low risk of systemic availability) and comprehensive data on the safety profile of the active substance, laboratory safety tests were not performed.

Furthermore the following data was evaluated for the safety set:

Local tolerability assessment of the application site, assessed by the investigator	The investigator will assess the local treatment tolerability on the application site at 1 h, and 24 h p.a. 1 = poor local tolerability 2 = moderate local tolerability 3 = good local tolerability 4 = very good local tolerability Frequencies and percentages (related to number of subjects with information) were given for each score as well as for the combined score "very good" / "good".

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Synopsis (continued)	
Summary – conclusion:	
Demographics:	In total, 162 subjects gave their informed consent to the study (one re-screened subject with two informed consent forms). One subject was classified as a screening failure, due to an inappropriate pain rating at screening. Therefore data from 161 subjects were included and all analyses were done, using the same population pool (ITT=PP=SAF). In age group I 129 subjects (verum N=63, placebo N=66) and in age group II (all verum N=32) were treated with Dynexan® Mundgel or placebo. There were 70 male and 91 female subjects included in the study. In age group I 54 male (verum N=30, placebo N=24) and 75 female subjects (verum N=33, placebo N=42) were included. In age group II 16 male and 16 female subjects (all verum) were included. The average age in the study was 5.5 ± 2.3 years (mean ± SD), ranging from 0.5 to 8.9 years. In age group I the average age was 6.4 ± 1.4 years, ranging from 4.0 to 8.9 years. In age group II the mean average age was 1.8 ± 0.9 years, ranging from 0.5 to 4.0 years. One-hundred and fifty-nine subjects (159) subjects were Caucasian, one subject was Black and one subject had a latvian-korean ethnic origin. The mean body weight in age group I was 24.3 ± 6.3 kg, ranging from 11.4 kg to 56.2 kg. The mean body weight in age group II was 11.7 ± 2.5 kg, ranging from 8.4 kg to 16.9 kg. The mean body height in age group I was 122.7 ± 9.0 cm, ranging from 98 cm to 146 cm. The mean body height in age group II was 84.0 ± 10.6 cm, ranging from 68 cm to 100 cm. <u>Description of painful sites:</u> **Number:** One-hundred and twelve (112) out of 161 subjects (69.6%) had only one painful site of the mouth. In age group I 101 subjects had one painful site (verum N=54, placebo N=47). Twenty-seven (27) subjects had between 2 and 5 painful sites (verum N=9, placebo N=18). Only one subject had more than 5 painful sites. In age group II 11 subjects had one, 18 subjects had between 2 and 5 and 3 subjects had more than 5 painful sites. **Average size:** In age group I the mean average size was similar in the verum (19.3 ± 19.1 mm^2) and the placebo (19.1 ± 10.4 mm^2) group. In age group II the mean size of the painful sites was slightly greater (23.1 ± 17.2 mm^2) than in age group I. **Location:** In total 189 locations were affected by pain (age group I 151 locations, age group II 38 locations). The gingiva and / or oral mucosa was affected in 140 cases in age group I (92.7%) and in 31 cases in age group II (81.6%). The mucosa of the lips or the tongue was more often affected in age group II (18.4%) than in age group I (7.3%). **Symptoms of indisposition of the child:** All 161 subjects in both age groups reported two or more indisposition signs. The parents in age group I often reported grouching (20.2%), changes in behaviour (24.1%) and a poorly feeding (26.0%), whereas in age group II weeping (14.2%), crying (13.5%), grouching (18.4%) and sleepiness (18.4%) were reported. **Cause:** In age group I aphthous ulcer (36.0%) was the main cause of painful sites (verum 40.0%, placebo 31.9%). In age group II teething (63.6%) was the main cause of painful sites.

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Synopsis (continued)	
	Previous painful sites: In age group I 76 (58.9%) subjects (; verum N=37, placebo N=39) and in age group II 20 (62.5%) subjects had no previous painful sites. Thirty (46.2%) out of 65 subjects had treated previous painful sites (age group I 41.5%, age group II 66.7%). Medical history: Sixty-eight (68) out of 161 subjects (42.2%) reported one or more findings in medical history (age group I 61, verum N=29, placebo N=32; age group II N=7). In age group I 11 subjects treated with verum and 12 subjects treated with placebo had more than 2 findings in medical history. In age group II no subject had more than 2 medical findings. No finding in medical history was reported for 93 (57.8%) out of 161 subjects. Frequent medical findings of the immune system (20.2%) and surgical and medical procedures (29.2%) were reported. Medical treatment prior to study: In total, 123 subjects (76.4%) reported no medical treatment one week before or during the study. Before inclusion of the patients the investigator ensured that no prohibited concomitant medication was used by the subjects. Particularly no systemic or local medication for pain relief (e.g. NSAR, paracetamol) and local drugs for treatment of the painful site were taken within 8 hours prior to enrolment. Indeed, 25 subjects (15.5%, age group I N=15; age group II N=10, verum N=16, placebo N=9) reported a concomitant medication prior to study due to an underlying diseases or a PTSS, in total 31 medications. For 5 subjects (age group I N=4; age group II N=1, verum N=4, placebo N=1) a medication was reported with a start and stop date at the day of administration. None of these medications was taken 8 hours before enrolment or during visit 1. Consequently, the intake was in accordance with the protocol and the pain rating was not influenced by this medications. General behaviour at screening: The most often assessed category was “distress” with 41 (25.5%) subjects (verum N=27, placebo N=14) followed by “playing” (N=17 (10.6% out of 161)), “laughing” (N=16 (9.9% out of 161) and “crying” (N=10 (6.2% out of 161)). 67.7% of subjects (additionally) contributed free-text entries related to general behaviour by answering category “other”. The most “other” descriptions of the general behaviour was “quiet” in 106 (97.3%) out of 109 subjects. Screening pain score: Most parents (93, 57.8%) stated a screening pain score of 3 “hurts even more”.

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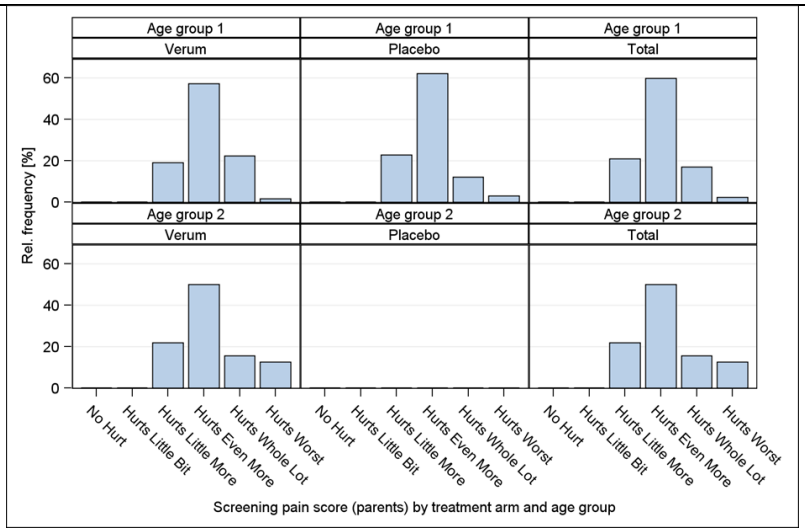
Synopsis (continued)	
	 **F 1: Screening pain score (parents) by treatment arm and age group** <u>Subject's ability for pain rating:</u> The subject's ability assessment results in: 113 (87.6%) age group I subjects with a valid pain rating. Additionally subject 31 of age group II had an advanced intellectual maturity, therefore the subject was deemed able to rate the pain by himself. Nine subjects in age group I were not able to rate their pain properly. For another 7 subjects of age group I the test could not be finished (e.g. unwillingness or lack of concentration of the child, lack of both validation ratings). In these cases the ratings of the parents were used for analysis of the primary parameter.
Efficacy results:	**<u>Primary efficacy parameter:</u>** The primary efficacy parameter was calculated for age group I, then in 129 subjects. The self-rating by the children was used in 107 cases (verum: 53 cases, placebo: 54 cases) at time T1 and in 109 cases (verum: 57 cases, placebo: 52 cases) at time T2. The assessments by parents were used in 22 cases at time T1 and in 20 cases at time T2. The mean pain score at baseline was 3.0 for the verum arm vs. 2.6 for the placebo arm. Ten minutes after treatment the pain score dropped to 1.0 for verum, and to 1.3 for placebo.

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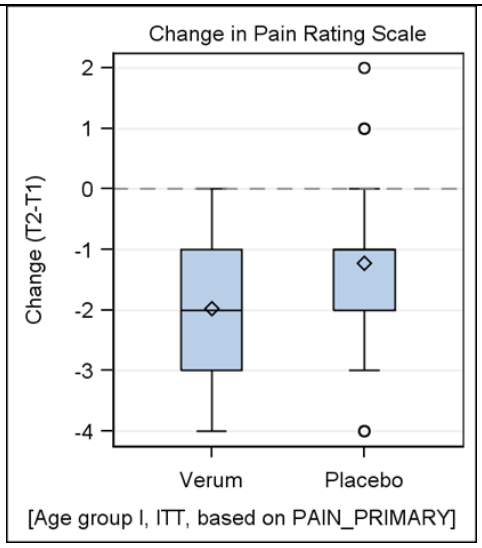
Synopsis (continued)



F 2: Boxplot related to difference T2-T1 of Wong-Baker FACES Pain Rating Scale assessments by treatment (age group I)

T 1: Difference T2-T1 in pain assessments by treatment (age group I)

Difference in pain assessment (T2-T1)	Verum	Placebo	Total
N	63	66	129
N(missing)	0	0	0
Mean	-2.0	-1.2	-1.6
StdDev	1.1	1.1	1.2
StdErr	0.1	0.1	0.1
Median	-2	-1	-1
25%P	-3	-2	-2
75%P	-1	-1	-1
Min	-4	-4	-4
Max	0	2	2

Non-parametric analysis (application of Mann Whitney U (MWU)-Test) of treatment related difference in pain assessment yielded statistically significance (p-value<0.001) of observed effect.

In order to assess the robustness of primary objective, sensitivity analyses have been performed. In scenario I (parents' assessment scenario) nonparametric statistical test does not yield statistical significance at α=0.05 level (p-value=0.054), whereas in minors' assessment scenario II statistical significance is shown (p-value=0.009), as it has been observed for primary objective. Scenario III (random assignment scenario) 75.8% (N=758) out of 1000 random sampling runs resulted in statistically significant finding in favour of verum arm.

The analysis of covariates showed a statistically significant treatment effect (related p-value=0.0208) in favour of the verum arm. In addition, baseline pain assessment was found to be statistically significant (p-value<0.0001). Within all calculated models, treatment arm and baseline pain assessment remained statistically significant whereas neither "age" nor "gender" were found to be statistically significant covariates in any considered model.

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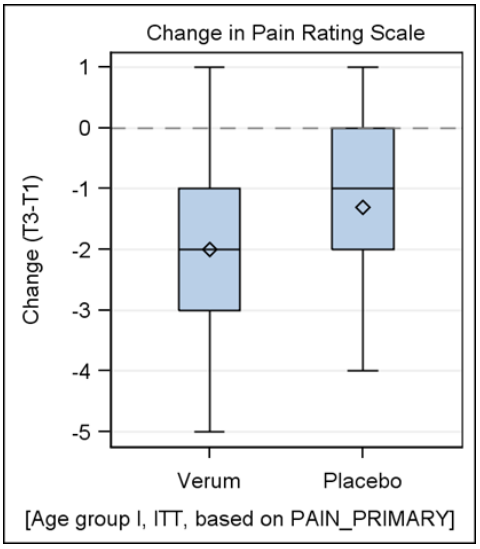
Synopsis (continued)

Secondary efficacy parameters:

Change of pain rating from T1 to T3

Change of pain rating from T1 to T3 was calculated for age group I, then in 129 subjects. The self-rating by the children was used in 107 cases (verum: 53 cases, placebo: 54 cases) at time T1 and in 108 cases (verum: 56 cases, placebo: 52 cases) at time T3. The assessments by parents were used in 22 cases at time T1 and in 21 cases at time T3.

The mean pain score at baseline was 3.0 for the verum arm vs. 2.6 for the placebo arm. Thirty minutes after treatment the pain score dropped to 1.0 for verum, and to 1.3 for placebo.



F 3: Boxplot related to difference T3-T1 of Wong-Baker FACES Pain Rating Scale assessments by treatment (age group I)

T 2: Difference in pain assessments T3-T1 by treatment (age group I)

Difference in pain assessment (T3-T1)	Verum	Placebo	Total
N	63	66	129
N(missing)	0	0	0
Mean	-2.0	-1.3	-1.6
StdDev	1.3	1.2	1.3
StdErr	0.2	0.1	0.1
Median	-2	-1	-2
25%P	-3	-2	-3
75%P	-1	0	-1
Min	-5	-4	-5
Max	1	1	1

The non-parametric analysis (application of Mann Whitney U (MWU)-Test) of treatment related difference in pain assessment yielded a statistically significance (p-value=0.002) of the observed effect.

Comparison of parents' and minors' pain rating

On average children rated their pain slightly lower than their parents. The evaluation was performed using signed rank test and corresponding p-values.

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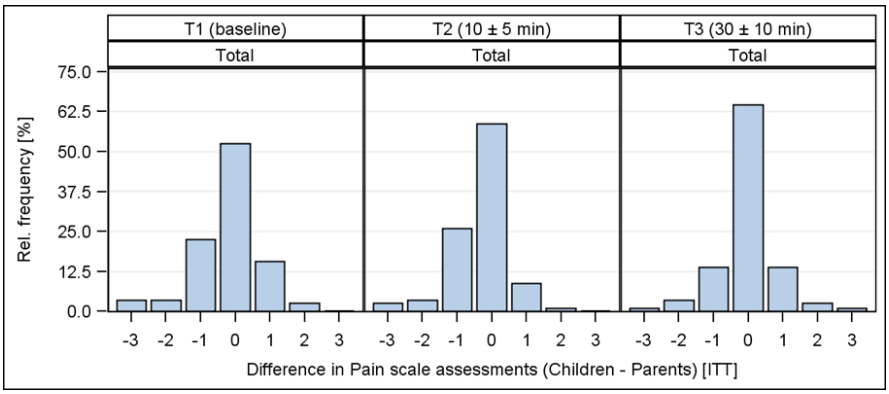
Synopsis (continued)

For T1 the mean difference between minors' and parents was -0.2 (Total: p-value=0.0467, verum arm p-value=0.9793, placebo arm p-value=0.0016).

For T2 the mean difference between minors' and parents was -0.3 (Total: p-value<0.0001; verum: p-value=0.0042; placebo: p-value=0.0060).

For T3 there was no mean difference between minors' and parents (Total: p-value=0.8076; verum: p-value=0.3257; placebo: p-value=0.5301).



F 4: Differences between parents and minors' assessment of primary variable, by time point, summarized over treatment arms (age group I only)

Subject's satisfaction

Within both treatment arms, "very satisfied" was the most often chosen answer. Within age group II (verum only) all assessments were either "very satisfied" or "satisfied". There were two age group I subjects (verum N=1, placebo N=1) where parents rated "very unsatisfied", 5 age group I (verum N=3, placebo N=2) subjects with "Somewhat unsatisfied" category assigned and additional 5 subjects (verum N=0, placebo N=5) where satisfaction has been assessed as "slightly satisfied".

T 3: Subjects satisfaction 1h after administration

Subjects satisfaction	Verum				Placebo		Total (both age groups)		Total (age group I)	
	Age groups I and II		Age groups I only							
	N	%	N	%	N	%	N	%	N	%
Very unsatisfied	1	1.1	1	1.6	1	1.5	2	1.2	2	1.6
Somewhat unsatisfied	3	3.2	3	4.8	2	3.0	5	3.1	5	3.9
Slightly satisfied	0	0.0	0	0.0	5	7.6	5	3.1	5	3.9
Satisfied	29	30.5	21	33.3	19	28.8	48	29.8	40	31.0
Very satisfied	62	65.3	38	60.3	39	59.1	101	62.7	77	59.7
Total	95	100	63	100	66	100	161	100	129	100

Safety results:

PTSS/AE:

Prior to the study drug administration 21 out of 161 subjects (13.0%) reported a PTSS (SAF). In total 24 PTSS were reported. 16 subjects (verum N=9, placebo N=7) in age group I reported 19 PTSS. In age group II 5 PTSS were recorded for 5 subjects (verum). For 12 subjects a concomitant medication due to PTSS was listed.

One (1) PTSS, a common cold of subject 56, age group II worsened after study drug intake and therefore changed into an AE (MedDRA LLT: bronchitis). The AE of moderate intensity was not related to the study drug. The AE resolved completely after the study.

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Synopsis (continued)

After administration of the study drug, 7 out of 161 subjects (4.3%) reported at one AE (4 subjects age group I, verum N=2, placebo N=2; 3 subjects age group II (verum). In total, none of the AEs were classified as study drug related according to the classification defined in protocol. Five (5) AEs had a mild and 2 had a moderate intensity. There were two subjects who reported the use of medication during the study (after first study drug administration) due to AEs. All 7 subjects (100% out of 7) have been categorized as being recovered at the end of the study.

No SAE was reported during the study.

Vital signs:

No clinically relevant changes in vital signs and physical parameters related to safety were observed between visit 1 and visit 2 considering mean values.

Physical examination

157 out of 161 subjects (97.5%) had a normal physical examination at the post study examination (verum N=92, placebo N=65). Only four subjects (verum N=3, placebo N=1) had an abnormal physical examination at visit 2 due to an AE.

T 4: Physical examination by treatment arm

Physical examination assessment		Verum		Placebo		Total	
		N	%	N	%	N	%
V1 (screening)	Normal	82	86.3	61	92.4	143	88.8
	Abnormal	13	13.7	5	7.6	18	11.2
	Total	95	100	66	100	161	100
Visit 2	Normal	92	96.8	65	98.5	157	97.5
	Abnormal	3	3.2	1	1.5	4	2.5
	Total	95	100	66	100	161	100

General well-being

The questioning on general well-being has been answered with “yes” for all assessments at any visit.

Local tolerability:

For most subjects (V1: 97.5%; V2: 98.1%) the tolerability has been rated ”very good” at both times. No treatment related differences can be assessed based on the counts observed.

T 5: Local tolerability (investigator’s assessment) by time and by treatment arm

Local tolerability assessment (investigator)		Verum				Placebo		Total (both age groups)		Total (age group I)	
		Age groups I and II		Age groups I only							
		N	%	N	%	N	%	N	%	N	%
V1	Poor	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Moderate	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Good	2	2.1	0	0.0	2	3.0	4	2.5	2	1.6
	Very good	93	97.9	63	100	64	97.0	157	97.5	127	98.4
	Total	95	100	63	100	66	100	161	100	129	100
V2	Poor	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Moderate	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Good	3	3.2	0	0.0	0	0.0	3	1.9	0	0.0
	Very good	92	96.8	63	100	66	100	158	98.1	129	100
	Total	95	100	63	100	66	100	161	100	129	100

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Synopsis (continued)	
Conclusions:	**Efficacy:** The primary aim of the study, to show superiority of treatment with verum compared to treatment with placebo in children from 4 to 8 years of age (age group I) is achieved. Evaluation of the primary endpoint based on pain assessment by child, if child's pain assessment was evaluated as reliable. If not, instead of child's assessment pain assessment by parents was used. Null hypothesis, pain reduction from T1 (prior to administration) to T2 (10 ± 5 min p.a.) is equal in both treatment arms, was rejected on α=0.05 level (p-value<0.001; Mann-Whitney U test). Additionally, a more intensive pain reduction with active treatment compared to placebo could be demonstrated. The baseline pain, which has been rated as 3 (median) in both treatment arms, was reduced by an amount of 2 scale-items in verum and 1 scale-item in placebo arm, indicating a treatment related effect in favour of verum. For the analysis of the efficacy parameters the minors' assessments were used in case of reliable children's ratings. The primary endpoint related analysis of covariates (ANCOVA) in pain reduction from T1 to T2 evaluation showed a statistically significant treatment effect (p-value=0.0208) and a statistically significant baseline pain assessment (p-value<0.0001). Further potentially relevant covariates "age" and "gender" were not found to be statistically significant in any of the considered models. Three sensitivity analysis scenarios were performed in order to assess the robustness of the primary objective. In scenario I, the non-parametric statistical test does not yield statistical significance at α=0.05 level (p-value=0.054), whereas in minors' assessment scenario II a statistical significance is shown (p-value=0.009). In scenario III 75.8% (N=758) out of 1000 random sampling runs resulted in a statistically significant finding in favour of verum arm. According to study protocol three secondary efficacy parameters were analysed. Also the result of the secondary objective, the difference in pain reduction from T1 (prior to administration) to T3 (30 ± 10 min p.a.), between verum and placebo arm was statistically significant (p-value=0.002; Mann-Whitney U test). The baseline pain, which has been rated as 3 (median) in both treatment arms, was reduced by an amount of 2 scale-items in verum and 1 scale-item in placebo arm, indicating a treatment related effect in favour of verum, as has been observed in primary analysis. The secondary endpoint related analysis of covariates (ANCOVA) in pain reduction from T1 to T3 evaluation showed a stable but not statistically significant treatment effect. The baseline pain assessment remained a highly statistically significant covariate in each model considered (p-values: <0.0001). Neither "age" nor "gender" effects were found to be statistically significant covariates, which is in accordance to primary analysis covariates assessment. The analysis of differences between parents' and minors' pain assessment (secondary objective, age group I only) showed an average (median) difference of "0" item scores consistently observed across treatments and time points. Individual assessment of pain between parents and children show a considerable range with observed differences of up to 3 scale items. The comparison of parents' and minors' pain rating showed that children rated their pain on average slightly lower than their parents. For T1 minors assessed a lower mean pain category compared to their parents (verum arm no statistical significance, placebo arm p-value=0.0016). For T2 minors assessed a lower mean pain category compared to their parents (verum arm p-value=0.0042, placebo arm p-value=0.0060). For T3 minors assessed the same pain category as their parents

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Synopsis (continued)	
	(verum and placebo arm no statistical significance). For subject's satisfaction the parents' assessment after 1h after administration has been rated. Most subjects could be classified as being "satisfied" or "very satisfied". The difference between the treatment arms did not reach statistical significance at α=0.05 level (p-value=0.060, χ^2-test). But the kind of binary categorization "satisfied Yes/No" tends to yield a higher proportion of verum arm subjects showing satisfaction. **Safety:** Dynexan® Mundgel can be considered as safe. No relevant changes in vital signs or physical examination were observed during the study. Seven out of 161 subjects (4.4%) reported in total 7 AEs. In age group I 2 AEs in verum and 2 AEs in placebo arm were reported. In age group II 3 AEs in verum subjects were reported. None of the AEs were assessed as study drug related (6 "not related", 1 "unlikely"). Five out of 7 AEs were classified as mild and 2 AEs were classified as moderate. Two subjects reported a concomitant medication during the study due to an AE. All AEs resolved completely until the end of the study. No adverse event was assessed as serious, as an unexpected adverse drug reaction or other as a clinically significant adverse event. The local tolerability has been rated for most subjects as "very good" one hour as well as 24 hours after treatment. No relevant differences between verum and placebo tolerability could be observed. In this study no laboratory safety tests were performed, due to the short treatment duration, the topical administration (associated with a low risk of systemic availability) and comprehensive data on the safety profile of the active substance. Subsuming the results of the safety evaluation, Dynexan® Mundgel can be evaluated as safe in paediatric groups, especially in minors from 6 month of age. **Discussion:** This randomised, placebo-controlled, double-blind comparative study was designed to evaluate the efficacy and safety of Dynexan® Mundgel in minors from 6 months to 8 years with acute painful sites of the mouth. In total 162 subjects (including one re-screened subject) with acute painful sites were included in this study, of which 161 were randomised and received study medication. The study population was divided in age group I (subjects ≥ 4 to 8 years) and age group II (subjects from 6 months to 3 years). Only age group I was placebo-controlled, and verum and placebo were approximately equally distributed. All study procedures were highly standardised and performed in accordance with the clinical trial protocol and the GCP regulations. Only minor deviations from the clinical trial protocol occurred, none of them was judged clinically relevant. No subject has been excluded from the analysis due to protocol deviations. The Wong-Baker FACES Pain Rating Scale for children and their parents was used in this study to evaluate pain. Compared to the treatment with placebo, the application of Dynexan® Mundgel resulted in a statistically significant higher pain reduction during the observation time of 30 minutes (T1 to T2 p-value < 0.001 and T1 to T3 p-value = 0.002). If only the parents' pain assessment was used for evaluation of the primary analysis instead of the minors' assessment the primary endpoint of the study was not achieved (no statistical significance, p-value = 0.054). If only the minors' assessment

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Synopsis (continued)	
	was used (unreliable/missing minors' assessment are taken into account instead of being replaced by parents' assessment), the primary endpoint of the study reached statistical significance (p-value=0.009). Paediatric pain measures are essential for determining the effectiveness of pain management. For parents it is sometimes difficult to assess the true degree of pain the child is experiencing and get a valid parents' rating. Many parents are unaware of the pain experienced by their children [19]. On average in our study parents rated the pain of their children slightly higher. Nevertheless the comparison of parents' and minors' assessment in this study showed an average (median) difference of "0" item scores across treatments and time points. The individual assessment of pain between parents and children showed a considerable range with observed differences of up to 3 scale items. A systematic review of faces scales for the self-report of pain intensity in children [20] had shown that children preferred the Wong-Baker FACES Pain Rating Scale. For the results obtained from the present study no inconsistencies between related measures were observed. The active ingredient lidocaine hydrochloride is a well-known pain reliever and the local tolerability was assessed as "very good" or "good" in all subjects in this study. The subject's satisfaction could be classified in most subjects as "very satisfied" or "satisfied". Within the course of the study no Serious Adverse Events occurred. No drug related AE was observed. There were no new or unexpected findings observed or reported during the course of the study, respectively. The risk-benefit relationship stated prior to the conduct of the present study was not affected by the obtained results.

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