

**Clinical trial results:**

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.

Summary

EudraCT number	2011-005336-25
Trial protocol	DE
Global end of trial date	04 July 2014

Results information

Result version number	v2 (current)
This version publication date	02 February 2016
First version publication date	15 May 2015
Version creation reason	• Correction of full data set Correction of "Routes of Administration" for IMP 2 (Placebo Gel)
Summary attachment (see zip file)	Clinical Study Report Synopsis (Synopsis_ISR_11ctam29dy_V01_2014-10-10.pdf)

Trial information**Trial identification**

Sponsor protocol code	DMKS-2011
-----------------------	-----------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Study Code CRO: 11ct/am29dy

Notes:

Sponsors

Sponsor organisation name	Chemische Fabrik Kreussler & Co. GmbH
Sponsor organisation address	Rheingaustraße 87-93, Wiesbaden, Germany, 65203
Public contact	Medical-Scientific Director, Kreussler Pharma Medical Scientific Department, 49 611 9271-0, info@kreussler.com
Scientific contact	Medical-Scientific Director, Kreussler Pharma Medical Scientific Department, 49 611 9271-0, info@kreussler.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 July 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 June 2014
Global end of trial reached?	Yes
Global end of trial date	04 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is the comparison of pain reduction after local application of Dynexan® Mundgel or placebo on painful sites in the mouth.

Protection of trial subjects:

The Guidelines of the World Medical Association Declaration of Helsinki 2013, the Guidelines of ICH Good Clinical Practice (GCP) (CPMP/ICH/135/95) as well as the requirements of national drug and data protection laws, and other applicable regulatory requirements were strictly followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 161
Worldwide total number of subjects	161
EEA total number of subjects	161

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	21
Children (2-11 years)	140
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0

Subject disposition

Recruitment

Recruitment details:

The first patient was included into the trial on 21.05.2012 and the last patient completed the trial on 14.06.2014. Posters, flyers as well as newspaper advertisements were used to recruit the patients and all recruitment materials were submitted to the Independent Ethics Committee for approval prior to use.

Pre-assignment

Screening details:

To find a pool of eligible subjects, 269 subjects were pre-screened by telephone, out of which 195 presented themselves at the study centre. In case of 33 patients it was obvious even before any investigations started that these patients could not pass the inclusion/exclusion criteria. In summary 161 individual subjects were included in the study.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Age Group II was treated with verum only.

Arms

Are arms mutually exclusive?	Yes
Arm title	Age Group I Verum

Arm description:

Minors from 4 years to 8 years

Arm type	Experimental
Investigational medicinal product name	Dynexan Mundgel
Investigational medicinal product code	IMP 1
Other name	
Pharmaceutical forms	Oral gel
Routes of administration	Topical use

Dosage and administration details:

Single local application of 0.2 g gel, corresponding to a pea size amount of gel

Arm title	Age Group I Placebo
------------------	---------------------

Arm description:

Minors from 4 years to 8 years

Arm type	Placebo
Investigational medicinal product name	Placebo Gel
Investigational medicinal product code	IMP 2
Other name	
Pharmaceutical forms	Oral gel
Routes of administration	Topical use

Dosage and administration details:

Single local application of 0.2 g gel, corresponding to a pea size amount of gel

Arm title	Age Group II
------------------	--------------

Arm description:

Minors from 6 months to 3 years

Arm type	Experimental
----------	--------------

Investigational medicinal product name	Dynexan Mundgel
Investigational medicinal product code	IMP 1
Other name	
Pharmaceutical forms	Oral gel
Routes of administration	Topical use

Dosage and administration details:

Single local application of 0.2 g gel, corresponding to a pea size amount of gel

Number of subjects in period 1	Age Group I Verum	Age Group I Placebo	Age Group II
Started	63	66	32
Completed	63	66	32

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial
-----------------------	---------------

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	161	161	
Age categorical			
Minors from 4 years to 8 years			
Units: Subjects			
Age group I 4 - 8 Years	129	129	
Age group II 6 months - 3 years	32	32	
Gender categorical			
Units: Subjects			
Female	91	91	
Male	70	70	

End points

End points reporting groups

Reporting group title	Age Group I Verum
Reporting group description: Minors from 4 years to 8 years	
Reporting group title	Age Group I Placebo
Reporting group description: Minors from 4 years to 8 years	
Reporting group title	Age Group II
Reporting group description: Minors from 6 months to 3 years	

Primary: Pain reduction from T1 (prior to administration) to T2

End point title	Pain reduction from T1 (prior to administration) to T2 ^[1]
End point description: The Wong-Baker FACES Pain Rating Scale is a self-report measure used to assess the intensity of children's pain. The minors were instructed to indicate their pain by pointing to one of the faces (0 No Hurt; 1 Hurts Little Bit; 2 Hurts Little More; 3 Hurts Even More; 4 Hurts Whole Lot; 5 Hurts Worst). Pain assessment using Wong-Baker FACES Pain Rating Scale was performed in children from 4 years on. Assessment by parents was done prior to assessment by the children. If the child was not old enough and/or not able to use this scale instead of child's assessment, the pain assessment by parents was used.	
End point type	Primary
End point timeframe: Pain reduction from T1 (prior to administration) to T2 (10 ± 5 min p.a.)	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Age Group II (aged < 4 years) subjects were all treated with verum, there was no control group. In order to assess the efficacy, individual pain rating shifts (before treatment - after treatment) have been evaluated. The Wilcoxon signed rank test has been applied in order to assess statistical significance of change in an explorative manner.

End point values	Age Group I Verum	Age Group I Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	66		
Units: Wong-Baker FACES Pain Rating Scale				
median (full range (min-max))	-2 (-4 to 0)	-1 (-4 to 2)		

Statistical analyses

Statistical analysis title	Mann Whitney U-Test
Statistical analysis description: MWU-Test of Treatment related difference in pain assessment	
Comparison groups	Age Group I Verum v Age Group I Placebo

Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [2]
Method	Wilcoxon (Mann-Whitney)

Notes:

[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 the observed effect.

Secondary: Pain reduction from T1 (prior to administration) to T3

End point title	Pain reduction from T1 (prior to administration) to T3 ^[3]
-----------------	---

End point description:

The Wong-Baker FACES Pain Rating Scale is a self-report measure used to assess the intensity of children's pain. The minors were instructed to indicate their pain by pointing to one of the faces (0 No Hurt; 1 Hurts Little Bit; 2 Hurts Little More; 3 Hurts Even More; 4 Hurts Whole Lot; 5 Hurts Worst). Pain assessment using Wong-Baker FACES Pain Rating Scale was performed in children from 4 years on. Assessment by parents was done prior to assessment by the children. If the child was not old enough and/or not able to use this scale instead of child's assessment, the pain assessment by parents was used.

End point type	Secondary
----------------	-----------

End point timeframe:

Pain reduction from T1 (prior to administration) to T3 (30 ± 10 min p.a.)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Age Group II (aged < 4 years) subjects were all treated with verum, there was no control group. In order to assess the efficacy, individual pain rating shifts (before treatment - after treatment) have been evaluated. The Wilcoxon signed rank test has been applied in order to assess statistical significance of change in an explorative manner.

End point values	Age Group I Verum	Age Group I Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	66		
Units: Wong-Baker FACES Pain Rating Scale				
median (full range (min-max))	-2 (-5 to 1)	-1 (-4 to 1)		

Statistical analyses

Statistical analysis title	Mann Whitney U-Test
Comparison groups	Age Group I Verum v Age Group I Placebo
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.002 [4]
Method	Wilcoxon (Mann-Whitney)

Notes:

[4] - 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.

Secondary: Comparison of children's and parent's assessment, whenever both ratings are eligible

End point title	Comparison of children's and parent's assessment, whenever
-----------------	--

End point description:

At times T1, T2 and T3 for N=115 subjects Wong-Baker FACES Pain Rating Scale assessments of minors and parents were available for evaluation of differences.

An average (median) difference of "0" item scores (difference between assessment of parent and child) was 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. On average children rated their pain slightly lower than their parents.

End point type

Secondary

End point timeframe:

T1, T2 and T3

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: There was only one age group II subject with available minor's assessment, where T1, T2 and T3 related minors' assessments were in accordance to parents' assessments.

End point values	Age Group I Verum	Age Group I Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	56		
Units: Wong-Baker FACES Pain Rating Scale				
median (full range (min-max))				
T1	0 (-3 to 2)	0 (-3 to 1)		
T2	0 (-3 to 2)	0 (-3 to 1)		
T3	0 (-3 to 3)	0 (-2 to 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of subject's satisfaction (parent's assessment) as rated on a 5-point verbal rating scale

End point title

Assessment of subject's satisfaction (parent's assessment) as rated on a 5-point verbal rating scale

End point description:

Assessment of subject's satisfaction (parent's assessment) as rated on a 5-point verbal rating scale:

1. Very unsatisfied
2. Somewhat unsatisfied
3. Slightly satisfied
4. Satisfied
5. Very satisfied

End point type

Secondary

End point timeframe:

Subject's satisfaction was assessed by parents 1 hour after administration on a 5 point verbal rating scale.

End point values	Age Group I Verum	Age Group I Placebo	Age Group II	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	63	66	32	
Units: 5 point verbal rating scale				
Very unsatisfied	1	1	0	
Somewhat unsatisfied	3	2	0	
Slightly unsatisfied	0	5	0	
Satisfied	21	19	8	
Very satisfied	38	39	24	

Statistical analyses

Statistical analysis title	Subject Satisfaction Differences: Verum/Placebo
Statistical analysis description:	
Binary categorization of subject satisfaction: Yes/No	
Comparison groups	Age Group I Verum v Age Group I Placebo v Age Group II
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.06 [6]
Method	Chi-squared

Notes:

[6] - Observed differences compared to placebo arm did not reach a statistical significance at $\alpha=0.05$ level (χ^2 -Test including age group II subjects: p-value=0.060)

Secondary: Characterisation of safety and tolerability of the investigational product considering Adverse Events in the study population, descriptive evaluation.

End point title	Characterisation of safety and tolerability of the investigational product considering Adverse Events in the study population, descriptive evaluation.
-----------------	--

End point description:

7 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.

End point type	Secondary
End point timeframe:	
Study Duration	

End point values	Age Group I Verum	Age Group I Placebo	Age Group II	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	63	66	32	
Units: Adverse events	2	2	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of local tolerability by the investigator

End point title	Assessment of local tolerability by the investigator
-----------------	--

End point description:

Assessment of local tolerability by the investigator (descriptive evaluation):

1. Poor
2. Moderate
3. Good
4. Very Good

End point type	Secondary
----------------	-----------

End point timeframe:

The local tolerability (secondary objective) has been assessed by the investigator with a 4-point verbal rating scale 1h after administration of IMP.

End point values	Age Group I Verum	Age Group I Placebo	Age Group II	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	63	66	32	
Units: 4 point verbal rating scale				
Poor	0	0	0	
Moderate	0	0	0	
Good	0	2	2	
Very good	63	64	30	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

21.05.2012 - 14.06.2014

Adverse event reporting additional description:

7 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.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	17.0
--------------------	------

Reporting groups

Reporting group title	Age Group II
-----------------------	--------------

Reporting group description:

Minors from 6 months to 3 years

Reporting group title	Age Group I Placebo
-----------------------	---------------------

Reporting group description:

Minors from 4 years to 8 years

Reporting group title	Age Group I Verum
-----------------------	-------------------

Reporting group description:

Minors from 4 years to 8 years

Serious adverse events	Age Group II	Age Group I Placebo	Age Group I Verum
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 32 (0.00%)	0 / 66 (0.00%)	0 / 63 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Age Group II	Age Group I Placebo	Age Group I Verum
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 32 (9.38%)	2 / 66 (3.03%)	2 / 63 (3.17%)
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 32 (3.13%)	0 / 66 (0.00%)	0 / 63 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			

subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	0 / 66 (0.00%) 0	1 / 63 (1.59%) 1
Oral pain subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 66 (1.52%) 1	0 / 63 (0.00%) 0
Mouth injury subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	0 / 66 (0.00%) 0	1 / 63 (1.59%) 1
Respiratory, thoracic and mediastinal disorders Bronchitis subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	0 / 66 (0.00%) 0	0 / 63 (0.00%) 0
Skin and subcutaneous tissue disorders Excoriation subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 66 (1.52%) 1	0 / 63 (0.00%) 0
Infections and infestations Hand-foot-and-mouth disease subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	0 / 66 (0.00%) 0	0 / 63 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported