Clinical trial results:
Efficacy of DC071 mouthwash (0,2 % chlorhexidine digluconate) in peri-surgical care for preventing alveolar osteitis after third molar extraction. Prospective, multicenter, randomised, double-blind, placebo controlled study in parallel groups

Summary

EudraCT number	2014-004682-24
Trial protocol	EE LV LT FR ES
Global end of trial date	17 February 2016

Results information

Result version number	v1 (current)
This version publication date	30 November 2018
First version publication date	30 November 2018

Trial information

Trial identification

Sponsor protocol code	DC0071BB405

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pierre Fabre Medicament
Sponsor organisation address	45 Place Abel Gance, Boulogne, France, 92100
Public contact	Centre de Recherche et Développement Pierre Fabre, Karim KEDDAD, MD, +33 (0)534506250, karim.keddad@pierre-fabre.com
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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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 February 2016
Global end of trial reached?	Yes
Global end of trial date	17 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy of chlorhexidine mouthwash in the prevention of alveolar osteitis following third molar extraction.

Protection of trial subjects:

The study was conducted according to Good Clinical Practice (GCP) (CPMP/ICH/135/95), the principles stated in the Declaration of Helsinki (1964) and its subsequent amendments thereto, and national regulations.
The request for authorization by the Competent Authority or its notification (depending on National Régulations) was carried out by the Sponsor.
The study protocol and related documents, including the informed consent forms (ICFs), were submitted for approval to independent, local or national Independent Ethics Committees (IECs) and to competent authorities (CAs) before the study set-up, according to national regulations.

Background therapy:

In the context of management of post-surgical care, the following medications were to be systematically prescribed to limit post-operative oedema and pain:
•Corticosteroids and level-2 analgesics (tramadol or paracetamol associated with codeine) were to be prescribed at a fixed dose during the first 48 hours post-surgery and progressively reduced over the subsequent 48 hours.

Evidence for comparator:

Alveolar osteitis (AO), or dry socket, is one of the most common postoperative complications following the extraction or surgical removal of a tooth. It is defined as postoperative pain inside and around the extraction site, which increases in severity at any time between the first and third day after extraction, accompanied by a partial or total disintegrated blood clot within the alveolar socket, with or without halitosis.
Antibacterial agents have been reported to reduce the incidence of AO and CHX digluconate is the most commonly used in dentistry and its efficacy has been widely validated. The use of a placebo was medically acceptable because all patients were followed by the investigator, informed that they may receive a placebo, and treated appropriately if needed

Actual start date of recruitment	30 January 2015
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	Estonia: 131
Country: Number of subjects enrolled	France: 72
Country: Number of subjects enrolled	Latvia: 103
Country: Number of subjects enrolled	Lithuania: 103

Worldwide total number of subjects	409
EEA total number of subjects	409

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)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	409
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 414 patients requiring an impacted mandibular third molar extraction were selected/enrolled, 413 of them randomised (206 patients in the DC071 group and 207 in the placebo group) and 409 were treated. 41 centres in 4 countries (France, Estonia, Lithuania and Latvia) were initiated, of which, 33 were active (selected at least 1 patient).

Pre-assignment

Screening details:

A total of 417 patients were screened for study participation and signed an ICF. Of these, 3 patients were not enrolled (could not commit to the study agenda, consent withdrawal) and 1 patient was enrolled but not randomised. Women were included in the last week of their menstrual cycle in order to perform surgery with lower oestrogen level.

Period 1

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

Blinding implementation details:

A randomisation list was established by the Clinical Pharmacy Department of the IRPF. This list was computer-generated with validated internal software. The randomisation methodology was validated by the Biometry Department of IRPF before generation. DC071 and placebo were formulated in mouthwash solutions identical in presentation (same size, same colour).

Arms

Are arms mutually exclusive?	Yes
Arm title	DC071

Arm description:

206 patients were randomised in the DC071 arm for seven days (Day -1 to Day 6). Of the 206 randomised patients, 203 of them received at least one dose treatment and 188 patients completed the treatment phase.

Arm type	Experimental
Investigational medicinal product name	DC071
Investigational medicinal product code	
Other name	Chlorhexidine digluconate 0.2%
Pharmaceutical forms	Mouthwash
Routes of administration	Buccal use

Dosage and administration details:

The DC071 mouthwashes (0.2% CHX digluconate) were ready for use and were to be used pure and undiluted. The teeth were to be brushed prior to each use and the mouth then rinsed thoroughly with water before using the mouthwash.
Patients rinsed with 10 mL for 1 min twice daily (in the morning and evening) for 7 days (Day -1 to Day 6).
Patients began taking the mouthwash treatment the day prior (Day -1) to surgical extraction of the mandibular third molar (Visit 3, Day 1). On the day of the surgery (Day 1), the mouthwash treatment was performed in the morning just before the start of surgery (at the investigational centre) and in the evening (with a passive rinsing).

Arm title	Placebo

Arm description:

207 patients were randomised in the Placebo arm for seven days (Day -1 to Day 6). Of the 207 randomised patients, 206 of them received at least one dose treatment and 185 patients completed the treatment phase.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Mouthwash
Routes of administration	Buccal use

Dosage and administration details:

The placebo mouthwashes were ready for use and were to be used pure and undiluted. The teeth were to be brushed prior to each use and the mouth then rinsed thoroughly with water before using the mouthwash.
Patients rinsed with 10 mL for 1 min twice daily (in the morning and evening) for 7 days (Day -1 to Day 6).
Patients began taking the mouthwash treatment the day prior (Day -1) to surgical extraction of the mandibular third molar (Visit 3, Day 1). On the day of the surgery (Day 1), the mouthwash treatment was performed in the morning just before the start of surgery (at the investigational centre) and in the evening (with a passive rinsing).

Number of subjects in period 1	DC071	Placebo
Started	203	206
Completed	188	185
Not completed	15	21
Consent withdrawn by subject	-	1
Adverse event, non-fatal	-	3
Personal reason	1	1
Lost to follow-up	2	-
Lack of efficacy	12	16

Baseline characteristics

Reporting groups	
Reporting group title	DC071
Reporting group description:	
206 patients were randomised in the DC071 arm for seven days (Day -1 to Day 6). Of the 206 randomised patients, 203 of them received at least one dose treatment and 188 patients completed the treatment phase.	
Reporting group title	Placebo
Reporting group description:	
207 patients were randomised in the Placebo arm for seven days (Day -1 to Day 6). Of the 207 randomised patients, 206 of them received at least one dose treatment and 185 patients completed the treatment phase.	

Reporting group values	DC071	Placebo	Total
Number of subjects	203	206	409
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	203	206	409
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Age at first study drug intake			
Units: years			
median	26	26	
inter-quartile range (Q1-Q3)	22 to 31	22 to 30	-
Gender categorical Units: Subjects			
Female	120	87	207
Male	83	119	202
Regular smoker Units: Subjects			
Yes	37	43	80
No	166	163	329
Number of cigarettes per day Units: number			
median	5	7	
inter-quartile range (Q1-Q3)	4 to 10	5 to 10	-

End points

End points reporting groups

Reporting group title	DC071

Reporting group description:

206 patients were randomised in the DC071 arm for seven days (Day -1 to Day 6). Of the 206 randomised patients, 203 of them received at least one dose treatment and 188 patients completed the treatment phase.

Reporting group title	Placebo

Reporting group description:

207 patients were randomised in the Placebo arm for seven days (Day -1 to Day 6). Of the 207 randomised patients, 206 of them received at least one dose treatment and 185 patients completed the treatment phase.

Primary: Absence of an alveolar osteitis

End point title	Absence of an alveolar osteitis

End point description:

The primary efficacy criterion was binary (success/failure) and was evaluated based on the absence/presence of an AO (alveolitis sicca, dry socket) within 7 days after the extraction of the third molar. A treatment failure was defined as the occurrence of an AO within 7 days after the extraction of the third molar.

End point type	Primary

End point timeframe:

The presence of Alveolar osteitis was recorded within 7 days following extraction of the third mandibular molar.

End point values	DC071	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	205		
Units: not applicable				
number (not applicable)				
Success	174	165		
Failure	26	40		

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

The objective was to test the equality of the proportion between DC071 and placebo (primary hypothesis [H0]: pDC071 = pplacebo against the alternative H1: pDC071 ≠ pplacebo).
The number of patients in failure was compared between DC071 and placebo, on the FAS, using a logistic regression adjusted for treatment, centre and smoker (Yes/No) and with the method of Firth's penalised likelihood. The Odds Ratio (OR) and the corresponding 95% Wald CI were provided as a measure of the treatment effect.

Comparison groups	DC071 v Placebo

Number of subjects included in analysis	405
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.074
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from the enrollment of patients to the end of study visit (Day 8 or Day 9 exceptionally)

Adverse event reporting additional description:

At each visit, the occurrence of AEs since the last visit was determined by the patient's spontaneous reporting, the investigator's non-leading questioning and his/her clinical evaluation. The occurrence of Alveolar Osteitis and any related signs (pain, halitosis, swelling, etc.) were not reported as AEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	DC071

Reporting group description: -

Reporting group title	Placebo

Reporting group description: -

Serious adverse events	DC071	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 203 (0.00%)	2 / 206 (0.97%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 203 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess jaw			
subjects affected / exposed	0 / 203 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.5 %

Non-serious adverse events	DC071	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 203 (15.27%)	33 / 206 (16.02%)	
Injury, poisoning and procedural complications			
Postoperative wound complication			
subjects affected / exposed	10 / 203 (4.93%)	12 / 206 (5.83%)	
occurrences (all)	10	12	
Post procedural swelling			
subjects affected / exposed	8 / 203 (3.94%)	9 / 206 (4.37%)	
occurrences (all)	8	9	
Post procedural oedema			
subjects affected / exposed	7 / 203 (3.45%)	6 / 206 (2.91%)	
occurrences (all)	7	6	
Procedural pain			
subjects affected / exposed	7 / 203 (3.45%)	9 / 206 (4.37%)	
occurrences (all)	7	9	
Overdose			
subjects affected / exposed	2 / 203 (0.99%)	0 / 206 (0.00%)	
occurrences (all)	2	0	
Post procedural complication			
subjects affected / exposed	2 / 203 (0.99%)	2 / 206 (0.97%)	
occurrences (all)	2	2	
Procedural haemorrhage			
subjects affected / exposed	0 / 203 (0.00%)	1 / 206 (0.49%)	
occurrences (all)	0	1	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 203 (0.00%)	1 / 206 (0.49%)	
occurrences (all)	0	1	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	3 / 203 (1.48%)	0 / 206 (0.00%)	
occurrences (all)	3	0	
Syncope			
subjects affected / exposed	0 / 203 (0.00%)	1 / 206 (0.49%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			

Ear pain			
subjects affected / exposed	0 / 203 (0.00%)	1 / 206 (0.49%)	
occurrences (all)	0	1	
Social circumstances			
Poor personal hygiene			
subjects affected / exposed	0 / 203 (0.00%)	1 / 206 (0.49%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Oral pruritus			
subjects affected / exposed	3 / 203 (1.48%)	0 / 206 (0.00%)	
occurrences (all)	3	0	
Tongue discolouration			
subjects affected / exposed	3 / 203 (1.48%)	0 / 206 (0.00%)	
occurrences (all)	3	0	
Tooth discolouration			
subjects affected / exposed	2 / 203 (0.99%)	0 / 206 (0.00%)	
occurrences (all)	2	0	
Gingival erythema			
subjects affected / exposed	1 / 203 (0.49%)	0 / 206 (0.00%)	
occurrences (all)	1	0	
Glossitis			
subjects affected / exposed	1 / 203 (0.49%)	0 / 206 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 203 (0.49%)	0 / 206 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 203 (0.99%)	2 / 206 (0.97%)	
occurrences (all)	2	2	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 203 (0.00%)	1 / 206 (0.49%)	
occurrences (all)	0	1	
Infections and infestations			

Post procedural cellulitis			
subjects affected / exposed	1 / 203 (0.49%)	0 / 206 (0.00%)	
occurrences (all)	1	0	
Post procedural infection			
subjects affected / exposed	1 / 203 (0.49%)	0 / 206 (0.00%)	
occurrences (all)	1	0	
Abscess jaw			
subjects affected / exposed	0 / 203 (0.00%)	1 / 206 (0.49%)	
occurrences (all)	0	1	
Abscess oral			
subjects affected / exposed	0 / 203 (0.00%)	1 / 206 (0.49%)	
occurrences (all)	0	1	
Alveolar osteitis			
subjects affected / exposed	0 / 203 (0.00%)	1 / 206 (0.49%)	
occurrences (all)	0	1	
Tooth abscess			
subjects affected / exposed	0 / 203 (0.00%)	1 / 206 (0.49%)	
occurrences (all)	0	1	

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