1. TITLE PAGE

Clinical Study Report

POSTOPERATIVE CARE BY A CHLORHEXIDINE MOUTHWASH AFTER PERIODONTAL SURGERY.

Randomised, parallel groups, blind study, DC071BB *versus* placebo, in patients presenting with periodontal surgery with suture

Protocol n°:	DC0071 BB 404 8b
Investigational product	DC071 BB 08b Mouthwash, chlorhexidine 0.1%
Date of first enrolment:	23 November 2005
Date of last completed:	03 June 2006
Date of the report:	04 June 2007
Coordinating Investigator:	Pr. Henri TENENBAUM
Eudract number	2005-000869-20

Study performed in compliance with Good Clinical Practice

2. SYNOPSIS

Name of Company: PIERRE FABRE MEDICAMENT **Name of finished product**: Chlorhexidine digluconate 0.1%, mouthwash solution **Name of active substance**: Chlorhexidine digluconate	TABULAR FORMAT Referring to Part IV of the Dossier Volume: Page:	*(For National Authority Use only)*

Title of the study:
Postoperative care by a chlorhexidine mouthwash after periodontal surgery.
Randomised, parallels groups, blind study, DC071BB *versus* placebo, in patients presenting with periodontal surgery with suture.

Coordinating Investigator:
Pr. H. TENENBAUM, D.D.S., Ph. D., Faculty of Dental Surgery, 4, rue Kirschleiger, 67000 – Strasbourg, France.

Study centres:
11 dental centres in: Estonia (2 centres), France (2 centres), Latvia (1 centre), Poland (2 centres), Romania (2 centres), Spain (2 centres).

Publication: None at the time of writing this report.

Study period:	**Clinical Phase:**
date of first enrolment: 23 November 2005 date of last completed: 03 June 2006	Phase IV in France Phase III in Estonia, Latvia, Poland, Romania, Spain

Objectives:
Main objective:
To assess the efficacy of DC071 BB 08b mouthwash for controlling the evolution of Plaque Index in peri-surgical area during the post-operative period.
Secondary objectives:
To evaluate the patient's satisfaction and the investigator's global judgement during the post-operative period.
To evaluate the suture healing.
To document the local and general tolerance.

Methodology:
This was a multicentre, international, randomised, placebo-controlled, blind study on two parallel groups involving a one-week treatment with either DC071 BB 08b or placebo.
Patients were recruited at the Dental Departments at the time of planning of dental surgery with suture. Treatment allocation was made at random. After surgery, patients had to make two mouthwashes per day for 7 days. The study involved two visits on Day 1 (inclusion) and Day 8 (end of treatment) and possibly a third visit between Day 10 and Day 21 if healing was not complete at Day 8.

Number of patients:
A sample of 200 patients was projected for the study. 201 patients were screened and 199 were included and randomised to treatment.

Diagnosis and main criteria for inclusion:
Inclusion criteria:
Were eligible patients (male or female) who met the following criteria:
- age over 18 years inclusive,
- regular user of manual toothbrush (at least once a day),
- who had a periodontitis,
- who had a periodontal surgery (flap, debridment with access flap, complicated tooth extraction, alveolectomy) with a gingival suture or several sutures on the same area, concerning one or several teeth,
- willing and able to understand and sign an approved Informed Consent Form,
- able to understand the protocol and to attend the control visits,
- registered with a social security system.

For women of child bearing potential: - use of an efficient contraceptive method.

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Diagnosis and main criteria for inclusion: (continued)

Non-inclusion criteria:

Criteria related to pathologies:

.dental surgery such as grafting of bone substitute material, membrane, gingivectomy, uncomplicated tooth extraction, scaling-root planing alone
.concomitant surgical procedure on different area of the mouth
.any surgery that required an antibiotic cover during or after the surgery
.more than 2 teeth missing between the suture and an existing tooth
.medical history of major medical or psychiatric illness or surgery which, in the judgement of the investigator, put the patient 'at risk' or was liable to modify the patient's handling of study treatment
.severe acute or chronic systemic disease or disorder that might interfere with the treatment or study assessments
.any coagulation disorder
.any buccal disorder which might interfere with the treatment or study assessments (hyposalivation or asialia, aphta, ulceration, lichen planus, stomatitis).

Criteria related to treatments:

- use of local antiseptics (mouthwash) within the 7 previous days,
- use of antibiotics (any route of administration) within the 7 previous days,
- use of any anticoagulant treatment,
- history of hypersensitivity (abnormal drug reaction or idiosyncrasy) to chlorhexidine**,** chlorobutanol or other ingredients in the solutions,
- start or change within the preceding month of any drug which could interfere with salivary flow: anticholinergic drug, atropine, scopolamine, quaternary ammoniums, imipraminic antidepressives, sedative antihistamines, phenothiazines neuroleptics, disopyramide,
- treatment with any other topical product (i.e. mouthwashes, gels…) that could interfere with the study treatment.

Criteria related to the population:

- smokers,
- participation to another clinical trial in the previous month or during the study,
- patient who, in the judgement of the investigator was not likely to be compliant during the study,
- patient who was unwilling to give a written informed consent,
- patient who had forfeited his freedom by administrative or legal award, or who is under guardianship,
- subject who could not be contacted in case of emergency.

For women:

- pregnancy or breast feeding.

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Test product, dose, and method of administration, batch number(s):

DC071 BB 08b mouthwash solution containing chlorhexidine digluconate 0.10%, twice a day, 7 days.
Patients brushed their teeth, excepted the peri-surgical area, in a usual manner.
Treatments were done at least 10 minutes after tooth wash and after a mouth rinse with water.
A mouthwash contained 15 mL of solution and the cup was filled up with water to the upper level.
The mouthwash was used divided in two rinses of 30 seconds each.
Batch number(s): SB0240

A toothbrush (15/100^{e}) and a non antiseptic toothpaste (Elgydium junior) was provided to the patients.
A toothbrush (7/100^{e}) was provided to the patients at the last visit to brush smoothly the surgical site after the end of treatment (D8).

Reference therapy, dose and mode of administration, batch number(s):

Placebo: mouthwash solution matched by appearance to the test solution.
A mouthwash contained 15 mL of solution and the cup was filled up with water to the upper level.
Batch number(s): SB0239

Duration of treatment:

After surgery, patients were to make two mouthwashes per day 1 mouthwash (two rinses of 30 seconds each) for 7 days, starting in the evening of the surgery day (Day 1) and ending in the morning of Day 8.

Criteria for evaluation:

Efficacy measurements:

- plaque accumulation in the perisurgical area was measured using the 4-point Pl I (Plaque Index: absence of dental plaque/film of plaque not visible by the naked eye/moderate accumulation/abundance of dental plaque) of Silness & Löe (1964)

The primary efficacy criterion was the mean of changes in measurements performed at:

6 sites per non-extracted tooth concerned by the surgery
plus the 2 distal sites for the mesial tooth and 2 mesial sites for the distal tooth (if the teeth were in the same sector and not the teeth 11, 21, 31 or 41)
or plus the 2 mesial sites for the distal and the mesial teeth (if the teeth were in the same sector and involved the teeth 11, 21 31 or 41) or the 2 mesial sites for the distal tooth (if the teeth were in two different sectors)

- healing was measured using the 3-point epithelialisation score (good/moderate/poor epithelialisation) of Sanz (1989)
- investigator's judgement on post-surgery evolution was assessed globally according to a 4-point scale (not satisfying/quite not satisfying/quite satisfying/very satisfying) and also when considering the surgical suture quality (cleanness, coalescence), suture healing (absent/partial/almost complete/complete), and gum inflammation (no/little/important residual redness and oedema)
- patient's satisfaction according to a 4-point scale (not satisfying/quite not satisfying/quite satisfying/very satisfying).

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Safety measurements:

General safety and tolerability:

- record of all adverse events (AEs) spontaneously reported, elicited through general questioning, or observed by the investigators: nature (signs, symptoms, diagnosis), intensity (mild/moderate/ severe), times of onset and end, seriousness, actions taken and outcome
- physical examination at Day 1 and Day 8.

Local tolerability:

- patients' comments and mouth examination (evaluation of erythema, oedema, ulceration and mucosal colouration according to a 3-point scale—mild/moderate/severe)
- tooth discoloration: tooth staining according to the 4-point scale (no/slight yellowish colouration/ moderate brownish discoloration/heavy brown and black discoloration) (mean value on all teeth) of Brecx (1993).

Statistical methods:

The APT population was defined as all randomised patients who had made at least one mouthwash with the study medication and for whom the main criterion was available.

The PP population was defined as all patients in the APT population without any major deviation.

The safety population was defined as all patients who had made at least one mouthwash with the study medication.

Patient characteristics at baseline were compared between treatment groups by an ANOVA with treatment and centre effects for quantitative variables, and by the Cochran-Mantel-Haenszel test with adjustment for centres for qualitative variables (with modified ridit scores in the case of ordinal variables).

Analysis of the primary efficacy criterion:

due to non-normality of study quantitative variables, the mean of changes in Pl I between Day 1 and Day 8 was analyzed by a non-parametric ANCOVA adjusted on the baseline value and stratified by centre; the main analysis was conducted on the APT population and a supportive analysis on the PP population; additional analyses were performed using an ANCOVA adjusted on the number of sites evaluated and stratified by centre, on the whole population and on the population of patients with at least 10 sites evaluated.

Analysis of the secondary efficacy criteria:

Treatments were compared using a Cochran-Mantel-Haenszel test for qualitative variables with modified ridit scores to allow for the ordinal nature of the criteria.

Analysis of safety criteria:

The number and percentage of patients with AEs were tabulated by system-organ class and preferred term according to the MedDRA classification.

The evolution of the tooth Discoloration Index was analyzed in the same fashion as Pl I on the population of patients with data available at both Day 1 and Day 8.

For mouth examination, the numbers of patients with abnormal signs improving, worsening or remaining unchanged between Day 1 and Day 8 have been tabulated by treatment group.

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SUMMARY – CONCLUSIONS

Study progress:
201 patients were screened, 199 were included and randomised to DC071 BB 08b (98 patients) or placebo (101 patients). 1 patient in the placebo group withdrew (for personal reasons) before Visit 2 (Day 8) and 2 patients of the DC071 BB 08b group (lost to follow-up, patient's decision) between Visit 2 and Visit 3. There was a total of 62 major deviations (mainly insufficient tooth cleaning after surgery—38 patients—which prevented adequate evaluation of the change in PI I during treatment, and/or incorrect evaluation of the primary efficacy criterion). The APT population consisted of 192 patients (DC071 BB 08b: 96; placebo: 96) and the PP population of 142 patients (71 and 71, respectively).

Patient characteristics:
There was no notable difference between patient groups at baseline in demography and physical characteristics, social habits (tobacco and alcohol consumption) and dental hygiene habits, except for a higher proportion of never smokers among the patients treated with DC071 BB 08b. History of periodontitis, medical and surgical history, and type of periodontal surgery were all comparable between the two patient groups. Analysis of concomitant treatments during the treatment period indicated a somewhat greater consumption of analgesics and non-steroidal anti-inflammatory drugs by the patients receiving placebo compared to/with patients treated with DC071 BB 08b.
PI I at baseline was higher in the APT population than in the PP population but comparable between the two treatment groups. The Discoloration Index was also comparable between groups at baseline. At baseline mouth examination, more patients in the DC071 BB 08b group than the placebo group showed mild mucosal or moderate mucosal colouration ($p<0.01$) and more of them had mild oedema (NS).

EFFICACY RESULTS:
.Primary efficacy variable:
The increase in PI/I from Day 1 to Day 8 in the APT population (main analysis) was significantly lower in the group of patients treated with DC071 BB 08b than in the group of patients who received placebo.

	DC071 BB 08b	Placebo	
APT population	0.42±0.48	0.58±0.64	p=0.017
PP population	0.53±0.43	0.71±0.59	p=0.053

In the PP population (supportive analysis), the between-group difference was very close to statistical significance, in favour of DC071 BB 08b.

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Efficacy results (continued):

An ANCOVA analysis allowing for centre, number of sites assessed at both Day 1 and Day 8 and treatment effects indicated a significant centre effect and a treatment effect in favour of DC071 BB 08b close to statistical significance (p=0.052).

The same analysis in the subset of patients with at least 10 sites evaluated at both Day 1 and Day 8 (159 patients) showed a significant difference in favour of DC071 BB 08b (p=0.033).

Analysis of treatment efficacy by type of surgery indicated efficacy of DC071 BB 08b over placebo in every type of surgery (debridement with access flap, complicated tooth extraction, other types of surgery) except flap alone.

.Secondary efficacy variables:

Post-surgery assessments at Day 8 (suture quality, healing, inflammation, epithelialisation score) showed a significant effect of DC071 BB 08b over placebo for suture cleanness (p=0.018 and p=0.012 in the APT and PP populations, respectively). More patients treated with DC071 BB 08b than receiving placebo exhibited complete healing and good epithelialisation (between-group differences not significant).

Based on these observations, overall investigator's judgement on the treatment was significantly in favour of DC071 BB 08b (p<0.001 in both the APT and PP populations). However, there was no significant between-group difference in patients' satisfaction.

Altogether, these results confirmed the better efficacy of DC0071BB08b and the interest of the use of this mouthwash solution after periodontal surgery: lower plaque accumulation, cleanness of the suture, good healing and epithelialisation of the buccal mucosa membrane.

SAFETY RESULTS:

A total of 199 patients used the study mouthwash at least once. Mean duration of treatment was 7.2±0.6 days. The incidence of AEs was lower in the group of patients treated with DC071 BB 08b than in the placebo group.

Patients with at least:	DC071 BB 08b	Placebo
one AE	9 (9.2%)	13 (12.9%)
one AE related to treatment	4 (4.1%)	4 (4.0%)
one serious AE	0 (0.0%)	0 (0.0%)
one AE leading to treatment discontinuation	0 (0.0%)	0 (0.0%)

Most AEs concerned the oral cavity and were linked to the disease and/or the surgical operation (oral pain, mouth ulceration, stomatitis). Some of these AEs were considered related to treatment (4 patients in each treatment group). Impaired healing and suture infection at Day 8 were noted only in the placebo group. Most AEs were of mild or moderate intensity. The 2 AEs of severe intensity (headache, allergic rhinitis in the DC071 BB 08b group) were not deemed related to treatment.

Tooth discoloration, a commonly reported untoward effect of chlorhexidine treatment, was not observed in this study: the change from baseline in tooth colouration was very slight after 7 days of treatment and similar with DC071 BB 08b and placebo.

Mouth examination at Day 8 indicated no change from baseline in most patients, but fewer increases and more frequent improvements in buccal abnormalities (erythema, oedema, ulceration, mucosal coloration) in the group of patients treated with DC071 BB 08b compared to/with placebo.

CONCLUSION:

Study results show that DC071 BB 08b mouthwash containing 0.10% chlorhexidine is effective at reducing plaque accumulation and safe and well tolerated in patients with periodontitis undergoing surgery. It reduces plaque accumulation and appears to exert favourable effects on suture cleanness, healing and epithelialisation. After 7 days of treatment, DC071 BB 08b produces no visible tooth staining and no more AEs or local intolerance than placebo.

Date of the report: 04 June 2007