Pierre Fabre Médicament
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1. TITLE PAGE

ABBREVIATED CLINICAL STUDY REPORT

"Effect of treatment with ossein-hydroxyapatite compound on the time of fracture-healing". A prospective, multicenter, double-blind, randomised, placebo controlled clinical trial.

Investigational product: L0006 CP / Ossein-hydroxyapatite compound / 830-mg film-coated tablets

EudraCT number: 2010-020973-18

Protocol number: L00006 CP 405

Phase of development: Phase IV

Date of first enrolment: 17 April 2011

Date of last completed: 20 June 2012

Coordinating Investigator: Prof. Stanislaw POMIANOWSKI, orthopaedist, Klinika Chirurgii Urazowej Narządu Ruchu i Ortopedii CMKP Samodzielny, Publiczny Szpital Kliniczny, im. Prof. Adama Grucy, ul. Konarskiego 13, 05-400 Otwock, Poland

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Date of report: 29 April 2013

Study performed in compliance with Good Clinical Practice.

2. SYNOPSIS

Name of Company: Pierre Fabre Médicament	**Individual Study Table**	**(For National Authority Use Only)**
Name of finished product: OSTEOGENON®	**Referring to Module 5 of the Dossier**	
Name of active substance *(or ingredient)***: ossein hydroxyapatite**	**Vol.: .....Page: .....**	

Title of study:	"Effect of treatment with ossein-hydroxyapatite compound on the time of fracture-healing". A prospective, multicenter, double-blind, randomised, placebo controlled clinical trial.	
Coordinating Investigator:	Prof. Stanislaw POMIANOWSKI, orthopaedist, Klinika Chirurgii Urazowej Narządu Ruchu i Ortopedii CMKP Samodzielny, Publiczny Szpital Kliniczny, im. Prof. Adama Grucy, ul. Konarskiego 13, 05-400 Otwock, Poland	
Study centre(s):	9 Polish centres	
Publication (reference):	Not applicable	
Studied period *(years, months …)***:** **(date of first enrolment)** **(date of last completed)**	date of first enrolment: 17 April 2011 date of last completed: 20 June 2012	**Phase of development:** Phase IV
Objectives: **Primary:** **Secondary:**	Main objective of the study was to compare the effect of a treatment with ossein-hydroxyapatite compound (L0006CP) versus a placebo on the time of fracture-healing in patients with a wrist fracture Secondary objectives were: • to assess the effect of the product on: o the functional improvement of upper limb, o the reduction of the time of return to normal function, • to evaluate safety and tolerability.	
Methodology:	This was a prospective, randomised, double-blind, placebo-controlled, parallel group, multicenter study.	
Number of patients (planned and analysed):	Planned: 90. Screened: 59. Included and randomised: 58. Treated: 57. Analysed for efficacy: 54.	
Diagnosis and main criteria for inclusion:	Inclusion criteria: • male or menopausal female (amenorrhea ≥6 months) between 50 and 80 years of age • patient with a recent (<48 hours) closed Colles' fracture (AO/ASIF type A2), correctly reduced and stabilised with Kirschner wires • patient willing, able to understand and sign an approved Informed Consent Form, • patient able to understand the protocol and to come to the control visits, • patient registered with a social security or health insurance system (if applicable). Non-inclusion criteria: • criteria connected to pathologies: o patient with an open fracture, o patient with a bilateral Colles' fracture or multiple concurrent fractures or injuries, o patient with fracture, which may require a surgical treatment during the study treatment,	

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Diagnosis and main criteria for inclusion:

- patient having had a fracture of the upper limb or a prolonged immobilization during the 12 months preceding the inclusion,
- patient having had a functional impairment of the hand or the forearm before injury,
- patient with a pathological fractures related to cancer,
- patient with hereditary bone disease,
- patient with bone necrosis,
- patient with chronic renal failure or chronic kidney disease or history of renal calculi,
- patient with history of calcium metabolism disorders (hypercalcemia, hypocalcemia…).

- criteria connected to previous or concomitant treatment:
  - patient receiving or having received treatment by chemotherapy, radiotherapy, immunosuppressive or systemic steroid treatment within 6 months prior to the inclusion visit,
  - patient receiving or expected to receive during the course of the study any medication (other than study medication) which might alter bone metabolism: calcium and phosphate preparations, calcitonin, hormone replacement therapy, anabolic agents, parathormone, heparins (long term treatment), barbiturates, hydantoin, insulin, thiazides,
  - patient with a known allergy to the study medication or one of its constituents,
  - patient requiring regular or intermittent steroid therapy.
- criteria connected to the study population:
  - patient with a body mass index (BMI) greater than 34,
  - patient with generalized rheumatic disease (rheumatoid arthritis, osteoarthritis…) which could impair severely the joint function of the upper limbs,
  - patient with concomitant disease known to delay the time of fracture-healing such as diabetes, respiratory insufficiency, anaemia, vascular insufficiency, thrombophlebitis…,
  - patient with an inflammatory bowel disease or any digestive disease which could modify calcium absorption,
  - patient with known history of lactose intolerance, hereditary galactose intolerance, the Lapp lactase deficiency or glucose / galactose malabsorption,
  - patient with a severe acute or chronic disease which the Investigator deems incompatible with study implementation,
  - patient with a disease which the Investigator considers likely to interfere with the study results or to expose the patient to additional risk,
  - patient liable not to comply with protocol instructions and/or with treatment, in the Investigator's opinion,
  - patient having taken part in a clinical trial in the preceding 30 days or taking part in a trial at the time of inclusion,

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Diagnosis and main criteria for inclusion:	o patient linguistically or psychologically unable to understand and sign the consent form, o patient who has forfeited his freedom by administrative or legal award, or who is under guardianship.
Test product, **Dose,** **Mode of administration,** **Batch number:**	Ossein-hydroxyapatite compound (Osteogenon®): L0006CP 830-mg film-coated tablets 1 tablet twice daily in the morning and in the evening before or during meal, to be swallowed with a glass of tap water. Batch number: G03600 - expiry date: 07/2015.
Other product, **Dose,** **Mode of administration,** **Batch number:**	Not applicable.
Duration of treatment:	12 weeks.
Reference therapy, **Dose,** **Mode of administration,** **Batch number:**	Placebo: film-coated tablets 1 tablet twice daily in the morning and in the evening before or during meal, to be swallowed with a glass of tap water. Batch number: SB0784 - expiry date: 09/2012.
Criteria for evaluation: **Efficacy:** **Safety:**	Efficacy criteria: • primary efficacy criterion: o time to cortical bridging of three cortices, • secondary efficacy criteria: o time to cortical bridging of 2 and 4 cortices, o time to disappearance of fracture line, o time to full normal activity of daily living involving the target upper limb, o time to full normal activity of daily living without pain, o change from baseline of pain scores while performing daily activities from inclusion to each visit, o value of pain score on palpation / examination of the fracture site at each visit as from Visit 3, o value of DASH score at Visits 4, 5, 6,7 and 8, o value of pain-free hand grip strength score at Visits 4, 5, 6,7 and 8 (as compared to the non-injured hand). Safety criteria: • percentage of patients with at least one adverse event occurring under treatment.
Statistical methods:	Analyses were conducted on the following patients' data sets: • the Full Analysis Set (FAS), which contains the patients having received at least one administration of the product and having at least one evaluation of the primary criterion post administration (as from Visit 3 [week 4]). This data set was used to perform the analysis of efficacy, • the Per-Protocol (PP) data set, which contains the patients of the FAS without any major protocol deviations. This data set was used for the supportive analysis of the primary efficacy criterion,

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Statistical methods:

- the Safety data set, which is composed of all the randomised patients having received at least one administration of the product. This data set was used to perform the analysis of safety.

Description at inclusion was done on the FAS (and PP data set if more than 15% of the FAS were excluded from the PP data set).

Efficacy analyses were conducted as follows:

- Main criterion

The two treatment groups were compared using the Mann-Whitney-Wilcoxon test. Hodges-Lehmann estimates (with their 95 % confidence intervals) were used to describe the distributions of the time to cortical bridging of the three cortices. This analysis was performed both on the FAS and the PP set.

Time to cortical bridging of the three cortices was also described using survival curves according to the Kaplan Meier method. The censoring was the date of the last radiography available. The two treatment groups were compared using the Gehan test, which is the extension of the Wilcoxon test to survival data analysis, on the FAS.

- Secondary criteria

The criteria defined as a time to event was analysed like the main criterion. The other criteria were analysed using a likelihood-based Mixed-effects Model for Repeated Measures (MMRM) to evaluate the global evolution of each criterion over time. The model will include treatment group and visit considered as fixed factors, the baseline value as covariate (if applicable), and the treatment group-by-visit and baseline-by-visit (if applicable) interactions. These analyses were performed only on the FAS.

Regarding safety data, descriptive analysis of the frequency of systemic adverse reactions according to MedDRA classification (last version in use) was performed.

Sample size was calculated based on the assumption that there would be a 4 day-difference in the time to cortical bridging of three cortices between the L0006CP group and the placebo group, the standard-deviation being assumed to be 5. Using a non-parametric test with a two-sided level of significance of 0.05 (5%), the sample size required was 78 patients assessable (39 per group) with a power of 90% for the analysis of the primary criterion on the FAS. Assuming a 15%-rate of not assessable patients, a minimum of 90 patients were to be randomised.

Due to early stop of the study, only 59 subjects were finally screened, 58 of them were randomised and 57 were treated. Taking into account the number of assessable patients (54), the power calculation leads to a power of 77% for the analysis of the primary criterion.

Summary - Conclusions:

Due to patient recruitment issues, the study was terminated early and only 58 patients of the 90 expected were included. Of them, 57 patients were treated and 54 patients were assessable (26 in Placebo group and 28 in L0006CP group).

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Efficacy results

No noticeable difference between the placebo and L0006CP was observed. In particular, and as expected for a reduced sample size, the study failed to demonstrate superiority of L0006CP over placebo in the FAS, as assessed by the reduction in time to cortical bridging of three cortices (see table below). However, the results observed on all the criteria have to be taken with high caution as the actual number of patients included and analysed is too small to allow any clinically relevant conclusion.

		Placebo N=26	**L0006CP N=28**
Cortical bridging of at least three cortices	No	0	1 (3.6%)
	Yes	26 (100.0%)	27 (96.4%)
Time to cortical bridging of at least three cortices (days)*	Mean (SD)	49.7 (7.9)	52.9 (11.3)
	[95% CI]	[46.5;52.8]	[48.6;57.3]
	Median	49.0	51.5
	Min / Max	41 / 72	42 / 100
	Hodges-Lehmann [95% CI]	48.5 [46.0;51.5]	51.0 [48.5;54.0]
	Hodges-Lehmann [95% CI] (L0006CP - Placebo)		2.0 [-1.0;6.0]
	Wilcoxon test		0.147

**For patients with no bridging of three cortices at the end of study, the time has been estimated by two times the median of the time to cortical bridging of the three cortices.*

Safety results

Nine patients (33.3%) experienced at least one AE during treatment with placebo versus seven patients (23.3%) during treatment with L0006CP. Two patients experienced at least one treatment-related or not assessable AE in both groups. One serious AE unrelated to treatment (deep vein thrombosis) and one treatment-related AE leading to patient withdrawal (abdominal pain upper) occurred, both during treatment with the placebo. The safety profiles of placebo and L0006CP were similar, with most AEs concerning the gastrointestinal (8 AEs) and general systems (5 AEs). No related AE was of severe intensity.

There was no noticeable change in mean values of vital signs nor in the results of clinical examination.

Conclusion

This study prematurely stopped due to difficulties to recruit the needed sample size in a reasonable delay (only 58 patients recruited over 12 months) leads to analyse the results only on a small sample size. The analysed sample size was too small to allow any valid or reliable conclusion on the clinical efficacy. Therefore, this study is considered as inconclusive on the efficacy of L0006CP on radiologic fracture healing.

Of note, results from this study clearly showed that the safety profile of L0006CP was comparable to that of placebo.

Date of report

29 April 2013