Pierre Fabre Médicament
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1. TITLE PAGE

CLINICAL STUDY REPORT

Exploratory study of besipirdine efficacy and safety in male patients with persistent stress urinary incontinence after radical prostatectomy

Investigational Product:	HP0749 / besipirdine hydrochloride / 20 mg capsules
Study Design:	Multicentre, randomised, double-blind, cross-over, placebo-controlled study
EudraCT number:	**2009-014049-10**
Protocol Number:	HP0749 GE 2 01
Phase of Development:	II
Date of First Enrolment:	14 December 2009
Date of Last Completed:	12 July 2010
Coordinating Investigator:	Prof François HAAB, Hôpital Tenon, 4 rue de la Chine 75020 PARIS, +33 (0) 1 56 01 64 95
Sponsor Representatives for Study Report:	Program Director: Athmane Bouroubi, IRPF, +33 (0)5 34 50 63 45 Clinical Monitor: Marlène Guiraud, IRPF, +33 (0)5 34 50 63 48 Project Statistician: Mélanie Groc, PFB, +33 (0)5 62 24 27 89 Medical Writer: Agnès Montagne, IRPF, +33 (0)5 34 50 63 50
Date of Report:	07 January 2011

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: Besipirdine	**Referring to Module 5 of the Dossier**	
Name of active substance *(or ingredient)***: besipirdine hydrochloride**	**Vol.: .....Page: .....**	

Title of study:	**Exploratory study of besipirdine efficacy and safety in male patients with persistent stress urinary incontinence after radical prostatectomy**	
Investigators:	8 investigators, specialists in urology or perineal exploration & rehabilitation – Coordinating investigator: Prof Haab – Department of Urological Surgery – Tenon Hospital – 75020 - Paris	
Study Centres:	4 French centres: hospital departments of Urology (Tenon Hospital – Paris), Neurological Rehabilitation & Perineal Exploration (Rothschild Hospital - Paris), or Urology (Rangueil Hospital – Toulouse, Michallon North Hospital – Grenoble).	
Publication:	None	
Study Period: **Date of First Enrolment** **Date of Last Completed**	7 months 14 Dec 2009 12 Jul 2010	**Phase of development: II**
Objectives: **Primary:**	To assess the efficacy of besipirdine (40 mg/day, *bid* administration) compared to placebo in male patients with persistent stress urinary incontinence (SUI) after radical prostatectomy.	
Secondary:	To assess the tolerability of besipirdine (40 mg/day, *bid* administration) compared to placebo in male patients with persistent SUI after radical prostatectomy.	
Methods:	Multicentre, double-blind, placebo-controlled, cross-over, randomised, repeated-dose trial of 13 weeks. After a 2-week single-blind placebo run-in period, patients received either besipirdine (40 mg/day, *bid* administration) or placebo for 4 weeks according to the randomisation schedule. At the end of this 1st comparative double-blind treatment period, patients entered a 2-week single blind placebo wash-out period, followed by the 2nd 4-week comparative double-blind treatment period where they received the study treatment non received during the 1st comparative treatment period. Six visits were planned: a Selection Visit (V1), 14 (± 2) days before the Randomisation Visit (V2), 3 assessment visits (V3 [Day 29], V4 [Day 43], V5 [Day 71] or premature withdrawal [PW]) and an End-of-Study Visit (V6), 7 days (± 1) after V5 / PW.	
Number of Patients	24 randomised patients: 10 in the placebo-besipirdine sequence and 14 in the besipirdine-placebo sequence.	
Diagnosis and Main Criteria for Inclusion:	Male 40-80 year-old patients with SUI persistent for ≥ 1 year after radical prostatectomy (for prostate cancer), stable urinary conditions (*i.e.*, no radiotherapy, start/modification of anti-androgen treatment, or urethral disease within the last 6 months, and no perineal re-education within the last 3 months), and daily urine leakage weight of 10 to 75 g at the 24 h home pad test (averaged over 3 consecutive days within the week preceding the Inclusion Visit).	
Duration of Treatment:	4-week treatment period with besirpirdine alternating with a 4-week placebo treatment period according to a cross-over design (2-week placebo period before each treatment period).	
Test Product, **Dose,** **Mode of Administration,** **Batch Number:**	**Besipirdine 20 mg capsules**, **40 mg/day** (2 capsules/day) during 1st or 2nd treatment period (depending on sequence randomisation) of 28 ± 3 days, *Per os*, *bid* administration: 1 capsule am at breakfast and 1 capsule pm at diner, CFS 230	

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Reference Therapy, Dose,	**Besipirdine placebo capsules**, 2 capsules/day during initial run-in period of 14 ± 2 days, during 1st or 2nd treatment period (depending on sequence randomisation) of 28 ± 3 days, and during wash-out or 2nd run-in period of 14 ± 2 days between both treatment periods,
Mode of Administration, Batch Number:	*Per os*, *bid* administration: 1 capsule am at breakfast and 1 capsule pm at diner, CFS 229
Criteria for Evaluation:	**Efficacy:** - **Primary efficacy criterion:** **Number of complete responders ("dry" patients) on the 24 h home pad test (*)** at V3 and V5, a "dry" patient being defined as a patient with an average 24 h urine leakage weight < 5 g on an assessment clinically validated by the Adjudication Committee(+). - **Secondary efficacy criteria/variables:** • **Daily urine leakage weight on the 24 h home pad test (*)** averaged on the 3 days of assessment, • **Number of 30% and 50% responders on the 24 h home pad test (*)** at V3 and V5, such responders being defined as patients with an average 24 h pad test weight having respectively decreased by [30-50%[and ≥ 50% (excluding "dry" patients) from the baseline of the period considered, • **Clinically Relevant Period Effect on Combined 24-HPT Response and PGIS** (Adjudication Committee (+) assessment), • **Patient Global Impression of Severity (PGIS)**, scored as: Normal/ Mild/ Moderate/ or Severe**)** at V2, V3, V4, and V5, • **Patient Global Impression of Change (PGIC)**, scored as: Very much better/ Much better/ A little better/ No Change/ A little worse/ Much worse/ or Very much worse**)** at V3 and V5 (as compared to V2), (*) the 24 h home pad test was performed by the Patient for 3 consecutive days within the 7 days prior to V2, V3 , V4 and V5 (+) the Adjudication Committee was composed of 4 investigators (including the Study Coordinating Investigator) each representing an Investigating Centre. In case of discrepancies, the Study Coordinating Investigator ruled on the final result. **Safety:** - **Adverse events (AEs)** reported at each visit after 1st study drug intake for the visit itself and the previous inter-visit period, - **Lab tests** in non-fasting conditions at V1, V3 , V4, and V5 / PW: • **Hepatic status**, in serum: ALP, ASAT, ALAT, γGT, LDH (IU/L), total and conjugated bilirubin (µmol/l), • **Renal status** : serum creatinine (µmol/l), - **Physical exam on** each body system at V1, V2, V5 / PW and V6 (final visit), - **Vital signs:** blood pressure (systolic and diastolic [SBP an DBP]) and pulse rate, at each visit from V1, - **ECG** (12 leads) at each visit from V1, - **Concomitant treatments** at each visit from V1.
Statistical Methods (1/2)	**Efficacy.** Descriptive analysis by treatment and period: - for qualitative criteria : n (%) of responses on each treatment - for quantitative criteria : mean, standard deviation, minimum, median and maximum values

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Statistical Methods (2/2)

Safety

Standard descriptive analysis by treatment group:

AEs:

- n (%) of patients: with at least one: AE, treatment-emergent AE (TEAE), serious AE (SAE), AE leading to a study treatment definitive discontinuation,
- n (%) of patients with at least one TEAE by System Organ Class and Preferred Term of MedDRA,
- Tabulated individual data for SAEs and for AEs leading to definitive study treatment discontinuation or change in dose,

Lab Tests:

- n (%) of patients with: i/ potentially clinically significant change (PC), and ii/ PC leading to out-of-range value (PCA),
- Tabulated individual data for clinically noteworthy abnormal lab values (CNALV);

Vital Signs:

- Descriptive statistics for values and changes over time,
- n (%) of patients with: i/ predefined potentially clinically significant changes (SC), ii/ PC leading to predefined potentially clinically significant value (SCV);

ECG: n (%) of patients by CHMP categories of QTc-Bazett and –Fridericia values and changes from baseline;

Concomitant Treatments: Frequencies by WHO-DRUG ATC classes.

Summary – Conclusions (1/2)

Patients

Totals of 36 (male) patients were screened, and 24 (66.7%) patients were randomised (10 into the Placebo-Besipirdine sequence group and 14 into the Besipirdine-Placebo sequence group). All randomised patients received at least one dose of study treatment; 5 of them (20.8%) prematurely withdrew from the study (2 on Placebo for non-inclusion criterion: daily urine leakage weight < 10 g, 3 on besipirdine for safety reason); thus, 19 (79.2%) patients completed the trial (7 [70.0%] in the Placebo-Besipirdine sequence group and 12 [85.7%] in the Besipirdine-Placebo sequence group).

The patient disposition across the different data sets analysed was the following:

	Placebo-Besipirdine 10	**Besipirdine-Placebo** 14	**Total** 24
Safety Set (= treated)	**10**	**14**	**24***
FAS (secondary efficacy analyses)	**9**	**13**	**22**
Completer Set (secondary efficacy analyses)	**7**	**12**	**19**
PP Set (primary and secondary efficacy analyses)	**7**	**8**	**15**

**22 patients in the Placebo group only, and 22 patients in the Besipirdine group only*

Sequence groups were similar for demographics, urological history and co-morbidity. Only the weight and height for demographics were globally higher in the Placebo–Besipirdine group (by ~9 kg and 5 cm, respectively), which had no consequence on the global body mass index (BMI) difference.

In the Safety patients, the mean (SD) 66.7 (6.1) years for age, 26.2 (3.2) kg/m^2 for BMI, and 4 (2.0) years for the SUI duration, were representative of the target population. The most frequent concomitant diseases (> 2 patients) were: erectile dysfunction (10 patients), hypercholesterolaemia (7 patients) and hypertension (6 patients).

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Summary – Conclusions (2/2):

Efficacy Results

The PP dataset, chosen as the primary analysis dataset in this exploratory study, consisted of 15 patients. The following summary efficacy results are presented in this dataset.

At Baseline 1, the mean weight of daily urine leakage was similar between groups (26.0 g and 26.6 g in the Placebo and Besipirdine groups, respectively), whereas the perception of patients of their SUI intensity (PGIS) was different, a higher proportion of patients reporting a moderate SUI intensity in the Placebo group (5/7) and a mild SUI intensity in the Besipirdine group (6/8).

At the End of Period 1, there was no marked effect of besipirdine on both:

- the complete responder rate (proportion of "dry" patients, primary criterion): 1/7 and 1/8 patients in the Placebo and Besipirdine group, respectively,
- and the 50% responder rate ("dry" patients excluded): 0/7 and 1/8 patients in the Placebo and Besipirdine group, respectively;

There was a trend to a besipirdine positive effect on:

- the daily urine leakage weight outcome with mean / median decreases of 11.9 / 12.4 g in the Besipirdine group *vs*. 3.6 / 6 g in the Placebo group,
- the ≥ 30% responder rate (50% and "dry" patients included) of 6/8 in the Besipirdine group *vs*. 3/7 in the Placebo group,
- and the proportion of patients with an at least minimally improved SUI reported on the PGIC of 8/8 Besipirdine patients vs. 2/7 Placebo patients.

The limited effect magnitude of besipirdine was confirmed on:

- the proportion of patients reporting to be much or very much improved on the PGIC (1/7 and 3/8 in the Placebo and Besipirdine group, respectively),
- and the proportion of patients with a besipirdine effect during Period 1 judged (on the pad test and PGIS results) clinically superior to the placebo effect during Period 2 by the AC Committee: 2/8 patients.

The 2-week run-in placebo interval was marked by an unexpected outcome of the urine leakage weight with a continuation of the reduction in the group previously treated by placebo and no change in the group previously treated by besipirdine. This phenomenon that led to a clinically relevant decrease in the mean / median urine leakage weight from Baseline 1 to Baseline 2 (by around 10 g) in both groups, is attributed to a "study" effect and makes difficult the interpretation of the Period 2 results.

During Period 2, the efficacy outcomes were almost unchanged in both groups.

Efficacy results in the wider samples of the CS (19) and FAS (22) patients were not relevantly different from those in the PP sample.

Safety Results (1/2)

AEs (1/2)

Overall, 33 TEAEs occurred in 17 patients on besipirdine *vs*. 2 TEAEs in 1 patient on placebo. The most frequent TEAEs (≥ 2 patients) were (number of affected patients into brackets): blood pressure increased (6), dry mouth (3), insomnia (3), heart rate decrease (2), myalgia or muscle spasms (2).

No deaths were reported. A single SAE (Wallenberg syndrome) was reported and occurred on besipirdine (Day 4 of Period 2) in a 72-year-old man with history of hypertension. The SAE was attributed to a cardiac embolism on supraventricular arrhythmia. The study drug causality was not suspected by the Investigator, but was not ruled out by the Sponsor. The event led to a temporary then definitive study drug discontinuation and to an hospitalisation; it needed a corrective (anticoagulant) treatment and was recovering at the hospital discharge.

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Summary – Conclusions (2/2):

Safety Results (2/2)

AEs (2/2)

In 10 patients, 18 occurrences of TEAEs were deemed related to the study drug by the Investigator (relationship suspected or unassessable): dry mouth (3), blood pressure increased (3), insomnia (2), heart rate decrease (2), myalgia or muscle spasm (2), dyspepsia (1), flatulence (1), nausea (1), blood pressure decreased (1), asthenia (1) and postural dizziness (1). Of them, 3 were severe in intensity: blood pressure increased (2), muscle spasms (1); 2 were ongoing at study end: moderate postural dizziness (1) and severe blood pressure increased (1); and 1 (moderate insomnia) needed a corrective treatment.

In 3 patients, 3 TEAEs (including the SAE) led to definitive study treatment discontinuation. As the SAE, both other TEAEs were experienced on besipirdine and were of cardio-vascular nature: a moderate postural dizziness (Day 4-Period 1) and a severe blood pressure increased (Day 10-Period 1). For both of them, the relationship with the study drug was suspected by the Investigator; in the patient with the blood pressure increased, a mild heart rate decrease (Day 2) and a first occurrence of severe blood pressure increase (Day 4) had been previously reported as AEs.

Lab Tests

Three patients presented PCA (of increase) in lab parameters (γGT [all 3 patients], and/or ALAT [1 patient] and/or creatinine [1 patient]), possibly imputable to besipirdine intake. Resulting values for ALAT and creatinine were not CNALV (*i.e.*, were < 2*ULN and < 150 µmol/L, respectively). Although no CNALV definition was given for γGT, the resulting value from the PCAi may be considered as potentially clinically significant in 2 patients (5.1*ULN and 6.1*ULN). In neither cases, these PCAis were deemed clinically significant by the Investigator. When available, the further controls were normal.

Vital Signs

Relative to vital sign outcome on placebo, besipirdine showed:

- During Period 1, a relevant increasing effect on SBP, a trend to an increasing effect on DBP, and a trend to a decreasing effect on HR (median changes from Baseline 1: +10 mmHg, +0.5 mmHg, and -4.5 bpm, respectively *vs*. 0 mmHg, –3.0 mmHg, and +1.0 bpm, respectively in the Placebo group);
- During Period 2, a lower decreasing effect on SBP, and a trend to a decreasing effect on both DBP and HR (median changes from Baseline 2: –3.0 mmHg, –6.5 mmHg, and –3.5 bpm, respectively, *vs*. –8.5 mmHg, 0 mmHg, and +1.0 bpm, respectively in the Placebo group);

During the last week off treatment, a relevant increasing effect on all vital signs.

Vital sign SCs toward increase (SCis) and toward decrease (SCds, mainly of HR), generally isolated, were possibly imputable to besipirdine intake in 12 and 9 patients, respectively. The vital sign SCVs reported in 5 patients (increased SBP in 4 patients and decreased HR in 1 patient), and the vital sign (supine) values deemed clinically significant by the Investigator for 5 patients (increased SBP in 4 patients [SCV in 3 of them], and concomitant [non SCV] decreased SBP, DBP and HR in 1 patient) were all possibly attributable to besipirdine intake.

ECG

There was no indication of QTc prolongation or any other ECG abnormalities with besipirdine intake.

Conclusion:

This cross-over designed exploratory trial conducted in post-prostatectomy SUI did not show any clinically significant efficacy of besipirdine 20 mg bid. The safety profile observed in the study was in line with the drug pharmacology.

Date of report: 07 January 2011

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