Pierre Fabre Médicament
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1. TITLE PAGE

CLINICAL STUDY REPORT

A Dose-Finding Study of Efficacy and Safety of F13640 (Befiradol) in Patients with Moderate to Severe Painful Peripheral Diabetic Polyneuropathy.
BEST-Diabetes Study (Befiradol Dose-Finding Study in diabetic patients)

Investigational Product:	Befiradol tablets (0.25 and 0.50 mg)
Study Design:	Multicentre, randomised, double-blind, placebo-controlled study on 4 parallel groups: 1, 2 or 3 mg/day and placebo
Protocol Number:	F13640 CP 2 01
EudraCT Number:	2009-012123-28
Phase of Development:	II
Date of First Enrolment:	27 October 2009
Date of Last Completed:	09 December 2010
Coordinator:	Prof Paul VALENSI, MD, *Hôpital Jean Verdier, Avenue du 14 juillet, 93140 Bondy*, France: +33 (0)1 48 02 65 96
Sponsor Representatives for Study Report:	Clinical Study Director: Marie-Thérèse Pétrissans, MD: +33 (0)5 34 50 63 42 Clinical Study Managers: Christine Métais / Carine Fabre: +33 (0)5 34 50 63 54 / 63 57 Pharmacokinetic Study Managers*:* Laurence Barthe / Laurence Del Frari: +33 (0)5 34 50 63 91/ 63 90 Project Statistician: Mélanie Groc: +33 (0)5 62 24 27 89 Medical Writer: Agnès Montagne, MD: +33 (0)5 34 50 63 50
Date of Report:	**07 November 2011**

Study performed in compliance with Good Clinical Practice.

2. SYNOPSIS

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Title of Study:	**A dose-finding study of efficacy and safety of F13640 (befiradol) in patients with moderate to severe painful peripheral diabetic polyneuropathy.**	
Abbrev.	BEfiradol Dose-Finding STudy in diabetic patients (BEST-Diabetes study).	
International Coordinating Investigator:	Prof Paul Valensi, MD, *Hôpital Jean Verdier*, *Avenue du 14 juillet*, 93140 Bondy, France	
Investigators:	317 potentially recruiting investigators in 10 European countries: Bulgaria (B), Croatia (C), Czech Republic (CR), France (F), Germany (G), Hungary (H), Lithuania (L), Russia (R), Serbia (Se), and Slovakia (Sl).	
Study Centres:	80 recruiting centres: B (4), C (4), CR (11), F (3), G (12), H (7), L (5), R (21), Se (5), and Sl (8), specialised in Endocrinology/Diabetology (71%), Neurology (25%) or Internal Medicine (4%); mainly hospital structures (59%).	
Publication (reference):	Not written	
Study Period: **date of first enrolment** **date of last completed**	13.4 months: 27 October 2009 09 December 2010	**Phase of development:** II
Objectives:	**Primary:** to define the dose-response relationship of befiradol (a selective 5-HT1A receptor agonist) compared to a placebo with respect to analgesic efficacy and safety in patients with moderate to severe diabetic peripheral neuropathic pain (DPNP); **Secondary:** - To evaluate, after study treatment discontinuation, potential rebound, addiction, or remanent effects; - To perform a descriptive analysis of befiradol plasma concentrations.	
Methods:	- Multicentre, randomised, double-blind, placebo-controlled study on 4 parallel groups (3 doses of befiradol: 1, 2 or 3 mg/day and placebo). - Maximum study duration: 108 days: • Selection period including a period of wash-out of the previous prohibited treatments up to 28 days (i.e., to a maximum of 5 T½ of the prohibited treatments) followed by a 7-day stabilisation period for the validation of the inclusion criteria related to the pain intensity score; • Treatment period (66 days) including an 11-day progressive up-titration, a fixed dose period and a 10-day progressive down titration; • Single-blind placebo follow-up period (7 days). - 7 study visits: Selection, Randomisation, Day (D)12, D29, D56 (or End of Fixed Dose [EFD]), D66 (or end of Down Titration [EDT]), D73 (or Study Termination [ST]); - 4 phone calls: at D-7, D6, D18 and D60. - Patient Electronic Diary (PED) to capture pain data for primary criterion calculation.	
Number of Patients:	456 randomised and treated patients: 112, 113, 114, and 117 patients in the Placebo, 1 mg, 2 mg, and 3 mg groups, respectively.	
Diagnosis and Main Criteria for Inclusion (1/2):	- Male or female patient aged 18 to 65, - Moderate-to-severe DPNP, with: • Michigan Neuropathy Screening Instrument (MNSI) score ≥ 3, • Pain persisting for ≥ 3 months, • Diabetes mellitus ≥ 3 years, stable glycaemic assessment for ≥ 3 months, Haemoglobin A1c (HbA1c) < 10% at Selection.	

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Diagnosis and Main Criteria for Inclusion (2/2):

- 24h-Recall Pain intensity score > 40 and < 90 on a paper 0-100 mm visual analogue scale (VAS) at Selection, and > 40 on average on a PED 0-100 VAS over the week preceding Randomisation (at least 4 assessable daily measurements),
- No potentially analgesic drugs authorised (except paracetamol).

Test Product,
Dose,
Mode of Administration,
Batch Numbers:

Befiradol (0.25 mg, 0.5 mg befiradol tablets),
Target doses: 0.5 mg *bid*, 1 mg *bid* and 1.5 mg *bid*, reached after up-titration started at 0.25 mg *qd*,
Oral, at breakfast (*qd* or *bid*) and dinner (*bid*)
0.25 mg tablets: CFS198, CFS225 (expiry [exp] Mar 2010, Mar 2011); 0.5 mg tablets: CFS210, CFS226 (exp Dec 2010, Sep 2011)

Duration of Treatment:

73 days on treatment:

- **66 days on comparative study treatment** according to the following schedule:
  - **56-day treatment period up to EFD (**including an **11-day up titration period):**

Step	**Placebo**	**1 mg**	**2 mg**	**3 mg**
1	placebo *qd* for 1 day	0.25 mg *qd* for 1 day		
2	placebo *bid* for 55 days	0.25 mg *bid* for 2 days		
3		0.5 mg *bid* for 53 days	0.50 mg *bid* for 2 days	
4			0.75 mg *bid* for 2 days	
5			1 mg *bid* for 49 days	1 mg *bid* for 2 days
6				1.25 mg *bid* for 2 days
7				1.5 mg *bid* for 45 days

  - **10-day down titration (DT) period**, at the end of the fixed dose period (D56), for all patients having reached their target dose:

Step	**Placebo**	**1 mg**	**2 mg**	**3 mg**
8	placebo *bid* for 10 days	0.25 mg *bid* for 10 days	0.75 mg *bid* for 2 days	1.25 mg *bid* for 2 days
9			0.5 mg *bid* for 2 days	1 mg *bid* for 2 days
10			0.25 mg *bid* for 6 days	0.75 mg *bid* for 2 days
11				0.5 mg *bid* for 2 days
12				0.25 mg *bid* for 2 days

- **7 days of follow-up (FU period)** on placebo (*bid*).

Reference therapy,
Dose,
Mode of Administration,
Batch Numbers:

(Befiradol-matching) Placebo tablets
See "Test Product"
See "Test Product"

- 0.25 mg-matching tablets: CFS200, CFS227 (exp May 2013, Sep 2014);
- 0.5 mg-matching tablets: CFS215, CFS231 (exp Feb 2014, Sep 2014)

Criteria for Evaluation (1/2):
Efficacy (1/2)

Primary Variable: 24 h-recall pain intensity VAS score: PED rating from Selection to D73.

Primary Criterion = responder rate on the weekly-averaged primary variable at Day 56/EFD, i.e., % of patients with a **reduction from baseline** (week preceding 1st study drug intake) **≥ 30%** and non PW for therapeutic failure.

Secondary Variables (except otherwise specified, assessed at D1, D29 and D56-EFD)**:**

- **Short-form McGill pain questionnaire** (SF-MPQ): Total, Sensory and Affective Intensity subscores; %improvers on Present Pain Intensity (PPI); Pain Intensity VAS;
- **Brief Pain Inventory Short Form** (BPI SF): Pain Intensity and Interference scores, **Pain Relief Score** (= item 8);
- **Neuropathic Pain Symptom Inventory** (NPSI): Total score, 5 subscores (burning, pressing, paroxysmal pain, evoked pain, parethaesiae/dysesthaesia), 2 item scores (duration of spontaneous pain, number of pain attacks);
- **Patient Global Impression of Change** (PGIC): on D29, D56, and D73 (ST);

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Criteria for Evaluation (2/2): **Efficacy (2/2)**	- **Beck Depression Inventory** (BDI-II) score; - **Short Form Medical Outcomes Study**: **Sleep Problems Index I**; - **Paracetamol rescue intake duration** (absolute in days and relative in % of study treatment duration up to EFD) **and dose**: at all visits.
Safety	Investigator's assessment or reporting on the CRF at each assessment visit from Selection unless otherwise specified: - **Adverse Events** including specific search for predefined withdrawal syndromes; - **General Physical Exam;** - **Vital Signs** (Systolic/Diastolic Blood Pressures [SBP/DBP] and Heart Rate [HR]) - **ECG** during selection period and Day73/ST-3 days; - **Lab Tests** during selection period, at D29, D56, and Day73/ST-3 days**:** • Blood tests: – Standard Haematology and Biochemistry, – HbA1c during selection period and at D73/ST, • Urinalysis for albuminuria/creatininuria ratio during selection period and at the last visit for the Patient; - **Concomitant Treatments.**
Pharmacokinetics	**Drug plasma concentrations** and **timing of sampling relative** to preceding study drug intake. Three blood samples were collected: - On D29 (PK1): in fasting condition with the lab test sampling before study drug intake; - On D56: 2 samples (PK2 and PK3): collected between the morning and the evening study drug intake: • PK2 in fasting condition simultaneously with the lab test sample, at least 30 min after the morning study drug intake; • PK3 at least 30 min after PK2. Concentrations of befiradol were quantified using a validated analytical LC-MS/MS method (LOQ: 0.1 ng/mL)
Statistical Methods (1/2): **Efficacy (1/2)**	In the Full Analysis Set (FAS), *i.e.*, data of all randomised and treated patients. Two-sided tests at a 5% level of significance. Unless otherwise specified: LOCF principle applied on incomplete or missing data and Hochberg adjustement for multiplicity. **Primary Analysis of the Primary Criterion:** Comparison of the 30%-responder rates at EFD using the Cochran Mantel Haenszel (CMH) test stratified by Country. **Supportive Analysis of the Primary Analysis:** Primary analysis repeated on the Per Protocol (PP) set. **Additional Analyses on the Primary Criterion:** - Description over time by week, - Dose effect relationship by MH Chi^2 test, - Search for prognostic demographic or other baseline factors: exploratory multiple factor logistic regression analysis. **Other Analyses derived from the Primary Variable (1/2):** - On the Weekly-averaged 24h-recall pain VAS: • ANCOVA on change (from baseline) at Week 8-LOCF with Treatment and Country as fixed effects and baseline value as covariate. + Dose effect relationship by appropriate contrasts; • Description over time of values, changes: by week; by day on D1-D14 period; • Contrasts on changes over time using the likelihood-based mixed-effect model for repeated measures (MMRM using observed case approach), • Postfixed dose outcome (rebound analysis): descriptive analysis of change during DT and FU periods ;

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Statistical Methods (2/2):

Other Analyses derived from the Primary Variable (2/2):

Efficacy (2/2)

- On response:
  - Time to 1st response (week);
  - Loss of therapeutic effect during fixed dose period (in first 3 weeks FAS responders); during down titration and follow-up periods;
  - 50% responder rates.

Analyses of Other Secondary Criteria

- Quantitative Variables (scores of SF-MPQ, BDI, BPI, MOS-Sleep, NPSI, Pain Relief):
  - Same ANCOVA model on Change from baseline to Week 8-LOCF as for primary variable
  - Description over time of values and changes from baseline (OC)
- Qualitative Criteria (SF-MPQ PPI Improvers, PGIC Responders): same analysis as primary analysis
- Paracetamol use for neuropathy: description of intake duration (days), daily and weekly dose during fixed dose, DT and FU periods.

Safety

AEs:

- N (%) of patients: with at least one: treatment-emergent AE (TEAE), serious AE (SAE), AE leading to a study treatment definitive discontinuation, TEAE by most severe intensity, drug-related* TEAE (*suspected or insufficient data),
- N (%) of patients with at least one TEAE by System Organ Class and Preferred Term (PT) of MedDRA,
- Tabulated individual data for SAEs and for AEs leading to definitive study treatment discontinuation or change in dose,
- 7-day FU period: descriptive analysis of post-TEAEs;

Lab Tests:

- Descriptive statistics for values and changes over time,
- N (%) of patients with: i/ potentially clinically significant change (PSC), and ii/ PSC leading to out-of-range value (PSCV),
- Scatter plots as a function of baseline values for D56/PW values,
- 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 (PSC), ii/ PSC leading to predefined potentially clinically significant value (PSCV); iii/ CS abnormalities (PSC $\geq$ 30 mmHg for SBP, $\geq$ 25 mmHg for DBP, PSCVs and corresponding AEs)
- N (%) of patients with changes from baseline to max. (and min.) post-baseline value.

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

Concomitant Treatments: Frequencies of use by WHO-DRUG ATC classes.

Pharmacokinetics

A descriptive analysis was performed on the PK set (*i.e.*, the data from all patients treated with befiradol with at least one quantified concentration and with available dose and time records: administration and sampling times): median and ranges of concentrations and relative times (between drug intake time and sampling time) were calculated by dose and day. Concentrations were tabulated and plotted *versus (vs.)* relative times, by dose and by visit.

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Summary – Conclusions (1/4)

Patients

Disposition

651 patients were screened, of whom, 457 (87.9%) were randomised (from 5 in France to 170 in Russia): 113, 113, 114, and 117 in the Placebo (PBO), Befiradol (BFL) 1 mg, BFL 2 mg, and BFL 3 mg groups, respectively. All randomised patients received at least one dose of study treatment except 1 PBO patient.

The patient disposition from randomisation to study completion is tabulated below (several reasons may have led to the PW). There was an increase with the dose in the incidence of PWs for safety concern, and no between-group difference for PWs due to other reasons than safety concern.

	Placebo	BFL 1mg	BFL 2mg	BFL 3mg	Total
Randomised	**113**	**113**	**114**	**117**	**457**
Prematurely Withdrawn	***13 (11.5 %)***	***9 (8.0 %)***	***14 (12.3 %)***	***24 (20.5 %)***	***60 (13.1 %)***
Safety Concern	*2 (1.8 %)*	*4 (3.5 %)*	*8 (7.0 %)*	*14 (12.0 %)*	*28 (6.1 %)*
Therapeutic Failure	*4 (3.5 %)*	*1 (0.9 %)*	*2 (1.8 %)*	*3 (2.6 %)*	*10 (2.2 %)*
*Other Reason**	*8 (7.1 %)*	*5 (4.4 %)*	*4 (3.5 %)*	*9 (7.7 %)*	*26 (7.7 %)*
Completers	**100 (88.5%)**	**104 (92.0%)**	**100 (87.7%)**	**93 (79.5%)**	**397 (86.9%)**

**exclusive of the other classes; including 1 loss to follow-up in the PBO group*

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

	Placebo	BFL 1mg	BFL 2mg	BFL 3mg	Total
FAS	112	113	114	117	456
PP Set	97	90	97	91	375
Rebound Analysis Set	98	100	100	90	388
PK Set	N/A	94	96	96	286

Baseline Characteristics (FAS sample)

Overall, 53.7% of patients were women, 98.2% of patients were Caucasians, the age was 55.1 years on average and ranged between 20 and 66 years, the BMI was 31.0 kg/m^2 on average and ranged between 12.1 and 48.6 kg/m^2; with 57.7% of obese patients.

Type 2 / type 1 diabetes ratio was ~4.8; the mean ages of diabetes and diabetic neuropathic pain (DNP) were 12.0 and 3.8 years, respectively. The mean HbA1C level was 7.6%; ~76% of patients had a concomitant hypertension.

The overall mean (SD) 24 h-recall pain VAS score at selection, 64.0 (11.5) mm, reflected a moderate-to-severe intensity of pain in the study sample.

Treatment groups did not relevantly differ (difference >10%) with respect to demographic and other baseline characteristics except:

- A higher proportion of female patients in the BFL 3 mg group (63.2% *vs*. 50.4% in the other groups as a whole);
- A higher proportion of smokers (including ex-smokers or not) in the PBO group (40.2% and 25.0% , respectively, *vs*. 30.5% and 13.6%, respectively in the BFL groups as a whole); among smokers (including ex-smokers), a higher daily consumption of cigarettes in the BFL 2 mg group: 20.2 *vs*. 15.1 in the other groups as a whole;
- A higher use of insulin and analogues in the BFL 1 mg and 3 mg groups (63.7% and 65.0%, respectively) than in the PBO (54.5%) and BFL 2 mg group (54.4%);
- A lower use in the BFL 3 mg group of antithrombotic agents (23.1% *vs*. 31.6% in the other groups as a whole) and calcium channel blockers (12.8% *vs* 23% in the other groups as a whole).

Efficacy Results (1/2)

In the FAS sample, the proportion of 30%-responders on the e-Diary 24 h-Recall Pain VAS Intensity weekly-averaged over the last fixed dose week (Week 8-LOCF), was non significantly higher in either BFL group than that in the PBO group (results in bold type in the following table; minimum CMH p_a value: 0.87 [BFL 3 mg group *vs*. PBO group]); a result unchanged in the PP data set. Although increasing with the dose, there was no significant dose effect on this 30% reponder rate.

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Summary – Conclusions (2/4):

Efficacy Results (2/2)

The following table summarises the main results of the efficacy criteria. Consistently with the results on the primary criterion (in bold type), improvements in pain and PGIC scales were higher (and tended to increase with the dose) in the BFL groups than in the PBO group, but the difference *vs*. PBO never reached the statistical significance for either BFL group.

Domain	**Variable [Worst-Best Scoring]**	**Outcome Statistics; p value**			
		PBO	**BFL 1mg**	**BFL 2mg**	**BFL 3mg**
		n=112	**n=113**	**n=114**	**n=117**
Pain		**% Patients over Last Week before EFD**			
	% of 30% responders on e-Diary 24h-Recall Pain VAS	**43.8%**	**44.0%; p=0.98**	**47.7%**; **p=1.00**	**50.4%**; **p=0.87**
	% of 50% responders on e-Diary 24h-Recall Pain VAS	33.0%	29.4%; p=1.00	30.6%; p=0.73	35%; p=1.00
		Mean (SE) Adj. Change at EFD			
	e-Diary 24h-Recall Pain VAS [100-0]	-19.4 (2.3)	-19.2 (2.3) ; p=0.94	-24.1 (2.3) ; p=0.33	-23.5 (2.2) ; p=0.32
	NPSI [100-0]	-7.2 (0.9)	-8.0 (0.9) ; p=0.50	-8.5 (0.8) ; p=0.75	-8.5 (0.8) ; p=0.52
	SF-MPQ Total [45-0]	-5.0 (0.8)	-5.4 (0.8) ; p=1.00	-5.6 (0.8) ; p=1.00	-5.1 (0.8) ; p=0.94
	BPI-SF Pain Intensity [10-0]	-6.9 (0.8)	-7.4 (0.8) ; p=1.00	-7.4 (0.8) ; p=0.61	-7.8 (0.7) ; p=1.00
	Pain Relief Score [0-100%]	23.0 (3.4)	23.6 (3.4) ; p=0.88	28.3 (3.3) ; p=0.44	29.9 (3.3) ; p=0.33
		Mean (SD) Value over Treatment Period up to EFD			
	% Days of Paracetamol (Rescue) Use	5.7 (19.3)%	6.4 (17.9)% ; N/A	7.7 (21.0)% ; N/A	7.7 (21.4)% ; N/A
PGIC		**% Patients at EFD**			
	% of PGIC responders	23.1%	28.4%; p=0.35	29.7%; p=0.60	30.6%; p=0.44
		Mean (SE) Adj. Change at EFD			
Depressive mood	BDI-II [63-0]	-4.3 (0.6)	-3.9 (0.6) ; p=0.59	-2.8 (0.6) ; p=0.14	-2.2 (0.6) ; p=0.032
Sleep	MOS-Sleep Index I [100-0]	-9.6 (1.6)	-9.5 (1.7) ; p=0.96	-7.6 (1.6) ; p=0.72	-6.1 (1.6) ; p=0.33

Pharmacokinetic (PK) Results

810 plasma concentrations from the 286 patients administered with befiradol were used to perform the descriptive PK analysis. Plasma concentrations of befiradol increased when administered dose increased. After close visual inspection of range of concentrations and graphs, no gender effect could be evidenced whatever the dose. In addition, the concentrations observed in patients who took concomitant CYP450 3A4 inducer or inhibitor, remained in the range of concentrations observed in patients without such concomitant medication.

Safety Results (1/3)

Adverse Events (1/2)

4 SAEs (1 in each group) were reported, all treatment-emergent, and none having been suspected as drug-related either by the Investigator or the Sponsor: a sudden death in the PBO group, an angina pectoris in the BFL 1 mg group, a pneumonia in the BFL 2 mg group and a hypertension (aggravated) in the BFL 3 mg group.

Overall, there was an increase (or trend to increase) with the dose (*i.e.*, predominantly in ≥ 1 of the 2 highest BFL doses) in the:

- Number of TEAE occurrences (67 in the PBO group, and 132, 167 and 180 in the BFL 1, 2 and 3 mg groups, respectively) and corresponding incidence (25.9% in the PBO group and 39.8%, 49.1% and 46.2% in the BFL 1, 2 and 3 mg groups, respectively);
- Proportion of drug-related TEAEs (46.3% in the PBO group, and 49.2%, 62.3% and 72.2% in the BFL 1, 2 and 3 mg groups, respectively) and corresponding incidence (11.6% in the PBO group and 19.5%, 32.5% and 35.0% in the BFL 1, 2 and 3 mg groups, respectively);
- Number and incidence of AEs leading to definitive study treatment discontinuation (8 in 0.9% of patients in the PBO group *vs*. 11 to 40 in 3.5% to 12.0% of patients in the BFL groups).

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Summary – Conclusions (3/4):

Safety Results (2/3)

Adverse Events (2/2)

The most common TEAEs (in ≥ 5% of patients in any group),

- With an increase (or trend to increase) with the dose in their incidence, were: dizziness (2.7%/PBO *vs*. 8.8% to 15.4%/BFL), nausea (4.5%/PBO *vs*. 7.1% to 15.4%/BFL), headache (4.5%/PBO *vs*. 8.8% to 11.1%/BFL), hypertension (0/PBO vs.1.8% to 5.1%/BFL), and withdrawal syndrome (2.7%/PBO and 3.5% to 5.1%/BFL);
- Of higher incidence in ≥ 1 BFL group than in the PBO group, with no apparent increase with the dose, were: insomnia (0.9%/PBO *vs*. 6.0 to 7.9%/BFL), and paraesthesia (2.7%/PBO and 2.6% to 5.3%/BFL); almost all TEAEs were of mild or moderate severity (~99% and ~97% TEAEs in the PBO group and BFL groups as a whole, respectively). The proportion of TEAEs of moderate severity was the highest in the BFL 3 mg group (mainly hypertension and psychiatric TEAEs).

The most common **drug-related** TEAEs (incidence > 2% of patients in either group) were the following:

PT	PBO	BFL 1 mg	BFL 2 mg	BFL 3 mg
	n=112	n=113	n=114	n=117
Dizziness	1 (0.9%)	8 (7.1%)	15 (13.2%)	15 (12.9%)
Nausea	4 (3.6%)	6 (5.3%)	12 (10.5%)	16 (13.7%)
Headache	3 (2.7%)	3 (2.7%)	6 (5.3%)	9 (7.7%)
Insomnia	-	3 (2.7%)	3 (2.6%)	6 (5.1%)
Withdrawal syndrome	1 (0.9%)	4 (3.5%)	4 (3.5%)	5 (4.3%)
Paraesthesia	1 (0.9%)	3 (2.7%)	4 (3.5%)	2 (1.7%)
Vomiting	-	-	-	5 (4.3%)
Hypotension	-	3 (2.7%)	2 (1.8%)	2 (1.7%)
Accidental overdose	1 (0.9%)	3 (2.7%)	3 (2.6%)	2 (1.7%)
Hypertension	-	1 (0.9%)	1 (0.9%)	3 (2.6%)
Mood Swings	2 (1.8%)	-	2 (1.8%)	3 (2.6%)
ALAT increased	1 (0.9%)	1 (0.9%)	3 (2.6%)	-

~70% of definitive treatment discontinuations due to drug-related TEAEs in the BFL groups occurred before the end of the 1st week of the fixed dose period. TEAEs leading to definitive treatment discontinuation were mainly (number of AEs in the PBO, BFL-1 mg, -2 mg, and -3 mg groups respectively): nausea (1, 2, 4, and 8 [+1 vomiting]) and dizziness (0, 1, 3 [+2 vertigo + 1 vestibular disorder], and 5).

TEAEs with the earliest onset were dizziness and nausea (generally during the up-titration period); then, hypotension and asthenia (generally within the first 4 weeks). Hypertension occurred more likely during the fixed dose period; whereas myalgia generally occurred during the down-titration or follow-up periods. The other AEs were either rare or had no specific onset period.12.6

Drug-related withdrawal syndromes with consistent date of onset (*i.e.*, at or after the end of fixed dose period) were reported in 1, 3, 3, and 2 patients in the PBO, BFL 1, 2 and 3 mg groups, respectively. The following withdrawal symptoms occurred specifically in the BFL groups: mood swings (3), dizziness (2), confusional state (1), visual hallucination (1), and nightmare (1).

Of the 18 accidental overdoses reported in the BFL group (*vs*. 1 in the PBO group), 3 possibly resulted in an AE: a dizziness in 2 cases, and a severe paroxysmal tachycardia + mild facial hypoesthesia in 1 case. The latter case led to a definitive treatment discontinuation.

Laboratory Tests (1/2)

At baseline, there were, in the whole study sample, trends to hyperglycemia, hypertriglyceridemia, and to poor hepatic (ALAT, GGT) and renal (creatininemia and MDRD creatinine clearance) functions. The BFL 2 mg group showed the most impaired means for most of these parameters, except for renal parameters.

The mean time profiles of all lab parameters showed no relevant between-group differences.

In post-baseline, the most relevant findings were the following:

- CNALVs resulting from potentially significant changes (PSCs) or drug-related TEAEs of increased hepatic parameters were reported in more patients in the BFL 1 mg and 2 mg groups (6 and 9, respectively) than in the PBO and BFL 3 mg groups (3 and 2, respectively) whereas significant increases (> 2 ULN) in hepatic enzymes were recorded in more patients in the BFL 2 mg group (8) than in the other groups: 2, 3 and 1 patients in the PBO, BFL 1 mg and BFL 3 mg groups, respectively;
- Incidence of PSCVs of increased creatininemia tended to increase with the dose (recorded in 1, 1, 3 and 4 patients in the PBO, BFL 1 mg, BFL 2 mg and BFL 3 mg groups, respectively). A similar trend was observed for the PSCVs of increased kaliemia (recorded in 2, 1, 1 and 5 patients in the PBO, BFL 1 mg, BFL 2 mg and BFL 3 mg groups, respectively). However, relevant CNALVs of increased creatininemia or drug-related TEAEs of renal impairment were reported in 1 to 2 patients of either group.

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

Summary – Conclusions (4/4):

Safety Results (3/3)

Vital Signs

The mean time profiles of all vital signs showed no relevant between- or within-group differences.

Clinically significant (CS) abnormalities of high blood pressure (BP) were presented by a higher number of patients in the BFL groups (with no increase with the dose) than in the PBO group: 7, 14, 13, and 15 patients in the PBO, BFL 1 mg, BFL 2 mg, and BFL 3 mg groups, respectively; the difference was mainly related to high PSCs of SBP (≥ 30 mmHg) or DBP (≥ 25 mmHg) increase (1, 6, 8 and 7 patients, respectively) and TEAEs of "hypertension"/"BP increased" (0, 5, 3 and 6 patients, respectively); the relationship of the TEAE with the study drug was not excluded in 0, 1 (suspected, but onset at D66/EDT Visit), 1 (insufficient data), and 3 (insufficient data in all cases, but onset at D66/EDT Visit in 1 case) patients, respectively.

CS abnormalities of low BP were presented by 6, 10, 4 and 8 patients in the PBO, BFL 1 mg, BFL 2 mg and BFL 3 mg groups, respectively. Among them, TEAEs of "hypotension" were reported in 0, 3, 2 and 2 (3 occurrences) patients, respectively; the relationship of the TEAE with the study drug was suspected in all cases (except for 1 occurrence in the BFL 3 mg patient). There was no signal of orthostatic hypotension occurrence related to BFL administration.

CS abnormalities of high HR were presented by 2, 2, 0 and 3 patients in the PBO, BFL 1 mg, BFL 2 mg and BFL 3 mg groups, respectively. Among them, PSCVs were only reported in both PBO patients and TEAEs of "tachycardia" were reported in 2 BFL 3 mg patients; the relationship of the TEAE with the study drug was suspected in 1 case.
CS abnormalities of low HR were presented by 3, 1, 4 and 0 patients in the PBO, BFL 1 mg, BFL 2 mg and BFL 3 mg groups, respectively. Among them, only 1 TEAE of "bradycardia" was reported in a BFL 2 mg patient; this TEAE was suspected to be related with the study drug.

ECG

At the on-treatment assessment (D56/PW), QTc prolongations > 30 ms resulting in a value > 450 ms were recorded in a higher proportion in the BFL 1 mg group (6 patients) than in the other groups (0 patient in the PBO and BFL 2 mg groups, 3 patients in the BFL 3 mg group); however, in only 1 case (BFL 1 mg patient), the QTc (QT_{CB}) increase was > 60 ms (+71 ms) and the resulting QTc (491 ms) was the only resulting QTc > 480 ms. The QTc values were normalised at D73/ST. No other clinically relevant ECG abnormalities were recorded or reported as AEs on BFL treatment.

Conclusion

The present trial did not allow to demonstrate befiradol efficacy in reducing pain associated with DPN at the doses of 1, 2 or 3 mg daily over 8 weeks of treatment. No bias in the study design, baseline characteristics of the population or study performance was identified that could explain such results. The nature of the most common drug-related AEs, whose incidence increases with the dose, is in line with the known pharmacological activity of befiradol.

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