



## Clinical trial results:

**An open-label naturalistic pragmatic study to assess the long-term safety of Pitolisant (BF2.649) in the treatment of Excessive Daytime Sleepiness (EDS) in narcolepsy (“HARMONY III”)**

**Part I : 12-month analysis**

### Summary

EudraCT number	2010-023804-28
Trial protocol	HU
Global end of trial date	12 September 2016

### Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

### Trial information

#### Trial identification

Sponsor protocol code	P09-10
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01399606
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Bioprojet
Sponsor organisation address	9, rue Rameau, Paris, France, 75002
Public contact	Clinical Development Director, Bioprojet , +33 1 47 03 66 33, contact@bioprojet.com
Scientific contact	Clinical Development Director, Bioprojet , +33 1 47 03 66 33, contact@bioprojet.com

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	30 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 October 2013
Global end of trial reached?	Yes
Global end of trial date	12 September 2016
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

- To assess the long-term safety of pitolisant (BF2.649) at 5, 10, 20 or 40 mg/d in the treatment of Excessive Daytime Sleepiness (EDS) in narcoleptic patients with or without cataplexy. The main objective was to get safety data from at least 50 complete patients treated for at least 12 months until BF2.649 commercialization.
- To assess the drug-drug interactions with possible concomitant therapies.
- To assess the efficacy of long-term therapy with pitolisant (BF2.649) on EDS after a prolonged treatment period.

Protection of trial subjects:

The study was conducted in accordance with International Conference on Harmonisation, Good Clinical Practice (ICH-GCP E6), the ethical principles that have their origins in the Declaration of Helsinki (revised Edinburgh, 2000), and applicable national and local regulatory requirements. Prior to the performance of any study-specific procedures, written informed consent was obtained from each patient. The subject was informed about the nature and purpose of the study, as well as of its risks and benefits.

It was explained that the subject could withdraw from the study at any time for any reason and that this would not have any effect on potential future medical care.

An independent Data Safety Monitoring Board (DSMB) was established to assess at intervals the progress of the trial as well as safety data and to recommend whether to continue, modify or terminate the study. It was composed of three independent experts selected by the sponsor, without any direct involvement in the conduct of the trial.

At each meeting, the DSMB members considered study-specific safety data (serious and non-serious AEs) as well as relevant background knowledge about narcolepsy, pitolisant (BF2.649) development (previous and ongoing studies), and patient population under study. DSMB members concluded each review with their recommendations as to whether the study should continue without change, be modified, or terminated.

Background therapy:

Previous participation in a Bioprojet narcolepsy study testing pitolisant (BF2.649) until completion (P05-03, P06-06, P07-03 HARMONY I or P09-15 HARMONY I bis or P07-07 HARMONY II) OR narcoleptic patients with EDS not able to participate in a double-blind study against placebo but who could benefit from testing a new therapy such as pitolisant in an open label study OR patient receiving pitolisant under condition of temporary authorization of use (ATU) delivered by the French Health Authorities.

Evidence for comparator:

no comparator was included

Actual start date of recruitment	11 May 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	France: 79
Country: Number of subjects enrolled	Hungary: 25
Worldwide total number of subjects	104
EEA total number of subjects	104

Notes:

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**Subjects enrolled per age group**

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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)	96
From 65 to 84 years	8
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

After a 1-week baseline period without investigational treatments, or at the end of the participation in a previous double blind controlled narcolepsy study testing pitolisant (BF2.649) (e.g., Studies P07-03, P07-07, P09-15), patients who fulfilled selection criteria started a 1-month individual dose titration phase.

### Pre-assignment

Screening details:

Previous participation in a Bioprojet narcolepsy study with pitolisant until completion OR narcoleptic patients with EDS not able to participate in a double-blind study against placebo but who could benefit from testing a new therapy such as pitolisant in an open label study OR patient receiving pitolisant under temporary authorization of use.

### Period 1

Period 1 title	12-month (Completers) (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

### Arms

<b>Arm title</b>	Baseline (12-month Completers)
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Arm description:

Subjects who completed the 12-month period with valid measurements at baseline and 12-month time point

Arm type	Experimental
Investigational medicinal product name	BF2.649
Investigational medicinal product code	
Other name	Pitolisant
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Pitolisant hydrochloride (BF2.649)

Dose: 5, 10, 20, 40 mg OD

Mode of administration: Per os

1-month individual dose titration phase: BF2.649 at 5 mg OD (1/4 tablet of BF2.649 at 20 mg) from D1 to D7, BF2.649 at 10 mg OD (1/2 tablet) from D8 to D14 and then increased to 20 mg OD (1 tablet) from D15 to D21 if safety and tolerability were good. At D21, doses could be adjusted according to the individual benefit/risk ratio (5, 10 or 20 mg OD). At 1-month, an individual dose adjustment could be performed again (5, 10, 20 or 40 mg OD if the investigator judged that the efficacy of 20 mg OD was not sufficient). Thereafter, the dose remained stable for a 2-month period. At 3-, 6-, 9-, 12-month visits, an individual dose adjustment could be performed again (5, 10, 20 or 40 mg OD).

<b>Number of subjects in period 1</b> <sup>[1]</sup>	Baseline (12-month Completers)
Started	68
Completed	68

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Subset of patients who completed the 12-month period, with baseline data - for Efficacy Endpoint

## Baseline characteristics

### Reporting groups

Reporting group title	12-month (Completers)
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Reporting group description:

Subjects who completed the 12-month period with baseline data - Efficacy endpoint

Reporting group values	12-month (Completers)	Total	
Number of subjects	68	68	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	64	64	
From 65-84 years	4	4	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Combined (M+F)	68	68	

### Subject analysis sets

Subject analysis set title	Safety Population
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Subjects who took at least one dose of study treatment

Subject analysis set title	12-month (Completers)
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Subject analysis set type	Per protocol
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Subject analysis set description:

Patients who completed the 12 months of treatment (n=68) with baseline data

Reporting group values	Safety Population	12-month (Completers)	
Number of subjects	102	68	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	

Adults (18-64 years)	95	64	
From 65-84 years	7	4	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Combined (M+F)	102	68	

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## End points

### End points reporting groups

Reporting group title	Baseline (12-month Completers)
Reporting group description: Subjects who completed the 12-month period with valid measurements at baseline and 12-month time point	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: Subjects who took at least one dose of study treatment	
Subject analysis set title	12-month (Completers)
Subject analysis set type	Per protocol
Subject analysis set description: Patients who completed the 12 months of treatment (n=68) with baseline data	

### Primary: Epworth Sleepiness Score

End point title	Epworth Sleepiness Score <sup>[1]</sup>
End point description:	
End point type	Primary
End point timeframe: Control visit at 12 months (Visit 7)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Efficacy was not the primary objective but safety.

No formal statistical analysis was planned other than descriptive statistics.

See attached Figure and Table with descriptive statistical results.

End point values	Baseline (12-month Completers)	12-month (Completers)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	68	68 <sup>[2]</sup>		
Units: number				
arithmetic mean (standard deviation)	16.76 (± 3.35)	12.13 (± 5.28)		

Notes:

[2] - Without replacement of missing values - ITT population

<b>Attachments (see zip file)</b>	2010-023804- 2010-023804-
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### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From Day 0 and then at Day 21 (Visit, V2), 1 month (V3), 3 month (V4), 6 month (V5), 9 month (V6) and 12 month (V7)

Adverse event reporting additional description:

Full data collected on the first 12 months period.

For non-serious adverse events, only Treatment Emergent Adverse Events (TEAEs) that were considered related (possibly or likely) to study drug.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.1
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### Reporting groups

Reporting group title	Safety Population
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Reporting group description: -

<b>Serious adverse events</b>	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 102 (6.86%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Carcinoid tumour pulmonary			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thoracic operation			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			

Pregnancy			
subjects affected / exposed	2 / 102 (1.96%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Abortion spontaneous			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Abortion			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 102 (1.96%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pilonidal cyst			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

<b>Non-serious adverse events</b>	Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 102 (42.16%)		
Investigations			
Weight increased			
subjects affected / exposed	7 / 102 (6.86%)		
occurrences (all)	7		
Weight decreased			
subjects affected / exposed	2 / 102 (1.96%)		
occurrences (all)	2		

Nervous system disorders			
Headache			
subjects affected / exposed	9 / 102 (8.82%)		
occurrences (all)	10		
Migraine			
subjects affected / exposed	2 / 102 (1.96%)		
occurrences (all)	2		
Dizziness			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		
Dyskinesia			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		
Sensory disturbance			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	3 / 102 (2.94%)		
occurrences (all)	3		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 102 (2.94%)		
occurrences (all)	3		
Abdominal discomfort			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		
Abdominal pain			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		
Gastritis			

<p>subjects affected / exposed occurrences (all)</p> <p>Gastrointestinal pain subjects affected / exposed occurrences (all)</p>	<p>1 / 102 (0.98%) 1</p> <p>1 / 102 (0.98%) 1</p>		
<p>Reproductive system and breast disorders</p> <p>Amenorrhoea subjects affected / exposed occurrences (all)</p>	<p>1 / 102 (0.98%) 1</p>		
<p>Skin and subcutaneous tissue disorders</p> <p>Rash subjects affected / exposed occurrences (all)</p>	<p>1 / 102 (0.98%) 1</p>		
<p>Psychiatric disorders</p> <p>Insomnia subjects affected / exposed occurrences (all)</p> <p>Anxiety subjects affected / exposed occurrences (all)</p> <p>Irritability subjects affected / exposed occurrences (all)</p> <p>Depression subjects affected / exposed occurrences (all)</p> <p>Dyssomnia subjects affected / exposed occurrences (all)</p> <p>Libido decreased subjects affected / exposed occurrences (all)</p> <p>Agitation subjects affected / exposed occurrences (all)</p> <p>Hallucination, visual</p>	<p>8 / 102 (7.84%) 8</p> <p>5 / 102 (4.90%) 5</p> <p>4 / 102 (3.92%) 5</p> <p>2 / 102 (1.96%) 2</p> <p>2 / 102 (1.96%) 2</p> <p>2 / 102 (1.96%) 2</p> <p>1 / 102 (0.98%) 1</p>		

<p>subjects affected / exposed occurrences (all)</p> <p>Premature ejaculation subjects affected / exposed occurrences (all)</p> <p>Sleep disorder subjects affected / exposed occurrences (all)</p>	<p>1 / 102 (0.98%) 1</p> <p>1 / 102 (0.98%) 1</p> <p>1 / 102 (0.98%) 1</p>		
<p>Infections and infestations</p> <p>Conjunctivitis subjects affected / exposed occurrences (all)</p> <p>Gingivitis subjects affected / exposed occurrences (all)</p>	<p>1 / 102 (0.98%) 1</p> <p>1 / 102 (0.98%) 1</p>		
<p>Metabolism and nutrition disorders</p> <p>Decreased appetite subjects affected / exposed occurrences (all)</p> <p>Diabetes mellitus subjects affected / exposed occurrences (all)</p> <p>Hypoglycaemia subjects affected / exposed occurrences (all)</p> <p>Increased appetite subjects affected / exposed occurrences (all)</p>	<p>2 / 102 (1.96%) 2</p> <p>1 / 102 (0.98%) 1</p> <p>1 / 102 (0.98%) 1</p> <p>1 / 102 (0.98%) 1</p>		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 June 2012	After having completed the first 12-month period, the cohort of French patients had the possibility to continue and receive prolonged treatment and follow-up until pitolisant (BF2.649) marketing authorization (Amendment N°2 of the 6th of June 2012 for France only).

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31529094>