



## Clinical trial results:

**A randomized, double blind study comparing BF2.649 (Pitolisant) to placebo in two parallel groups on the weekly frequency of cataplexy attacks and Excessive Daytime Sleepiness in narcoleptic patients with cataplexy**

### Summary

EudraCT number	2012-003076-39
Trial protocol	HU BG CZ
Global end of trial date	28 January 2015

### Results information

Result version number	v1 (current)
This version publication date	28 November 2024
First version publication date	28 November 2024

### Trial information

#### Trial identification

Sponsor protocol code	P11-05
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	abbreviated name: HARMONY CTP

Notes:

### Sponsors

Sponsor organisation name	Bioprojet
Sponsor organisation address	9 Rue Rameau, Paris, France, 75002
Public contact	Clinical Development Director, Bioprojet Pharma, (33) 147 03 66 33, contact@bioprojet.com
Scientific contact	Clinical Development Director, Bioprojet Pharma, (33) 147 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	14 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 January 2015
Global end of trial reached?	Yes
Global end of trial date	28 January 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The main objective was to confirm the efficacy of pitolisant (BF2.649) compared to placebo to decrease the frequency of cataplexy attacks and to reduce EDS (Excessive Daytime Sleepiness) in patients suffering from narcolepsy with cataplexy.

Protection of trial subjects:

An independent Safety Data Monitoring Committee (SDMC) was implemented and served to monitor the study progress and safety data. The SDMC reviewed blinded study information during the conduct of the study and provided the sponsor with recommendations regarding study modification, continuation or termination.

Monitoring visits to the study centers were conducted periodically during the study, in order to ensure that the clinical investigators continued to meet their contractual, clinical and regulatory obligations with regard to protocol compliance, adherence to regulatory and ethical requirements and the protection of the patients' rights and safety.

Background therapy:

Several antiepileptic treatments (e.g. sodium oxybate, fluoxetine, venlafaxine) were authorized on the condition that treatment at stable doses had been taken for at least 1 month prior to the trial and the dose was not changed throughout the trial.

Evidence for comparator: -

Actual start date of recruitment	19 April 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Czech Republic: 6
Country: Number of subjects enrolled	Hungary: 19
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 1
Country: Number of subjects enrolled	Serbia: 16
Country: Number of subjects enrolled	Turkey: 9
Country: Number of subjects enrolled	Russian Federation: 40
Country: Number of subjects enrolled	Ukraine: 8
Worldwide total number of subjects	106
EEA total number of subjects	32

Notes:

<b>Subjects enrolled per age group</b>	
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)	105
From 65 to 84 years	1
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Date of first patient enrolled: April 19th 2013, recruitment ended mid November 2014

### Pre-assignment

Screening details:

During the screening visit, the investigator checked the inclusion and exclusion criteria and performed all required screening assessments. For patients treated with prohibited treatments, a 1 week wash-out period was conducted. 117 patients were screened for inclusion. Of those, 106 patients were eligible for entry into the study.

### Pre-assignment period milestones

Number of subjects started	106
Number of subjects completed	105

### Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 1
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### Period 1

Period 1 title	Double-Blind (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Blinding implementation details:

BF2.649 and placebo at different doses were provided in capsules. The capsules were identical in appearance to ensure that neither the patient nor the investigator or members of the clinical staff knew the identity of the study medication.

### Arms

Are arms mutually exclusive?	Yes
Arm title	BF2.649 Treatment arm (Double-blind)

Arm description:

Participants who qualified for treatment were administered a Pitolisant (BF2.649) capsule by escalating doses (5-, 10-, 20-, or 40 mg/d) orally daily (OD), before breakfast with a glass of water.

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

Dosage and administration details:

Patients started with BF2.649 at 5 mg OD during first week and then took BF2.649 at 10 mg OD during second week.

For the third week, the dose could be increased up to 20 mg OD or remained at medium dose (10 mg OD) or even decreased at low dose (5 mg OD), on the basis of individual efficacy and tolerance results. At D21, an individual dose adjustment could be performed again: the investigator determined the optimum dose of study treatment (i.e 5, 10, 20 mg or 40 mg OD) based on efficacy and tolerability, and assigned the patient to receive this optimum dose for the following 4 weeks.

Arm title	Placebo arm (Double-blind)
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**Arm description:**

Participants who qualified for treatment were administered a placebo capsule orally daily before breakfast with a glass of water

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

**Dosage and administration details:**

Same dosage regimen than BF2.649 Treatment arm, but with placebo capsules.

<b>Number of subjects in period 1</b> <sup>[1]</sup>	BF2.649 Treatment arm (Double-blind)	Placebo arm (Double-blind)
Started	54	51
Completed	50	48
Not completed	4	3
Consent withdrawn by subject	2	1
Patient's decision/lack of efficacy/adverse event	1	-
Patient's decision and lack of efficacy	1	1
Protocol deviation	-	1

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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: One included patient was prematurely withdrawn.

## Baseline characteristics

### Reporting groups

Reporting group title	BF2.649 Treatment arm (Double-blind)
Reporting group description:	
Participants who qualified for treatment were administered a Pitolisant (BF2.649) capsule by escalating doses (5-, 10-, 20-, or 40 mg/d) orally daily (OD), before breakfast with a glass of water.	
Reporting group title	Placebo arm (Double-blind)
Reporting group description:	
Participants who qualified for treatment were administered a placebo capsule orally daily before breakfast with a glass of water	

Reporting group values	BF2.649 Treatment arm (Double-blind)	Placebo arm (Double-blind)	Total
Number of subjects	54	51	105
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	54	50	104
From 65-84 years	0	1	1
85 years and over	0	0	0
Age continuous			
Units: years			
median	34	39	
full range (min-max)	18 to 64	18 to 66	-
Gender categorical			
Units: Subjects			
Female	28	24	52
Male	26	27	53

## End points

### End points reporting groups

Reporting group title	BF2.649 Treatment arm (Double-blind)
Reporting group description: Participants who qualified for treatment were administered a Pitolisant (BF2.649) capsule by escalating doses (5-, 10-, 20-, or 40 mg/d) orally daily (OD), before breakfast with a glass of water.	
Reporting group title	Placebo arm (Double-blind)
Reporting group description: Participants who qualified for treatment were administered a placebo capsule orally daily before breakfast with a glass of water	

### Primary: Change in the Weekly Rate of Cataplexy (WRC)

End point title	Change in the Weekly Rate of Cataplexy (WRC)
End point description: The measure of anticataplectic efficacy was assessed by the change in the average number of cataplexy attacks per week between the 2 weeks of baseline (Day-14 to Day 0) and the 4 weeks of stable treatment period.	
End point type	Primary
End point timeframe: Between the 2 weeks of baseline (Day-14 to Day 0) and the 4 weeks of stable treatment period (Double-Bind).	

End point values	BF2.649 Treatment arm (Double-blind)	Placebo arm (Double-blind)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	51		
Units: number of cataplexy attacks per week				
geometric mean (confidence interval 95%)				
Baseline rate of WRC	9.15 (7.60 to 11.01)	7.31 (6.02 to 8.87)		
Stable treatment period rate of WRC	2.27 (1.51 to 3.41)	4.51 (2.90 to 7.02)		

### Statistical analyses

Statistical analysis title	Reduction of cataplexy attacks
Statistical analysis description: The reduction of cataplexy by 75% (WCRs/b=0.25) in the pitolisantgroup, higher than with placebo (38%; WCRs/b=0.62), was shown highly significant (Poisson regression adjusted for baseline, rate Ratio rR=0.51, 95%CI 0.43 to 0.60; p<0.0001;	
Comparison groups	BF2.649 Treatment arm (Double-blind) v Placebo arm (Double-blind)

Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Poisson regression adjusted for baseline
Parameter estimate	Rate Ratio
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	0.6

### Secondary: Number of cataplexy attacks per week (as recorded in CRF): change during the 2 weeks of end of treatment period

End point title	Number of cataplexy attacks per week (as recorded in CRF): change during the 2 weeks of end of treatment period
End point description:	Change in the average number of cataplexy attacks per week (as recorded in CRF) between the 2 weeks of baseline [(V1+V2) / 2], and the 2 weeks of end treatment period [(V5+V6) / 2];
End point type	Secondary
End point timeframe:	Change in the average number of cataplexy attacks per week (as recorded in CRF) between the 2 weeks of baseline [(V1+V2) / 2], and the 2 weeks of end treatment period [(V5+V6) / 2];

End point values	BF2.649 Treatment arm (Double-blind)	Placebo arm (Double-blind)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	51		
Units: Number of cataplexy attacks per week				
geometric mean (confidence interval 95%)				
Baseline (BL) - (Wk1+Wk2)/2	9.15 (7.60 to 11.01)	7.31 (6.02 to 8.87)		
Final (F) - (Wk8+Wk9)/2	1.99 (1.29 to 3.05)	4.26 (2.72 to 6.66)		
F/BL	0.22 (0.15 to 0.32)	0.58 (0.40 to 0.85)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of patients with high frequency cataplexy episodes

End point title	Proportion of patients with high frequency cataplexy episodes
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End point description:	
Proportion of patients with high frequency cataplexy episodes	
End point type	Secondary
End point timeframe:	
During whole double blind treatment duration	

End point values	BF2.649 Treatment arm (Double-blind)	Placebo arm (Double-blind)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	51		
Units: Patients with high frequency of cataplex				
High frequency at baseline > 15	15	9		
High frequency at stable dose > 15	4	12		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Epworth Sleepiness Scale (ESS) score

End point title	Epworth Sleepiness Scale (ESS) score
End point description:	
ESS score: difference between the mean value during baseline $[(V1+V2) / 2]$ and the mean value during end treatment period $[(V5+V6) / 2]$	
End point type	Secondary
End point timeframe:	
During study double blind treatment	

End point values	BF2.649 Treatment arm (Double-blind)	Placebo arm (Double-blind)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	51		
Units: Score				
arithmetic mean (standard deviation)				
Baseline (BL)	17.4 (± 3.3)	17.3 (± 3.3)		
Final (F)	12.0 (± 5.4)	15.4 (± 5)		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events AEs were reported during the study course and up to one month after the last study visit.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

### Reporting groups

Reporting group title	Pitolisant (BF2.649)
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Pitolisant (BF2.649)	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 54 (0.00%)	0 / 51 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 1.9 %

Non-serious adverse events	Pitolisant (BF2.649)	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 54 (35.19%)	17 / 51 (33.33%)	
Cardiac disorders			
Heart rate increased			
subjects affected / exposed	2 / 54 (3.70%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Bundle branch block right			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Electrocardiogram T wave inversion			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Hypertension			

subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Palpitations			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Sinus tachycardia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 54 (9.26%)	5 / 51 (9.80%)	
occurrences (all)	5	6	
Dizziness			
subjects affected / exposed	0 / 54 (0.00%)	2 / 51 (3.92%)	
occurrences (all)	0	2	
Migraine			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Sciatica			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 54 (3.70%)	2 / 51 (3.92%)	
occurrences (all)	2	2	
Blood and lymphatic system disorders			
Blood cholesterol increased			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Blood glucose increased			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Blood triglycerides increased			

subjects affected / exposed occurrences (all)	0 / 54 (0.00%) 0	1 / 51 (1.96%) 1	
Immune system disorders Monocyte count increased subjects affected / exposed occurrences (all)	0 / 54 (0.00%) 0	1 / 51 (1.96%) 1	
Neutrophil count increased subjects affected / exposed occurrences (all)	0 / 54 (0.00%) 0	1 / 51 (1.96%) 1	
White blood cell analysis abnormal subjects affected / exposed occurrences (all)	0 / 54 (0.00%) 0	1 / 51 (1.96%) 1	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	3 / 54 (5.56%) 3	0 / 51 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 54 (3.70%) 2	0 / 51 (0.00%) 0	
Upper respiratory tract inflammation subjects affected / exposed occurrences (all)	0 / 54 (0.00%) 0	1 / 51 (1.96%) 1	
Hepatobiliary disorders Cholecystitis chronic subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1	0 / 51 (0.00%) 0	
Skin and subcutaneous tissue disorders Wound subjects affected / exposed occurrences (all)	0 / 54 (0.00%) 0	1 / 51 (1.96%) 1	
Psychiatric disorders Irritability subjects affected / exposed occurrences (all)	3 / 54 (5.56%) 4	1 / 51 (1.96%) 1	
Somnolence			

subjects affected / exposed	1 / 54 (1.85%)	3 / 51 (5.88%)	
occurrences (all)	1	3	
Anxiety			
subjects affected / exposed	3 / 54 (5.56%)	0 / 51 (0.00%)	
occurrences (all)	3	0	
Apathy			
subjects affected / exposed	1 / 54 (1.85%)	2 / 51 (3.92%)	
occurrences (all)	1	2	
Dyssomnia			
subjects affected / exposed	2 / 54 (3.70%)	1 / 51 (1.96%)	
occurrences (all)	2	1	
Fatigue			
subjects affected / exposed	1 / 54 (1.85%)	1 / 51 (1.96%)	
occurrences (all)	1	1	
Depressed mood			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Hallucination			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Hypersomnia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Sleep disorder			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	

**More information**

**Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 October 2012	Addition of the pitolisant 40 mg once daily dose in the treatment scheme

Notes:

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**Interruptions (globally)**

Were there any global interruptions to the trial? No

**Limitations and caveats**

None reported