Clinical trial results:
Randomized placebo controlled trial assessing the efficacy and safety of BP1.4979 in smoking cessation

Summary

EudraCT number	2012-002731-28
Trial protocol	CZ PL
Global end of trial date	09 October 2014

Results information

Result version number	v1 (current)
This version publication date	26 June 2022
First version publication date	26 June 2022

Trial information

Trial identification

Sponsor protocol code	P12-01/BP1.4979

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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 Pharma, +33 1 47 03 66 33, contact@bioprojet.com
Scientific contact	Clinical Development Director, Bioprojet Pharma, +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	18 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 July 2014
Global end of trial reached?	Yes
Global end of trial date	09 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess efficacy on smoking abstinence of BP1.4979 administered at 3, 10, 15 mg o.d. vs placebo during 12 weeks in healthy male or female heavy smokers.

Protection of trial subjects:

The study was conducted according to ICH and GCP guidelines related to subject's welfare. A Data Safety Monitoring Board (DSMB) 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: -

Evidence for comparator: -

Actual start date of recruitment	18 February 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: 81
Country: Number of subjects enrolled	Czechia: 41
Country: Number of subjects enrolled	France: 96
Worldwide total number of subjects	218
EEA total number of subjects	218

Notes:

Subjects enrolled per age group

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)	217
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

During the screening visit, the investigator checked the inclusion and exclusion criteria and performed all required screening assessments. 290 patients were screened for inclusion. Of those, 219 patients were randomized and 218 were enrolled and started study treatment.

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, Data analyst

Blinding implementation details:

Prior to the start of the study, a copy of the master randomization code was supplied in sealed envelopes to the Investigator and pharmacist, and the bioanalytical centre. These copies were stored in confidential manner up to the unblinding after database lock. The study blind was to be only broken after database lock except in the case of emergency to protect patients.

Arms

Are arms mutually exclusive?	Yes
Arm title	BP1.4979 3mg treatment arm (Double-blind period)

Arm description:

Patients receiving one tablet of BP1.4979 3 mg orally daily.

Arm type	Experimental
Investigational medicinal product name	BP1.4979
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were to take one tablet of 3mg per day in the morning during breakfast with a glass of water for 12 weeks.

Arm title	BP1.4979 10 mg treatment arm (Double-blind period)

Arm description:

Patients receiving one tablet of BP1.4979 10 mg orally daily.

Arm type	Experimental
Investigational medicinal product name	BP1.4979
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were to take one tablet of 10mg per day in the morning during breakfast with a glass of water for 12 weeks.

Arm title	BP1.4979 15 mg treatment arm (Double-blind period)

Arm description:

Patients receiving one tablet of BP1.4979 15 mg orally daily.

Arm type	Experimental

Investigational medicinal product name	BP1.4979
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were to take one tablet of 15 mg per day in the morning during breakfast with a glass of water for 12 weeks.

Arm title	Placebo treatment arm (Double-blind period)

Arm description:

Patients taking one placebo tablet orally daily

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

Dosage and administration details:

Patients were to take one tablet of placebo per day in the morning during breakfast with a glass of water for 12 weeks.

Number of subjects in period 1	BP1.4979 3mg treatment arm (Double-blind period)	BP1.4979 10 mg treatment arm (Double-blind period)	BP1.4979 15 mg treatment arm (Double-blind period)
Started	52	53	58
Completed	37	35	30
Not completed	15	18	28
Other	15	18	28

Number of subjects in period 1	Placebo treatment arm (Double-blind period)
Started	55
Completed	33
Not completed	22
Other	22

Baseline characteristics

Reporting groups	
Reporting group title	BP1.4979 3mg treatment arm (Double-blind period)
Reporting group description:	
Patients receiving one tablet of BP1.4979 3 mg orally daily.	
Reporting group title	BP1.4979 10 mg treatment arm (Double-blind period)
Reporting group description:	
Patients receiving one tablet of BP1.4979 10 mg orally daily.	
Reporting group title	BP1.4979 15 mg treatment arm (Double-blind period)
Reporting group description:	
Patients receiving one tablet of BP1.4979 15 mg orally daily.	
Reporting group title	Placebo treatment arm (Double-blind period)
Reporting group description:	
Patients taking one placebo tablet orally daily	

Reporting group values	BP1.4979 3mg treatment arm (Double-blind period)	BP1.4979 10 mg treatment arm (Double-blind period)	BP1.4979 15 mg treatment arm (Double-blind period)
Number of subjects	52	53	58
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)	52	53	57
From 65-84 years	0	0	1
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	45.9	48.4	46.2
standard deviation	± 10.8	± 10.4	± 9.1
Gender categorical Units: Subjects			
Female	28	20	26
Male	24	33	32

Reporting group values	Placebo treatment arm (Double-blind period)	Total	
Number of subjects	55	218	
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)	55	217	
From 65-84 years	0	1	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	43.4		
standard deviation	± 8.7	-	
Gender categorical			
Units: Subjects			
Female	32	106	
Male	23	112	

End points

End points reporting groups

Reporting group title	BP1.4979 3mg treatment arm (Double-blind period)
Reporting group description:	
Patients receiving one tablet of BP1.4979 3 mg orally daily.	
Reporting group title	BP1.4979 10 mg treatment arm (Double-blind period)
Reporting group description:	
Patients receiving one tablet of BP1.4979 10 mg orally daily.	
Reporting group title	BP1.4979 15 mg treatment arm (Double-blind period)
Reporting group description:	
Patients receiving one tablet of BP1.4979 15 mg orally daily.	
Reporting group title	Placebo treatment arm (Double-blind period)
Reporting group description:	
Patients taking one placebo tablet orally daily	

Primary: Continuous Abstinence Proportion (CAP)

End point title	Continuous Abstinence Proportion (CAP)
End point description:	
The primary efficacy criterion was the CAP defined as the ratio of abstinence period over the treatment period (Double-blind). The continuous abstinence was measured from the patient's diary and was to be confirmed by exhaled CO (≤10 ppm).	
End point type	Primary
End point timeframe:	
From beginning of treatment to end of double-blind treatment period	

End point values	BP1.4979 3mg treatment arm (Double-blind period)	BP1.4979 10 mg treatment arm (Double-blind period)	BP1.4979 15 mg treatment arm (Double-blind period)	Placebo treatment arm (Double-blind period)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10[1]	9[2]	8[3]	14[4]
Units: CAP				
arithmetic mean (standard deviation)	57.0 (± 36.1)	45.9 (± 27.0)	59.1 (± 28.1)	53.3 (± 24.8)

Notes:

[1] - The CAP was calculated in patients who were abstinent during the study.

[2] - The CAP was calculated in patients who were abstinent during the study.

[3] - The CAP was calculated in patients who were abstinent during the study.

[4] - The CAP was calculated in patients who were abstinent during the study.

Statistical analyses

Statistical analysis title	Linear mixed model adjusted
Statistical analysis description:	
No statistically significant difference between treatment groups was shown using the linear mixed model adjusted for the baseline FTND (Fagerström Test of Nicotine Dependence).	
Comparison groups	BP1.4979 10 mg treatment arm (Double-blind period) v BP1.4979 3mg treatment arm (Double-blind period) v

	mg treatment arm (Double-blind period) v Placebo treatment arm (Double-blind period)
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Mixed models analysis

Secondary: Daily cigarettes consumption

End point title	Daily cigarettes consumption
End point description:	
Mean change in the daily cigarette consumption from baseline to V4.	
End point type	Secondary
End point timeframe:	
From beginning of treatment to end of double-blind treatment period.	

End point values	BP1.4979 3mg treatment arm (Double-blind period)	BP1.4979 10 mg treatment arm (Double-blind period)	BP1.4979 15 mg treatment arm (Double-blind period)	Placebo treatment arm (Double-blind period)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	35	35	33
Units: Number of cigarettes per day				
arithmetic mean (standard deviation)	-9.3 (± 7.0)	-10.6 (± 8.9)	-11.7 (± 7.2)	-11.6 (± 7.4)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From beginning of treatment to 1 week after end of treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	6.1

Reporting groups	
Reporting group title	BP1.4979 3mg treatment arm
Reporting group description: Patients who received BP1.4979 3mg during Double-blind period.	
Reporting group title	BP1.4979 10 mg treatment arm
Reporting group description: Patients who received BP1.4979 10 mg during Double-blind period.	
Reporting group title	P1.4979 15 mg treatment arm
Reporting group description: Patients who received BP1.4979 15 mg during Double-blind period.	
Reporting group title	Placebo arm
Reporting group description: Patients taking placebo during Double-blind period.	

Serious adverse events	BP1.4979 3mg treatment arm	BP1.4979 10 mg treatment arm	P1.4979 15 mg treatment arm
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	1 / 58 (1.72%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0		
Investigations			
Investigation	Additional description: The patient was hospitalized to perform a Ventilatory Polygraphy for Obstructive Sleep Apnea syndrome (OSA) suspicion with a complaint of blockpnea.		
subjects affected / exposed	0 / 52 (0.00%)	0 / 53 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Surgery	Additional description: Surgery for inguinal hernia (10mg treatment arm) Surgery for discal hernia (placebo arm)		
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			

Depression			
subjects affected / exposed	0 / 52 (0.00%)	0 / 53 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 55 (3.64%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Investigations			
Investigation	Additional description: The patient was hospitalized to perform a Ventilatory Polygraphy for Obstructive Sleep Apnea syndrome (OSA) suspicion with a complaint of blockpnea.		
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Surgery	Additional description: Surgery for inguinal hernia (10mg treatment arm) Surgery for discal hernia (placebo arm)		
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	BP1.4979 3mg treatment arm	BP1.4979 10 mg treatment arm	P1.4979 15 mg treatment arm
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 52 (50.00%)	37 / 53 (69.81%)	42 / 58 (72.41%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	1 / 58 (1.72%)
occurrences (all)	0	1	1
General disorders and administration			

site conditions			
Asthenia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	1 / 58 (1.72%)
occurrences (all)	0	1	1
Influenza like illness			
subjects affected / exposed	1 / 52 (1.92%)	1 / 53 (1.89%)	3 / 58 (5.17%)
occurrences (all)	1	1	3
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 52 (3.85%)	0 / 53 (0.00%)	0 / 58 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 52 (0.00%)	3 / 53 (5.66%)	2 / 58 (3.45%)
occurrences (all)	0	3	2
Cough			
subjects affected / exposed	0 / 52 (0.00%)	0 / 53 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 52 (0.00%)	4 / 53 (7.55%)	3 / 58 (5.17%)
occurrences (all)	0	4	4
Anxiety			
subjects affected / exposed	1 / 52 (1.92%)	1 / 53 (1.89%)	2 / 58 (3.45%)
occurrences (all)	1	1	2
Depression			
subjects affected / exposed	0 / 52 (0.00%)	0 / 53 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Sleep disorder			
subjects affected / exposed	1 / 52 (1.92%)	2 / 53 (3.77%)	0 / 58 (0.00%)
occurrences (all)	1	2	0
Investigations			
Laboratory test abnormal			
subjects affected / exposed	0 / 52 (0.00%)	2 / 53 (3.77%)	2 / 58 (3.45%)
occurrences (all)	0	2	2
Weight increased			

subjects affected / exposed	1 / 52 (1.92%)	2 / 53 (3.77%)	0 / 58 (0.00%)
occurrences (all)	1	2	0
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	0 / 52 (0.00%)	2 / 53 (3.77%)	0 / 58 (0.00%)
occurrences (all)	0	2	0
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 52 (9.62%)	5 / 53 (9.43%)	7 / 58 (12.07%)
occurrences (all)	6	8	8
Migraine			
subjects affected / exposed	2 / 52 (3.85%)	1 / 53 (1.89%)	2 / 58 (3.45%)
occurrences (all)	3	1	3
Dizziness			
subjects affected / exposed	0 / 52 (0.00%)	2 / 53 (3.77%)	0 / 58 (0.00%)
occurrences (all)	0	2	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 52 (0.00%)	0 / 53 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 52 (1.92%)	1 / 53 (1.89%)	4 / 58 (6.90%)
occurrences (all)	1	1	4
Diarrhoea			
subjects affected / exposed	1 / 52 (1.92%)	1 / 53 (1.89%)	3 / 58 (5.17%)
occurrences (all)	1	1	3
Toothache			
subjects affected / exposed	0 / 52 (0.00%)	2 / 53 (3.77%)	1 / 58 (1.72%)
occurrences (all)	0	2	1
Abdominal discomfort			
subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Dry mouth			
subjects affected / exposed	0 / 52 (0.00%)	0 / 53 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 52 (0.00%)	1 / 53 (1.89%)	2 / 58 (3.45%)
occurrences (all)	0	1	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 52 (11.54%)	7 / 53 (13.21%)	8 / 58 (13.79%)
occurrences (all)	7	8	10
Bronchitis			
subjects affected / exposed	3 / 52 (5.77%)	1 / 53 (1.89%)	2 / 58 (3.45%)
occurrences (all)	3	1	2
Urinary tract infection			
subjects affected / exposed	0 / 52 (0.00%)	0 / 53 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Tooth abscess			
subjects affected / exposed	0 / 52 (0.00%)	0 / 53 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	1 / 52 (1.92%)	1 / 53 (1.89%)	2 / 58 (3.45%)
occurrences (all)	1	1	2

Non-serious adverse events	Placebo arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 55 (61.82%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	3		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Influenza like illness			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Immune system disorders			

Hypersensitivity			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Anxiety			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Sleep disorder			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Investigations			
Laboratory test abnormal			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Weight increased			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Nervous system disorders			

Headache subjects affected / exposed occurrences (all) Migraine subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all)	5 / 55 (9.09%) 11 0 / 55 (0.00%) 0 0 / 55 (0.00%) 0		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	2 / 55 (3.64%) 2		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Toothache subjects affected / exposed occurrences (all) Abdominal discomfort subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1 0 / 55 (0.00%) 0 1 / 55 (1.82%) 1 2 / 55 (3.64%) 2 3 / 55 (5.45%) 3		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1		
Infections and infestations Nasopharyngitis			

subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	4		
Bronchitis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Tooth abscess			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 July 2012	The name of visit 2 (V2) was changed to V-TQD (Tobacco Quit Date visit) leading to the change in the name of subsequent visits. A phone contact was decided 15 days before the follow-up visits V6, V7, and V8. If the patient was abstinent, the visit was maintained and in case of smoking resumption, the patient was withdrawn from the study. Modification of inclusion criteria No. 4 and No. 6, and non-inclusion criteria No. 4, No. 11, and No. 16. Update of the center/investigator list.
22 October 2012	Addition of questionnaires to assess sexual (PATHOS) and gambling addictions (BBGS) and extrapyramidal symptoms (SAS). Modification of inclusion criterion No. 10 to allow the inclusion of patients treated with fluoxetine and paroxetine. Update of the center/investigator list.
07 November 2012	Reduction of the follow-up period from 9 months to 3 months (Consequently, the telephone call approved in Amendment No1 was cancelled). Follow-up of all patients whether or not they had stop smoking. For Poland only: modification of inclusion criterion No. 11: "females of child-bearing potential must use a medically accepted highly effective method of birth control (e.g. combined contraceptive pills, progestogen-only pill (POP), intrauterine device (IUD), contraceptive implant (inserted for less than 3 years) and contraceptive patch (oestrogen and progestogen)).
18 December 2013	Modification of the exclusion criterion No. 11 in order to select patients without bias of smoking cigars or pipes and No. 16 in order to select patients without Nicotine treatment. In addition, based on the safety and efficacy analysis of the 46 patients who completed the 12-weeks double-blind period (at V4 as planned in the protocol) and on pharmacokinetic considerations, the possibility was accepted to increase the number of randomized patients from 250 to 350 in order to assess the effect of an additional arm of patients treated with 15 mg BP1.4979 b.i.d. for 12 weeks. The enrolment of new randomized patients had to lead to 5 balanced groups of 60 patients.
23 May 2014	Based on the futility analysis planned in the protocol and detailed in the Futility Analysis Plan (See Appendix 16.3.1) dated on 17 January 2014, the inclusion of randomized patients to assess the effect of an additional arm consisting in 15 mg BP1.4979 b.i.d. was not implemented. Addition of an interim analysis on both efficacy and safety results before the study completion, but after the completion of the treatment period. This required intermediate database lock on 01 April 2015.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported