Clinical trial results:
A Phase 2, Single-Arm, Open-Label Study to Evaluate the Safety and Tolerability of PBI-4050 and of its Effects on the Inflammatory, Fibrosis, Diabetes and Obesity Biomarkers in Subjects with Alström Syndrome

Summary

EudraCT number	2015-001625-16
Trial protocol	GB
Global end of trial date	04 June 2018

Results information

Result version number	v1 (current)
This version publication date	23 July 2021
First version publication date	23 July 2021

Trial information

Trial identification

Sponsor protocol code	PBI-4050-ATX-9-05

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02739217
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Liminal BioSciences
Sponsor organisation address	Unit 1 Iconix Park, Cambridge, United Kingdom, CB22 3EG
Public contact	Catherine Simcock, Liminal BioSciences, c.simcock@liminalbiosciences.com
Scientific contact	Catherine Simcock, Liminal BioSciences, c.simcock@liminalbiosciences.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	08 July 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 June 2018
Global end of trial reached?	Yes
Global end of trial date	04 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the safety and tolerability of 800 mg PBI-4050 (the Investigational Medicinal Product), administered orally once daily for 24 weeks, in subjects with Alström Syndrome.

Protection of trial subjects:

A Data Safety Monitoring Board (DSMB) reviewed individual subject safety data in an ongoing fashion during the course of the study, including safety data collected during the 36- or 48-week Extension Period (EP). When 8 subjects completed 1 month of study drug treatment, the DSMB met formally and determined, based on the adverse event profile, whether the study should be stopped or continued with either the current 800 mg dose of PBI-4050 or a reduced dose of 400 mg. The DSMB also determined if the safety data continued to support an additional 36 or 48 weeks of study drug treatment.

Background therapy:

Subjects were allowed to continue their individual current therapy during the study, with dose adjustments (if deemed necessary by the Investigator) documented in the subjects' medical records and in the electronic case report form.

Evidence for comparator:

This was an uncontrolled study with all subjects receiving the same dose and frequency of PBI-4050 (800 mg/day for up to 72 weeks).

Actual start date of recruitment	22 February 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Regulatory reason, Scientific research
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 12
Worldwide total number of subjects	12
EEA total number of subjects	12

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)	1
Adults (18-64 years)	11
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a single-center study conducted at a specialized Alström syndrome (ALMS) center in the United Kingdom (Queen Elizabeth Hospital in Birmingham).

Pre-assignment

Screening details:

15 subjects were screened from 22 February 2016 to 04 June 2018, with 3 subjects not meeting eligibility criteria (i.e., screen failures).

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	800 mg PBI-4050

Arm description:

Each daily oral dose of 800 mg PBI-4050 consisted of 4 × 200 mg gel capsules taken once daily at approximately the same time each day with a glass of water, at least 1 hour before or 2 hours after a meal for 24 weeks (main study) and, if consented, for up to an additional 36 or 48 weeks in the extension period.

Arm type	Experimental
Investigational medicinal product name	Fezagepras
Investigational medicinal product code	PBI-4050
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Each daily oral dose of 800 mg PBI-4050 consisted of 4 × 200 mg gel capsules taken once daily approximately at the same time each day with a glass of water, at least 1 hour before or 2 hours after a meal for 24 weeks (main study) and, if consented, for up to an additional 36 or 48 weeks in an Extension Period.

Number of subjects in period 1	800 mg PBI-4050
Started	12
Completed	12

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial (overall period)
Reporting group description:	
The Safety Population included all subjects who signed an informed consent form and received at least 1 dose of PBI4050.	

Reporting group values	Overall Trial (overall period)	Total	
Number of subjects	12	12	
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)	1	1	
Adults (18-64 years)	11	11	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	26.1		
standard deviation	± 9.56	-	
Gender categorical			
Units: Subjects			
Female	4	4	
Male	8	8	
Duration of ALMS			
ALMS duration was measured from the diagnosis date to the informed consent form date.			
Units: Years			
arithmetic mean	10.8		
standard deviation	± 5.92	-	

End points

End points reporting groups

Reporting group title	800 mg PBI-4050

Reporting group description:

Each daily oral dose of 800 mg PBI-4050 consisted of 4 × 200 mg gel capsules taken once daily at approximately the same time each day with a glass of water, at least 1 hour before or 2 hours after a meal for 24 weeks (main study) and, if consented, for up to an additional 36 or 48 weeks in the extension period.

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Population included all subjects who signed an informed consent form and received at least 1 dose of PBI4050.

Subject analysis set title	Baseline
Subject analysis set type	Full analysis

Subject analysis set description:

Baseline for comparison of endpoints

Subject analysis set title	Week 12
Subject analysis set type	Full analysis

Subject analysis set description:

Week 12

Subject analysis set title	Week 24
Subject analysis set type	Full analysis

Subject analysis set description:

Week 24

Subject analysis set title	EP Week 12
Subject analysis set type	Full analysis

Subject analysis set description:

EP week 12

Subject analysis set title	EP Week 24
Subject analysis set type	Full analysis

Subject analysis set description:

Week 24

Subject analysis set title	EP Week 36
Subject analysis set type	Full analysis

Subject analysis set description:

EP Week 36

Subject analysis set title	EP Week 48
Subject analysis set type	Full analysis

Subject analysis set description:

EP Week 48

Primary: Safety and Tolerability

End point title	Safety and Tolerability[1]

End point description:

Number of subjects with at least 1 of the following events: treatment-emergent adverse event (TEAE) or treatment-emergent serious adverse event (TESAE); study drug related TEAE/TESAE (TEAEs/TESAEs assessed as possibly, probably, or definitely related to study drug); TEAE leading to permanent discontinuation of study; TEAE leading to death; protocol-defined hypoglycemia; clinically significant clinical laboratory tests; ECG; vital signs; physical examination.

End point type	Primary

End point timeframe:

Week 1 (after first dose of study drug) to Week 72

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: This study was exploratory and aimed to evaluate the safety and tolerability of PBI-4050 and its effects on biomarkers. The study collected data to derive descriptive statistics on secondary endpoints for future studies but no statistical hypotheses were tested. Therefore, a minimum of 8 subjects was deemed necessary for this study.

End point values	800 mg PBI-4050			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Measurable				
TEAEs	12			
TESAEs	2			
Study drug related TEAEs	9			
Study drug related TESAEs	0			
TEAEs - discontinuation	0			
TESAEs - discontinuation	0			
TEAEs - death	0			
Protocol-defined Hypoglycemia	9			
Clinically significant haematology:Haemoglobin	1			
Clinically significant biochemistry:Hypoglycaemia	4			
Clinically significant biochemistry:Triglycerides	1			
Clinically significant biochemistry:Cholesterol	1			
Clinically significant biochemistry:GGT	1			
Clinically significant biochemistry:LFT	4			
Clinically significant ECG	0			
Clinically significant vital signs:Hypertension	1			
Change in phys.exam.:Decreased body weight	6			
Change in phys.exam.:Decreased waist circumference	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Effect of 800 mg PBI-4050 on FPG

End point title	Effect of 800 mg PBI-4050 on FPG

End point description:

To compare the effect of 800 mg PBI-4050 on the change from baseline in FPG at Weeks 12 (n=11; missing value), 24 (n=12), EP 12 (n=10), EP 24 (n=10), EP 36 (n=9), and EP 48 (n=3).

End point type	Secondary

End point timeframe:

Week 1 (baseline) to Week 72

End point values	Baseline	Week 12	Week 24	EP Week 12
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	12	12	12
Units: mmol/L				
arithmetic mean (standard deviation)	8.81 (± 5.29)	0.30 (± 4.96)	0.33 (± 3.59)	0.63 (± 5.23)

End point values	EP Week 24	EP Week 36	EP Week 48	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	12	12	
Units: mmol/L				
arithmetic mean (standard deviation)	0.70 (± 4.57)	1.49 (± 5.38)	-0.93 (± 2.07)	

Statistical analyses

Statistical analysis title	Change from Baseline to Week 12
Statistical analysis description: Statistical analyses based on paired t-test. No changes of note were seen.	
Comparison groups	Baseline v Week 12
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.845
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.03
upper limit	3.63

Statistical analysis title	Change from Baseline to Week 24
Statistical analysis description: Statistical analyses based on paired t-test. No changes of note were seen.	
Comparison groups	Baseline v Week 24
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.76
Method	Paired t-test

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.96
upper limit	2.61

Statistical analysis title	Change from Baseline to EP Week 12
Statistical analysis description:	
Statistical analyses based on paired t-test. No changes of note were seen.	
Comparison groups	EP Week 12 v Baseline
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7123
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.11
upper limit	4.37

Statistical analysis title	Change from Baseline to EP Week 24
Statistical analysis description:	
Statistical analyses based on paired t-test. No changes of note were seen.	
Comparison groups	Baseline v EP Week 24
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6397
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.57
upper limit	3.97

Statistical analysis title	Change from Baseline to EP Week 36
Statistical analysis description:	
Statistical analyses based on paired t-test. No changes of note were seen.	
Comparison groups	Baseline v EP Week 36

Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4305
Method	paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.65
upper limit	5.62

Statistical analysis title	Change from Baseline to EP Week 48
Statistical analysis description:	
Statistical analyses based on paired t-test. No changes of note were seen.	
Comparison groups	Baseline v EP Week 48
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5157
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.06
upper limit	4.2

Secondary: Effect of 800 mg PBI-4050 on HbA1c

End point title	Effect of 800 mg PBI-4050 on HbA1c
End point description:	
To compare the effect of 800 mg PBI-4050 on the change from baseline in HbA1c at Weeks 12 (n=12), 24 (n=12), EP 12 (n=10), EP 24 (n=10), EP 36 (n=9), and EP 48 (n=3).	
End point type	Secondary
End point timeframe:	
Week 1 (baseline) to Week 72	

End point values	Baseline	Week 12	Week 24	EP Week 12
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	12	12	12
Units: percent				
arithmetic mean (standard deviation)	7.34 (± 2.25)	-0.53 (± 0.63)	-0.24 (± 0.83)	0.24 (± 1.88)

End point values	EP Week 24	EP Week 36	EP Week 48	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	12	12	
Units: percent				
arithmetic mean (standard deviation)	-0.28 (± 1.42)	-0.18 (± 1.00)	0.13 (± 0.15)	

Statistical analyses

Statistical analysis title	Change from Baseline to Week 12
Statistical analysis description:	
Statistical analyses based on paired t-test. Some small changes were noted at isolated timepoints but no consistent changes over time were seen.	
Comparison groups	Baseline v Week 12
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0144
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.92
upper limit	-0.13

Statistical analysis title	Change from Baseline to Week 24
Statistical analysis description:	
Statistical analyses based on paired t-test. Some small changes were noted at isolated timepoints but no consistent changes over time were seen.	
Comparison groups	Baseline v Week 24
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.337
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.92
upper limit	-0.13

Statistical analysis title	Change from Baseline to EP Week 12
Statistical analysis description:	
Statistical analyses based on paired t-test. Some small changes were noted at isolated timepoints but no consistent changes over time were seen.	
Comparison groups	Baseline v EP Week 12

Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6958
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	1.58

Statistical analysis title	Change from Baseline to EP Week 24

Statistical analysis description:

Statistical analyses based on paired t-test. Some small changes were noted at isolated timepoints but no consistent changes over time were seen.

Comparison groups	Baseline v EP Week 24
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5476
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.29
upper limit	0.73

Statistical analysis title	Change from Baseline to EP Week 36

Statistical analysis description:

Statistical analyses based on paired t-test. Some small changes were noted at isolated timepoints but no consistent changes over time were seen.

Comparison groups	Baseline v EP Week 36
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6078
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.95
upper limit	0.59

Statistical analysis title	Change from Baseline to EP Week 48

Statistical analysis description:

Statistical analyses based on paired t-test. Some small changes were noted at isolated timepoints but no consistent changes over time were seen.

Comparison groups	Baseline v EP Week 48
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2697
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.25
upper limit	0.51

Secondary: Effect of 800 mg PBI-4050 on fasting insulin

End point title	Effect of 800 mg PBI-4050 on fasting insulin

End point description:

To compare the effect of 800 mg PBI-4050 on the change from baseline in fasting insulin at Weeks 12 (n=12), 24 (n=12), EP 12 (n=10), EP 24 (n=9), EP 36 (n=8; missing value), and EP 48 (n=3).

End point type	Secondary

End point timeframe:

Week 1 (baseline) to Week 72

End point values	Baseline	Week 12	Week 24	EP Week 12
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	12	12	12
Units: picomole(s)/litre				
median (full range (min-max))	360.50 (110.0 to 12750.0)	9.00 (-4350.0 to 2765.0)	-86.00 (-3850.0 to 355.0)	-53.50 (-8550.0 to 126.0)

End point values	EP Week 24	EP Week 36	EP Week 48	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	12	12	
Units: picomole(s)/litre				
median (full range (min-max))	-24.00 (-12369.0 to 395.0)	7.00 (-12548.0 to 1970.0)	193.00 (-12290.0 to 298.0)	

Statistical analyses

Statistical analysis title	Change from Baseline to Week 12
Statistical analysis description: Statistical analyses based on Wilcoxon signed-rank test. No changes of note were seen.	
Comparison groups	Baseline v Week 12
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9658
Method	Wilcoxon signed-rank test

Statistical analysis title	Change from Baseline to Week 24
Statistical analysis description: Statistical analyses based on Wilcoxon signed-rank test. No changes of note were seen.	
Comparison groups	Baseline v Week 24
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4238
Method	Wilcoxon signed-rank test

Statistical analysis title	Change from Baseline to EP Week 12
Statistical analysis description: Statistical analyses based on Wilcoxon signed-rank test. No changes of note were seen.	
Comparison groups	Baseline v EP Week 12
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2324
Method	Wilcoxon signed-rank test

Statistical analysis title	Change from Baseline to EP Week 24
Statistical analysis description: Statistical analyses based on Wilcoxon signed-rank test. No changes of note were seen.	
Comparison groups	Baseline v EP Week 24
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5703
Method	Wilcoxon signed-rank test

Statistical analysis title	Change from Baseline to EP Week 36

Statistical analysis description:	
Statistical analyses based on Wilcoxon signed-rank test. No changes of note were seen.	
Comparison groups	Baseline v EP Week 36
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8438
Method	Wilcoxon signed-rank test

Statistical analysis title	Change from Baseline to EP Week 48
Statistical analysis description:	
Statistical analyses based on Wilcoxon signed-rank test. No changes of note were seen.	
Comparison groups	Baseline v EP Week 48
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon signed-rank test

Secondary: Effect of 800 mg PBI-4050 on HOMA-B Based on C-Peptide and FPG

End point title	Effect of 800 mg PBI-4050 on HOMA-B Based on C-Peptide and FPG
End point description:	
To compare the effect of 800 mg PBI-4050 on the change from baseline in homeostasis model assessment for steady state beta-cell function (HOMA-B) based on C-peptide and fasting plasma glucose at Weeks 12 (n=11; missing value), 24 (n=12), EP 12 (n=10), EP 24 (n=9), EP 36 (n=8; missing value), and EP 48 (n=3).	
End point type	Secondary
End point timeframe:	
Week 1 (baseline) to Week 72	

End point values	Baseline	Week 12	Week 24	EP Week 12
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	12	12	12
Units: None				
arithmetic mean (standard deviation)	158.12 (± 100.81)	52.58 (± 65.82)	-1.60 (± 78.46)	1.70 (± 102.62)

End point values	EP Week 24	EP Week 36	EP Week 48	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	12	12	
Units: None				

arithmetic mean (standard deviation)	24.57 (± 96.75)	1.42 (± 62.99)	60.17 (± 51.68)	

Statistical analyses

Statistical analysis title	Change from Baseline to Week 12
Statistical analysis description:	
Statistical analyses based on paired t-test. Some small changes were noted at isolated timepoints but no consistent changes over time were seen.	
Comparison groups	Baseline v Week 12
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0243
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.36
upper limit	96.8

Statistical analysis title	Change from Baseline to Week 24
Statistical analysis description:	
Statistical analyses based on paired t-test. Some small changes were noted at isolated timepoints but no consistent changes over time were seen.	
Comparison groups	Baseline v Week 24
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.945
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-54.45
upper limit	48.25

Statistical analysis title	Change from Baseline to EP Week 12
Statistical analysis description:	
Statistical analyses based on paired t-test. Some small changes were noted at isolated timepoints but no consistent changes over time were seen.	
Comparison groups	Baseline v EP Week 12

Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9594
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-71.71
upper limit	75.11

Statistical analysis title	Change from Baseline to EP Week 24

Statistical analysis description:

Statistical analyses based on paired t-test. Some small changes were noted at isolated timepoints but no consistent changes over time were seen.

Comparison groups	Baseline v EP Week 24
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4681
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-49.8
upper limit	98.94

Statistical analysis title	Change from Baseline to EP Week 36

Statistical analysis description:

Statistical analyses based on paired t-test. Some small changes were noted at isolated timepoints but no consistent changes over time were seen.

Comparison groups	EP Week 36 v Baseline
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9508
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.24
upper limit	54.09

Statistical analysis title	Change from Baseline to EP Week 48

Statistical analysis description:	
Statistical analyses based on paired t-test. Some small changes were noted at isolated timepoints but no consistent changes over time were seen.	
Comparison groups	Baseline v EP Week 48
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1813
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-68.2
upper limit	188.54

Secondary: Effect of 800 mg PBI-4050 on HOMA-S Based on C-Peptide and FPG

End point title	Effect of 800 mg PBI-4050 on HOMA-S Based on C-Peptide and FPG

End point description:

To compare the effect of 800 mg PBI-4050 on the change from baseline in homeostasis model assessment for insulin sensitivity (HOMA-S) based on C-peptide and FPG at Weeks 12 (n=11; missing value), 24 (n=12), EP 12 (n=10), EP 24 (n=9; missing value), EP 36 (n=8; missing value), and EP 48 (n=3).

End point type	Secondary

End point timeframe:

Week 1 (baseline) to Week 72

End point values	Baseline	Week 12	Week 24	EP Week 12
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	12	12	12
Units: None				
median (full range (min-max))	22.70 (10.8 to 160.7)	-1.30 (-114.9 to 33.6)	-1.90 (-97.0 to 85.5)	-0.40 (-42.4 to 34.3)

End point values	EP Week 24	EP Week 36	EP Week 48	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	12	12	
Units: None				
median (full range (min-max))	2.70 (-120.7 to 30.8)	-4.70 (-120.2 to 29.6)	-9.50 (-25.5 to 142.1)	

Statistical analyses

Statistical analysis title	Change from Baseline to Week 12
Statistical analysis description: Statistical analyses based on Wilcoxon signed-rank test. No changes of note were seen.	
Comparison groups	Baseline v Week 12
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6377
Method	Wilcoxon signed-rank test

Statistical analysis title	Change from Baseline to Week 24
Statistical analysis description: Statistical analyses based on Wilcoxon signed-rank test. No changes of note were seen.	
Comparison groups	Baseline v Week 24
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8501
Method	Wilcoxon signed-rank test

Statistical analysis title	Change from Baseline to EP Week 12
Statistical analysis description: Statistical analyses based on Wilcoxon signed-rank test. No changes of note were seen.	
Comparison groups	Baseline v EP Week 12
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9219
Method	Wilcoxon signed-rank test

Statistical analysis title	Change from Baseline to EP Week 24
Statistical analysis description: Statistical analyses based on Wilcoxon signed-rank test. No changes of note were seen.	
Comparison groups	Baseline v EP Week 24
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon signed-rank test

Statistical analysis title	Change from Baseline to EP Week 36

Statistical analysis description:	
Statistical analyses based on Wilcoxon signed-rank test. No changes of note were seen.	
Comparison groups	Baseline v EP Week 36
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4609
Method	Wilcoxon signed-rank test

Statistical analysis title	Change from Baseline to EP Week 48
Statistical analysis description:	
Statistical analyses based on Wilcoxon signed-rank test. No changes of note were seen.	
Comparison groups	Baseline v EP Week 48
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon signed-rank test

Secondary: Effect of 800 mg PBI-4050 on ACR	
End point title	Effect of 800 mg PBI-4050 on ACR
End point description:	
To compare the effect of 800 mg PBI-4050 on the change from baseline in ACR at Weeks 12 (n=12), 24 (n=11; missing value), EP 12 (n=10), EP 24 (n=10), EP 36 (n=9), and EP 48 (n=3).	
End point type	Secondary
End point timeframe:	
Week 1 (baseline) to Week 72	

End point values	Baseline	Week 12	Week 24	EP Week 12
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	12	12	12
Units: mg/mmol				
median (full range (min-max))	10.30 (0.7 to 44.5)	0.90 (-3.2 to 61.4)	0.30 (-8.4 to 35.9)	1.25 (-9.8 to 50.5)

End point values	EP Week 24	EP Week 36	EP Week 48	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	12	12	
Units: mg/mmol				
median (full range (min-max))	1.30 (-11.0 to 67.2)	1.60 (-0.2 to 133.8)	1.60 (-11.3 to 13.8)	

Statistical analyses

Statistical analysis title	Change from Baseline to Week 12
Statistical analysis description:	
Statistical analyses based on Wilcoxon signed-rank test. Some small changes were noted at isolated timepoints but no consistent changes over time were seen.	
Comparison groups	Baseline v Week 12
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2334
Method	Wilcoxon signed-rank test

Statistical analysis title	Change from Baseline to Week 24
Statistical analysis description:	
Statistical analyses based on Wilcoxon signed-rank test. Some small changes were noted at isolated timepoints but no consistent changes over time were seen.	
Comparison groups	Baseline v Week 24
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9658
Method	Wilcoxon signed-rank test

Statistical analysis title	Change from Baseline to EP Week 12
Statistical analysis description:	
Statistical analyses based on Wilcoxon signed-rank test. Some small changes were noted at isolated timepoints but no consistent changes over time were seen.	
Comparison groups	Baseline v EP Week 12
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2324
Method	Wilcoxon signed-rank test

Statistical analysis title	Change from Baseline to EP Week 24
Statistical analysis description:	
Statistical analyses based on Wilcoxon signed-rank test. Some small changes were noted at isolated timepoints but no consistent changes over time were seen.	

Comparison groups	Baseline v EP Week 24
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2754
Method	Wilcoxon signed-rank test

Statistical analysis title	Change from Baseline to EP Week 36

Statistical analysis description:

Statistical analyses based on Wilcoxon signed-rank test. Some small changes were noted at isolated timepoints but no consistent changes over time were seen.

Comparison groups	Baseline v EP Week 36
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0117
Method	Wilcoxon signed-rank test

Statistical analysis title	Change from Baseline to EP Week 48

Statistical analysis description:

Statistical analyses based on Wilcoxon signed-rank test. Some small changes were noted at isolated timepoints but no consistent changes over time were seen.

Comparison groups	Baseline v EP Week 48
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.75
Method	Wilcoxon signed-rank

Secondary: Effect of 800 mg PBI-4050 on ELF Test

End point title	Effect of 800 mg PBI-4050 on ELF Test

End point description:

To compare the effect of 800 mg PBI-4050 on the change from baseline in ELF test at Weeks 12 (n=12), 24 (n=12), EP 12 (n=10), EP 24 (n=9; missing value), EP 36 (n=8; missing value), and EP 48 (n=3). ELF test score: None to mild fibrosis < 7.7; moderate fibrosis ≥ 7.7 to < 9.8; and severe fibrosis ≥ 9.8.

End point type	Secondary

End point timeframe:

Week 1 (baseline) to Week 72

End point values	Baseline	Week 12	Week 24	EP Week 12
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	12	12	12
Units: None				
arithmetic mean (standard deviation)	9.12 (± 1.38)	0.02 (± 1.02)	-0.26 (± 0.93)	-0.24 (± 1.06)

End point values	EP Week 24	EP Week 36	EP Week 48	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	12	12	
Units: None				
arithmetic mean (standard deviation)	-0.22 (± 1.09)	-0.26 (± 1.19)	-0.03 (± 1.21)	

Statistical analyses

Statistical analysis title	Change from Baseline to Week 12
Statistical analysis description:	
Statistical analyses based on paired t-test. No changes of note were seen.	
Comparison groups	Baseline v Week 12
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9472
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.63
upper limit	0.67

Statistical analysis title	Change from Baseline to Week 24
Statistical analysis description:	
Statistical analyses based on paired t-test. No changes of note were seen.	
Comparison groups	Baseline v Week 24
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3564
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.85
upper limit	0.33

Statistical analysis title	Change from Baseline to EP Week 12
Statistical analysis description:	
Statistical analyses based on paired t-test. No changes of note were seen.	
Comparison groups	Baseline v EP Week 12
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4923
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.99
upper limit	0.52

Statistical analysis title	Change from Baseline to EP Week 24
Statistical analysis description:	
Statistical analyses based on paired t-test. No changes of note were seen.	
Comparison groups	Baseline v EP Week 24
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5565
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.06
upper limit	0.61

Statistical analysis title	Change from Baseline to EP Week 36
Statistical analysis description:	
Statistical analyses based on paired t-test. No changes of note were seen.	
Comparison groups	Baseline v EP Week 36
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5551
Method	Paired t-test

Confidence interval	
level	95 %
sides	1-sided
lower limit	-1.26
upper limit	0.74

Statistical analysis title	Change from Baseline to EP Week 8
Statistical analysis description:	
Statistical analyses based on paired t-test. No changes of note were seen.	
Comparison groups	Baseline v EP Week 48
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9697
Method	Paired t-test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.04
upper limit	2.98

Secondary: Effect of 800 mg PBI-4050 on NT-pro-BNP	
End point title	Effect of 800 mg PBI-4050 on NT-pro-BNP
End point description:	
To compare the effect of 800 mg PBI-4050 on the change from baseline in NT-pro-BNP at Weeks 12 (n=12), 24 (n=12), EP 12 (n=10), EP 24 (n=10), EP 36 (n=9), and EP 48 (n=3).	
End point type	Secondary
End point timeframe:	
Week 1 (baseline) to Week 72	

End point values	Baseline	Week 12	Week 24	EP Week 12
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	12	12	12
Units: ng/L				
median (full range (min-max))	34.00 (8.0 to 279.0)	0.00 (-26.0 to 296.0)	0.00 (-26.0 to 67.0)	0.00 (-26.0 to 77.0)

End point values	EP Week 24	EP Week 36	EP Week 48	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	12	12	
Units: ng/L				

median (full range (min-max))	1.00 (-16.3 to 92.68)	0.00 (-24.0 to 355.0)	-8.00 (-17.0 to 2.0)	

Statistical analyses

Statistical analysis title	Change from Baseline to Week 12
Statistical analysis description:	
Statistical analyses based on Wilcoxon signed-rank test. No changes of note were seen.	
Comparison groups	Baseline v Week 12
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4063
Method	Wilcoxon signed-rank test

Statistical analysis title	Change from Baseline to Week 24
Statistical analysis description:	
Statistical analyses based on Wilcoxon signed-rank test. No changes of note were seen.	
Comparison groups	Baseline v Week 24
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7188
Method	Wilcoxon signed-rank test

Statistical analysis title	Change from Baseline to EP Week 12
Statistical analysis description:	
Statistical analyses based on Wilcoxon signed-rank test. No changes of note were seen.	
Comparison groups	Baseline v EP Week 12
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8438
Method	Wilcoxon signed-rank test

Statistical analysis title	Change from Baseline to EP Week 24
Statistical analysis description:	
Statistical analyses based on Wilcoxon signed-rank test. No changes of note were seen.	
Comparison groups	Baseline v EP Week 24

Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.25
Method	Wilcoxon signed-rank test

Statistical analysis title	Change from Baseline to EP Week 36
Statistical analysis description: Statistical analyses based on Wilcoxon signed-rank test. No changes of note were seen.	
Comparison groups	Baseline v EP Week 36
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4063
Method	Wilcoxon signed-rank test

Statistical analysis title	Change from Baseline to EP Week 48
Statistical analysis description: Statistical analyses based on Wilcoxon signed-rank test. No changes of note were seen.	
Comparison groups	Baseline v EP Week 48
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5
Method	Wilcoxon signed-rank test

Secondary: Effect of 800 mg PBI-4050 on pro-Inflammatory/Inflammatory, Diabetes, and Obesity Biomarkers

End point title	Effect of 800 mg PBI-4050 on pro-Inflammatory/Inflammatory, Diabetes, and Obesity Biomarkers
End point description: To compare the effect of 800 mg PBI-4050 on the change from baseline in pro- inflammatory/ inflammatory, diabetes, or obesity biomarkers at Week 24 (n=12). Immunoassays were used to analyse the subjects' plasma/urine samples and to determine the concentration of each biomarker.	
End point type	Secondary
End point timeframe: Week 1 (baseline) to Week 24	

End point values	Baseline	Week 24		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	12		
Units: None				
arithmetic mean (standard deviation)				
Monocyte chemoattractant protein 1 (urine)	0.00005 (± 0.00003)	0.00004 (± 0.00003)		
Adiponectin (plasma)	1478800 (± 789925)	1522242 (± 782070)		
High-specificity C-reactive protein (plasma)	14855 (± 18610)	17875 (± 25831)		
Cystatin C (plasma)	1016 (± 663)	998 (± 653)		
Glucagon (plasma)	4440 (± 746)	4457 (± 745)		
Interleukin-6 (plasma)	8.40 (± 6.06)	9.94 (± 5.86)		
Interleukin-8 (plasma)	15.80 (± 8.58)	17.56 (± 7.34)		
Interleukin-10 (plasma)	47.28 (± 83.80)	27.41 (± 33.98)		
Interferon-gamma (plasma)	57.68 (± 41.25)	63.48 (± 37.69)		
Monocyte chemoattractant protein 1 (plasma)	18.65 (± 21.82)	13.98 (± 9.91)		
Tumor necrosis factor alpha (plasma)	70.62 (± 35.91)	77.56 (± 34.29)		
Vascular endothelial growth factor (plasma)	39.87 (± 27.76)	46.12 (± 31.94)		

Statistical analyses

Statistical analysis title	Urine MCP-1 Change from Baseline to Week 24

Statistical analysis description:

Urine monocyte chemoattractant protein 1 was the only biomarker that showed a statistically significant (p=0.05) change from baseline at Week 24.

Comparison groups	Week 24 v Baseline
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Paired t-test

Statistical analysis title	Plasma Adiponectin Change from Baseline to Week 24

Statistical analysis description:

Statistical analyses based on paired t-test. No changes of note were seen.

Comparison groups	Week 24 v Baseline

Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78
Method	Paired t-test

Statistical analysis title	Plasma hsCRP Change from Baseline to Week 24
Statistical analysis description: Statistical analyses based on paired t-test. No changes of note were seen..	
Comparison groups	Week 24 v Baseline
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.24
Method	Paired t-test

Statistical analysis title	Plasma Cystatin C Change from Baseline to Week 24
Statistical analysis description: Statistical analyses based on paired t-test. No changes of note were seen.	
Comparison groups	Week 24 v Baseline
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.62
Method	Paired t-test

Statistical analysis title	Plasma Glucagon Change from Baseline to Week 24
Statistical analysis description: Statistical analyses based on paired t-test. No changes of note were seen.	
Comparison groups	Week 24 v Baseline
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.86
Method	Paired t-test

Statistical analysis title	Plasma IL-6 Change from Baseline to Week 24
Statistical analysis description: Statistical analyses based on paired t-test. No changes of note were seen.	
Comparison groups	Week 24 v Baseline

Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.25
Method	Paired t-test

Statistical analysis title	Plasma IL-8 Change from Baseline to Week 24
Statistical analysis description: Statistical analyses based on paired t-test. No changes of note were seen.	
Comparison groups	Week 24 v Baseline
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.28
Method	Paired t-test

Statistical analysis title	Plasma IL-10 Change from Baseline to Week 24
Statistical analysis description: Statistical analyses based on paired t-test. No changes of note were seen.	
Comparison groups	Week 24 v Baseline
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.35
Method	Paired t-test

Statistical analysis title	Plasma IFNγ Change from Baseline to Week 24
Statistical analysis description: Statistical analyses based on paired t-test. No changes of note were seen.	
Comparison groups	Week 24 v Baseline
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.45
Method	Paired t-test

Statistical analysis title	Plasma MCP-1 Change from Baseline to Week 24
Statistical analysis description: Statistical analyses based on paired t-test. No changes of note were seen.	
Comparison groups	Week 24 v Baseline

Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.27
Method	Paired t-test

Statistical analysis title	Plasma TNFα Change from Baseline to Week 24
Statistical analysis description: Statistical analyses based on paired t-test. No changes of note were seen.	
Comparison groups	Week 24 v Baseline
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.37
Method	Paired t-test

Statistical analysis title	Plasma VEGF Change from Baseline to Week 24
Statistical analysis description: Statistical analyses based on paired t-test. No changes of note were seen.	
Comparison groups	Week 24 v Baseline
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.17
Method	Paired t-test

Secondary: Effect of 800 mg PBI-4050 on Changes in Anti-Diabetic Treatment	
End point title	Effect of 800 mg PBI-4050 on Changes in Anti-Diabetic Treatment
End point description: To compare the effect of 800 mg PBI-4050 on the change from baseline in anti-diabetic treatment in subjects with diabetes (N=10).	
End point type	Secondary
End point timeframe: Week 1 (baseline) to Week 72	

End point values	800 mg PBI-4050			
Subject group type	Reporting group			
Number of subjects analysed	10[2]			
Units: Measurable				
Change in anti-diabetic medications	6			
Stopped anti-diabetic medications	3			
Added anti-diabetic medications	4			
Changed their anti-diabetic medications	1			
Dose/frequency of anti-diabetic medication changed	2			
No change in anti-diabetic medications	4			

Notes:

[2] - Number of subjects who had type 2 diabetes at baseline.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day -44 to the end of the study visit

Adverse event reporting additional description:

The condition of the subject was monitored throughout the study. At each visit and during each weekly telephone contact, study personnel reviewed the subject diary card and elicited adverse events (AEs) from each subject using a standard, non-leading question, such as “How have you been since the last visit/during the previous study period?"

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	800 mg PBI-4050

Reporting group description:

All subjects who received at least 1 dose of PBI-4050

Serious adverse events	800 mg PBI-4050		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 12 (16.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Cardiac ventricular thrombosis	Additional description: Left ventricular thrombus		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	800 mg PBI-4050		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)		
Investigations			
Haemoglobin decreased			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		
Abdominal discomfort			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	5		
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Nasopharyngitis			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		

Urinary tract infection subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 4		
Metabolism and nutrition disorders Hypoglycaemia subjects affected / exposed occurrences (all)	4 / 12 (33.33%) 28		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 March 2016	Substantial changes were: 1) The objective related to the hyperinsulinaemic-euglycaemic clamp was moved from a secondary to an exploratory objective; 2) The 4-point and 7-point glucose profiles were removed as secondary endpoints, as they were not sensitive enough to detect potential effects; 3) Adequate contraception was required for females of childbearing potential who were sexually active with a non-sterile male partner;4) Discontinuation criteria related to dropping heart rate and systolic blood pressure were clarified to be accompanied by symptoms; 5) Storage condition of study drug was changed for consistency with the study drug label and EU labeling for solid dosage forms; 6) Laboratory tests for FPG and fasting insulin were removed from the Week 4, 8, 16, and 20 visits; and 7) Provision was added to allow the Investigator’s discretion on the performance of the hyperinsulinemic-euglycemic clamp procedure for certain subjects if appropriate.
22 August 2016	Substantial changes were: 1) A 36-week Extension Period (EP) was added to capture longer term safety and exploratory efficacy data of PBI-4050 in subjects with ALMS; 2) The time period to collect historical data relevant to the disease course was extended from 3 to 10 years; 3) The Data Safety Monitoring Board reviewed individual safety data during the 36-week EP and determined if the safety data supported an additional 36 weeks of study drug treatment; 4) Glycated hemoglobin was performed at every visit during the initial 24 weeks of study drug treatment to capture more data; 5) Exclusion criterion 10 was added to exclude subjects who had a history of an allergic reaction to PBI-4050 or any of its excipients; 6) Based on the addition of a 36-week EP, the primary analysis was to be conducted after the initial 24 weeks of study drug treatment and a final analysis was to be completed at the end of the EP; 7) Subjects were required to give informed consent in order to enter into the 36-week EP; 8) According to the Investigator's Brochure, organic anion transporter (OAT) inhibition could lead to a clinically relevant drug interaction at efficacious human exposures of PBI-4050 based on in vitro inhibitory potency. Therefore, concomitant use of substrates for OAT1 and OAT3 was to be avoided or Investigators were to closely monitor the subject for possible dose adjustments of concomitant substrates for OAT1 and OAT3; 9) Subjects who had already stopped study drug at Week 24 and completed an End of Study (EoS) visit recommenced capture of concomitant therapy at the Start of Extension Study visit; 10) Subjects who had stopped study drug and completed an EoS visit and wanted to continue treatment in the EP were required to meet inclusion and exclusion criteria in order to be treated during the EP; and 11) Secondary and exploratory biomarkers of glucose metabolism were only analyzed at visits that the subject was required to attend fasted.

09 December 2016	Substantial changes were: 1) Added 12 weeks to the 36-week Extension Period (EP) to allow subjects who completed the 36-week EP to continue study drug treatment without a break until the rollover study was open for enrolment (i.e., approved and initiated); 2) A Data Safety Monitoring Board continued to review individual subject safety data through the EP, regardless of whether it was 36- or 48-weeks in duration; 3) Clarified that subjects who entered the EP at Week 24 signed informed consent; 4) Liver and cardiac magnetic resonance imaging scans were removed from the EP Week 12 and EP Week 24 visits to reduce subjects' burden and radiological exposure in the study; 5) Subjects who completed study drug treatment through the EP Week 48 visit were eligible to enter a rollover study in order to continue ongoing study drug without any break in treatment; 6) Removed Inclusion Criterion #6 restricting subjects who had a body mass index of at least 25 kg/m2 to broaden the subject population; 7) Revised Exclusion Criterion #6 to add use of any moderate/potent inducer or inhibitor of cytochrome P450 (CYP) 2C9 isozyme, based on preclinical data showing that CYP2C9 is the major isoform responsible for the metabolism of PBI-4050 and that co-administration of drugs known to be inducers or inhibitors of CYP2C9 could alter the rate of metabolic clearance of PBI 4050; 8) Added telephone contacts for subjects who could not enroll in the rollover study because it was not open for enrolment and for subjects who completed the 48-week EP but chose not to enter the rollover study; and 9) Since subjects could enroll in a rollover study at either the EP Week 36 or EP Week 48 visit without completing the End of Study visit, the defined end of the study was changed to the final visit of the final subject in the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported