Clinical trial results:
A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Phase 2b Study to Assess the Efficacy, Safety, and Tolerability of Velusetrag for the Treatment of Diabetic or Idiopathic Gastroparesis

Summary

EudraCT number	2014-003250-13
Trial protocol	CZ PL
Global end of trial date	05 June 2017

Results information

Result version number	v1 (current)
This version publication date	28 October 2019
First version publication date	28 October 2019

Trial information

Trial identification

Sponsor protocol code	0099

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02267525
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Theravance Biopharma R&D, Inc.
Sponsor organisation address	901 Gateway Boulevard, South San Francisco, United States, 94080
Public contact	Theravance Biopharma R&D, Inc., Theravance Biopharma R&D, Inc., 650 808-6000,
Scientific contact	Theravance Biopharma R&D, Inc., Theravance Biopharma R&D, Inc., 650 808-6000,

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	05 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 June 2017
Global end of trial reached?	Yes
Global end of trial date	05 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of velusetrag on symptoms in participants with gastroparesis.

Protection of trial subjects:

This study was conducted in accordance with the protocol, the principles of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice, the United States Code of Federal Regulations, the principles of the World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects, and all applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 February 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	Poland: 12
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United States: 217
Worldwide total number of subjects	233
EEA total number of subjects	16

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)	200

From 65 to 84 years	33
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The screening period was 1 to 5 weeks in duration. The last consecutive 7 days were assessed for eligibility and served as the baseline period.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description: -

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:

Administered once daily, 30 minutes prior to eating, for 12 weeks.

Arm title	Velusetrag 5 mg

Arm description: -

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

Dosage and administration details:

Administered once daily, 30 minutes prior to eating, for 12 weeks.

Arm title	Velusetrag 15 mg

Arm description: -

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

Dosage and administration details:

Administered once daily, 30 minutes prior to eating, for 12 weeks.

Arm title	Velusetrag 30 mg

Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Velusetrag
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Administered once daily, 30 minutes prior to eating, for 12 weeks.

Number of subjects in period 1[1]	Placebo	Velusetrag 5 mg	Velusetrag 15 mg
Started	59	59	56
Completed	50	49	44
Not completed	9	10	12
Physician decision	1	-	1
Consent withdrawn by subject	3	7	5
Adverse event, non-fatal	5	2	6
Miscellaneous	-	-	-
Lost to follow-up	-	1	-

Number of subjects in period 1[1]	Velusetrag 30 mg
Started	58
Completed	51
Not completed	7
Physician decision	1
Consent withdrawn by subject	1
Adverse event, non-fatal	4
Miscellaneous	1
Lost to follow-up	-

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 participant in the velusetrag 15 mg arm did not receive any study drug and is not included in the baseline period.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Velusetrag 5 mg
Reporting group description: -	
Reporting group title	Velusetrag 15 mg
Reporting group description: -	
Reporting group title	Velusetrag 30 mg
Reporting group description: -	

Reporting group values	Placebo	Velusetrag 5 mg	Velusetrag 15 mg
Number of subjects	59	59	56
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	47.0	51.8	49.9
standard deviation	± 13.91	± 13.29	± 14.63
Gender categorical Units: Subjects			
Female	43	46	45
Male	16	13	11
Race Units: Subjects			
White	53	52	46
Black or African American	5	7	7
Asian	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
American Indian or Alaska Native	1	0	1
Multiple	0	0	1
Gastroparesis Type Units: Subjects			
Idiopathic Gastroparesis	27	29	26
Diabetic Gastroparesis	32	30	30

Weight			
Units: kg			
arithmetic mean	81.52	82.29	82.85
standard deviation	± 20.960	± 19.177	± 18.784
Height			
Units: cm			
arithmetic mean	167.75	165.70	165.93
standard deviation	± 9.132	± 9.826	± 9.133
Body Mass Index (BMI)			
Units: kg/m^2			
arithmetic mean	28.90	29.95	29.94
standard deviation	± 6.795	± 6.273	± 5.666
HbA1c			
Units: percent			
arithmetic mean	7.75	6.92	7.42
standard deviation	± 1.474	± 1.246	± 1.545

Reporting group values	Velusetrag 30 mg	Total	
Number of subjects	58	232	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	52.4		
standard deviation	± 12.02	-	
Gender categorical			
Units: Subjects			
Female	49	183	
Male	9	49	
Race			
Units: Subjects			
White	53	204	
Black or African American	4	23	
Asian	0	1	
Native Hawaiian or Other Pacific Islander	1	1	
American Indian or Alaska Native	0	2	
Multiple	0	1	
Gastroparesis Type			
Units: Subjects			
Idiopathic Gastroparesis	31	113	

Diabetic Gastroparesis	27	119	

Weight			
Units: kg			
arithmetic mean	78.32		
standard deviation	± 15.906	-	
Height			
Units: cm			
arithmetic mean	164.51		
standard deviation	± 7.460	-	
Body Mass Index (BMI)			
Units: kg/m^2			
arithmetic mean	28.89		
standard deviation	± 5.218	-	
HbA1c			
Units: percent			
arithmetic mean	6.95		
standard deviation	± 1.314	-	

End points

End points reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Velusetrag 5 mg
Reporting group description: -	
Reporting group title	Velusetrag 15 mg
Reporting group description: -	
Reporting group title	Velusetrag 30 mg
Reporting group description: -	

Primary: Change from baseline in the 7-day mean Gastroparesis Cardinal Symptoms Index – 24−Hour Recall (GCSI-24H) total score at week 4	
End point title	Change from baseline in the 7-day mean Gastroparesis Cardinal Symptoms Index – 24−Hour Recall (GCSI-24H) total score at week 4
End point description: The GCSI was developed to quantifying symptom severity in participants with functional upper gastrointestinal symptoms. The daily version was developed to assess short-term changes in symptoms. The GCSI-24H contains 9 items in 3 subscales covering nausea/vomiting (3 items), postprandial fullness/early satiety (4 items), and bloating (2 items). A negative change from baseline indicates a reduction in gastroparesis-related symptoms.	
End point type	Primary
End point timeframe: Baseline and Week 4	

End point values	Placebo	Velusetrag 5 mg	Velusetrag 15 mg	Velusetrag 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	59	59	53	57
Units: Score on a scale				
least squares mean (standard error)	-1.1 (± 0.13)	-1.5 (± 0.13)	-1.2 (± 0.14)	-1.0 (± 0.13)

Statistical analyses

Statistical analysis title	Velusetrag 5 mg vs. Placebo
Comparison groups	Placebo v Velusetrag 5 mg
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0327
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.75
upper limit	-0.03

Statistical analysis title	Velusetrag 15 mg vs. Placebo
Comparison groups	Placebo v Velusetrag 15 mg
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5758
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.48
upper limit	0.27

Statistical analysis title	Velusetrag 30 mg vs. Placebo
Comparison groups	Velusetrag 30 mg v Placebo
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6743
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.45

Secondary: Change from baseline in the 7-day mean Gastroparesis Cardinal Symptoms Index – 24−Hour Recall (GCSI-24H) total score

End point title	Change from baseline in the 7-day mean Gastroparesis Cardinal Symptoms Index – 24−Hour Recall (GCSI-24H) total score

End point description:

The GCSI was developed to quantifying symptom severity in subjects with functional upper gastrointestinal symptoms. The daily version was developed to assess short-term changes in symptoms. The GCSI-24H contains 9 items in 3 subscales covering nausea/vomiting (3 items), postprandial

fullness/early satiety (4 items), and bloating (2 items). A negative change from baseline indicates a reduction in gastroparesis-related symptoms.

End point type	Secondary

End point timeframe:

Baseline, Week 8 and Week 12

End point values	Placebo	Velusetrag 5 mg	Velusetrag 15 mg	Velusetrag 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	55[1]	57[2]	48[3]	53[4]
Units: Score on a scale				
least squares mean (standard error)				
Week 8 Change from Baseline	-1.3 (± 0.14)	-1.6 (± 0.14)	-1.3 (± 0.15)	-1.3 (± 0.14)
Week 12 Change from Baseline	-1.4 (± 0.15)	-1.7 (± 0.15)	-1.4 (± 0.16)	-1.5 (± 0.15)

Notes:

[1] - ITT analysis set: 59

[2] - ITT analysis set: 59

[3] - ITT analysis set: 53

[4] - ITT analysis set: 57

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the 7-day mean Gastroparesis Cardinal Symptoms Index – 24−Hour Recall (GCSI-24H) individual component scores

End point title	Change from baseline in the 7-day mean Gastroparesis Cardinal Symptoms Index – 24−Hour Recall (GCSI-24H) individual component scores

End point description:

Assessed with the 7-day mean Gastroparesis Rating Scale PRO (GRS PRO) Factor 2 scores. The GRS was developed for use in participants with diabetic or idiopathic gastroparesis and is sensitive to the range of symptoms experienced by participants within this study. A negative change from baseline indicates a reduction in gastroparesis-related symptoms.

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 8 and Week 12

End point values	Placebo	Velusetrag 5 mg	Velusetrag 15 mg	Velusetrag 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	55[5]	57[6]	48[7]	53[8]
Units: Score on scale				
least squares mean (standard error)				
Week 4 Change from Baseline	-0.7 (± 0.09)	-0.8 (± 0.08)	-0.7 (± 0.09)	-0.6 (± 0.09)
Week 8 Change from Baseline	-0.8 (± 0.09)	-0.9 (± 0.09)	-0.8 (± 0.10)	-0.8 (± 0.09)
Week 12 Change from Baseline	-0.8 (± 0.08)	-1.0 (± 0.08)	-0.9 (± 0.09)	-1.0 (± 0.08)

Notes:

[5] - ITT analysis set: 59

[6] - ITT analysis set: 59

[7] - ITT analysis set: 53

[8] - ITT analysis set: 57

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Gastroparesis Cardinal Symptoms Index – 24−Hour Recall (GCSI-24H) weekly responders

End point title	Number of Gastroparesis Cardinal Symptoms Index – 24−Hour Recall (GCSI-24H) weekly responders

End point description:

Weekly responders experienced at least 1 point decrease from baseline in GCSI-24H individual domain scores.

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 8 and Week 12

End point values	Placebo	Velusetrag 5 mg	Velusetrag 15 mg	Velusetrag 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	55[9]	57[10]	48[11]	53[12]
Units: Participants				
Week 4	30	39	22	24
Week 8	30	37	27	31
Week 12	31	37	26	34

Notes:

[9] - ITT analysis set: 59

[10] - ITT analysis set: 59

[11] - ITT analysis set: 53

[12] - ITT analysis set: 57

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the 7-day mean Gastroparesis Rating Scale (GRS) total score

End point title	Change from baseline in the 7-day mean Gastroparesis Rating Scale (GRS) total score

End point description:

The GRS was developed for use in participants with diabetic or idiopathic gastroparesis and is sensitive to the range of symptoms experienced by participants within this study. A negative change from baseline indicates a reduction in gastroparesis-related symptoms.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8 and 12

End point values	Placebo	Velusetrag 5 mg	Velusetrag 15 mg	Velusetrag 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	55[13]	57[14]	48[15]	53[16]
Units: Score on a scale				
least squares mean (standard error)				
Week 4 Change from Baseline	-0.9 (± 0.12)	-1.3 (± 0.11)	-1.1 (± 0.12)	-0.8 (± 0.12)
Week 8 Change from Baseline	-1.1 (± 0.13)	-1.4 (± 0.13)	-1.2 (± 0.14)	-1.1 (± 0.13)
Week 12 Change from Baseline	-1.1 (± 0.13)	-1.5 (± 0.13)	-1.3 (± 0.14)	-1.3 (± 0.13)

Notes:

[13] - ITT analysis set: 59

[14] - ITT analysis set: 59

[15] - ITT analysis set: 53

[16] - ITT analysis set: 57

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the 7-day mean Gastroparesis Rating Scale (GRS) individual component scores

End point title	Change from baseline in the 7-day mean Gastroparesis Rating Scale (GRS) individual component scores

End point description:

The GRS was developed for use in participants with diabetic or idiopathic gastroparesis and is sensitive to the range of symptoms experienced by participants within this study. A negative change from baseline indicates a reduction in gastroparesis-related symptoms.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8 and 12

End point values	Placebo	Velusetrag 5 mg	Velusetrag 15 mg	Velusetrag 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	55[17]	57[18]	48[19]	53[20]
Units: Score on a scale				
least squares mean (standard error)				
New GRS PRO Factor 1: Week 4 Change from Baseline	-0.9 (± 0.12)	-1.3 (± 0.11)	-1.2 (± 0.12)	-0.8 (± 0.12)
New GRS PRO Factor 1: Week 8 Change from Baseline	-1.1 (± 0.13)	-1.4 (± 0.13)	-1.2 (± 0.14)	-1.1 (± 0.13)
New GRS PRO Factor 1: Week 12 Change from Baseline	-1.1 (± 0.14)	-1.5 (± 0.13)	-1.3 (± 0.15)	-1.2 (± 0.14)
New GRS PRO Factor 2: Week 4 Change from Baseline	-0.7 (± 0.09)	-0.8 (± 0.08)	-0.7 (± 0.09)	-0.6 (± 0.09)
New GRS PRO Factor 2: Week 8 Change from Baseline	-0.8 (± 0.09)	-0.9 (± 0.09)	-0.8 (± 0.10)	-0.8 (± 0.09)
New GRS PRO Factor 2: Week 12 Change from Baseline	-0.8 (± 0.08)	-1.0 (± 0.08)	-0.9 (± 0.09)	-1.0 (± 0.08)

Notes:

[17] - ITT analysis set: 59

[18] - ITT analysis set: 59

[19] - ITT analysis set: 53

[20] - ITT analysis set: 57

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with an improvement from baseline of at least 1 point in Gastroparesis Rating Scale (GRS) individual summary scores

End point title	Number of participants with an improvement from baseline of at least 1 point in Gastroparesis Rating Scale (GRS) individual summary scores

End point description:

The GRS was developed for use in participants with diabetic or idiopathic gastroparesis and is sensitive to the range of symptoms experienced by participants within this study. A negative change from baseline indicates a reduction in gastroparesis-related symptoms. Responders experienced at least 1 point decrease in GRS individual summary scores. Responders for at least 6 of 12 weeks (Weeks 1-12) (Responder Criteria 1) and responders for at least 6 of 12 weeks (Weeks 1-12) and for at least 3 weeks (Weeks 9-12) (Responder Criteria 2) are reported for GRS PRO Factor 1 and GRS PRO Factor 2 scores.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo	Velusetrag 5 mg	Velusetrag 15 mg	Velusetrag 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	59	59	53	57
Units: Participants				
GRS PRO Factor 1: Responder Criteria 1	22	33	26	27
GRS PRO Factor 1: Responder Criteria 2	22	32	24	27
GRS PRO Factor 2: Responder Criteria 1	24	34	27	29
GRS PRO Factor 2: Responder Criteria 2	20	32	23	28

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Day 28 Gastric Emptying Scintigraphy (GES) Hour 4 percentage retention

End point title	Summary of Day 28 Gastric Emptying Scintigraphy (GES) Hour 4 percentage retention

End point description:

Participants received a standardized test meal consisting of a 4-ounce (oz) egg white meal radiolabelled with 0.5-1 millicurie (mCi) technetium, 2 slices of white bread/toast, jam and water. Gamma camera images were obtained immediately after meal ingestion and at 1, 2, 3, and 4 hours after meal ingestion. The geometric mean of the anterior and posterior gastric counts for each time point were calculated and corrected for radioactive decay. Results are expressed as a percentage of food remaining in the stomach

4 hours after meal ingestion.

End point type	Secondary

End point timeframe:

Day 28

End point values	Placebo	Velusetrag 5 mg	Velusetrag 15 mg	Velusetrag 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23[21]	23[22]	20[23]	21[24]
Units: Percentage of food remaining				
least squares mean (standard error)	29.5 (± 4.0)	13.4 (± 3.9)	16.1 (± 4.2)	12.4 (± 4.3)

Notes:

[21] - ITT analysis set: 59

[22] - ITT analysis set: 59

[23] - ITT analysis set: 53

[24] - ITT analysis set: 57

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 to Week 14	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Velusetrag 15 mg
Reporting group description: -	
Reporting group title	Velusetrag 30 mg
Reporting group description: -	
Reporting group title	Velusetrag 5 mg
Reporting group description: -	

Serious adverse events	Placebo	Velusetrag 15 mg	Velusetrag 30 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 59 (5.08%)	2 / 56 (3.57%)	3 / 58 (5.17%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 59 (0.00%)	0 / 56 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 59 (0.00%)	0 / 56 (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
General disorders and administration site conditions			
Chest pain			

subjects affected / exposed	0 / 59 (0.00%)	0 / 56 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 59 (3.39%)	0 / 56 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal adhesions			
subjects affected / exposed	1 / 59 (1.69%)	0 / 56 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired gastric emptying			
subjects affected / exposed	0 / 59 (0.00%)	1 / 56 (1.79%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 59 (0.00%)	1 / 56 (1.79%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 59 (0.00%)	0 / 56 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 59 (1.69%)	0 / 56 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			

subjects affected / exposed	0 / 59 (0.00%)	0 / 56 (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
Pneumonia			
subjects affected / exposed	0 / 59 (0.00%)	0 / 56 (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
Bronchitis			
subjects affected / exposed	0 / 59 (0.00%)	0 / 56 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 59 (0.00%)	1 / 56 (1.79%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Velusetrag 5 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 59 (6.78%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			

subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal adhesions			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Impaired gastric emptying			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Influenza			

subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 59 (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	Placebo	Velusetrag 15 mg	Velusetrag 30 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 59 (64.41%)	38 / 56 (67.86%)	29 / 58 (50.00%)
Investigations			
Electrocardiogram T wave abnormal			
subjects affected / exposed	0 / 59 (0.00%)	1 / 56 (1.79%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Muscle strain			
subjects affected / exposed	0 / 59 (0.00%)	0 / 56 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 59 (0.00%)	2 / 56 (3.57%)	1 / 58 (1.72%)
occurrences (all)	0	2	1
Headache			

subjects affected / exposed	8 / 59 (13.56%)	5 / 56 (8.93%)	2 / 58 (3.45%)
occurrences (all)	9	6	2
Paraesthesia			
subjects affected / exposed	0 / 59 (0.00%)	0 / 56 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 59 (3.39%)	0 / 56 (0.00%)	0 / 58 (0.00%)
occurrences (all)	2	0	0
Chest pain			
subjects affected / exposed	3 / 59 (5.08%)	1 / 56 (1.79%)	1 / 58 (1.72%)
occurrences (all)	3	1	2
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 59 (1.69%)	2 / 56 (3.57%)	0 / 58 (0.00%)
occurrences (all)	1	2	0
Constipation			
subjects affected / exposed	2 / 59 (3.39%)	2 / 56 (3.57%)	0 / 58 (0.00%)
occurrences (all)	2	3	0
Abdominal pain upper			
subjects affected / exposed	2 / 59 (3.39%)	0 / 56 (0.00%)	1 / 58 (1.72%)
occurrences (all)	3	0	1
Abdominal pain			
subjects affected / exposed	3 / 59 (5.08%)	1 / 56 (1.79%)	1 / 58 (1.72%)
occurrences (all)	3	3	1
Diarrhoea			
subjects affected / exposed	4 / 59 (6.78%)	17 / 56 (30.36%)	11 / 58 (18.97%)
occurrences (all)	4	19	12
Flatulence			
subjects affected / exposed	1 / 59 (1.69%)	1 / 56 (1.79%)	2 / 58 (3.45%)
occurrences (all)	1	1	2
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 59 (0.00%)	2 / 56 (3.57%)	2 / 58 (3.45%)
occurrences (all)	0	2	2
Toothache			

subjects affected / exposed	0 / 59 (0.00%)	0 / 56 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	2 / 59 (3.39%)	4 / 56 (7.14%)	8 / 58 (13.79%)
occurrences (all)	2	4	8
Vomiting			
subjects affected / exposed	0 / 59 (0.00%)	2 / 56 (3.57%)	4 / 58 (6.90%)
occurrences (all)	0	2	4
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 59 (1.69%)	2 / 56 (3.57%)	0 / 58 (0.00%)
occurrences (all)	1	2	0
Cough			
subjects affected / exposed	2 / 59 (3.39%)	0 / 56 (0.00%)	0 / 58 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 59 (0.00%)	3 / 56 (5.36%)	1 / 58 (1.72%)
occurrences (all)	0	3	1
Gastroenteritis viral			
subjects affected / exposed	2 / 59 (3.39%)	1 / 56 (1.79%)	1 / 58 (1.72%)
occurrences (all)	2	1	1
Influenza			
subjects affected / exposed	1 / 59 (1.69%)	0 / 56 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	5 / 59 (8.47%)	0 / 56 (0.00%)	0 / 58 (0.00%)
occurrences (all)	5	0	0
Localised infection			
subjects affected / exposed	0 / 59 (0.00%)	0 / 56 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 59 (0.00%)	0 / 56 (0.00%)	3 / 58 (5.17%)
occurrences (all)	0	0	3
Urinary tract infection			

subjects affected / exposed	3 / 59 (5.08%)	2 / 56 (3.57%)	4 / 58 (6.90%)
occurrences (all)	3	2	4
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 59 (1.69%)	1 / 56 (1.79%)	2 / 58 (3.45%)
occurrences (all)	1	1	2
Hypoglycaemia			
subjects affected / exposed	0 / 59 (0.00%)	0 / 56 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Velusetrag 5 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 59 (59.32%)		
Investigations			
Electrocardiogram T wave abnormal			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Muscle strain			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences (all)	0		
Paraesthesia			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences (all)	2		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences (all)	0		
Chest pain			

subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Abdominal pain			
subjects affected / exposed	6 / 59 (10.17%)		
occurrences (all)	6		
Diarrhoea			
subjects affected / exposed	7 / 59 (11.86%)		
occurrences (all)	7		
Flatulence			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences (all)	0		
Toothache			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	4		
Vomiting			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Gastroenteritis viral			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Localised infection			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences (all)	3		
Nasopharyngitis			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Hypoglycaemia			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 November 2014	• Changed Inclusion Criterion #10 to clarify the concomitant medications restriction for entry to the study as well as the use of concomitant medications that affect gastroparesis symptoms in order for symptoms to remain stable throughout the study. • Added Exclusion Criterion #12 to exclude participants with an underlying condition that may have been the cause of the gastroparesis. • Added 2 new study endpoints: the proportion of participants with at least 1-point improvement from baseline in the GCSI-DD and GRS individual components at each week (1-12) to further assess changes. • Added predose and postdose 12-lead electrocardiograms (ECGs) to Visit 7 (Day 56) to closely monitor participants' cardiac health while they were being dosed. • Added HbA1c sample collection to Visit 8 (Day 84) for diabetic participants to monitor the results for these participants from Screening to the end of the study to determine effect of the study drug. • Added blinded interim assessment of sample size assumptions to ensure an adequate sample size. • Added a statement that the proportion endpoints would be evaluated using chi-square methodology. • Changed the PK assessment at Visit 7 (Day 56) from serial pharmacokinetics (PK) sampling to a trough level and at Visit 8 (Day 84) from a trough level to serial PK sampling to better correlate blood levels with gastric motility breath test (GMBT) results. • Added a statement that the final interpretation of all ECGs collected during the study would be completed by a central reviewer. • Removed or changed certain statements related to abstaining from smoking and alcohol and strenuous exercise to clarify these requirements in relationship to gastric motility breath test (GMBT) or GES testing. • Clarified that the GES was not required if a participant had a comparable, qualifying 4-hour GES performed within 1 year of Screening.
30 November 2015	• Clarified details of the study design (added the Screening Treatment Satisfaction Questionnaire, clarified the description of the 2 daily PRO measures, added that participants must have had a 7-day mean score of ≥2.5 and <5 points on the GCSI-24H at Day 1 and that eligible participants completed the Patient Assessment of Upper Gastrointestinal Quality of Life (PAGI-QOL) questionnaire to establish baseline QOL metrics at Day 1) for consistency between the study procedures section and the Schedule of Study Procedures. • Added the use of comparable, qualifying 4-hour 99mTc GES within 1 year of Screening to decrease participants' exposure to radiation and decrease the number of long visits required by the protocol. The GES was used to diagnose participants with delayed gastric emptying and the Sponsor did not believe a confirmatory test was needed if a GES was performed within 1 year of Screening. • Added a statement that at least 50% of the participantsenrolled must have had a GES performed during the Screening Period of the study to allow the Sponsor to assess any difference in treatment effect due to historical GES (within 1 year of Screening) compared to the GES performed at the time of study entry. • Changed the GCSI-2W composite score range for eligibility to between ≥2 and <5 to enlarge the pool of participants eligible for Screening. Also revised the GCSI-DD to GCSI-24H for consistency with the naming convention of the questionnaire. • Removed all references to the 13C-octanoate GMBT. The GMBT was removed from the study to decrease the number of long visits and the study burden for participants as well as streamline study procedures for study sites. • Deleted references to GE t1/2 using 99mTc GES since the GMBT was removed from the study. • Added a statement that participants also completed the PAGI-QOL questionnaire to assess QOL metrics and completed the Treatment Satisfaction Question to provide an impression of study treatment.

30 November 2015	Continuation of protocol amendment 2: • Changed the serial PK assessments to a substudy. Decreasing the serial PK sampling to a subset of participants allowed participants who were unable to stay for numerous long visits to participate in the study. The trough PK sample at Day 14 was deleted, as it was the only blood draw for the visit and sufficient PK data were collected using the remaining PK samples. • Changed Inclusion Criterion #7 to increase the BMI range from 18 to 35 kg/m^2 to 18 to 42 kg/m^2, inclusive. • Changed Inclusion Criterion #11 (and revised similar language globally) to decrease the period for abstaining from prohibited medications from 72 hours to 24 hours prior to GES during Screening and start of Baseline Period to be less restrictive to potential participants, and to clarify that certain medications could have been used but their use was documented during the study in the Treatment and Follow-Up Periods so that participants did not withhold treatment for an extended period. • Added text to clarify that Visit 2 could have been combined with Screening if a Screening GES was not needed. • Changed the following inclusion/exclusion criteria to allow more potential participants to screen for the study: o Changed Exclusion Criterion #3 to allow a type 1 or type 2 diabetic to have an HbA1c level >11% instead of >10%. o Changed Exclusion Criterion #6 to allow a history of intrapyloric botulinum toxin injection within 3 months instead of 6 months of Screening. o Changed Exclusion Criterion #10 to allow a history of eating disorder but not a concurrent eating disorder. o Changed Exclusion Criterion #14 to exclude participants who were unwilling or unable to perform 99mTc GES, if applicable, for consistency with global removal of GMBT from the study. o Changed Exclusion Criterion #15 to increase the upper limit of normal for aspartate aminotransferase and alanine aminotransferase from >1.5 times to >2 times the upper limit of normal.
30 November 2015	Continuation of protocol amendment 2: o Changed Exclusion Criterion #16 and concomitant medications language to clarify the use of opioids, with the intention to exclude chronic opioid use but not restrict or prohibit use of opioids for potential AEs. o Changed Exclusion Criterion #18 and concomitant medications language to clarify the use of moderate P-gp inhibitors based on the Sponsor’s assessment that the risk of moderate inhibitors and inducers was anticipated to be relatively low. o Deleted Exclusion Criterion #19 and modified concomitant medications language that prohibited the use of 2 or more psychotropic medications to be less restrictive to potential participants. o Changed Exclusion Criterion #21 to clarify examples of psychiatric conditions that were exclusionary. • Deleted Visit 3 from the study since the primary purpose of this visit was to conduct the GMBT; all Visit 3 procedures were moved to Visit 4. • Clarified the allowable window for the postdose ECGs and increased certain visit windows to allow more flexibility in scheduling visits to accommodate participants. • Added follow-up telephone calls on Day 42 and Day 70 in the Schedule of Study Procedures for clarity and consistency with the study procedures section. • Updated the total amount of blood drawn if participating in the main study only, and if also participating in the PK substudy. • Added predose meal requirements for Visit 5 (Day 14) and Visit 7 (Day 56) and postdose meal requirements for Visit 6 (Day 28) and Visit 8 (Day 84) for consistency with the Schedule of Study Procedures.

09 May 2016	• Added a 4-hour gastric emptying breath test (GEBT) option during the Screening Period to allow for a nonradioactive alternative for gastric emptying testing. • Clarified that a participant could qualify for the study with either a GES or a GEBT, and added text to allow for an additional GEBT at Screening for qualification if needed. • Changed Inclusion Criterion #6 to define entry criteria for the GEBT results that qualified the participant for the study, and to allow a participant to perform a second gastric emptying test if they failed either the GES or GEBT at Screening. • Changed Exclusion Criterion #13 and study procedures language to add additional exclusions pertaining to nicotine-containing products specific for the GEBT. • Changed Exclusion Criterion #14 to add additional exclusions for the GEBT (allergies to lactose and Spirulina). • Changed Exclusion Criterion #23 to clarify which drugs in the urine drug screen were exclusionary. • Broadened the study endpoints to include both the GES and the GEBT. • Increased certain visit windows to increase participant compliance with the scheduled visits per protocol. • Clarified that the Follow-up Visit was to occur 14 days after the Day 84/Early Termination Visit. • Added cannabinoids and tramadol to urine drug screen testing. • Clarified which participants would be included in the full analysis set and included new variables added to the protocol in the subgroup analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported