Clinical trial results:
A Phase III, Multicentre, Single-arm, Open-label Study to Evaluate the Long-term Safety of Z-338 in Subjects with Functional Dyspepsia

Summary

EudraCT number	2013-003342-16
Trial protocol	BE SK GB LV LT BG
Global end of trial date	30 September 2016

Results information

Result version number	v1 (current)
This version publication date	14 October 2017
First version publication date	14 October 2017

Trial information

Trial identification

Sponsor protocol code	Z338-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01973790
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Zeria Pharmaceutical Co., Ltd. London Office
Sponsor organisation address	Building 3, Chiswick Park, 566 Chiswick High Road, London, United Kingdom, W4 5YA
Public contact	Project Manager, Zeria Pharmaceutical Co., Ltd. London Office, +81 336611183, tomoharu-miyagawa@zeria.co.jp
Scientific contact	Project Manager, Zeria Pharmaceutical Co., Ltd. London Office, +81 336611183, tomoharu-miyagawa@zeria.co.jp

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	17 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2016
Global end of trial reached?	Yes
Global end of trial date	30 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety of 100 mg Z-338 three times a day (TID) in subjects with Functional Dyspepsia.

Protection of trial subjects:

The study procedures outlined in this protocol will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the International Conference on Harmonisation (ICH) consolidated Guideline E6 for GCP, and applicable national/regional laws and regulatory requirement(s).
In general, if a subject is injured as a direct result of the study drug, the Sponsor will pay for reasonable and necessary medical treatment for the injury, to the extent the expenses are not covered by the subject's medical insurance, a government program, or other responsible third party. If laws or regulations of the locality in which the trial is taking place require additional payment of expenses, the Sponsor shall comply with such law or regulation. Where applicable, the Sponsor has taken specific national insurance.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 March 2014
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	Latvia: 49
Country: Number of subjects enrolled	Russian Federation: 10
Country: Number of subjects enrolled	Ukraine: 35
Country: Number of subjects enrolled	Romania: 22
Country: Number of subjects enrolled	Slovakia: 21
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Bulgaria: 16
Country: Number of subjects enrolled	Lithuania: 41
Worldwide total number of subjects	207
EEA total number of subjects	162

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)	196
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study Centers: Total of 62 sites initiated in 10 European countries: 1 in Belgium, 7 in Bulgaria, 8 in Latvia, 8 in Lithuania, 10 in Romania, 7 in Russia, 10 in Slovakia, 3 in Sweden, 5 in the Ukraine, and 3 in the United Kingdom.
Study Period ('First patient in' to 'Last patient out'): First patient in: 28-Mar-2014 Last patient out: 30-Sep-2016

Pre-assignment

Screening details:

Male and female patients who were at least 18 years old and with a diagnosis of FD (PDS) as defined by the ROME III criteria, who presented with early satiation
or postprandial fullness with a severity of at least moderate and a frequency of at least 2 days a week during the run-in period

Period 1

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

Blinding implementation details:

Not blinded

Arms

Arm title	100 mg Z-338 group

Arm description:

Subjects entering the open-label treatment period will receive Z-338 supplied as a white film-coated tablet containing 100 mg Z-338.

Arm type	Experimental
Investigational medicinal product name	Acotiamide
Investigational medicinal product code	Z-338
Other name	Acofide
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects will take 1 tablet of 100 mg acotiamide TID before food (subjects should be encouraged to eat 3 meals a day, i.e. morning, afternoon and evening).

Number of subjects in period 1	100 mg Z-338 group
Started	207
Completed	168
Not completed	39
Consent withdrawn by subject	12
Adverse event, non-fatal	6
Other	5
Pregnancy	1
Lost to follow-up	2

Lack of efficacy	7
Protocol deviation	3
Noncompliance	3

Baseline characteristics

Reporting groups	
Reporting group title	100 mg Z-338 group
Reporting group description:	
Subjects entering the open-label treatment period will receive Z-338 supplied as a white film-coated tablet containing 100 mg Z-338.	

Reporting group values	100 mg Z-338 group	Total	
Number of subjects	207	207	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	196	196	
From 65-84 years	11	11	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	64	64	
Male	143	143	

Subject analysis sets	
Subject analysis set title	Safety analysis
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety Analysis Set Population: all enrolled subjects who receive at least one dose of open-label study treatment	
Subject analysis set title	Full analysis
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Analysis Set Population: all enrolled subjects who receive at least one dose of open-label study treatment and have at least one post-baseline efficacy assessment.	

Reporting group values	Safety analysis	Full analysis	
Number of subjects	207	207	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	

Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	196	196	
From 65-84 years	11	11	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	64	64	
Male	143	143	

End points

End points reporting groups

Reporting group title	100 mg Z-338 group
Reporting group description:	
Subjects entering the open-label treatment period will receive Z-338 supplied as a white film-coated tablet containing 100 mg Z-338.	
Subject analysis set title	Safety analysis
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety Analysis Set Population: all enrolled subjects who receive at least one dose of open-label study treatment	
Subject analysis set title	Full analysis
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Analysis Set Population: all enrolled subjects who receive at least one dose of open-label study treatment and have at least one post-baseline efficacy assessment.	

Primary: Safety - number of subjects with AEs

End point title	Safety - number of subjects with AEs[1]
End point description:	
End point type	Primary
End point timeframe:	
Treatment-emergent Adverse events (TEAEs) will be monitored throughout the study for all subjects from the time of signing informed consent until 2 weeks after the End of Treatment (Visit 11 [Week 52]) or Early Termination visit, as applicable	

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: Statistical analyses not applicable due to the nature of the trial

End point values	100 mg Z-338 group			
Subject group type	Reporting group			
Number of subjects analysed	207			
Units: subjects				
Patients with at least 1 TEAE	92			
Patients with at least 1 Treatment related TEAE	18			
Patients with at least 1 Serious TEAE	6			
Patients with at least 1 TEAE led to discontinue	7			
Deaths	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Early satiation by time point

End point title	Change from baseline in Early satiation by time point

End point description:

Subjects will be asked to record the severity of each individual FD symptom on a daily basis during the 7-day run-in period (Visit 2 [Week -1] to Visit 3 [Week 0]) using the LPDS incorporated in an ePRO system.
During the open-label treatment period, subjects will be asked to record the severity of each individual symptom on a daily basis from Visit 3 (Week 0) to Visit 6 (Week 12), Visit 7 (Week 24) to Visit 8 (Week 26), and Visit 10 (Week 50) to Visit 11 (Week 52), using the LPDS incorporated in an ePRO system.
The LPDS has been developed and validated by Professor Jan Tack of the University of Leuven, Belgium.

End point type	Secondary

End point timeframe:

Baseline, Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8, Week 9, Week 10, Week 11, Week 12, Week 25, Week 26, Week 51, Week 52, End of treatment

End point values	100 mg Z-338 group			
Subject group type	Reporting group			
Number of subjects analysed	207			
Units: Score				
arithmetic mean (standard deviation)				
Week 1	-0.46 (± 0.649)			
Week 2	-0.65 (± 0.769)			
Week 3	-0.76 (± 0.841)			
Week 4	-0.85 (± 0.839)			
Week 5	-0.86 (± 0.839)			
Week 6	-0.89 (± 0.893)			
Week 7	-0.93 (± 0.859)			
Week 8	-0.99 (± 0.896)			
Week 9	-1.05 (± 0.896)			
Week 10	-1.06 (± 0.909)			
Week 11	-1.07 (± 0.883)			
Week 12	-1.16 (± 0.91)			
Week 25	-1.3 (± 0.912)			
Week 26	-1.35 (± 0.929)			
Week 51	-1.46 (± 0.977)			
Week 52	-1.48 (± 0.979)			
End of treatment	-1.38 (± 0.975)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Postprandial fullness by time point

End point title	Change from baseline in Postprandial fullness by time point

End point description:

"Subjects will be asked to record the severity of each individual FD symptom on a daily basis during the 7-day run-in period (Visit 2 [Week -1] to Visit 3 [Week 0]) using the LPDS incorporated in an ePRO system.
During the open-label treatment period, subjects will be asked to record the severity of each individual symptom on a daily basis from Visit 3 (Week 0) to Visit 6 (Week 12), Visit 7 (Week 24) to Visit 8 (Week 26), and Visit 10 (Week 50) to Visit 11 (Week 52), using the LPDS incorporated in an ePRO system.
The LPDS has been developed and validated by Professor Jan Tack of the University of Leuven, Belgium."

End point type	Secondary

End point timeframe:

Baseline, Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8, Week 9, Week 10, Week 11, Week 12, Week 25, Week 26, Week 51, Week 52, End of treatment

End point values	100 mg Z-338 group			
Subject group type	Reporting group			
Number of subjects analysed	207			
Units: Score				
arithmetic mean (standard deviation)				
Week 1	-0.57 (± 0.666)			
Week 2	-0.71 (± 0.801)			
Week 3	-0.91 (± 0.84)			
Week 4	-1.04 (± 0.848)			
Week 5	-1.08 (± 0.849)			
Week 6	-1.09 (± 0.85)			
Week 7	-1.15 (± 0.891)			
Week 8	-1.22 (± 0.906)			
Week 9	-1.27 (± 0.903)			
Week 10	-1.32 (± 0.904)			
Week 11	-1.37 (± 0.899)			
Week 12	-1.4 (± 0.893)			
Week 25	-1.58 (± 0.867)			
Week 26	-1.62 (± 0.895)			
Week 51	-1.8 (± 0.886)			
Week 52	-1.81 (± 0.909)			
End of treatment	-1.69 (± 0.941)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Upper Abdominal Bloating by time point

End point title	Change from baseline in Upper Abdominal Bloating by time point

End point description:

"Subjects will be asked to record the severity of each individual FD symptom on a daily basis during the 7-day run-in period (Visit 2 [Week -1] to Visit 3 [Week 0]) using the LPDS incorporated in an ePRO system.
During the open-label treatment period, subjects will be asked to record the severity of each individual symptom on a daily basis from Visit 3 (Week 0) to Visit 6 (Week 12), Visit 7 (Week 24) to Visit 8 (Week 26), and Visit 10 (Week 50) to Visit 11 (Week 52), using the LPDS incorporated in an ePRO system.
The LPDS has been developed and validated by Professor Jan Tack of the University of Leuven, Belgium."

End point type	Secondary

End point timeframe:

Baseline, Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8, Week 9, Week 10, Week 11, Week 12, Week 25, Week 26, Week 51, Week 52, End of treatment

End point values	100 mg Z-338 group			
Subject group type	Reporting group			
Number of subjects analysed	207			
Units: Score				
arithmetic mean (standard deviation)				
Week 1	-0.16 (± 0.612)			
Week 2	-0.31 (± 0.689)			
Week 3	-0.34 (± 0.746)			
Week 4	-0.39 (± 0.773)			
Week 5	-0.42 (± 0.781)			
Week 6	-0.45 (± 0.834)			
Week 7	-0.49 (± 0.839)			
Week 8	-0.5 (± 0.855)			
Week 9	-0.54 (± 0.778)			
Week 10	-0.56 (± 0.812)			
Week 11	-0.6 (± 0.789)			

Week 12	-0.59 (± 0.739)			
Week 25	-0.71 (± 0.855)			
Week 26	-0.73 (± 0.895)			
Week 51	-0.84 (± 0.847)			
Week 52	-0.85 (± 0.874)			
End of treatment	-0.8 (± 0.904)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Epigastric Pain by time point

End point title	Change from baseline in Epigastric Pain by time point

End point description:

"Subjects will be asked to record the severity of each individual FD symptom on a daily basis during the 7-day run-in period (Visit 2 [Week -1] to Visit 3 [Week 0]) using the LPDS incorporated in an ePRO system.
During the open-label treatment period, subjects will be asked to record the severity of each individual symptom on a daily basis from Visit 3 (Week 0) to Visit 6 (Week 12), Visit 7 (Week 24) to Visit 8 (Week 26), and Visit 10 (Week 50) to Visit 11 (Week 52), using the LPDS incorporated in an ePRO system.
The LPDS has been developed and validated by Professor Jan Tack of the University of Leuven, Belgium."

End point type	Secondary

End point timeframe:

Baseline, Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8, Week 9, Week 10, Week 11, Week 12, Week 25, Week 26, Week 51, Week 52, End of treatment

End point values	100 mg Z-338 group			
Subject group type	Reporting group			
Number of subjects analysed	207			
Units: Score				
arithmetic mean (standard deviation)				
Week 1	0.13 (± 0.457)			
Week 2	0.11 (± 0.447)			
Week 3	0.1 (± 0.464)			
Week 4	0.09 (± 0.453)			
Week 5	0.1 (± 0.529)			
Week 6	0.11 (± 0.518)			
Week 7	0.06 (± 0.474)			
Week 8	0.08 (± 0.535)			
Week 9	0.03 (± 0.4)			
Week 10	0.02 (± 0.382)			
Week 11	0.02 (± 0.362)			

Week 12	0.01 (± 0.367)			
Week 25	0.02 (± 0.375)			
Week 26	0.02 (± 0.387)			
Week 51	-0.02 (± 0.352)			
Week 52	-0.01 (± 0.384)			
End of treatment	0.02 (± 0.506)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Epigastric Burning by time point

End point title	Change from baseline in Epigastric Burning by time point

End point description:

"Subjects will be asked to record the severity of each individual FD symptom on a daily basis during the 7-day run-in period (Visit 2 [Week -1] to Visit 3 [Week 0]) using the LPDS incorporated in an ePRO system.
During the open-label treatment period, subjects will be asked to record the severity of each individual symptom on a daily basis from Visit 3 (Week 0) to Visit 6 (Week 12), Visit 7 (Week 24) to Visit 8 (Week 26), and Visit 10 (Week 50) to Visit 11 (Week 52), using the LPDS incorporated in an ePRO system.
The LPDS has been developed and validated by Professor Jan Tack of the University of Leuven, Belgium."

End point type	Secondary

End point timeframe:

Baseline, Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8, Week 9, Week 10, Week 11, Week 12, Week 25, Week 26, Week 51, Week 52, End of treatment

End point values	100 mg Z-338 group			
Subject group type	Reporting group			
Number of subjects analysed	207			
Units: Score				
arithmetic mean (standard deviation)				
Week 1	0.08 (± 0.349)			
Week 2	0.08 (± 0.349)			
Week 3	0.09 (± 0.375)			
Week 4	0.07 (± 0.322)			
Week 5	0.09 (± 0.374)			
Week 6	0.11 (± 0.419)			
Week 7	0.08 (± 0.384)			
Week 8	0.11 (± 0.406)			
Week 9	0.07 (± 0.258)			
Week 10	0.06 (± 0.249)			
Week 11	0.04 (± 0.237)			
Week 12	0.04 (± 0.231)			
Week 25	0.06 (± 0.233)			

Week 26	0.06 (± 0.262)			
Week 51	0.01 (± 0.21)			
Week 52	0.02 (± 0.286)			
End of treatment	0.06 (± 0.418)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Belching by time point

End point title	Change from baseline in Belching by time point

End point description:

"Subjects will be asked to record the severity of each individual FD symptom on a daily basis during the 7-day run-in period (Visit 2 [Week -1] to Visit 3 [Week 0]) using the LPDS incorporated in an ePRO system.
During the open-label treatment period, subjects will be asked to record the severity of each individual symptom on a daily basis from Visit 3 (Week 0) to Visit 6 (Week 12), Visit 7 (Week 24) to Visit 8 (Week 26), and Visit 10 (Week 50) to Visit 11 (Week 52), using the LPDS incorporated in an ePRO system.
The LPDS has been developed and validated by Professor Jan Tack of the University of Leuven, Belgium."

End point type	Secondary

End point timeframe:

Baseline, Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8, Week 9, Week 10, Week 11, Week 12, Week 25, Week 26, Week 51, Week 52, End of treatment

End point values	100 mg Z-338 group			
Subject group type	Reporting group			
Number of subjects analysed	207			
Units: Score				
arithmetic mean (standard deviation)				
Week 1	0.01 (± 0.589)			
Week 2	-0.04 (± 0.599)			
Week 3	-0.07 (± 0.628)			
Week 4	-0.1 (± 0.616)			
Week 5	-0.07 (± 0.651)			
Week 6	-0.1 (± 0.679)			
Week 7	-0.12 (± 0.645)			
Week 8	-0.14 (± 0.644)			
Week 9	-0.15 (± 0.638)			
Week 10	-0.18 (± 0.606)			
Week 11	-0.2 (± 0.606)			

Week 12	-0.18 (± 0.621)			
Week 25	-0.22 (± 0.688)			
Week 26	-0.22 (± 0.655)			
Week 51	-0.29 (± 0.656)			
Week 52	-0.28 (± 0.665)			
End of treatment	-0.23 (± 0.71)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Nausea by time point

End point title	Change from baseline in Nausea by time point

End point description:

"Subjects will be asked to record the severity of each individual FD symptom on a daily basis during the 7-day run-in period (Visit 2 [Week -1] to Visit 3 [Week 0]) using the LPDS incorporated in an ePRO system.
During the open-label treatment period, subjects will be asked to record the severity of each individual symptom on a daily basis from Visit 3 (Week 0) to Visit 6 (Week 12), Visit 7 (Week 24) to Visit 8 (Week 26), and Visit 10 (Week 50) to Visit 11 (Week 52), using the LPDS incorporated in an ePRO system.
The LPDS has been developed and validated by Professor Jan Tack of the University of Leuven, Belgium."

End point type	Secondary

End point timeframe:

Baseline, Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8, Week 9, Week 10, Week 11, Week 12, Week 25, Week 26, Week 51, Week 52, End of treatment

End point values	100 mg Z-338 group			
Subject group type	Reporting group			
Number of subjects analysed	207			
Units: Score				
arithmetic mean (standard deviation)				
Week 1	0 (± 0.425)			
Week 2	-0.02 (± 0.448)			
Week 3	-0.01 (± 0.435)			
Week 4	-0.01 (± 0.441)			
Week 5	0.02 (± 0.447)			
Week 6	0.01 (± 0.473)			
Week 7	0 (± 0.454)			
Week 8	0 (± 0.472)			
Week 9	-0.02 (± 0.41)			

Week 10	-0.06 (± 0.381)			
Week 11	-0.06 (± 0.38)			
Week 12	-0.1 (± 0.366)			
Week 25	-0.07 (± 0.376)			
Week 26	-0.06 (± 0.404)			
Week 51	-0.1 (± 0.365)			
Week 52	-0.1 (± 0.358)			
End of treatment	-0.05 (± 0.475)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Heartburn by time point

End point title	Change from baseline in Heartburn by time point

End point description:

"Subjects will be asked to record the severity of each individual FD symptom on a daily basis during the 7-day run-in period (Visit 2 [Week -1] to Visit 3 [Week 0]) using the LPDS incorporated in an ePRO system.
During the open-label treatment period, subjects will be asked to record the severity of each individual symptom on a daily basis from Visit 3 (Week 0) to Visit 6 (Week 12), Visit 7 (Week 24) to Visit 8 (Week 26), and Visit 10 (Week 50) to Visit 11 (Week 52), using the LPDS incorporated in an ePRO system.
The LPDS has been developed and validated by Professor Jan Tack of the University of Leuven, Belgium."

End point type	Secondary

End point timeframe:

Baseline, Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8, Week 9, Week 10, Week 11, Week 12, Week 25, Week 26, Week 51, Week 52, End of treatment

End point values	100 mg Z-338 group			
Subject group type	Reporting group			
Number of subjects analysed	207			
Units: Score				
arithmetic mean (standard deviation)				
Week 1	0.08 (± 0.331)			
Week 2	0.1 (± 0.354)			
Week 3	0.08 (± 0.358)			
Week 4	0.07 (± 0.302)			
Week 5	0.09 (± 0.37)			
Week 6	0.12 (± 0.04)			
Week 7	0.09 (± 0.356)			
Week 8	0.09 (± 0.364)			
Week 9	0.06 (± 0.227)			
Week 10	0.07 (± 0.237)			

Week 11	0.06 (± 0.234)			
Week 12	0.04 (± 0.217)			
Week 25	0.05 (± 0.18)			
Week 26	0.04 (± 0.204)			
Week 51	0.04 (± 0.178)			
Week 52	0.05 (± 0.273)			
End of treatment	0.07 (± 0.383)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall treatment evaluation by time point

End point title	Overall treatment evaluation by time point

End point description:

The OTE will be used to measure subjects' global outcome on a weekly basis, from the start of open-label treatment (Day 1 to Visit 6 [Week 12], Visit 7 [Week 24] to Visit 8 [Week 26], and Visit 10 [Week 50] to Visit 11 [Week 52]).

End point type	Secondary

End point timeframe:

Baseline, Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8, Week 9, Week 10, Week 11, Week 12, Week 25, Week 26, Week 51, Week 52, End of treatment

End point values	100 mg Z-338 group			
Subject group type	Reporting group			
Number of subjects analysed	207			
Units: Improvement rate				
number (confidence interval 95%)				
Week 1	13.1 (8.6 to 18.9)			
Week 2	18.7 (13.4 to 24.9)			
Week 3	21 (15.5 to 27.4)			
Week 4	26.2 (20.1 to 33)			
Week 5	26.9 (20.6 to 34)			
Week 6	33.3 (26.6 to 40.6)			
Week 7	32.2 (25.5 to 39.5)			
Week 8	39.1 (32 to 46.6)			
Week 9	41.2 (34 to 48.7)			
Week 10	45.7 (38.2 to 53.4)			

Week 11	40.6 (33.2 to 48.2)			
Week 12	41.5 (30.7 to 52.9)			
Week 25	52.9 (45.1 to 60.6)			
Week 26	50.3 (42.3 to 58.3)			
Week 51	70.6 (62.9 to 77.6)			
Week 52	70.2 (62.2 to 77.4)			
End of treatment	61.6 (54.5 to 68.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in SF-36 physical component by time point

End point title	Change from baseline in SF-36 physical component by time point

End point description:

The SF-36 is a 36-item survey that includes 1 multi-item scale measuring each of the following 8 health concepts: 1) physical functioning; 2) role limitations because of physical health problems; 3) bodily pain; 4) social functioning; 5) general mental health; 6) role limitations because of emotional problems; 7) vitality; and 8) general health perceptions.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 26, Week 38, Week 52, End of treatment

End point values	100 mg Z-338 group			
Subject group type	Reporting group			
Number of subjects analysed	207			
Units: Score				
arithmetic mean (standard deviation)				
Week 12	3.4 (± 7.09)			
Week 26	4.5 (± 7.19)			
Week 38	4.4 (± 7.25)			
Week 52	5.2 (± 7.54)			
End of treatment	4.2 (± 7.43)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in SF-36 mental component by time point

End point title	Change from baseline in SF-36 mental component by time point

End point description:

The SF-36 is a 36-item survey that includes 1 multi-item scale measuring each of the following 8 health concepts: 1) physical functioning; 2) role limitations because of physical health problems; 3) bodily pain; 4) social functioning; 5) general mental health; 6) role limitations because of emotional problems; 7) vitality; and 8) general health perceptions.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 26, Week 38, Week 52, End of treatment

End point values	100 mg Z-338 group			
Subject group type	Reporting group			
Number of subjects analysed	207			
Units: Score				
arithmetic mean (standard deviation)				
Week 12	4.2 (± 11.03)			
Week 26	6.5 (± 11.07)			
Week 38	6.1 (± 10.36)			
Week 52	7.6 (± 11.31)			
End of treatment	5.7 (± 10.68)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in SF-NDI scale (total) by time point

End point title	Change from baseline in SF-NDI scale (total) by time point

End point description:

The SF-NDI comprises a 15-symptom checklist and a 10-item survey specifically for FD measuring symptoms and health-related QoL. For the symptom checklist, subjects will be asked to score the frequency, intensity and bothersomeness of 15 upper gastrointestinal symptoms. For the 10-item QoL survey, subjects will be asked to answer 2 questions in each of 5 clinically relevant factors (subscales): tension; interference with daily activities; eating/drinking; knowledge/control; and work/study.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 26, Week 38, Week 52, End of treatment

End point values	100 mg Z-338 group			
Subject group type	Reporting group			
Number of subjects analysed	207			
Units: Score				
arithmetic mean (standard deviation)				
Week 12	-0.9 (± 0.9)			
Week 26	-1 (± 0.89)			
Week 38	-1 (± 0.86)			
Week 52	-1.1 (± 0.86)			
End of treatment	-1 (± 0.84)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in WPAI absenteeism by time point

End point title	Change from baseline in WPAI absenteeism by time point

End point description:

The WPAI is an assessment of the amount of absenteeism (work time missed), presenteeism (impairment at work/reduced on-the-job effectiveness) and activity impairment. Subjects will be asked to answer a maximum of 6 questions on whether they are currently employed; hours missed due to health problems; hours missed due to other reasons; hours actually worked; degree that health affected productivity while working; and the degree that health affected regular activities.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 26, Week 38, Week 52, End of treatment

End point values	100 mg Z-338 group			
Subject group type	Reporting group			
Number of subjects analysed	207			
Units: Score				
arithmetic mean (standard deviation)				
Week 12	0.7 (± 17.37)			
Week 26	-1 (± 13.29)			
Week 38	1.3 (± 15.54)			
Week 52	0.2 (± 15.27)			
End of treatment	0.9 (± 14.66)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in WPAI presenteeism by time point

End point title	Change from baseline in WPAI presenteeism by time point

End point description:

The WPAI is an assessment of the amount of absenteeism (work time missed), presenteeism (impairment at work/reduced on-the-job effectiveness) and activity impairment. Subjects will be asked to answer a maximum of 6 questions on whether they are currently employed; hours missed due to health problems; hours missed due to other reasons; hours actually worked; degree that health affected productivity while working; and the degree that health affected regular activities.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 26, Week 38, Week 52, End of treatment

End point values	100 mg Z-338 group			
Subject group type	Reporting group			
Number of subjects analysed	207			
Units: Score				
arithmetic mean (standard deviation)				
Week 12	-11.9 (± 21.81)			
Week 26	-14.2 (± 23.27)			
Week 38	-13.9 (± 25.48)			
Week 52	-15.5 (± 19.94)			
End of treatment	-13.4 (± 24.54)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in WPAI work productivity loss by time point

End point title	Change from baseline in WPAI work productivity loss by time point

End point description:

The WPAI is an assessment of the amount of absenteeism (work time missed), presenteeism (impairment at work/reduced on-the-job effectiveness) and activity impairment. Subjects will be asked to answer a maximum of 6 questions on whether they are currently employed; hours missed due to health problems; hours missed due to other reasons; hours actually worked; degree that health affected productivity while working; and the degree that health affected regular activities.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 26, Week 38, Week 52, End of treatment

End point values	100 mg Z-338 group			
Subject group type	Reporting group			
Number of subjects analysed	207			
Units: Score				
arithmetic mean (standard deviation)				
Week 12	-10.9 (± 23.85)			
Week 26	-13.4 (± 24.76)			
Week 38	-12.6 (± 27.23)			
Week 52	-14 (± 23.36)			
End of treatment	-12.4 (± 26.11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in WPAI activity impairment by time point

End point title	Change from baseline in WPAI activity impairment by time point

End point description:

The WPAI is an assessment of the amount of absenteeism (work time missed), presenteeism (impairment at work/reduced on-the-job effectiveness) and activity impairment. Subjects will be asked to answer a maximum of 6 questions on whether they are currently employed; hours missed due to health problems; hours missed due to other reasons; hours actually worked; degree that health affected productivity while working; and the degree that health affected regular activities.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 26, Week 38, Week 52, End of treatment

End point values	100 mg Z-338 group			
Subject group type	Reporting group			
Number of subjects analysed	207			
Units: Score				
arithmetic mean (standard deviation)				
Week 12	-12.4 (± 24.44)			
Week 26	-16.7 (± 25.16)			
Week 38	-15.1 (± 25.7)			

Week 52 End of treatment	-17.2 (± 24.56) -15.1 (± 25.14)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events will be monitored throughout the study for all subjects from the time of signing informed consent and will continue until 2 weeks after the End of Treatment (Visit 11 [Week 52]) or Early Termination visit, as applicable.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	100 mg Z-338 group

Reporting group description: -

Serious adverse events	100 mg Z-338 group		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 207 (2.90%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Ovarian cancer			
subjects affected / exposed	1 / 207 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostate cancer stage I			
subjects affected / exposed	1 / 207 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Ligament rupture			
subjects affected / exposed	1 / 207 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rib fracture			

subjects affected / exposed	1 / 207 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lumbar vertebral fracture			
subjects affected / exposed	1 / 207 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	1 / 207 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Uterine haemorrhage			
subjects affected / exposed	1 / 207 (0.48%)		
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	100 mg Z-338 group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 207 (17.87%)		
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 207 (6.76%)		
occurrences (all)	17		
Infections and infestations			
Influenza			
subjects affected / exposed	15 / 207 (7.25%)		
occurrences (all)	15		
Nasopharyngitis			
subjects affected / exposed	12 / 207 (5.80%)		
occurrences (all)	12		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 August 2015	Modification 1: The CRO Project Physician was changed from Dr Tandy Amure to Dr Katerina Cooper. Modification 2: The language on sample size was modified to reduce the total number of subjects to be screened due to challenges in recruitment. Modification 3: The reference to the ICH E1 Guideline was updated for clarity.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported