



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

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|--|----|
| 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.

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|--|--------------------|
| 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.

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|----------------|-----------|
| 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

Secondary: Change from baseline in Postprandial fullness by time point

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|-----------------|---|
| 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."

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|----------------|-----------|
| 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

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|-----------------|--|
| End point title | Change from baseline in Upper Abdominal Bloating by time point |
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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."

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|----------------|-----------|
| 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 (\pm 0.739) | | | |
| Week 25 | -0.71 (\pm 0.855) | | | |
| Week 26 | -0.73 (\pm 0.895) | | | |
| Week 51 | -0.84 (\pm 0.847) | | | |
| Week 52 | -0.85 (\pm 0.874) | | | |
| End of treatment | -0.8 (\pm 0.904) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Epigastric Pain by time point

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|-----------------|---|
| 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."

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|----------------|-----------|
| 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 (\pm 0.457) | | | |
| Week 2 | 0.11 (\pm 0.447) | | | |
| Week 3 | 0.1 (\pm 0.464) | | | |
| Week 4 | 0.09 (\pm 0.453) | | | |
| Week 5 | 0.1 (\pm 0.529) | | | |
| Week 6 | 0.11 (\pm 0.518) | | | |
| Week 7 | 0.06 (\pm 0.474) | | | |
| Week 8 | 0.08 (\pm 0.535) | | | |
| Week 9 | 0.03 (\pm 0.4) | | | |
| Week 10 | 0.02 (\pm 0.382) | | | |
| Week 11 | 0.02 (\pm 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."

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|----------------|-----------|
| 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 (\pm 0.262) | | | |
| Week 51 | 0.01 (\pm 0.21) | | | |
| Week 52 | 0.02 (\pm 0.286) | | | |
| End of treatment | 0.06 (\pm 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."

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|----------------|-----------|
| 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 (\pm 0.589) | | | |
| Week 2 | -0.04 (\pm 0.599) | | | |
| Week 3 | -0.07 (\pm 0.628) | | | |
| Week 4 | -0.1 (\pm 0.616) | | | |
| Week 5 | -0.07 (\pm 0.651) | | | |
| Week 6 | -0.1 (\pm 0.679) | | | |
| Week 7 | -0.12 (\pm 0.645) | | | |
| Week 8 | -0.14 (\pm 0.644) | | | |
| Week 9 | -0.15 (\pm 0.638) | | | |
| Week 10 | -0.18 (\pm 0.606) | | | |
| Week 11 | -0.2 (\pm 0.606) | | | |

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

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Nausea by time point

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|---|--|
| End point title | Change from baseline in Nausea by time point |
| End point description: | |
| <p>"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.</p> <p>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."</p> | |
| 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 (\pm 0.425) | | | |
| Week 2 | -0.02 (\pm 0.448) | | | |
| Week 3 | -0.01 (\pm 0.435) | | | |
| Week 4 | -0.01 (\pm 0.441) | | | |
| Week 5 | 0.02 (\pm 0.447) | | | |
| Week 6 | 0.01 (\pm 0.473) | | | |
| Week 7 | 0 (\pm 0.454) | | | |
| Week 8 | 0 (\pm 0.472) | | | |
| Week 9 | -0.02 (\pm 0.41) | | | |

| | | | | |
|------------------|----------------------|--|--|--|
| Week 10 | -0.06 (\pm 0.381) | | | |
| Week 11 | -0.06 (\pm 0.38) | | | |
| Week 12 | -0.1 (\pm 0.366) | | | |
| Week 25 | -0.07 (\pm 0.376) | | | |
| Week 26 | -0.06 (\pm 0.404) | | | |
| Week 51 | -0.1 (\pm 0.365) | | | |
| Week 52 | -0.1 (\pm 0.358) | | | |
| End of treatment | -0.05 (\pm 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 (\pm 0.331) | | | |
| Week 2 | 0.1 (\pm 0.354) | | | |
| Week 3 | 0.08 (\pm 0.358) | | | |
| Week 4 | 0.07 (\pm 0.302) | | | |
| Week 5 | 0.09 (\pm 0.37) | | | |
| Week 6 | 0.12 (\pm 0.04) | | | |
| Week 7 | 0.09 (\pm 0.356) | | | |
| Week 8 | 0.09 (\pm 0.364) | | | |
| Week 9 | 0.06 (\pm 0.227) | | | |
| Week 10 | 0.07 (\pm 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 | -17.2 (± 24.56) | | | |
| End of treatment | -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