



Clinical trial results:

Effects of Linagliptin on endothelial function and global arginine bioavailability ratio in coronary artery disease patients with early diabetes

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2013-000330-35 |
| Trial protocol | AT |
| Global end of trial date | 28 April 2018 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 01 January 2020 |
| First version publication date | 01 January 2020 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | HS-2012-1 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02350478 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Medical University of Graz |
| Sponsor organisation address | Auenbruggerplatz 2, Graz, Austria, 8010 |
| Public contact | Harald Sourij, Medizinische Universität Graz, 0043 31638581310, ha.sourij@medunigraz.at |
| Scientific contact | Harald Sourij, Medical University of Graz, 0043 31638581310, ha.sourij@medunigraz.at |

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 | 13 November 2017 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 April 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to investigate the impact of a 12 week linagliptin treatment on endothelial function in patients with early type 2 diabetes.

Protection of trial subjects:

All laboratory results will be reviewed and the reports signed by the study physician who will record whether it is normal, abnormal but not clinically significant, or abnormal and clinically significant. In the latter case, the eligibility of the subject will be reviewed.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------|
| Actual start date of recruitment | 06 May 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Austria: 49 |
| Worldwide total number of subjects | 49 |
| EEA total number of subjects | 49 |

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) | 35 |
| From 65 to 84 years | 14 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

In total 49 randomizations were performed. After randomization, two subjects were excluded due to screening failures without receiving the study medication. Therefore 47 subjects were enrolled in the study and received the study medication. Of those, 3 subjects were lost to follow up without available follow-up data and 1 subject was excluded.

Period 1

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

Arms

| | |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Linagliptin |

Arm description:

Linagliptin 5mg /daily oral

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Linagliptin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

5mg oral daily

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Placebo

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

Dosage and administration details:

5mg daily oral

| Number of subjects in period 1 | Linagliptin | Placebo |
|---------------------------------------|-------------|---------|
| Started | 25 | 24 |
| Completed | 20 | 23 |
| Not completed | 5 | 1 |
| Lost to follow-up | 3 | 1 |
| Protocol deviation | 2 | - |

Baseline characteristics

Reporting groups

| | |
|---|-------------|
| Reporting group title | Linagliptin |
| Reporting group description: Linagliptin 5mg /daily oral | |
| Reporting group title | Placebo |
| Reporting group description: Placebo | |

| Reporting group values | Linagliptin | Placebo | Total |
|---|-------------|---------|-------|
| Number of subjects | 25 | 24 | 49 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 10 | 12 | 22 |
| From 65-84 years | 15 | 12 | 27 |
| Age continuous Units: years | | | |
| arithmetic mean | 63.3 | 63.3 | |
| standard deviation | ± 7.8 | ± 8.7 | - |
| Gender categorical Units: Subjects | | | |
| Female | 9 | 5 | 14 |
| Male | 16 | 19 | 35 |
| Blood pressure systolic Units: mmHg | | | |
| arithmetic mean | 134 | 128 | |
| standard deviation | ± 17 | ± 18 | - |
| Blood pressure diastolic Units: mmHg | | | |
| arithmetic mean | 79 | 78 | |
| standard deviation | ± 14 | ± 10 | - |

End points

End points reporting groups

| | |
|------------------------------|-------------|
| Reporting group title | Linagliptin |
| Reporting group description: | |
| Linagliptin 5mg /daily oral | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Placebo | |

Primary: Changes in Flow Mediated Dilatation

| | |
|---|-------------------------------------|
| End point title | Changes in Flow Mediated Dilatation |
| End point description: | |
| Changes in Flow Mediated Dilatation from baseline to 12 weeks | |
| End point type | Primary |
| End point timeframe: | |
| 12 weeks | |

| End point values | Linagliptin | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 23 | | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | 0.4 (± 4.8) | -0.5 (± 3.0) | | |

Statistical analyses

| | |
|---|-------------------------|
| Statistical analysis title | Group comparison |
| Comparison groups | Placebo v Linagliptin |
| Number of subjects included in analysis | 43 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 |
| Method | Wilcoxon (Mann-Whitney) |

Secondary: Changes in Global Arginine Bioavailability Ratio

| | |
|--|--|
| End point title | Changes in Global Arginine Bioavailability Ratio |
| End point description: | |
| Changes in Global Arginine Bioavailability Ratio from Baseline to 12 weeks | |
| End point type | Secondary |

End point timeframe:

12 weeks

| End point values | Linagliptin | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 23 | | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | -0.11 (± 0.35) | -0.06 (± 0.39) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in Arginine to Ornithine Ratio

| | |
|------------------------|--|
| End point title | Changes in Arginine to Ornithine Ratio |
| End point description: | Changes in Arginine to Ornithine Ratio from Baseline to 12 weeks |
| End point type | Secondary |
| End point timeframe: | 12 weeks |

| End point values | Linagliptin | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 23 | | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | -0.13 (± 0.45) | -0.05 (± 0.53) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in Soluble cell adhesion molecules-1

| | |
|------------------------|--|
| End point title | Changes in Soluble cell adhesion molecules-1 |
| End point description: | Changes in Soluble cell adhesion molecules-1 from Baseline to 12 weeks |
| End point type | Secondary |
| End point timeframe: | 12 weeks |

| End point values | Linagliptin | Placebo | | |
|---------------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 23 | | |
| Units: ng/mL | | | | |
| median (inter-quartile range (Q1-Q3)) | -15 (-272 to 103) | -21 (-134 to 310) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in Soluble vascular cell adhesion molecule-1

| | |
|------------------------|--|
| End point title | Changes in Soluble vascular cell adhesion molecule-1 |
| End point description: | Changes in Soluble vascular cell adhesion molecule-1 from Baseline to 12 weeks |
| End point type | Secondary |
| End point timeframe: | 12 weeks |

| End point values | Linagliptin | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 23 | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | -34 (\pm 84) | 5 (\pm 130) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in Area under curve for glucose

| | |
|------------------------|---|
| End point title | Changes in Area under curve for glucose |
| End point description: | Changes in Area under curve for glucose from Baseline to 12 weeks |
| End point type | Secondary |
| End point timeframe: | 12 weeks |

| End point values | Linagliptin | Placebo | | |
|--------------------------------------|---------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 23 | | |
| Units: mg/dL | | | | |
| arithmetic mean (standard deviation) | -1135 (\pm 2619) | 481 (\pm 3185) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Area under curve for free fatty acids

| | |
|------------------------|---|
| End point title | Change in Area under curve for free fatty acids |
| End point description: | Change in Area under curve for free fatty acids from baseline to 12 weeks |
| End point type | Secondary |
| End point timeframe: | 12 weeks |

| End point values | Linagliptin | Placebo | | |
|--------------------------------------|-----------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 23 | | |
| Units: μ mol/L | | | | |
| arithmetic mean (standard deviation) | 2 (\pm 28.4) | -3.1 (\pm 18.3) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in Area under curve for insulin

| | |
|------------------------|---|
| End point title | Changes in Area under curve for insulin |
| End point description: | changes in Area under curve for insulin from baseline to 12 weeks |
| End point type | Secondary |
| End point timeframe: | 12 weeks |

| End point values | Linagliptin | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 23 | | |
| Units: mU/L | | | | |
| arithmetic mean (standard deviation) | 249 (± 4766) | 40 (± 6357) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in Area under curve for c-peptide

| | |
|------------------------|---|
| End point title | Changes in Area under curve for c-peptide |
| End point description: | Changes in Area under curve for c-peptide from Baseline to 12 weeks |
| End point type | Secondary |
| End point timeframe: | 12 weeks |

| End point values | Linagliptin | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 23 | | |
| Units: mg/dL | | | | |
| arithmetic mean (standard deviation) | -3 (± 161) | -34 (± 211) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

12 weeks

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 22.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Linagliptin |
|-----------------------|-------------|

Reporting group description:

Verum Group

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo group

| Serious adverse events | Linagliptin | Placebo | |
|---|-----------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 20 (15.00%) | 1 / 23 (4.35%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Nervous system disorders | | | |
| Coordination abnormal | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 23 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 23 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Prolapse | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 23 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |

| | | | |
|---|----------------|----------------|--|
| Borrelia infection | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 23 (4.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Linagliptin | Placebo | |
|---|-----------------|-----------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 3 / 20 (15.00%) | 3 / 23 (13.04%) | |
| Vascular disorders | | | |
| Intermittent claudication | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 23 (4.35%) | |
| occurrences (all) | 0 | 0 | |
| Cardiac disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 23 (4.35%) | |
| occurrences (all) | 0 | 0 | |
| Nervous system disorders | | | |
| Pain | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 23 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| General disorders and administration site conditions | | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 23 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Gastrointestinal disorders | | | |
| Toothache | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 23 (0.00%) | |
| occurrences (all) | 0 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 05 August 2013 | Combination of Screening and Baseline Visits |
| 22 October 2013 | Inclusion criterion (max age changed from 75 to 80 years) |
| 30 April 2014 | Exclusion criteria: HbA1c <6.0% (42mmol/mol) instead of HbA1c <6.5 (48mmol/mol) |
| 24 October 2014 | Storage of blood samples in the Biobank (Medical University of Graz) |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29773079>

<http://www.ncbi.nlm.nih.gov/pubmed/27733180>