



Clinical trial results:

The Role of Tetracyclines in the Personalised Management of MMP-9 and Cardiovascular Function in Type 2 Diabetes

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-002387-16 |
| Trial protocol | IE |
| Global end of trial date | 10 April 2017 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 26 April 2018 |
| First version publication date | 26 April 2018 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | SI-C-060 |
|-----------------------|----------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Solvotrin Innovations Ltd |
| Sponsor organisation address | Hoffman Park, Little Island, Cork, Ireland, T45 YX04 |
| Public contact | Fiona Ryan, Solvotrin Innovations Ltd, 353 214510220, Fionaryan@solvotrin.com |
| Scientific contact | Fiona Ryan, Solvotrin Innovations Ltd, 353 214510220, Fionaryan@solvotrin.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 10 April 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 10 April 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 10 April 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To investigate the impact of one year therapy with minocycline on MMP-9 in patients with with Type 2 diabetes and the MMP-9, 1562 C>T promoter single nucleotide polymorphism

Protection of trial subjects:

This study was carried out in accordance with the ethical principles that have their origins in the Declaration of Helsinki. Before initiating the study, all relevant documentation including the study protocol and patient information and informed consent form were reviewed and approved by the relevant competent authority and the St Vincent's University Hospital Ethics Committee. Each participant was provided with an information and consent form in clear, simple language and was given ample time to inquire about details of the study and to decide whether or not to participate in the study. Participants anonymity was maintained at all times throughout the study.

Background therapy:

Usual medical care

Evidence for comparator:

The comparator group was usual medical care. There was no placebo.

| | |
|---|-----------------|
| Actual start date of recruitment | 13 January 2016 |
| 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 | Ireland: 22 |
| Worldwide total number of subjects | 22 |
| EEA total number of subjects | 22 |

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) | 8 |
| From 65 to 84 years | 14 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Trial participants were recruited from the STOP-HF Unit of St Michael's Hospital, Dun Laoghaire, Co Dublin. Male and female patients >18 years of age were eligible to participate once eligibility criteria were met.

Pre-assignment

Screening details:

The STOP-HF database was screened to identify patients that met the inclusion criteria (age, diabetes, MMP-9 1562 C>T promoter single nucleotide polymorphism). Potentially eligible patients were invited to a 'Screening visit' at which eligibility was further assessed/confirmed.

Period 1

| | |
|------------------------------|-------------------------|
| Period 1 title | Baseline |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

Unblinded study

Arms

| | |
|------------------------------|----------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Intervention (minocycline) |

Arm description:

Usual medical care and additional treatment with minocycline 100mg daily (orally) for 12 months.

| | |
|--|--------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Minocycline 100mg capsules |
| Investigational medicinal product code | |
| Other name | Minosil |
| Pharmaceutical forms | Modified-release capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Minocycline 100mg once daily (orally) for 12 months

| | |
|------------------|---------|
| Arm title | Control |
|------------------|---------|

Arm description:

Usual medical care (no minocycline)

| | |
|---|-----------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 1 | Intervention (minocycline) | Control |
|--------------------------------|----------------------------|---------|
| Started | 10 | 12 |
| Completed | 10 | 12 |

| | |
|--|--------------------------------|
| Period 2 | |
| Period 2 title | Overall Trial |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |
| Blinding implementation details: Unblinded study | |
| Arms | |
| Are arms mutually exclusive? | Yes |
| Arm title | Intervention (Minocycline) |
| Arm description: Usual medical care and additional treatment with minocycline 100mg daily (orally) for 12 months. | |
| Arm type | Experimental |
| Investigational medicinal product name | Minocycline |
| Investigational medicinal product code | |
| Other name | Minosil |
| Pharmaceutical forms | Modified-release capsule, hard |
| Routes of administration | Oral use |
| Dosage and administration details: Minocycline 100mg once daily (orally) for 12 months | |
| Arm title | Control |
| Arm description: Usual medical care | |
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 2 | Intervention (Minocycline) | Control |
|--------------------------------|----------------------------|---------|
| Started | 10 | 12 |
| Completed | 7 | 11 |
| Not completed | 3 | 1 |
| Consent withdrawn by subject | - | 1 |
| Adverse event, non-fatal | 3 | - |

Baseline characteristics

Reporting groups

| | |
|--|----------------------------|
| Reporting group title | Intervention (minocycline) |
| Reporting group description: Usual medical care and additional treatment with minocycline 100mg daily (orally) for 12 months. | |
| Reporting group title | Control |
| Reporting group description: Usual medical care (no minocycline) | |

| Reporting group values | Intervention (minocycline) | Control | Total |
|--|-------------------------------|--------------|-------|
| Number of subjects | 10 | 12 | 22 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 4 | 4 | 8 |
| From 65-84 years | 6 | 8 | 14 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous Units: years | | | |
| median | 68.2 | 69 | |
| inter-quartile range (Q1-Q3) | 60.7 to 73.8 | 62.6 to 73.7 | - |
| Gender categorical Units: Subjects | | | |
| Female | 2 | 4 | 6 |
| Male | 8 | 8 | 16 |
| Diabetes Units: Subjects | | | |
| Diabetes mellitus | 10 | 12 | 22 |
| No diabetes mellitus | 0 | 0 | 0 |
| Hypertension Units: Subjects | | | |
| Hypertension | 8 | 11 | 19 |
| No hypertension | 2 | 1 | 3 |
| Dyslipidemia Units: Subjects | | | |
| Dyslipidemia | 8 | 11 | 19 |
| No dyslipidemia | 2 | 1 | 3 |
| Atrial fibrillation Units: Subjects | | | |
| AF | 0 | 0 | 0 |
| No AF | 10 | 12 | 22 |
| Coronary artery disease Units: Subjects | | | |
| CAD | 0 | 1 | 1 |
| No CAD | 10 | 11 | 21 |
| Smoking history Units: Subjects | | | |
| Smoker | 3 | 1 | 4 |

| | | | |
|---|----|----|----|
| Non-smoker | 7 | 11 | 18 |
| Medication history. Beta-blocker Units: Subjects | | | |
| Beta-blocker | 3 | 3 | 6 |
| No beta-blocker | 7 | 9 | 16 |
| Medication history. Alpha-blocker Units: Subjects | | | |
| Alpha-blocker | 0 | 1 | 1 |
| No alpha-blocker | 10 | 11 | 21 |
| Medication history. CCB (calcium channel blocker) Units: Subjects | | | |
| CCB | 6 | 6 | 12 |
| No CCB | 4 | 6 | 10 |
| Medication history. AA (aldosterone antagonist) Units: Subjects | | | |
| AA | 0 | 0 | 0 |
| No AA | 10 | 12 | 22 |
| Medication history. Statin Units: Subjects | | | |
| Statin | 10 | 9 | 19 |
| No statin | 0 | 3 | 3 |
| Medication history. Diuretic Units: Subjects | | | |
| Diuretic | 0 | 2 | 2 |
| No diuretic | 10 | 10 | 20 |
| Medication history. Antiplatelet Units: Subjects | | | |
| Antiplatelet | 8 | 12 | 20 |
| No antiplatelet | 2 | 0 | 2 |
| Medication history. Metformin Units: Subjects | | | |
| Metformin | 10 | 8 | 18 |
| No metformin | 0 | 4 | 4 |
| Medication history (Gliclazide) Units: Subjects | | | |
| Gliclazide | 4 | 4 | 8 |
| No gliclazide | 6 | 8 | 14 |
| Medication history (Insulin) Units: Subjects | | | |
| Insulin | 2 | 0 | 2 |
| No insulin | 8 | 12 | 20 |
| Family history of CVD Units: Subjects | | | |
| Family history of CVD | 2 | 3 | 5 |
| No family history of CVD | 8 | 9 | 17 |
| Medication history. ACEI or ARB Units: Subjects | | | |
| ACEI or ARB | 7 | 9 | 16 |
| No ACEI or ARB | 3 | 3 | 6 |

| | | | |
|-------------------------------------|--------------|--------------|----|
| Medication history. Warfarin | | | |
| Units: Subjects | | | |
| Warfarin | 0 | 0 | 0 |
| No warfarin | 10 | 12 | 22 |
| Body mass index (BMI) | | | |
| Units: kg/m2 | | | |
| median | 28.05 | 29.4 | |
| inter-quartile range (Q1-Q3) | 27.1 to 31.1 | 26.0 to 30.9 | - |
| Height | | | |
| Units: cm | | | |
| median | 184 | 168 | |
| inter-quartile range (Q1-Q3) | 175 to 186 | 168 to 174 | - |
| Weight | | | |
| Units: kg | | | |
| median | 90 | 85 | |
| inter-quartile range (Q1-Q3) | 81 to 109 | 79 to 94 | - |
| Body surface area | | | |
| Units: m2 | | | |
| median | 2.12 | 1.98 | |
| inter-quartile range (Q1-Q3) | 1.96 to 2.35 | 1.90 to 2 | - |
| Glucose | | | |
| Units: mmol/L | | | |
| median | 8.2 | 10.8 | |
| inter-quartile range (Q1-Q3) | 6.7 to 8.8 | 8.8 to 12.5 | - |
| Total cholesterol | | | |
| Units: mmol/L | | | |
| median | 3.9 | 4.1 | |
| inter-quartile range (Q1-Q3) | 3.6 to 4.5 | 3.5 to 4.6 | - |
| Intraocular pressure | | | |
| Units: mmHg | | | |
| median | 15 | 15 | |
| inter-quartile range (Q1-Q3) | 12.5 to 16.5 | 13 to 17 | - |
| ABPM. Systolic BP (24h) | | | |
| Units: mmHg | | | |
| median | 129 | 131 | |
| inter-quartile range (Q1-Q3) | 126 to 131 | 122 to 136 | - |
| ABPM. Diastolic BP (24h) | | | |
| Units: mmHg | | | |
| median | 72 | 73 | |
| inter-quartile range (Q1-Q3) | 67 to 75 | 66 to 73 | - |
| ABPM. Heart Rate (24hour) | | | |
| Units: bpm | | | |
| median | 80 | 71 | |
| inter-quartile range (Q1-Q3) | 75 to 83 | 63 to 78 | - |
| ABPM. Pulse Pressure (24 hour) | | | |
| Units: mmHg | | | |
| median | 54 | 57 | |
| inter-quartile range (Q1-Q3) | 52 to 59 | 54 to 64 | - |
| Echocardiography. Ejection fraction | | | |
| Units: %, Teicholtz | | | |
| median | 68 | 65 | |
| inter-quartile range (Q1-Q3) | 63 to 73 | 63 to 68 | - |

| | | | |
|---|----------------------|----------------------|---|
| Echocardiography. End Diastolic Volume Units: millilitre(s) median inter-quartile range (Q1-Q3) | 97 69 to 108 | 92 77 to 110 | - |
| Echocardiography. End Systolic Volume Units: millilitre(s) median inter-quartile range (Q1-Q3) | 31 23 to 37 | 27 25 to 42 | - |
| Echocardiography. Left ventricular mass index (LVMI) Units: gram(s)/square meter median inter-quartile range (Q1-Q3) | 92 84 to 98 | 109 83 to 119 | - |
| Echocardiography. E/E' lateral Units: Ratio median inter-quartile range (Q1-Q3) | 8.75 7.3 to 11.1 | 9.77 8.9 to 10.6 | - |
| Echocardiography. Left Atrial Volume Index (LAVI) Units: mL/m2 median inter-quartile range (Q1-Q3) | 22.4 19.1 to 25 | 21.3 17.8 to 24.2 | - |
| Brain natriuretic peptide (BNP) Units: Normalised protein expression units (NPX) median inter-quartile range (Q1-Q3) | 12.2 8.0 to 21.5 | 24.3 12.0 to 34.1 | - |
| Matrix metalloproteinase-2 (MMP-2) Units: Normalised protein expression units (NPX) median inter-quartile range (Q1-Q3) | 3.86 3.66 to 4.12 | 3.91 3.66 to 4.18 | - |
| Matrix metalloproteinase-9 (MMP-9) Units: Normalised protein expression units (NPX) median inter-quartile range (Q1-Q3) | 5.29 4.56 to 5.53 | 5.83 5.29 to 6.19 | - |
| Interleukin 6 receptor antagonist (IL6RA) Units: Normalised protein expression units (NPX) median inter-quartile range (Q1-Q3) | 11.1 10.9 to 11.3 | 10.9 10.8 to 11.1 | - |
| Collagen 1 (Col1a1) Units: Normalised protein expression units (NPX) median inter-quartile range (Q1-Q3) | 3.6 3.3 to 3.9 | 3.5 3.3 to 3.8 | - |
| Galectin-3 (Gal-3) Units: Normalised protein expression units (NPX) median inter-quartile range (Q1-Q3) | 4.9 4.8 to 5.3 | 5.1 4.8 to 5.5 | - |
| Tumor necrosis factor 1 receptor 1 (TNFr1) | | | |

| | | | |
|--|-------------------|-------------------|---|
| Units: Normalised protein expression units (NPX median inter-quartile range (Q1-Q3) | 5.2 4.9 to 5.4 | 5.3 5.2 to 5.6 | - |
| Monocyte chemotactic protein-1 (MCP-1) Units: Normalised protein expression units (NPX median inter-quartile range (Q1-Q3) | 3.4 2.7 to 3.5 | 3.5 3.0 to 3.7 | - |
| Triglycerides Units: mmol/L median inter-quartile range (Q1-Q3) | 2.4 1.9 to 2.9 | 1.9 1.3 to 2.4 | - |

End points

End points reporting groups

| | |
|--|----------------------------|
| Reporting group title | Intervention (minocycline) |
| Reporting group description: Usual medical care and additional treatment with minocycline 100mg daily (orally) for 12 months. | |
| Reporting group title | Control |
| Reporting group description: Usual medical care (no minocycline) | |
| Reporting group title | Intervention (Minocycline) |
| Reporting group description: Usual medical care and additional treatment with minocycline 100mg daily (orally) for 12 months. | |
| Reporting group title | Control |
| Reporting group description: Usual medical care | |

Primary: Baseline to 1 year change in matrix metalloproteinase-9 (MMP-9)

| | |
|-----------------------------------|---|
| End point title | Baseline to 1 year change in matrix metalloproteinase-9 (MMP-9) |
| End point description: | |
| End point type | Primary |
| End point timeframe: 12 months | |

| End point values | Intervention (Minocycline) | Control | | |
|--|-------------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 11 | | |
| Units: Normalised protein expression units (NPX) | | | | |
| median (inter-quartile range (Q1-Q3)) | 0.66 (-0.02 to 1.32) | 0.04 (-0.88 to 0.59) | | |

Statistical analyses

| | |
|----------------------------|--------------------------------------|
| Statistical analysis title | Wilcoxon (Mann Whitney) |
| Comparison groups | Intervention (Minocycline) v Control |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 21 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.22 |
| Method | Wilcoxon (Mann-Whitney) |

Secondary: Baseline to 1 year change in matrix metalloproteinase-2 (MMP-2)

| | |
|-----------------------------------|---|
| End point title | Baseline to 1 year change in matrix metalloproteinase-2 (MMP-2) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: 12 months | |

| End point values | Intervention (Minocycline) | Control | | |
|--|-------------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 11 | | |
| Units: Normalised protein expression units (NPX) | | | | |
| median (inter-quartile range (Q1-Q3)) | 0.16 (0.02 to 0.33) | 0.09 (-0.06 to 0.17) | | |

Statistical analyses

| | |
|---|--------------------------------------|
| Statistical analysis title | T-test |
| Comparison groups | Intervention (Minocycline) v Control |
| Number of subjects included in analysis | 21 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.35 |
| Method | t-test, 2-sided |

Secondary: Baseline to 1 year change in interleukin 6 receptor antagonist (IL6RA)

| | |
|-----------------------------------|--|
| End point title | Baseline to 1 year change in interleukin 6 receptor antagonist (IL6RA) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: 12 months | |

| End point values | Intervention (Minocycline) | Control | | |
|--|----------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 11 | | |
| Units: Normalised protein expression units (NPX) | | | | |
| arithmetic mean (standard deviation) | 0.1 (\pm 0.23) | 0.01 (\pm 0.26) | | |

Statistical analyses

| | |
|---|--------------------------------------|
| Statistical analysis title | T-test |
| Comparison groups | Intervention (Minocycline) v Control |
| Number of subjects included in analysis | 21 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.31 |
| Method | t-test, 2-sided |

Secondary: Baseline to 1 year change in collagen 1 (Col1a1)

| | |
|------------------------|--|
| End point title | Baseline to 1 year change in collagen 1 (Col1a1) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 12 months | |

| End point values | Intervention (Minocycline) | Control | | |
|--|----------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 11 | | |
| Units: Normalised protein expression units (NPX) | | | | |
| arithmetic mean (standard deviation) | -0.03 (\pm 0.41) | 0.15 (\pm 0.19) | | |

Statistical analyses

| | |
|----------------------------|--------------------------------------|
| Statistical analysis title | T-test |
| Comparison groups | Intervention (Minocycline) v Control |

| | |
|---|-----------------|
| Number of subjects included in analysis | 21 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.39 |
| Method | t-test, 2-sided |

Secondary: Baseline to 1 year change in galectin-3 (Gal-3)

| | |
|------------------------|---|
| End point title | Baseline to 1 year change in galectin-3 (Gal-3) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 12 months | |

| End point values | Intervention (Minocycline) | Control | | |
|---|-------------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 11 | | |
| Units: Normalised protein expression units (NPX | | | | |
| arithmetic mean (standard deviation) | 0.03 (\pm 0.33) | 0.03 (\pm 0.49) | | |

Statistical analyses

| | |
|---|--------------------------------------|
| Statistical analysis title | T-test |
| Comparison groups | Intervention (Minocycline) v Control |
| Number of subjects included in analysis | 21 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.91 |
| Method | t-test, 2-sided |

Secondary: Baseline to 1 year change in tumor necrosis factor 1 receptor 1 (TNFa R1)

| | |
|------------------------|---|
| End point title | Baseline to 1 year change in tumor necrosis factor 1 receptor 1 (TNFa R1) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 12 months | |

| End point values | Intervention (Minocycline) | Control | | |
|--|-------------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 11 | | |
| Units: Normalised protein expression units (NPX) | | | | |
| arithmetic mean (standard deviation) | 0.12 (\pm 0.45) | 0.05 (\pm 0.36) | | |

Statistical analyses

| | |
|---|--------------------------------------|
| Statistical analysis title | T-test |
| Comparison groups | Intervention (Minocycline) v Control |
| Number of subjects included in analysis | 21 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.66 |
| Method | t-test, 2-sided |

Secondary: Baseline to 1 year change in monocyte chemotactic protein 1 (MCP-1)

| | |
|------------------------|---|
| End point title | Baseline to 1 year change in monocyte chemotactic protein 1 (MCP-1) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | 12 months |

| End point values | Intervention (Minocycline) | Control | | |
|--|-------------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 11 | | |
| Units: Normalised protein expression units (NPX) | | | | |
| arithmetic mean (standard deviation) | 0.27 (\pm 0.47) | 0.29 (\pm 0.71) | | |

Statistical analyses

| | |
|----------------------------|--------------------------------------|
| Statistical analysis title | T-test |
| Comparison groups | Intervention (Minocycline) v Control |

| | |
|---|-----------------|
| Number of subjects included in analysis | 21 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.85 |
| Method | t-test, 2-sided |

Secondary: Baseline to 1 year change in ejection fraction (echo)

| | |
|------------------------|---|
| End point title | Baseline to 1 year change in ejection fraction (echo) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 12 months | |

| End point values | Intervention (Minocycline) | Control | | |
|--------------------------------------|-------------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 9 | 10 | | |
| Units: percentage | | | | |
| arithmetic mean (standard deviation) | 2.8 (± 7.1) | 3.46 (± 10.1) | | |

Statistical analyses

| | |
|---|--------------------------------------|
| Statistical analysis title | T test |
| Comparison groups | Intervention (Minocycline) v Control |
| Number of subjects included in analysis | 19 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.81 |
| Method | t-test, 2-sided |

Secondary: Baseline to 1 year change in left atrial volume index (LAVI) (echo)

| | |
|------------------------|---|
| End point title | Baseline to 1 year change in left atrial volume index (LAVI) (echo) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 12 months | |

| End point values | Intervention (Minocycline) | Control | | |
|--------------------------------------|-------------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 9 | 11 | | |
| Units: ml/m2 | | | | |
| arithmetic mean (standard deviation) | 0.39 (± 4.1) | 1.19 (± 5.4) | | |

Statistical analyses

| | |
|---|--------------------------------------|
| Statistical analysis title | T-test |
| Comparison groups | Intervention (Minocycline) v Control |
| Number of subjects included in analysis | 20 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.56 |
| Method | t-test, 2-sided |

Secondary: Baseline to 1 year change in left ventricular mass index (LVMI) (echo)

| | |
|-----------------------------------|--|
| End point title | Baseline to 1 year change in left ventricular mass index (LVMI) (echo) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: 12 months | |

| End point values | Intervention (Minocycline) | Control | | |
|--------------------------------------|-------------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 10 | | |
| Units: g/m2 | | | | |
| arithmetic mean (standard deviation) | 13.4 (± 24.7) | 1.6 (± 18.7) | | |

Statistical analyses

| | |
|-----------------------------------|--------------------------------------|
| Statistical analysis title | T-test |
| Comparison groups | Intervention (Minocycline) v Control |

| | |
|---|-----------------|
| Number of subjects included in analysis | 18 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.73 |
| Method | t-test, 2-sided |

Secondary: Baseline to 1 year change in systolic BP (24 hour)

| | |
|------------------------|--|
| End point title | Baseline to 1 year change in systolic BP (24 hour) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 12 months | |

| End point values | Intervention (Minocycline) | Control | | |
|--------------------------------------|-------------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 11 | | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | -3.6 (± 7.4) | 0 (± 11.3) | | |

Statistical analyses

| | |
|---|--------------------------------------|
| Statistical analysis title | T-test |
| Comparison groups | Intervention (Minocycline) v Control |
| Number of subjects included in analysis | 19 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.61 |
| Method | t-test, 2-sided |

Secondary: Baseline to 1 year change in diastolic BP (24 hour)

| | |
|------------------------|---|
| End point title | Baseline to 1 year change in diastolic BP (24 hour) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 12 months | |

| End point values | Intervention (Minocycline) | Control | | |
|--------------------------------------|----------------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 11 | | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | -1.5 (\pm 3.8) | -0.4 (\pm 5.6) | | |

Statistical analyses

| Statistical analysis title | T-test |
|---|--------------------------------------|
| Comparison groups | Intervention (Minocycline) v Control |
| Number of subjects included in analysis | 19 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.66 |
| Method | t-test, 2-sided |

Secondary: Baseline to 1 year change in pulse pressure (24 hour)

| | |
|------------------------|---|
| End point title | Baseline to 1 year change in pulse pressure (24 hour) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 12 months | |

| End point values | Intervention (Minocycline) | Control | | |
|--------------------------------------|----------------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 11 | | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | -1.9 (\pm 4.6) | 0.6 (\pm 5.4) | | |

Statistical analyses

| Statistical analysis title | T-test |
|----------------------------|--------------------------------------|
| Comparison groups | Intervention (Minocycline) v Control |

| | |
|---|-----------------|
| Number of subjects included in analysis | 19 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.67 |
| Method | t-test, 2-sided |

| | |
|---|--------------------------------------|
| Statistical analysis title | T-test |
| Comparison groups | Intervention (Minocycline) v Control |
| Number of subjects included in analysis | 19 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.67 |
| Method | t-test, 2-sided |

Secondary: Baseline to 1 year change in intraocular pressure

| | |
|------------------------|---|
| End point title | Baseline to 1 year change in intraocular pressure |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 12 months | |

| End point values | Intervention (Minocycline) | Control | | |
|--------------------------------------|-------------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 4 | 5 | | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | -1.8 (± 0.5) | -2.0 (± 1.6) | | |

Statistical analyses

| | |
|---|--------------------------------------|
| Statistical analysis title | T-test |
| Comparison groups | Intervention (Minocycline) v Control |
| Number of subjects included in analysis | 9 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.73 |
| Method | t-test, 2-sided |

Secondary: Baseline to 1 year change in E/E' (echo)

| | |
|-----------------|--|
| End point title | Baseline to 1 year change in E/E' (echo) |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

12 months

| End point values | Intervention (Minocycline) | Control | | |
|--------------------------------------|-------------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 | 9 | | |
| Units: ratio | | | | |
| arithmetic mean (standard deviation) | -0.22 (\pm 1.47) | 0.01 (\pm 1.54) | | |

Statistical analyses

| | |
|---|--------------------------------------|
| Statistical analysis title | T-test |
| Comparison groups | Intervention (Minocycline) v Control |
| Number of subjects included in analysis | 15 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.94 |
| Method | t-test, 2-sided |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization

Adverse event reporting additional description:

Safety information was provided spontaneously by the participant and/or through questioning by the investigator. If any changes to medication suggested a new illness or worsening of a pre-existing condition, the participant was questioned further. Abnormal laboratory/test results, if deemed medically significant, were considered adverse events

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 20 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|----------------------------|
| Reporting group title | Intervention (Minocycline) |
|-----------------------|----------------------------|

Reporting group description:

Minocycline 100mg daily orally in addition to usual medical care.

| | |
|-----------------------|---------|
| Reporting group title | Control |
|-----------------------|---------|

Reporting group description:

Usual medical care

| Serious adverse events | Intervention (Minocycline) | Control | |
|---|-------------------------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 10 (30.00%) | 0 / 12 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Phrenic nerve paralysis | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Speech disorder | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Atelectasis | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Intervention (Minocycline) | Control | |
|---|-------------------------------|-----------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 9 / 10 (90.00%) | 9 / 12 (75.00%) | |
| Vascular disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 1 | 1 | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Cardiac disorders | | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Palpitations | | | |

| | | | |
|---|--|--|--|
| subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 0 / 12 (0.00%) 0 | |
| Surgical and medical procedures Knee operation subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 12 (8.33%) 1 | |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Influenza like illness subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) | 3 / 10 (30.00%) 3 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 | 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 2 / 12 (16.67%) 2 | |
| Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) Inguinal hernia subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Gastrointestinal disorder subjects affected / exposed occurrences (all) | 2 / 10 (20.00%) 2 0 / 10 (0.00%) 0 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 0 / 10 (0.00%) 0 1 / 10 (10.00%) 0 | 0 / 12 (0.00%) 0 1 / 12 (8.33%) 1 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 1 / 12 (8.33%) 1 0 / 12 (0.00%) 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|--|----------------------|----------------------|--|
| Cough subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 0 / 12 (0.00%) 0 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 0 / 12 (0.00%) 0 | |
| Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 0 / 12 (0.00%) 0 | |
| Pruritus subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 0 / 12 (0.00%) 0 | |
| Skin cyst excision subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 0 / 12 (0.00%) 0 | |
| Psychiatric disorders Depression subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 0 / 12 (0.00%) 0 | |
| Sleep disorder subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 0 / 12 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 12 (8.33%) 1 | |
| Joint swelling subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 0 / 12 (0.00%) 0 | |
| Infections and infestations Lower respiratory tract infection subjects affected / exposed occurrences (all) | 2 / 10 (20.00%) 2 | 2 / 12 (16.67%) 2 | |
| Sinusitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 12 (16.67%) | |
| occurrences (all) | 0 | 2 | |
| Metabolism and nutrition disorders | | | |
| Blood glucose increased | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|---|
| 22 March 2016 | <p>Screening and baseline visits can be combined.</p> <p>Update to eligibility criteria. Subjects with a contraindication to cardiac MRI can be randomized into the study; however, they will not undergo MRI.</p> <p>Update to exclusion criteria. Subjects with a soya or peanut allergy can be randomized into the study as the study drug does not contain these ingredients.</p> <p>Follow up visits at month 2, 4, 8 and 10 deleted so that subjects are followed up at 6 and 12 months only.</p> <p>Schedule of assessments: Measurement of natriuretic peptide (NT-proBNP) added at baseline, 6 and 12 months (previously captured under 'biomarkers' but separated out for clarity).</p> <p>Schedule of assessments: Pulse wave velocity. A more comprehensive analysis of arterial stiffness will be done on a sub-set of subjects that are willing to travel to another site (Tallaght Hospital).</p> <p>Schedule of assessments: Some changes to the retinopathy assessment were made (measurement of IOP using non-contact tonometry instead of applanation tonometry and Schnellan chart instead of Log Mar visual acuity chart).</p> <p>Cardiac MRI: The site for performing cMRI was changed and the need for gadolinium contrast media was removed as this is not necessary.</p> <p>Alk Phos measurement not required during screening visit. Glucose monitoring was removed from the protocol.</p> <p>Randomisation: A method of sealed envelopes at the investigator site was implemented and replaced the need to contact the study monitor during this process.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported