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

Units: Normalised protein expression units (NPX			
median	5.2	5.3	
inter-quartile range (Q1-Q3)	4.9 to 5.4	5.2 to 5.6	-
Monocyte chemotactic protein-1 (MCP-1)			
Units: Normalised protein expression units (NPX			
median	3.4	3.5	
inter-quartile range (Q1-Q3)	2.7 to 3.5	3.0 to 3.7	-
Triglycerides			
Units: mmol/L			
median	2.4	1.9	
inter-quartile range (Q1-Q3)	1.9 to 2.9	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 (± 0.23)	0.01 (± 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 (± 0.41)	0.15 (± 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 (± 0.33)	0.03 (± 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 (± 0.45)	0.05 (± 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 (± 0.47)	0.29 (± 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 (± 3.8)	-0.4 (± 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 (± 4.6)	0.6 (± 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 (± 1.47)	0.01 (± 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	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Knee operation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 10 (30.00%)	1 / 12 (8.33%)	
occurrences (all)	3	1	
Influenza like illness			
subjects affected / exposed	1 / 10 (10.00%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Oedema peripheral			
subjects affected / exposed	1 / 10 (10.00%)	2 / 12 (16.67%)	
occurrences (all)	1	2	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 10 (20.00%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Inguinal hernia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Gastrointestinal disorder			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			

Cough			
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	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Skin cyst excision			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Sleep disorder			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Joint swelling			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	2 / 10 (20.00%)	2 / 12 (16.67%)	
occurrences (all)	2	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	Screening and baseline visits can be combined. Update to eligibility criteria. Subjects with a contraindication to cardiac MRI can be randomized into the study; however, they will not undergo MRI. 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. Follow up visits at month 2, 4, 8 and 10 deleted so that subjects are followed up at 6 and 12 months only. 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). 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). 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). Cardiac MRI: The site for performing cMRI was changed and the need for gadolinium contrast media was removed as this is not necessary. Alk Phos measurement not required during screening visit. Glucose monitoring was removed from the protocol. Randomisation: A method of sealed envelopes at the investigator site was implemented and replaced the need to contact the study monitor during this process.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported