Clinical trial results:
Myomet: A randomized, double blind, placebo-controlled phase II study of metformin in myotonic dystrophy type 1 patients

Summary

EudraCT number	2013-001732-21
Trial protocol	FR
Global end of trial date	17 November 2017

Results information

Result version number	v1 (current)
This version publication date	16 October 2019
First version publication date	16 October 2019

Trial information

Trial identification

Sponsor protocol code	MET001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	CECS/Istem
Sponsor organisation address	CRCT, 28 rue Henri Desbruères, Corbeil-Essonnes, France, 91100
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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	17 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 June 2016
Global end of trial reached?	Yes
Global end of trial date	17 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of metformin on ambulation in patients with myotonic dystrophy type 1.

Protection of trial subjects:

After the enrolment of the first 5 patients in each arm, a blinded assessment of the tolerance has been performed in order to take appropriate measures if required.
Additionally, blinded safety reviews have occurred on a regular basis during the course of the study for the same purpose.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 February 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	France: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	40
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 40 patients with myotonic dystrophy type I (DM1) was included in order to evaluate 30 patients (expected dropout rate of 25%). Patients were to be aged between 18 and 60 years.

Pre-assignment

Screening details:

Screening included:
- informed consent process
- diagnosis of DM1 confirmed by DM1 genetic mutation
- Muscular Impairment Rating Scale (MIRS) score 2 or 3
- ambulatory, able to perform the 6MWT

Period 1

Period 1 title	Controlled phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	metformin group - Controlled phase

Arm description:

All enrolled randomised patients in the controlled phase in the metformin arm who actually received at least one dose of study drug

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

Dosage and administration details:

- From D1 to D14, the patient received 500 mg oral tablets of metformin BID at the total daily dose of 1,000 mg/d for 14 days
- From D15 to D28, the patient received 2 oral tablets of 500 mg BID of metformin at the total daily dose of 2,000 mg/d for 14 days
- From D29 to the end of the study period, the patient received 2 oral tablets of 500 mg TID of metformin at the total daily dose of 3,000 mg/d for 48 weeks

Arm title	Placebo group

Arm description:

All enrolled randomised patients in the controlled phase in the placebo arm who actually received at least one dose of 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:

- From D1 to D14, the patient received one oral tablet of placebo BID for 14 days
- From D15 to D28, the patient received 2 oral tablets of placebo BID for 14 days
- From D29 to the end of the study period, the patient received 2 oral tablets of 500 mg TID of placebo for 48 weeks

Number of subjects in period 1	metformin group - Controlled phase	Placebo group
Started	20	20
Completed	12	17
Not completed	8	3
Non-Compliance	1	-
Consent withdrawn by subject	-	1
Patient's Decision	4	2
Adverse event, non-fatal	3	-

Period 2	
Period 2 title	Open-label extension phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	metformin group - Extension phase
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

- From D1 to D14, the patient received 500 mg oral tablets of metformin BID at the total daily dose of 1,000 mg/d for 14 days
- From D15 to D28, the patient received 2 oral tablets of 500 mg BID of metformin at the total daily dose of 2,000 mg/d for 14 days
- From D29 to the end of the study period, the patient received 2 oral tablets of 500 mg TID of metformin at the total daily dose of 3,000 mg/d for 48 weeks

Number of subjects in period 2[1]	metformin group - Extension phase
Started	20
Completed	13
Not completed	7
Consent withdrawn by subject	4
Adverse event, non-fatal	3

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: At the end of the 52 weeks study period, all patients were proposed to enter in the open-label extension phase in which they received the active treatment according to the same dose escalation performed at study entry. 20 patients consented to participate.

Baseline characteristics

Reporting groups	
Reporting group title	metformin group - Controlled phase
Reporting group description:	
All enrolled randomised patients in the controlled phase in the metformin arm who actually received at least one dose of study drug	
Reporting group title	Placebo group
Reporting group description:	
All enrolled randomised patients in the controlled phase in the placebo arm who actually received at least one dose of placebo	

Reporting group values	metformin group - Controlled phase	Placebo group	Total
Number of subjects	20	20	40
Age categorical Units: Subjects			
Adults (18-64 years)	20	20	40
Gender categorical Units: Subjects			
Female	11	11	22
Male	8	8	16
Not reported	1	1	2

Subject analysis sets	
Subject analysis set title	ITT Complete D1-W52_Metformin controlled phase
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients having received metformin and completed the controlled phase of the Study (ie from D1 until Week 52 visit)	
Subject analysis set title	ITT Complete D1-W52_Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients having received the placebo and completed the controlled phase of the Study (ie from D1 until Week 52 visit)	
Subject analysis set title	Per protocol population N°1_Metformin controlled phase
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects who did not substantially deviate from the protocol as to be determined on a per-subject basis discussed with the Investigator regarding any protocol deviation related to study inclusion or exclusion criteria, conduct of the trial, patient management, or patient assessment in the metformin arm	
Subject analysis set title	Per protocol population N°1_Placebo
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects who did not substantially deviate from the protocol as to be determined on a per-subject basis discussed with the Investigator regarding any protocol deviation related to study inclusion or exclusion criteria, conduct of the trial, patient management, or patient assessment in the placebo arm	

Reporting group values	ITT Complete D1-W52_Metformin controlled phase	ITT Complete D1-W52_Placebo	Per protocol population N°1_Metformin controlled phase
Number of subjects	12	17	9
Age categorical Units: Subjects			
Adults (18-64 years)	12	17	9
Gender categorical Units: Subjects			
Female Male Not reported	12	17	9

Reporting group values	Per protocol population N°1_Placebo		
Number of subjects	14		
Age categorical Units: Subjects			
Adults (18-64 years)	14		
Gender categorical Units: Subjects			
Female Male Not reported	14		

End points

End points reporting groups

Reporting group title	metformin group - Controlled phase
Reporting group description:	
All enrolled randomised patients in the controlled phase in the metformin arm who actually received at least one dose of study drug	
Reporting group title	Placebo group
Reporting group description:	
All enrolled randomised patients in the controlled phase in the placebo arm who actually received at least one dose of placebo	
Reporting group title	metformin group - Extension phase
Reporting group description: -	
Subject analysis set title	ITT Complete D1-W52_Metformin controlled phase
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients having received metformin and completed the controlled phase of the Study (ie from D1 until Week 52 visit)	
Subject analysis set title	ITT Complete D1-W52_Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients having received the placebo and completed the controlled phase of the Study (ie from D1 until Week 52 visit)	
Subject analysis set title	Per protocol population N°1_Metformin controlled phase
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects who did not substantially deviate from the protocol as to be determined on a per-subject basis discussed with the Investigator regarding any protocol deviation related to study inclusion or exclusion criteria, conduct of the trial, patient management, or patient assessment in the metformin arm	
Subject analysis set title	Per protocol population N°1_Placebo
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects who did not substantially deviate from the protocol as to be determined on a per-subject basis discussed with the Investigator regarding any protocol deviation related to study inclusion or exclusion criteria, conduct of the trial, patient management, or patient assessment in the placebo arm	

Primary: Ambulation measured by the 6 Minute Walk Test (6MWT): absolute changes from baseline

End point title	Ambulation measured by the 6 Minute Walk Test (6MWT): absolute changes from baseline
End point description:	
At week 52, absolute change from baseline in distance walked at the 6MWT: Delta W52 - W0	
End point type	Primary
End point timeframe:	
52 weeks (change from baseline)	

End point values	metformin group - Controlled phase	metformin group - Extension phase	Placebo group	ITT Complete D1-W52_Metformin controlled phase
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	12	17	17	12
Units: meters				
arithmetic mean (standard deviation)	14.6 (± 47.6)	-13.0 (± 25.7)	3.1 (± 32.0)	14.6 (± 47.6)

End point values	ITT Complete D1-W52_Placebo	Per protocol population N°1_Metformin controlled phase	Per protocol population N°1_Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	17	9	14	
Units: meters				
arithmetic mean (standard deviation)	3.1 (± 32.0)	32.9 (± 32.8)	3.7 (± 32.4)	

Statistical analyses

Statistical analysis title	Primary analysis ITT population
Statistical analysis description: 6MWT: absolute changes from baseline	
Comparison groups	metformin group - Controlled phase v Placebo group
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [1]
Method	t-test, 2-sided
Confidence interval	
level	95 %

Notes:

[1] - No statistically significant differences were detected (p=0.441)

Statistical analysis title	Primary analysis PP1 population
Comparison groups	Per protocol population N°1_Placebo v Per protocol population N°1_Metformin controlled phase
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [2]
Method	t-test, 2-sided

Notes:

[2] - Statistically significant differences were detected (p=0.048)

Secondary: Ambulation measured by the 6 Minute Walk Test (6MWT): relative

changes from baseline	
End point title	Ambulation measured by the 6 Minute Walk Test (6MWT): relative changes from baseline
End point description:	
Relative change from baseline in 6MWT at week 52 (% Delta W52-W0)	
End point type	Secondary
End point timeframe:	
Week 52 (change from baseline)	

End point values	metformin group - Controlled phase	metformin group - Extension phase	Placebo group	Per protocol population N°1_Metformin controlled phase
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	12	17	17	9
Units: meters				
arithmetic mean (standard deviation)	3.6 (± 9.2)	-3.0 (± 5.3)	0.9 (± 8.1)	7.1 (± 6.9)

End point values	Per protocol population N°1_Placebo			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: meters				
arithmetic mean (standard deviation)	0.9 (± 8.3)			

Statistical analyses

Statistical analysis title	6MWT: relative change from baseline_ITT population
Comparison groups	metformin group - Controlled phase v Placebo group
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [3]
Method	t-test, 2-sided
Confidence interval	
sides	2-sided

Notes:

[3] - No statistically significant differences were detected (p=0.419)

Statistical analysis title	6MWT: relative change from baseline_PP1 population
Comparison groups	metformin group - Controlled phase v Placebo group

Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [4]
Method	t-test, 2-sided

Notes:

[4] - No statistically significant differences were detected (p=0.07)

Secondary: Myotone at W52: grip strength_changes from baseline

End point title	Myotone at W52: grip strength_changes from baseline

End point description:

MIE Handgrip: changes from baseline (Delta W52-W0)

End point type	Secondary

End point timeframe:

Week 52 (change from baseline)

End point values	metformin group - Controlled phase	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	18		
Units: mm				
arithmetic mean (standard deviation)	0.0 (± 0.0)	0.0 (± 0.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Handgrip Relaxation Time (RT) 90

End point title	Handgrip Relaxation Time (RT) 90

End point description:

Myotonia RT 90 (Delta W52-W0)

End point type	Secondary

End point timeframe:

Week 52 (change from baseline)

End point values	metformin group - Controlled phase	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	18		
Units: ms				

median (inter-quartile range (Q1-Q3))	-11.2 (-31.3 to 121.5)	5.40 (-28.6 to 48.1)		

Statistical analyses

Statistical analysis title	Myotonia RT 90 change from baseline_ITT population
Comparison groups	metformin group - Controlled phase v Placebo group
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [5]
Method	t-test, 2-sided

Notes:

[5] - No statistically significant differences were detected (p=0.637)

Secondary: Handgrip Relaxation Time (RT) 10

End point title	Handgrip Relaxation Time (RT) 10
End point description: Myotonia RT10 (Delta W52-W0)	
End point type	Secondary
End point timeframe: Week 52 (change from baseline)	

End point values	metformin group - Controlled phase	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	18		
Units: ms				
median (inter-quartile range (Q1-Q3))	2.1 (-25.2 to 70.3)	28.5 (2.5 to 74.9)		

Statistical analyses

Statistical analysis title	Myotonia RT 10 change from baseline_ITT population
Comparison groups	metformin group - Controlled phase v Placebo group
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [6]
Method	t-test, 2-sided

Notes:
[6] - No statistically significant differences were detected (p=0.337)

Secondary: HandHeld Test_fingers extension

End point title	HandHeld Test_fingers extension
End point description:	
Extension of fingers: changes from baseline (Delta W52-W0)	
End point type	Secondary
End point timeframe:	
W 52 (change from baseline)	

End point values	metformin group - Controlled phase	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	18		
Units: N.m				
median (inter-quartile range (Q1-Q3))	0.1 (-0.32 to 0.42)	-0.1 (-0.32 to 0.06)		

Statistical analyses

Statistical analysis title	Fingers extension (W52-W0)_ITT population
Comparison groups	metformin group - Controlled phase v Placebo group
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [7]
Method	t-test, 2-sided

Notes:
[7] - No statistically significant differences were detected (p=0.969)

Secondary: HandHeld Test_knee extension

End point title	HandHeld Test_knee extension
End point description:	
Extension of knee: changes from baseline (Delta W52-W0)	
End point type	Secondary
End point timeframe:	
W52 (change from baseline)	

End point values	metformin group - Controlled phase	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	18		
Units: N.m				
median (inter-quartile range (Q1-Q3))	2.9 (-31.2 to 8.5)	-5.0 (-15.5 to 1.0)		

Statistical analyses

Statistical analysis title	Knee extension (W52-W0)_ITT population
Comparison groups	Placebo group v metformin group - Controlled phase
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [8]
Method	t-test, 2-sided

Notes:

[8] - No statistically significant differences were detected (p=0.382)

Secondary: HandHeld Test_elbow flexion

End point title	HandHeld Test_elbow flexion
End point description:	
Flexion of elbow: changes from baseline (Delta W52-W0)	
End point type	Secondary
End point timeframe:	
W52 (changes from baseline)	

End point values	metformin group - Controlled phase	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	18		
Units: N.m				
median (inter-quartile range (Q1-Q3))	-0.8 (-20.9 to 1.6)	-0.7 (-6.3 to 3.1)		

Statistical analyses

Statistical analysis title	Elbow flexion (W52-W0)_ITT population
Comparison groups	metformin group - Controlled phase v Placebo group

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [9]
Method	t-test, 2-sided

Notes:

[9] - No statistically significant differences were detected (p=0.266)

Secondary: Proportion of patients with an improvement ≥5% of the muscle strength for fingers extension

End point title	Proportion of patients with an improvement ≥5% of the muscle strength for fingers extension

End point description:

% of patients with an improvement ≥5% of the muscle strength for fingers extension (Delta W52-W0)

End point type	Secondary

End point timeframe:

Week 52

End point values	metformin group - Controlled phase	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	18		
Units: Percentage	50	16		

Statistical analyses

No statistical analyses for this end point

Secondary: Muscle MRI right side for VL

End point title	Muscle MRI right side for VL

End point description:

Muscle MRI of Vastus Lateralis (right side): Delta W52-W0

End point type	Secondary

End point timeframe:

W52 (change from baseline)

End point values	metformin group - Controlled phase	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	13		
Units: muscle fat fraction				
arithmetic mean (standard deviation)	-2.0 (± 5.0)	-4.0 (± 23.5)		

Statistical analyses

Statistical analysis title	MRI right side (VL) (Delta W52-W0)
Comparison groups	metformin group - Controlled phase v Placebo group
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [10]
Method	t-test, 2-sided

Notes:

[10] - No statistically significant differences were detected (p=0.846)

Secondary: Muscle MRI right side for VM

End point title	Muscle MRI right side for VM
End point description:	
Change from baseline in MRI assessment for Vastus Medialis (Delta W52-W0)	
End point type	Secondary
End point timeframe:	
Week 52 (change from baseline)	

End point values	metformin group - Controlled phase	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	12		
Units: muscle fat fraction				
arithmetic mean (standard deviation)	-1.5 (± 3.6)	-8.3 (± 16.9)		

Statistical analyses

Statistical analysis title	MRI right side (VM)(Delta W52-W0)
Comparison groups	metformin group - Controlled phase v Placebo group

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [11]
Method	t-test, 2-sided

Notes:

[11] - No statistically significant differences were detected (p=0.352)

Secondary: Muscle MRI right side for Soleus

End point title	Muscle MRI right side for Soleus

End point description:

Change from baseline in MRI assessment for Soleus (Delta W52-W0)

End point type	Secondary

End point timeframe:

W52 (Change from baseline)

End point values	metformin group - Controlled phase	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	11		
Units: Muscle Fat Fraction				
arithmetic mean (standard deviation)	-2.1 (± 5.1)	-20.8 (± 28.1)		

Statistical analyses

Statistical analysis title	MRI right side (Soleus) (Delta W52-W0)
Comparison groups	metformin group - Controlled phase v Placebo group
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [12]
Method	t-test, 2-sided

Notes:

[12] - No statistically significant differences were detected (p=0.131)

Secondary: Muscle MRI right side for Tibialis Ant

End point title	Muscle MRI right side for Tibialis Ant

End point description:

Change from baseline in MRI assessment for Tibialis Ant (Delta W52-W0)

End point type	Secondary

End point timeframe:

W52 (Change from baseline)

End point values	metformin group - Controlled phase	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	11		
Units: Muscle Fat Fraction				
arithmetic mean (standard deviation)	-1.45 (± 3.53)	-8.59 (± 15.50)		

Statistical analyses

Statistical analysis title	MRI right side (Tibialis Ant) (Delta W52-W0)
Comparison groups	metformin group - Controlled phase v Placebo group
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [13]
Method	t-test, 2-sided

Notes:

[13] - No statistically significant differences were detected (p=0.29)

Secondary: Muscle MRI right side for Lateral GM

End point title	Muscle MRI right side for Lateral GM
End point description:	
Change from baseline in MRI assessment for Lateral Gluteus Medius	
End point type	Secondary
End point timeframe:	
W52 (Change from baseline)	

End point values	metformin group - Controlled phase	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	11		
Units: Muscle Fat Fraction				
arithmetic mean (standard deviation)	-1.3 (± 3.3)	-14.5 (± 24.3)		

Statistical analyses

Statistical analysis title	MRI right side (Lateral GM)
Comparison groups	metformin group - Controlled phase v Placebo group
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [14]
Method	t-test, 2-sided

Notes:

[14] - No statistically significant differences were detected (p=0.215)

Secondary: DM1 assessments (original version)

End point title	DM1 assessments (original version)

End point description:

Dystrophy type 1 activity and social participation scale (DM1 scale) - original version (Delta W52-W0)

End point type	Secondary

End point timeframe:

W52 (change from baseline)

End point values	metformin group - Controlled phase	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	8		
Units: Score				
arithmetic mean (standard deviation)	0.8 (± 10.1)	6.8 (± 10.9)		

Statistical analyses

Statistical analysis title	DM1 original version (delta W52-W0)
Comparison groups	metformin group - Controlled phase v Placebo group
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [15]
Method	t-test, 2-sided

Notes:

[15] - No statistically significant differences were detected (p=0.297)

Secondary: DM1 scale - Active C version

End point title	DM1 scale - Active C version

End point description:

Dystrophy type 1 activity and social participation scale (DM1 scale) - Active C version (Delta W52-W0)

End point type	Secondary

End point timeframe:

W52 (change from baseline)

End point values	metformin group - Controlled phase	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	11		
Units: score				
arithmetic mean (standard deviation)	2.2 (± 3.2)	2.5 (± 5.7)		

Statistical analyses

Statistical analysis title	DM1 Active C version(Delta W52-W0)
Comparison groups	Placebo group v metformin group - Controlled phase
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [16]
Method	t-test, 2-sided

Notes:

[16] - No statistically significant differences were detected (p=0.906)

Secondary: INQoL scores per dimension (Delta W52-W0)_(20 subjects)

End point title	INQoL scores per dimension (Delta W52-W0)_(20 subjects)

End point description:

INQoL scores per dimension (Delta W52-W0)_20 subjects : 9 in the metformin group and 11 in the placebo group

End point type	Secondary

End point timeframe:

W52 (changes from baseline)

End point values	metformin group - Controlled phase	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	11		
Units: Score				
median (inter-quartile range (Q1-Q3))				
weakness	5.3 (-5.3 to 26.3)	5.3 (-21.1 to 10.5)		
pain	0.0 (-10.5 to 0.0)	0.0 (-15.8 to 5.3)		
activities	0.0 (-3.7 to 8.3)	-5.6 (-11.1 to 15.7)		

independence	2.8 (0.0 to 11.1)	-2.8 (-19.4 to 12.5)		
social relationships	1.9 (0.0 to 12.0)	-8.3 (-20.4 to 1.9)		
body image	2.78 (0.0 to 16.7)	-2.8 (-13.9 to 13.9)		
perceived treatment effects	-25.0 (-41.7 to 0.0)	0.0 (-16.7 to 25.0)		
expected treatment effects	-16.7 (-25.0 to 0.0)	16.7 (-16.7 to 25.0)		

Statistical analyses

Statistical analysis title	INQoL questionnaire_Weakness (Delta W52-W0)
Comparison groups	metformin group - Controlled phase v Placebo group
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	> 0.05
Method	t-test, 2-sided

Notes:

[17] - No statistically significant differences were detected (p=0.175)

Statistical analysis title	INQoL questionnaire_Pain (Delta W52-W0)
Comparison groups	metformin group - Controlled phase v Placebo group
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [18]
Method	t-test, 2-sided

Notes:

[18] - No statistically significant differences were detected (p=0.698)

Statistical analysis title	INQoL questionnaire_Activities (Delta W52-W0)
Comparison groups	metformin group - Controlled phase v Placebo group
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [19]
Method	t-test, 2-sided

Notes:

[19] - No statistically significant differences were detected (p=0.333)

Statistical analysis title	INQoL questionnaire_Independence (Delta W52-W0)
Comparison groups	metformin group - Controlled phase v Placebo group

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [20]
Method	t-test, 2-sided

Notes:

[20] - No statistically significant differences were detected (p=0.124)

Statistical analysis title	INQoL questionnaire_Social Relation (Delta W52-W0)

Statistical analysis description:

INQoL: Social Relationships

Comparison groups	metformin group - Controlled phase v Placebo group
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [21]
Method	t-test, 2-sided

Notes:

[21] - No statistically significant differences were detected (p=0.13)

Statistical analysis title	INQoL questionnaire_Body image (Delta W52-W0)
Comparison groups	metformin group - Controlled phase v Placebo group
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [22]
Method	t-test, 2-sided

Notes:

[22] - No statistically significant differences were detected (p=0.393)

Statistical analysis title	INQoL questionnaire_Perceived treat (Delta W52-W0)

Statistical analysis description:

INQoL: Perceived treatment effects

Comparison groups	metformin group - Controlled phase v Placebo group
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [23]
Method	t-test, 2-sided

Notes:

[23] - Statistically significant differences were detected (p=0.034)

Statistical analysis title	INQoL questionnaire_Expected treat. (Delta W52-W0)

Statistical analysis description:

INQoL questionnaire: Expected treatment effects

Comparison groups	metformin group - Controlled phase v Placebo group

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [24]
Method	t-test, 2-sided

Notes:

[24] - Statistically significant differences were detected (p=0.043)

Secondary: INQoL scores per dimension (Delta W52-W0)_(19 subjects)	
End point title	INQoL scores per dimension (Delta W52-W0)_(19 subjects)

End point description:

INQoL scores per dimension (Delta W52-W0)_19 subjects : 8 in the metformin group and 11 in the placebo group

End point type	Secondary

End point timeframe:

W52 (Change from baseline)

End point values	metformin group - Controlled phase	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	11		
Units: score				
median (inter-quartile range (Q1-Q3))				
fatigue	0.0 (-2.6 to 13.2)	0.0 (-21.1 to 15.8)		
emotions	2.31 (0.0 to 7.4)	-13.9 (-26.9 to 1.9)		
NMD related QoL	1.9 (0.3 to 4.2)	-0.6 (-5.6 to 1.7)		

Statistical analyses

Statistical analysis title	INQoL scores_Fatigue (Delta W52-W0)
Comparison groups	metformin group - Controlled phase v Placebo group
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [25]
Method	t-test, 2-sided

Notes:

[25] - No statistically significant differences were detected (p=0.462)

Statistical analysis title	INQoL scores_Emotions (Delta W52-W0)
Comparison groups	metformin group - Controlled phase v Placebo group

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [26]
Method	t-test, 2-sided

Notes:

[26] - No statistically significant differences were detected (p=0.112)

Statistical analysis title	INQoL scores_NMD-related QoL (Delta W52-W0)
Comparison groups	metformin group - Controlled phase v Placebo group
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [27]
Method	t-test, 2-sided

Notes:

[27] - No statistically significant differences were detected (p=0.06)

Secondary: INQoL scores per dimension (Delta W52-W0)_(18 subjects)

End point title	INQoL scores per dimension (Delta W52-W0)_(18 subjects)

End point description:

INQoL scores per dimension (Delta W52-W0)_19 subjects : 8 in the metformin group and 10 in the placebo group

End point type	Secondary

End point timeframe:

W52 (change from baseline)

End point values	metformin group - Controlled phase	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	10		
Units: score				
median (inter-quartile range (Q1-Q3))				
Muscle lock	2.6 (-2.6 to 10.5)	-2.6 (-15.8 to 5.3)		

Statistical analyses

Statistical analysis title	INQoL scores-muscle lock

Statistical analysis description:

INQoL scores for muscle lock (Delta W52-W0)

Comparison groups	metformin group - Controlled phase v Placebo group

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [28]
Method	t-test, 2-sided

Notes:

[28] - No statistically significant differences were detected (p=0.539)

Secondary: ECG_results at W52

End point title	ECG_results at W52

End point description:

Cardiac 12-lead resting ECG: results at Week 52

End point type	Secondary

End point timeframe:

Week 52

End point values	metformin group - Controlled phase	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	18		
Units: Percentage				
number (not applicable)				
Normal	66.7	83.3		
Abnormal, not clinically significant	33.3	16.7		

Statistical analyses

Statistical analysis title	ECG_results at Week 52
Comparison groups	metformin group - Controlled phase v Placebo group
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [29]
Method	t-test, 2-sided

Notes:

[29] - No statistically significant differences were detected (p=0.29)

Secondary: Biomarker evaluation_FAS exon 6

End point title	Biomarker evaluation_FAS exon 6

End point description:

Absolute changes from baseline in evaluation of biomarker FAS exon 6 (Delta W52-W0)

End point type	Secondary

End point timeframe:

Week 52

End point values	metformin group - Controlled phase	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	18		
Units: not applicable				
arithmetic mean (standard deviation)				
Standardization on a common calibrator	0.01 (± 0.15)	0.04 (± 0.16)		
Standardization on D1	0.01 (± 0.12)	0.03 (± 0.13)		

Statistical analyses

Statistical analysis title	FAS exon 6_standardization on a common calibrator
Statistical analysis description: Absolute change from baseline (delta W52-W0)	
Comparison groups	metformin group - Controlled phase v Placebo group
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [30]
Method	t-test, 2-sided

Notes:
[30] - No statistically significant differences were detected (p=0.615)

Statistical analysis title	FAS exon 6_standardization on D1
Statistical analysis description: Delta W52-W0	
Comparison groups	metformin group - Controlled phase v Placebo group
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [31]
Method	t-test, 2-sided

Notes:
[31] - No statistically significant differences were detected (p=0.677)

Secondary: Biomarker evaluation_LaminA/LaminC

End point title	Biomarker evaluation_LaminA/LaminC
End point description: Absolute changes from baseline in evaluation of biomarker LaminA/LaminC (Delta W52-W0)	
End point type	Secondary
End point timeframe: Week 52 (changes from baseline)	

End point values	metformin group - Controlled phase	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	18		
Units: not applicable				
arithmetic mean (standard deviation)				
Standardization on a common calibrator	0.06 (± 0.49)	-0.22 (± 0.48)		
Standardization on D1	0.07 (± 0.22)	-0.05 (± 0.31)		

Statistical analyses

Statistical analysis title	LaminA/LaminC_Standardization on a common calibr.
Comparison groups	Placebo group v metformin group - Controlled phase
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [32]
Method	t-test, 2-sided

Notes:

[32] - no statistically significant differences were detected (p=0.126)

Statistical analysis title	LaminA/LaminC_Standardization on D1

Statistical analysis description:

Delta W52-W0

Comparison groups	Placebo group v metformin group - Controlled phase
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [33]
Method	t-test, 2-sided

Notes:

[33] - No statistically significant differences were detected (p=0.238)

Secondary: Biomarker evaluation_INSR exon 11 (irba)	
End point title	Biomarker evaluation_INSR exon 11 (irba)

End point description:

Absolute changes from baseline in evaluation of biomarker INSR exon 11 (irba) (Delta W52-W0)

End point type	Secondary

End point timeframe:

W52 (changes from baseline)

End point values	metformin group - Controlled phase	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	18		
Units: not applicable				
arithmetic mean (standard deviation)				
Standardization on a common calibrator	-0.05 (± 0.06)	-0.03 (± 0.06)		
Standardization on D1	-0.08 (± 0.08)	-0.04 (± 0.08)		

Statistical analyses

Statistical analysis title	INSR exon 11_Standardization on a common calibrat.
Statistical analysis description: Delta W52-W0	
Comparison groups	metformin group - Controlled phase v Placebo group
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [34]
Method	t-test, 2-sided

Notes:

[34] - No statistically significant differences were detected (p=0.299)

Statistical analysis title	INSR exon 11_Standardization on D1
Statistical analysis description: Delta W52-W0	
Comparison groups	metformin group - Controlled phase v Placebo group
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [35]
Method	t-test, 2-sided

Notes:

[35] - No statistically significant differences were detected (p=0.263)

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From 18 February 2014 to 17 November 2017	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0
Reporting groups	
Reporting group title	Metformin group, Safety population
Reporting group description: -	
Reporting group title	Placebo group, Safety population
Reporting group description: -	

Serious adverse events	Metformin group, Safety population	Placebo group, Safety population	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 20 (15.00%)	1 / 18 (5.56%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung adenocarcinoma			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine prolapse			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Bronchopneumopathy			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 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	Metformin group, Safety population	Placebo group, Safety population	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 20 (100.00%)	18 / 18 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung adenocarcinoma			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hot flush			
subjects affected / exposed	2 / 20 (10.00%)	1 / 18 (5.56%)	
occurrences (all)	2	1	
Lymphoedema			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Phlebitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	8 / 20 (40.00%)	3 / 18 (16.67%)	
occurrences (all)	12	3	
Chest pain			

subjects affected / exposed	2 / 20 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	3	0	
Oedema peripheral			
subjects affected / exposed	1 / 20 (5.00%)	1 / 18 (5.56%)	
occurrences (all)	1	2	
Pyrexia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Social circumstances			
Menopause			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Breast discharge			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Dysmenorrhoea			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Ejaculation disorder			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Ovarian cyst			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Ovarian prolapse			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Uterine prolapse			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Vaginal haemorrhage			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			

Bronchopneumopathy			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 20 (5.00%)	2 / 18 (11.11%)	
occurrences (all)	1	2	
Depression			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences (all)	3	0	
Libido decreased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Sleep disorder			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Stress			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Investigations			
Weight decreased			
subjects affected / exposed	5 / 20 (25.00%)	0 / 18 (0.00%)	
occurrences (all)	10	0	
Lipase increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Weight increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			

Ligament sprain			
subjects affected / exposed	3 / 20 (15.00%)	1 / 18 (5.56%)	
occurrences (all)	3	1	
Fall			
subjects affected / exposed	1 / 20 (5.00%)	2 / 18 (11.11%)	
occurrences (all)	1	2	
Joint injury			
subjects affected / exposed	0 / 20 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	3	
Head injury			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Spinal column injury			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Thermal burn			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 20 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Dysgeusia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Neuralgia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Sciatica			

subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 20 (5.00%)	2 / 18 (11.11%)	
occurrences (all)	2	3	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	2	
Dry eye			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Eye irritation			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	15 / 20 (75.00%)	5 / 18 (27.78%)	
occurrences (all)	30	10	
Abdominal pain			
subjects affected / exposed	10 / 20 (50.00%)	6 / 18 (33.33%)	
occurrences (all)	18	10	
Nausea			
subjects affected / exposed	7 / 20 (35.00%)	3 / 18 (16.67%)	
occurrences (all)	8	4	
Vomiting			
subjects affected / exposed	4 / 20 (20.00%)	3 / 18 (16.67%)	
occurrences (all)	4	3	
Constipation			
subjects affected / exposed	3 / 20 (15.00%)	3 / 18 (16.67%)	
occurrences (all)	3	3	
Dyspepsia			

subjects affected / exposed	4 / 20 (20.00%)	0 / 18 (0.00%)	
occurrences (all)	4	0	
Dry mouth			
subjects affected / exposed	2 / 20 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Dysphagia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Abdominal pain upper			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Dermal cyst			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Psoriasis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 20 (10.00%)	2 / 18 (11.11%)	
occurrences (all)	3	2	
Arthralgia			

subjects affected / exposed	1 / 20 (5.00%)	2 / 18 (11.11%)	
occurrences (all)	1	3	
Neck pain			
subjects affected / exposed	2 / 20 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Pain in extremity			
subjects affected / exposed	1 / 20 (5.00%)	1 / 18 (5.56%)	
occurrences (all)	2	1	
Bursitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Musculoskeletal pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 20 (10.00%)	8 / 18 (44.44%)	
occurrences (all)	4	12	
Pharyngitis			
subjects affected / exposed	2 / 20 (10.00%)	5 / 18 (27.78%)	
occurrences (all)	2	6	
Nasopharyngitis			
subjects affected / exposed	4 / 20 (20.00%)	2 / 18 (11.11%)	
occurrences (all)	4	3	
Gastroenteritis			
subjects affected / exposed	2 / 20 (10.00%)	3 / 18 (16.67%)	
occurrences (all)	2	3	
Ear infection			
subjects affected / exposed	1 / 20 (5.00%)	2 / 18 (11.11%)	
occurrences (all)	1	3	
Influenza			
subjects affected / exposed	1 / 20 (5.00%)	2 / 18 (11.11%)	
occurrences (all)	1	2	
Rhinitis			
subjects affected / exposed	1 / 20 (5.00%)	2 / 18 (11.11%)	
occurrences (all)	1	2	

Conjunctivitis			
subjects affected / exposed	0 / 20 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Laryngitis			
subjects affected / exposed	0 / 20 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	4	
Eye infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Furuncle			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Gingivitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Herpes zoster			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Tonsillitis			
subjects affected / exposed	2 / 20 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Urinary tract infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 April 2014	- Modification of inclusion and exclusion criteria - Modification of the blood sampling plan and volume - A urine pregnancy test was added to guarantee the safety of women who participated in the study - A fatigue evaluation scale was added at D1, W16, W28, W52 and end of visit to determine the impact of the 6-minute test on the state of fatigue of the patients - A time window for visits (from 1 to 7 days) was added to guarantee the comfort of the patients
17 October 2014	- To introduce editorials changes and modify the name and contact details of the Clinical Project Manager - To extend the study period to Q2 2016 instead of Q3 2015 - To amend the study design with an additional paragraph: "After the enrolment of the first 5 patients of each arm, a blinded assessment of the tolerance will be performed in order to check the patients' compliance to the study treatment and take appropriate measures if required Additional blinded safety reviews may occur on a regular basis during the course of the study for the same purpose" - To add complementary information for the end of study visit as follows: "In addition any patient having successfully completed the dose escalation phase and reached the 3000 mg/day dose of treatment will be assessed at week 52 in case of withdrawal from the study for 6 MWT with Locometrix and Fatigue Visual Analogue Scale" - To amend the evaluation period of the study flow chart with an additional W8 visit, with AEs reporting, and a review of concomitant medications/treatments.
12 June 2015	- To add an open-label extension phase for patients who had completed their 52-week follow-up in the randomised phase of the study in order to not deprive these patients of potentially effective treatment. In order to take part to the open-label extension phase, the patients must have completed the 52 weeks study period, given their written informed consent for the open label extension study and a positive benefit/risk assessment according to the investigator's opinion.
18 February 2016	- To introduce a list of biomarkers relevant to the assessment of the efficiency of a drug tested in the a clinical trial for DM1 - To add information regarding the end-of-study visit of the open extension phase. In addition, a biological analysis including the clearance of creatinine was added at the end of the participation of patients in the open extension phase to check the renal function of patients and ensure their good tolerance to metformin - To provide clarifications on the analysis and reporting issues for the randomised and open label phases of the study
04 August 2016	- Modification and clarification of exclusion criteria
21 November 2016	- To extend the openlabel extension phase of the MYOMET study for a period of 1 year until December 2017 in order to collect long term exposure data for an additional year

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/30169600

http://www.ncbi.nlm.nih.gov/pubmed/26528939