Clinical trial results:
A Placebo-Controlled, Randomized, Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Biological Activity of ATYR1940 in Adult Patients with Molecularly Defined Genetic Muscular Dystrophies

Summary

EudraCT number	2014-001753-17
Trial protocol	NL IT
Global end of trial date	04 January 2017

Results information

Result version number	v1 (current)
This version publication date	30 November 2018
First version publication date	30 November 2018
Summary attachment (see zip file)	ATYR1940-C-002 CSR synopsis (ATYR1940-C-002 FINAL CSR Synopsis 12JUN17.pdf)

Trial information

Trial identification

Sponsor protocol code	ATYR1940-C-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	IND number: 122045

Notes:

Sponsors

Sponsor organisation name	aTyr Pharma, Inc.
Sponsor organisation address	3545 John Hopkins Court, Suite #250, San Diego, CA, United States, 92121
Public contact	Clinical Trial Operations, Voisin Consulting, clinicaltrialinformation@voisinconsulting.com
Scientific contact	Clinical Trial Operations, Voisin Consulting, clinicaltrialinformation@voisinconsulting.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	12 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 December 2015
Global end of trial reached?	Yes
Global end of trial date	04 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate the safety, tolerability, pharmacokinetics (PK), and immunogenicity of multiple doses of intravenous (IV) ATYR1940 in adults 18 to 65 years of age, inclusive, with FSHD.

All clinically significant laboratory abnormalities were reported as adverse events and therefore appear in the Adverse events section of this dataset. As a consequence, the endpoints reported in this dataset are limited to the most relevant safety endpoints, as well as the pharmacodynamic endpoints.

Cohort 4 was optional in the study and the Sponsor elected to not move forward with Cohort 4.

Protection of trial subjects:

The study process, benefits and risks of participating in the study were explained to each subject. In addition, if the study drug needed to be stopped for safety, the doctor, his/her staff along with the medical monitor, were to continue to monitor participant's health and determine what treatment should be given (if any) until the symptoms or findings had resolved or until a satisfactory conclusion was reached.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 September 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	20
EEA total number of subjects	18

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	18
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Cohorts 1 to 3 were completed and the data are described herein. The sponsor elected not to move forward with cohort 4.

Pre-assignment

Screening details:

A total of 44 patients were screened. Out of that number, 20 patients were randomized.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Cohort 1 - 0.3 mg/kg

Arm description:

Cohort 1 included 4 patients randomized 3 (ATYR1940) : 1 (placebo). For the purpose of reporting the results, separate arms were created for the placebo patients.

Arm type	Experimental
Investigational medicinal product name	ATYR1940
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received an initial Study Drug infusion of placebo, followed by once weekly IV Study Drug administration (ATYR1940) for 4 weeks. All Study Drug was administered via IV infusion over 30 minutes.

Arm title	Cohort 2 - 1 mg/kg

Arm description:

Cohort 2 included 8 patients randomized 3 (ATYR1940) : 1 (placebo). For the purpose of reporting the results, separate arms were created for the placebo patients.

Arm type	Experimental
Investigational medicinal product name	ATYR1940
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received an initial Study Drug infusion of placebo, followed by once weekly IV Study Drug administration (ATYR1940) for 4 weeks. All Study Drug was administered via IV infusion over 30 minutes.

Arm title	Cohort 3 - 3 mg/kg

Arm description:

Cohort 3 included 8 patients randomized 3 (ATYR1940) : 1 (placebo). For the purpose of reporting the results, separate arms were created for the placebo patients.

Arm type	Experimental

Investigational medicinal product name	ATYR1940
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received an initial Study Drug infusion of placebo, followed by once weekly IV Study Drug administration (ATYR1940) for 12 weeks. All Study Drug was administered via IV infusion over 30 minutes.

Arm title	Cohorts 1, 2 and 3 - Placebo

Arm description:

Cohort 1 included 4 patients randomized 3 (ATYR1940) : 1 (placebo). Cohorts 2 and 3 included 8 patients randomized 3 (ATYR1940) : 1 (placebo). This arm includes the placebo patient from Cohort 1, the 2 placebo patients from Cohort 2 and the 2 placebo patients from Cohort 3.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received an initial Study Drug infusion of placebo, followed by once weekly IV Study Drug administration (placebo) for 4 weeks. All Study Drug was administered via IV infusion over 30 minutes.

Arm title	Cohort 3 - Placebo

Arm description:

Cohort 3 included 8 patients randomized 3 (ATYR1940) : 1 (placebo). This arm includes the 2 placebo patients from Cohort 3.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received an initial Study Drug infusion of placebo, followed by once weekly IV Study Drug administration (placebo) for 12 weeks. All Study Drug was administered via IV infusion over 30 minutes.

Number of subjects in period 1	Cohort 1 - 0.3 mg/kg	Cohort 2 - 1 mg/kg	Cohort 3 - 3 mg/kg
Started	3	6	6
Completed	3	6	6

Number of subjects in period 1	Cohorts 1, 2 and 3 - Placebo	Cohort 3 - Placebo
Started	5	2
Completed	5	2

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1 - 0.3 mg/kg
Reporting group description:	
Cohort 1 included 4 patients randomized 3 (ATYR1940) : 1 (placebo). For the purpose of reporting the results, separate arms were created for the placebo patients.	
Reporting group title	Cohort 2 - 1 mg/kg
Reporting group description:	
Cohort 2 included 8 patients randomized 3 (ATYR1940) : 1 (placebo). For the purpose of reporting the results, separate arms were created for the placebo patients.	
Reporting group title	Cohort 3 - 3 mg/kg
Reporting group description:	
Cohort 3 included 8 patients randomized 3 (ATYR1940) : 1 (placebo). For the purpose of reporting the results, separate arms were created for the placebo patients.	
Reporting group title	Cohorts 1, 2 and 3 - Placebo
Reporting group description:	
Cohort 1 included 4 patients randomized 3 (ATYR1940) : 1 (placebo). Cohorts 2 and 3 included 8 patients randomized 3 (ATYR1940) : 1 (placebo). This arm includes the placebo patient from Cohort 1, the 2 placebo patients from Cohort 2 and the 2 placebo patients from Cohort 3.	
Reporting group title	Cohort 3 - Placebo
Reporting group description:	
Cohort 3 included 8 patients randomized 3 (ATYR1940) : 1 (placebo). This arm includes the 2 placebo patients from Cohort 3.	

Reporting group values	Cohort 1 - 0.3 mg/kg	Cohort 2 - 1 mg/kg	Cohort 3 - 3 mg/kg
Number of subjects	3	6	6
Age categorical Units: Subjects			
Adults (18-64 years)	3	6	5
From 65-84 years	0	0	1
Age continuous Units: years			
arithmetic mean	44.3	44.5	45.3
full range (min-max)	25 to 55	33 to 52	25 to 72
Gender categorical Units: Subjects			
Female	1	4	2
Male	2	2	4

Reporting group values	Cohorts 1, 2 and 3 - Placebo	Cohort 3 - Placebo	Total
Number of subjects	5	2	20
Age categorical Units: Subjects			
Adults (18-64 years)	4	2	18
From 65-84 years	1	0	2
Age continuous Units: years			
arithmetic mean	54	56.5	
full range (min-max)	39 to 66	49 to 64	-

Gender categorical Units: Subjects			
Female	1	0	8
Male	4	2	12

End points

End points reporting groups

Reporting group title	Cohort 1 - 0.3 mg/kg
Reporting group description:	
Cohort 1 included 4 patients randomized 3 (ATYR1940) : 1 (placebo). For the purpose of reporting the results, separate arms were created for the placebo patients.	
Reporting group title	Cohort 2 - 1 mg/kg
Reporting group description:	
Cohort 2 included 8 patients randomized 3 (ATYR1940) : 1 (placebo). For the purpose of reporting the results, separate arms were created for the placebo patients.	
Reporting group title	Cohort 3 - 3 mg/kg
Reporting group description:	
Cohort 3 included 8 patients randomized 3 (ATYR1940) : 1 (placebo). For the purpose of reporting the results, separate arms were created for the placebo patients.	
Reporting group title	Cohorts 1, 2 and 3 - Placebo
Reporting group description:	
Cohort 1 included 4 patients randomized 3 (ATYR1940) : 1 (placebo). Cohorts 2 and 3 included 8 patients randomized 3 (ATYR1940) : 1 (placebo). This arm includes the placebo patient from Cohort 1, the 2 placebo patients from Cohort 2 and the 2 placebo patients from Cohort 3.	
Reporting group title	Cohort 3 - Placebo
Reporting group description:	
Cohort 3 included 8 patients randomized 3 (ATYR1940) : 1 (placebo). This arm includes the 2 placebo patients from Cohort 3.	

Primary: Anti-drug antibodies (ADA)

End point title	Anti-drug antibodies (ADA)[1]
End point description:	
End point type	Primary
End point timeframe:	
Screening and weeks 3 to 9 for Cohorts 1 and 2, screening and weeks 3 to 6, 10, 14, 17, 25 for Cohort 3	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was performed for any of the primary/safety endpoints.

End point values	Cohort 1 - 0.3 mg/kg	Cohort 2 - 1 mg/kg	Cohort 3 - 3 mg/kg	Cohorts 1, 2 and 3 - Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	6	6	5
Units: number (frequency) of confirmed positive	2	1	3	0

End point values	Cohort 3 - Placebo			
Subject group type	Reporting group			
Number of subjects analysed	2			

Units: number (frequency) of confirmed positive	0			

Statistical analyses

No statistical analyses for this end point

Primary: Jo-1 antibodies

End point title	Jo-1 antibodies[2]

End point description:

End point type	Primary

End point timeframe:

Screening and weeks 3 to 9 for Cohorts 1 and 2, screening and weeks 3 to 14, 17, 25 for Cohort 3

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was performed for any of the primary/safety endpoints.

End point values	Cohort 1 - 0.3 mg/kg	Cohort 2 - 1 mg/kg	Cohort 3 - 3 mg/kg	Cohorts 1, 2 and 3 - Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	6	6	5
Units: number of patients positive or equivocal	0	0	0	0

End point values	Cohort 3 - Placebo			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: number of patients positive or equivocal	0			

Statistical analyses

No statistical analyses for this end point

Primary: Treatment Emergent Adverse Events (TEAEs)

End point title	Treatment Emergent Adverse Events (TEAEs)[3]

End point description:

End point type	Primary

End point timeframe:

All study visits until the end of the study

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was performed for any of the primary/safety endpoints.

End point values	Cohort 1 - 0.3 mg/kg	Cohort 2 - 1 mg/kg	Cohort 3 - 3 mg/kg	Cohorts 1, 2 and 3 - Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	6	6	5
Units: number of subjects with at least 1 TEAE	3	6	6	5

End point values	Cohort 3 - Placebo			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: number of subjects with at least 1 TEAE	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Manual Muscle Testing (MMT)

End point title	Manual Muscle Testing (MMT)

End point description:

End point type	Secondary

End point timeframe:

Cohorts 1 and 2: shift from baseline to Week 6
Cohort 3: shift from baseline to Week 14

End point values	Cohort 1 - 0.3 mg/kg	Cohort 2 - 1 mg/kg	Cohort 3 - 3 mg/kg	Cohorts 1, 2 and 3 - Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	6	6	5
Units: percentage				
arithmetic mean (full range (min-max))	2.83 (1.0 to 4.4)	3.07 (0.7 to 5.6)	0.70 (-5.9 to 9.2)	1.34 (-3.3 to 7.8)

End point values	Cohort 3 - Placebo			
Subject group type	Reporting group			
Number of subjects analysed	2			

Units: percentage				
arithmetic mean (full range (min-max))	-1.40 (-1.5 to -1.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Individualized Neuromuscular Quality of Life (INQoL) - Overall QoL

End point title	Individualized Neuromuscular Quality of Life (INQoL) - Overall QoL

End point description:

End point type	Secondary

End point timeframe:

Cohorts 1 and 2: shift from baseline to Week 6
Cohort 3: shift from baseline to Week 14

End point values	Cohort 1 - 0.3 mg/kg	Cohort 2 - 1 mg/kg	Cohort 3 - 3 mg/kg	Cohorts 1, 2 and 3 - Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	5	6	5
Units: PP				
arithmetic mean (full range (min-max))	2.77 (-5.0 to 6.7)	-2.98 (-16.1 to 8.4)	-9.90 (-19.4 to 5.0)	4.12 (-8.3 to 22.2)

End point values	Cohort 3 - Placebo			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: PP				
arithmetic mean (full range (min-max))	15.55 (3.9 to 27.2)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug to the last follow-up assessment (EOS Visit) or after the end of the study if the TEAE was thought to be related to study drug

Adverse event reporting additional description:

TEAEs reported for ≥ 2 patients treated with ATYR1940 are listed in the section below.

The number of occurrences per TEAE is not available in the source data, the field "Occurrences all number" therefore corresponds to the number of subjects affected per TEAE.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Cohorts 1, 2 and 3 - Placebo
Reporting group description: -	
Reporting group title	Cohort 1 - 0.3 mg/kg
Reporting group description: -	
Reporting group title	Cohort 2 - 1 mg/kg
Reporting group description: -	
Reporting group title	Cohort 3 - 3 mg/kg
Reporting group description: -	

Serious adverse events	Cohorts 1, 2 and 3 - Placebo	Cohort 1 - 0.3 mg/kg	Cohort 2 - 1 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Infusion related reaction	Additional description: Not assessed by the Investigator as serious; upgraded by Sponsor as medically-important, and therefore, an SAE		
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 3 - 3 mg/kg		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

General disorders and administration site conditions			
Infusion related reaction	Additional description: Not assessed by the Investigator as serious; upgraded by Sponsor as medically-important, and therefore, an SAE		
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cohorts 1, 2 and 3 - Placebo	Cohort 1 - 0.3 mg/kg	Cohort 2 - 1 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	3 / 3 (100.00%)	6 / 6 (100.00%)
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 5 (40.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Presyncope			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 3 (66.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Back pain			

subjects affected / exposed	1 / 5 (20.00%)	1 / 3 (33.33%)	3 / 6 (50.00%)
occurrences (all)	1	1	3
Myalgia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	1 / 6 (16.67%)
occurrences (all)	0	1	1

Non-serious adverse events	Cohort 3 - 3 mg/kg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)		
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Presyncope			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Myalgia			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 September 2014	2.0 (Amendment 1; 02 September 2014)
10 January 2015	3.0 (Amendment 2; 10 January 2015)
05 February 2015	4.0 (Amendment 3; 05 February 2015)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported