Clinical trial results:
An Open-Label, Intrapatient Dose-Escalation Study to Evaluate the Safety, Tolerability, Immunogenicity, and Biological Activity of ATYR1940 in Patients With Early Onset and Other Pediatric Onset Facioscapulohumeral Muscular Dystrophy

Summary

EudraCT number	2014-003346-27
Trial protocol	IT
Global end of trial date	14 February 2017

Results information

Result version number	v1 (current)
This version publication date	20 May 2018
First version publication date	20 May 2018

Trial information

Trial identification

Sponsor protocol code	ATYR1940-C-003

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	13 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 February 2017
Global end of trial reached?	Yes
Global end of trial date	14 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety, tolerability, and immunogenicity of the intravenous (IV) administration of ATYR1940, at doses of 0.3, 1.0, and 3.0 mg/kg, to patients with early onset FSHD

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	01 September 2015
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	France: 1
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	8
EEA total number of subjects	3

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)	3
Adults (18-64 years)	5

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Per the original study design enrollment was to be performed in 2 stages. Stage 1 was conducted and completed and the data are described herein. The sponsor elected not to conduct Stage 2.

The key patient disease characteristics included an established genetically confirmed diagnosis of FSHD with FSHD signs or symptoms presenting < 10 years.

Pre-assignment

Screening details:

The study actually had 3 periods distinct periods - screening, treatment (13 weeks including 1 dose of placebo at Week 1) and follow-up (12 weeks).

Pre-assignment period milestones

Number of subjects started	9[1]
Number of subjects completed	8

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screen failure: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The worldwide number corresponds to the number of patients randomized (8) and not to the number of patients screened (9).

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	ATYR1940

Arm description:

Enrollment into the study was to be conducted in 2 stages, based on patient age. In Stage 1, up to 8 patients between the ages of 16 and 25 years with early onset FSHD who met study entry criteria were enrolled. Stage 2 of enrollment, which was planned to include patients with early onset FSHD between the ages of 12 and 15 years, was to be initiated following an amendment to the study, based on consideration of safety data of ATYR1940 gathered in Stage 1 of this study, along with clinical safety data obtained in other studies of ATYR1940. The Sponsor elected not to conduct Stage 2.

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:

Three dose levels of ATYR1940 were to be evaluated using intrapatient dose escalation: 0.3, 1.0, and 3.0 mg/kg. Following a single, 90-minute IV placebo (normal saline Week 1) infusion, ATYR1940 was to be administered as a 90-minute IV infusion once a week for 12 weeks, starting at a dose of 0.3 mg/kg, with the potential for intrapatient dose escalation over the dosing period.

During the 13-week treatment period, patients visited the clinic weekly for dosing and assessments of safety, immunogenicity, and PD activity. Patients also returned to the clinic 1, 4, and 12 weeks after the last dose of ATYR1940 for assessment of safety, immunogenicity, and biological and PD activity. The maximum duration of patient participation in the study was 28 weeks.

Number of subjects in period 1	ATYR1940
Started	8
Completed	7
Not completed	1
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	ATYR1940

Reporting group description:

Enrollment into the study was to be conducted in 2 stages, based on patient age. In Stage 1, up to 8 patients between the ages of 16 and 25 years with early onset FSHD who met study entry criteria were enrolled. Stage 2 of enrollment, which was planned to include patients with early onset FSHD between the ages of 12 and 15 years, was to be initiated following an amendment to the study, based on consideration of safety data of ATYR1940 gathered in Stage 1 of this study, along with clinical safety data obtained in other studies of ATYR1940. The Sponsor elected not to conduct Stage 2.

Reporting group values	ATYR1940	Total	
Number of subjects	8	8	
Age categorical Units: Subjects			
Adolescents (12-17 years)	3	3	
Adults (18-64 years)	5	5	
Age continuous Units: years			
arithmetic mean	17.9		
full range (min-max)	16 to 20	-	
Gender categorical Units: Subjects			
Female	3	3	
Male	5	5	

End points

End points reporting groups

Reporting group title	ATYR1940

Reporting group description:

Enrollment into the study was to be conducted in 2 stages, based on patient age. In Stage 1, up to 8 patients between the ages of 16 and 25 years with early onset FSHD who met study entry criteria were enrolled. Stage 2 of enrollment, which was planned to include patients with early onset FSHD between the ages of 12 and 15 years, was to be initiated following an amendment to the study, based on consideration of safety data of ATYR1940 gathered in Stage 1 of this study, along with clinical safety data obtained in other studies of ATYR1940. The Sponsor elected not to conduct Stage 2.

Primary: Anti-drug antibodies

End point title	Anti-drug antibodies[1]

End point description:

End point type	Primary

End point timeframe:

Screening and weeks 4, 6, 8, 10, 13, 14, 17 and 25. The visits through week 13 were on-treatment, and visits 14, 17, 25 are post-treatment follow-up.

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	ATYR1940			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: number (frequency) of confirmed positive	4			

Statistical analyses

No statistical analyses for this end point

Primary: Anti-Jo1 antibodies

End point title	Anti-Jo1 antibodies[2]

End point description:

End point type	Primary

End point timeframe:

Screening and weeks 3 to 25

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	ATYR1940			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: number of patients positive or equivocal	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Heart Rate

End point title	Heart Rate

End point description:

End point type	Secondary

End point timeframe:

Change from baseline at 1-week post-treatment follow-up

End point values	ATYR1940			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: BEATS/MIN				
arithmetic mean (full range (min-max))	-2.5 (-12 to 8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Electrocardiogram - PR Duration

End point title	Electrocardiogram - PR Duration

End point description:

End point type	Secondary

End point timeframe:

Change from baseline at 1-week post-treatment follow-up

End point values	ATYR1940			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: msec				
arithmetic mean (full range (min-max))	-7.7 (-32 to 8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Electrocardiogram - QRS Duration

End point title	Electrocardiogram - QRS Duration

End point description:

End point type	Secondary

End point timeframe:

Change from baseline at 1-week post-treatment follow-up

End point values	ATYR1940			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: msec				
arithmetic mean (full range (min-max))	-4.8 (-12 to 3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Electrocardiogram - QTcF Interval

End point title	Electrocardiogram - QTcF Interval

End point description:

End point type	Secondary

End point timeframe:

Change from baseline at 1-week post-treatment follow-up

End point values	ATYR1940			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: msec				
arithmetic mean (full range (min-max))	-1.8 (-13 to 13)			

Statistical analyses

No statistical analyses for this end point

Secondary: PFT - FEV1/FVC Ratio

End point title	PFT - FEV1/FVC Ratio

End point description:

End point type	Secondary

End point timeframe:

Change from baseline at week 13

End point values	ATYR1940			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: %				
arithmetic mean (full range (min-max))	2.6 (-8 to 38)			

Statistical analyses

No statistical analyses for this end point

Secondary: Manual Muscle Testing - Overall total score

End point title	Manual Muscle Testing - Overall total score

End point description:

End point type	Secondary

End point timeframe:

Percent change from baseline at 1-week post-treatment follow-up

End point values	ATYR1940			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: percent				
arithmetic mean (full range (min-max))	3.8 (-6.5 to 19.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: INQoL - QoL Score

End point title	INQoL - QoL Score

End point description:

End point type	Secondary

End point timeframe:

Change from baseline at 1-week post-treatment follow-up

End point values	ATYR1940			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: None				
arithmetic mean (full range (min-max))	-1.2 (-17.3 to 13.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Hematocrit

End point title	Hematocrit

End point description:

End point type	Secondary

End point timeframe:

Change from baseline at 1-week post-treatment follow-up

End point values	ATYR1940			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: percent				
arithmetic mean (full range (min-max))	-0.01 (-2.5 to 3.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Hemoglobin

End point title	Hemoglobin

End point description:

End point type	Secondary

End point timeframe:

Change from baseline at 1-week post-treatment follow-up

End point values	ATYR1940			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: g/L				
arithmetic mean (full range (min-max))	0.7 (-7 to 11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Erythrocytes

End point title	Erythrocytes

End point description:

End point type	Secondary

End point timeframe:

Change from baseline at 1-week post-treatment follow-up

End point values	ATYR1940			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: 10^12/L				
arithmetic mean (full range (min-max))	0.027 (-0.16 to 0.36)			

Statistical analyses

No statistical analyses for this end point

Secondary: Leukocytes

End point title	Leukocytes

End point description:

End point type	Secondary

End point timeframe:

Change from baseline at 1-week post-treatment follow-up

End point values	ATYR1940			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: 10^9/L				
arithmetic mean (full range (min-max))	-0.10 (-1.2 to 1.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Platelets

End point title	Platelets

End point description:

End point type	Secondary

End point timeframe:

Change from baseline at 1-week post-treatment follow-up

End point values	ATYR1940			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: 10^9/L				
arithmetic mean (full range (min-max))	11.9 (-24 to 82)			

Statistical analyses

No statistical analyses for this end point

Secondary: Neutrophils

End point title	Neutrophils

End point description:

End point type	Secondary

End point timeframe:

Change from baseline at 1-week post-treatment follow-up

End point values	ATYR1940			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: percent				
arithmetic mean (full range (min-max))	1.84 (-6.2 to 7.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Lymphocytes

End point title	Lymphocytes

End point description:

End point type	Secondary

End point timeframe:

Change from baseline at 1-week post-treatment follow-up

End point values	ATYR1940			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: percent				
arithmetic mean (full range (min-max))	-1.13 (-7.3 to 6.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Monocytes

End point title	Monocytes

End point description:

End point type	Secondary

End point timeframe:

Change from baseline at 1-week post-treatment follow-up

End point values	ATYR1940			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: percent				
arithmetic mean (full range (min-max))	-0.50 (-1.4 to 0.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Eosinophils

End point title	Eosinophils

End point description:

End point type	Secondary

End point timeframe:

Change from baseline at 1-week post-treatment follow-up

End point values	ATYR1940			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: percent				
arithmetic mean (full range (min-max))	-0.39 (-1.3 to 0.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Basophils

End point title	Basophils

End point description:

End point type	Secondary

End point timeframe:

Change from baseline at 1-week post-treatment follow-up

End point values	ATYR1940			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: percent				
arithmetic mean (full range (min-max))	0.17 (0.0 to 0.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Aspartate Aminotransferase

End point title	Aspartate Aminotransferase

End point description:

End point type	Secondary

End point timeframe:

Change from baseline at 1-week post-treatment follow-up

End point values	ATYR1940			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: U/L				
arithmetic mean (full range (min-max))	2.1 (-9 to 8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Alanine Aminotransferase

End point title	Alanine Aminotransferase

End point description:

End point type	Secondary

End point timeframe:

Change from baseline at 1-week post-treatment follow-up

End point values	ATYR1940			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: U/L				
arithmetic mean (full range (min-max))	-0.3 (-10 to 10)			

Statistical analyses

No statistical analyses for this end point

Secondary: Bilirubin

End point title	Bilirubin

End point description:

End point type	Secondary

End point timeframe:

Change from baseline at 1-week post-treatment follow-up

End point values	ATYR1940			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: mcmol/L				
arithmetic mean (full range (min-max))	1.69 (-0.7 to 5.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Blood Urea Nitrogen

End point title	Blood Urea Nitrogen

End point description:

End point type	Secondary

End point timeframe:

Change from baseline at 1-week post-treatment follow-up

End point values	ATYR1940			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: mmol/L				
arithmetic mean (full range (min-max))	-0.359 (-1.43 to 0.71)			

Statistical analyses

No statistical analyses for this end point

Secondary: Creatinine

End point title	Creatinine

End point description:

End point type	Secondary

End point timeframe:

Change from baseline at 1-week post-treatment follow-up

End point values	ATYR1940			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: mcmol/L				
arithmetic mean (full range (min-max))	0.0 (-9 to 9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Creatine Kinase

End point title	Creatine Kinase

End point description:

End point type	Secondary

End point timeframe:

Change from baseline at 1-week post-treatment follow-up

End point values	ATYR1940			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: U/L				
arithmetic mean (full range (min-max))	99.4 (-296 to 485)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cholesterol

End point title	Cholesterol

End point description:

End point type	Secondary

End point timeframe:

Change from baseline at 1-week post-treatment follow-up

End point values	ATYR1940			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: mmol/L				
arithmetic mean (full range (min-max))	-0.100 (-1.22 to 0.54)			

Statistical analyses

No statistical analyses for this end point

Secondary: Sodium

End point title	Sodium

End point description:

End point type	Secondary

End point timeframe:

Change from baseline at 1-week post-treatment follow-up

End point values	ATYR1940			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: mmol/L				
arithmetic mean (full range (min-max))	0.1 (-3 to 3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Potassium

End point title	Potassium

End point description:

End point type	Secondary

End point timeframe:

Change from baseline at 1-week post-treatment follow-up

End point values	ATYR1940			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: mmol/L				
arithmetic mean (full range (min-max))	-0.04 (-0.3 to 0.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Bicarbonate

End point title	Bicarbonate

End point description:

End point type	Secondary

End point timeframe:

Change from baseline at 1-week post-treatment follow-up

End point values	ATYR1940			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: mmol/L				
arithmetic mean (full range (min-max))	-1.9 (-7 to 3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Calcium

End point title	Calcium

End point description:

End point type	Secondary

End point timeframe:

Change from baseline at 1-week post-treatment follow-up

End point values	ATYR1940			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: mmol/L				
arithmetic mean (full range (min-max))	0.030 (-0.03 to 0.15)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout the study

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	18.1

Reporting groups

Reporting group title	ATYR1940

Reporting group description: -

Serious adverse events	ATYR1940		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	ATYR1940		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)		
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	3 / 8 (37.50%)		
occurrences (all)	3		
Headache			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Gastrointestinal disorders			
Nausea			

subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 2		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	 3 / 8 (37.50%) 3		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 2 / 8 (25.00%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 January 2016	Protocol version 2.0 dated 12 January 2016

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported