Clinical trial results:
Restoring Dystrophin Expression in Duchenne Muscular Dystrophy: A Phase I/II Clinical Trial Using AVI-4658

Summary

EudraCT number	2006-003833-33
Trial protocol	GB
Global end of trial date	31 March 2009

Results information

Result version number	v1 (current)
This version publication date	18 December 2019
First version publication date	18 December 2019

Trial information

Trial identification

Sponsor protocol code	CRO490

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00159250
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	South Kensington Campus, London, United Kingdom, SW7 2AZ
Public contact	Francesco Muntoni , Imperial College London, f.muntoni@ucl.ac.uk
Scientific contact	Francesco Muntoni , Imperial College London, f.muntoni@ucl.ac.uk

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	05 April 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2009
Global end of trial reached?	Yes
Global end of trial date	31 March 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this trial is to evaluate the safety and tolerability of a single intramuscular (IM) dose of AVI-4658, a phosphorodiamidate Morpholino oligomer (PMO) at increasing dosages compared to placebo in up to 9 DMD subjects divided into three groups.

Protection of trial subjects:

Standard-of-care treatment, including glucocorticoids and cardioprotective drugs, was continued in all patients.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 October 2007
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	United Kingdom: 7
Worldwide total number of subjects	7
EEA total number of subjects	7

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)	7
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This single-site, non-randomised, single-blind (investigator) study was done at Imperial College NHS Trust, London, UK, in patients with DMD who were recruited nationally.

Pre-assignment

Screening details:

Participants were boys with a classic clinical diagnosis of DMD26 who were aged between 10 and 17 years inclusive when the study drug was given.

Period 1

Period 1 title	Treatments (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Low dose AVI-4658

Arm description:

Low dose of AVI-4658 was injected into the EDB muscle; the contralateral muscle received saline.

Arm type	Experimental
Investigational medicinal product name	AVI-4658
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.09 mg doses were diluted in 900 µL normal saline (0·9%) and injected to the extensor digitorum brevis (EDB) muscle

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

900 µL normal saline injected to the contralateral extensor digitorum brevis (EDB) muscle

Arm title	High dose AVI-4658

Arm description:

High dose of AVI-4658 was injected into the EDB muscle; the contralateral muscle received saline.

Arm type	Experimental
Investigational medicinal product name	AVI-4658
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.9 mg doses were diluted in 900 µL normal saline (0·9%) and injected to the extensor digitorum brevis (EDB) muscle

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

900 µL normal saline injected to the contralateral extensor digitorum brevis (EDB) muscle

Number of subjects in period 1	Low dose AVI-4658	High dose AVI-4658
Started	2	5
Completed	2	5

Baseline characteristics

Reporting groups	
Reporting group title	Low dose AVI-4658
Reporting group description:	
Low dose of AVI-4658 was injected into the EDB muscle; the contralateral muscle received saline.	
Reporting group title	High dose AVI-4658
Reporting group description:	
High dose of AVI-4658 was injected into the EDB muscle; the contralateral muscle received saline.	

Reporting group values	Low dose AVI-4658	High dose AVI-4658	Total
Number of subjects	2	5	7
Age categorical Units: Subjects			
Adolescents (12-17 years)	2	5	7
Age continuous Units: years			
geometric mean	14.5	11.8	
full range (min-max)	13 to 16	10 to 15	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	2	5	7
Mobility Units: Subjects			
Wheelchair for 11 years	1	0	1
Wheelchair for 10 years; rides static bike for 10	1	0	1
Wheelchair for 10 years	0	1	1
Walks indoors	0	1	1
Walks unaided	0	3	3

End points

End points reporting groups

Reporting group title	Low dose AVI-4658
Reporting group description:	
Low dose of AVI-4658 was injected into the EDB muscle; the contralateral muscle received saline.	
Reporting group title	High dose AVI-4658
Reporting group description:	
High dose of AVI-4658 was injected into the EDB muscle; the contralateral muscle received saline.	

Primary: Number of participants with adverse events related to AVI-4568

End point title	Number of participants with adverse events related to AVI-4568[1]
End point description:	
Number of Subjects with Treatment Emergent Adverse Events (TEAEs) and Serious TEAEs Adverse events assessed by light microscopy and immunocytochemistry to detect the differences in inflammatory infiltrates between the AVI-4568 and placebo-treated EDB muscles	
End point type	Primary
End point timeframe:	
Baseline up to Day 120	

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 analyses due to the low number of participants

End point values	Low dose AVI-4658	High dose AVI-4658		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	5		
Units: Number of participants	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with Injection Site Reactions

End point title	Number of participants with Injection Site Reactions[2]
End point description:	
End point type	Primary
End point timeframe:	
From the Day of Screening to Day 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 analyses due to the low number of participants

End point values	Low dose AVI-4658	High dose AVI-4658		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	5		
Units: Number of participants	2	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Increased expression of dystrophin

End point title	Increased expression of dystrophin
End point description: Western blot analysis	
End point type	Secondary
End point timeframe: 4 weeks	

End point values	Low dose AVI-4658	High dose AVI-4658		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	5		
Units: Number of participants	0	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Induced Skipping of Exon 51 in the Treated Extensor Digitorum Brevis (EDB) Muscle Determined by Reverse Transcription Polymerase Chain Reaction

End point title	Number of participants with Induced Skipping of Exon 51 in the Treated Extensor Digitorum Brevis (EDB) Muscle Determined by Reverse Transcription Polymerase Chain Reaction
End point description: Sequencing of the RT-PCR products	
End point type	Secondary
End point timeframe: Day 14 to Day 28	

End point values	Low dose AVI-4658	High dose AVI-4658		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	5		
Units: Number of participants	2	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Restoration of Dystrophin Protein Expression Measured by Immunocytochemistry

End point title	Number of participants with Restoration of Dystrophin Protein Expression Measured by Immunocytochemistry

End point description:

End point type	Secondary

End point timeframe:

Day 14 to Day 28

End point values	Low dose AVI-4658	High dose AVI-4658		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	5		
Units: Number of participants	0	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Restoration of Dystrophin Protein Expression Measured by Western blot analysis

End point title	Number of participants with Restoration of Dystrophin Protein Expression Measured by Western blot analysis

End point description:

End point type	Secondary

End point timeframe:

Day 14 to Day 28

End point values	Low dose AVI-4658	High dose AVI-4658		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	5		
Units: Number of participants	0	5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 120 days	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	10
Reporting groups	
Reporting group title	Low dose AVI-4658
Reporting group description: AVI-4658 was injected into the EDB muscle; the contralateral muscle received saline.	
Reporting group title	High dose AVI-4658
Reporting group description: Participants received a high dose of AVI-4658	

Serious adverse events	Low dose AVI-4658	High dose AVI-4658	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	0 / 5 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Low dose AVI-4658	High dose AVI-4658	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	4 / 5 (80.00%)	
Cardiac disorders			
Decline in cardiac function	Additional description: The decline in cardiac function (FS=22%)		
subjects affected / exposed	1 / 2 (50.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Myoglobinuria			
subjects affected / exposed	0 / 2 (0.00%)	3 / 5 (60.00%)	
occurrences (all)	0	3	
Skin and subcutaneous tissue disorders			

Bilateral erythema	Additional description: Bilateral erythema at the injection sites		
subjects affected / exposed	2 / 2 (100.00%)	1 / 5 (20.00%)	
occurrences (all)	2	1	
Ecchymosis			
subjects affected / exposed	1 / 2 (50.00%)	3 / 5 (60.00%)	
occurrences (all)	1	4	
Bilateral oedema			
subjects affected / exposed	1 / 2 (50.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 May 2008	the investigators had identified considerable comorbidity that precluded recruitment of some of the older patients, it also requested and obtained permission to lower the age at inclusion to 10 years and to be able to recruit ambulant patients.

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/19713152