Clinical trial results:
A Phase II Randomised, Open-Label, Parallel Group Study of the Safety, Tolerability, Pharmacokinetics and Efficacy of Two Subcutaneous Dosing Regimens of ATL1103 in Adult Patients with Acromegaly.

Summary

EudraCT number	2012-003147-30
Trial protocol	GB ES HU
Global end of trial date	12 September 2014

Results information

Result version number	v1 (current)
This version publication date	14 August 2022
First version publication date	14 August 2022

Trial information

Trial identification

Sponsor protocol code	1103-CT02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	ANZCTR: ACTRN12612000989842

Notes:

Sponsors

Sponsor organisation name	Antisense Therapeutics Limited
Sponsor organisation address	Level 1, 14 Wallace Avenue, Toorak, Australia, 3142
Public contact	Director, Drug Discovery & Patents, Antisense Therapeutics Ltd, 61 39827 8999, info@antisense.com.au
Scientific contact	Dr George Tachas, Antisense Therapeutics Limited, 61 39827 8999, george.tachas@antisense.com.au

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	31 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 September 2014
Global end of trial reached?	Yes
Global end of trial date	12 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of ATL1103 in patients with acromegaly.

To evaluate the single dose and multiple dose pharmacokinetic profiles of ATL1103 via the subcutaneous route in patients with acromegaly.

Protection of trial subjects:

An independent Data Safety Monitoring Board (DSMB) was established prior to recruitment start, with an appropriate charter to direct decisions, and monitor the trial safety results at intervals throughout the study. The DSMB was comprised of 4 individuals with appropriate experience in the area of acromegaly, endocrine disorders, statistics, and the conduct of clinical trials. These included at least 2 clinicians involved in treating patients with acromegaly or other endocrine disorders.
The DSMB conveyed to Antisense Therapeutics Limited (ATL) their recommendations as to whether the trial could continue as planned or whether there were any concerns. The final decision on whether the study should be stopped at any time was the responsibility of ATL. Any decision to stop was to be communicated to investigators and regulatory agencies by ATL.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 February 2013
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	Australia: 3
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	United Kingdom: 7
Worldwide total number of subjects	26
EEA total number of subjects	16

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)	20
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Screening/recruitment commenced 15 February 2013. First patient dosed 9 April 2013 last patient completed 12 September 2014. Countries UK- 6 sites , France 2- sites, Spain- 3 sites Australia- 2 sites.

Pre-assignment

Screening details:

Screened for patients with Acromegaly due to pituitary adenoma, serum IGF-I levels >1.3 times the upper limit of normal (ULN) and not on acromegaly treatment or who have undergone washout period from acromegaly medications, ranging from 6 weeks to 4 months depending on medication.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Regimen 1

Arm description:

ATL1103 200 mg administered three times in the first week (Days 1, 4 and 7) then 200 mg once weekly (Day 4 each week) in Week 2 through to Week 13 for a total of 15 doses.

Arm type	Active comparator
Investigational medicinal product name	Atesidorsen (ATL1103)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial, Solution for injection
Routes of administration	Injection , Subcutaneous use

Dosage and administration details:

ATL1103 was administered subcutaneously (sc) with patients given a loading dose of 200 mg administered three times in the first week, followed by weekly doses of 200 mg of ATL1103 for an additional 12 weeks.

Arm title	Regimen 2

Arm description:

ATL1103 200 mg administered three times in the first week (Days 1, 4 and 7), then 200 mg twice weekly (Days 4 and 7 each week) in Weeks 2 through to Week 13 for a total of 27 doses.

Arm type	Active comparator
Investigational medicinal product name	Atesidorsen (ATL1103)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Injection

Dosage and administration details:

ATL1103 was administered subcutaneously (sc) with patients given a loading dose of 200 mg administered three times in the first week, followed by twice weekly doses of 200 mg of ATL1103 for an additional 12 weeks.

Number of subjects in period 1	Regimen 1	Regimen 2
Started	13	13
Completed	13	13

Baseline characteristics

Reporting groups	
Reporting group title	Regimen 1
Reporting group description:	
ATL1103 200 mg administered three times in the first week (Days 1, 4 and 7) then 200 mg once weekly (Day 4 each week) in Week 2 through to Week 13 for a total of 15 doses.	
Reporting group title	Regimen 2
Reporting group description:	
ATL1103 200 mg administered three times in the first week (Days 1, 4 and 7), then 200 mg twice weekly (Days 4 and 7 each week) in Weeks 2 through to Week 13 for a total of 27 doses.	

Reporting group values	Regimen 1	Regimen 2	Total
Number of subjects	13	13	26
Age categorical			
Regimen 1 Median Age 49 and age range 26-72 Regimen 2 Median Age 49 and age range 32-80			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	12	9	21
From 65-84 years	1	4	5
85 years and over	0	0	0
Age continuous			
Units: years			
median	49	49	
full range (min-max)	26 to 72	32 to 80	-
Gender categorical			
Regimen 1 - 5 males & 8 females Regimen 2 - 6 males & 7 females			
Units: Subjects			
Female	8	7	15
Male	5	6	11

Subject analysis sets	
Subject analysis set title	Regimen 1
Subject analysis set type	Safety analysis
Subject analysis set description:	
200mg per week group	
Subject analysis set title	Regimen 2
Subject analysis set type	Safety analysis
Subject analysis set description:	
400 mg per week	

Reporting group values	Regimen 1	Regimen 2	
Number of subjects	13	13	
Age categorical			
Regimen 1 Median Age 49 and age range 26-72 Regimen 2 Median Age 49 and age range 32-80			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	12	21	
From 65-84 years	1	5	
85 years and over	0	0	
Age continuous			
Units: years			
median	49	49	
full range (min-max)	26 to 72	32 to 80	
Gender categorical			
Regimen 1 - 5 males & 8 females Regimen 2 - 6 males & 7 females			
Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Regimen 1
Reporting group description:	
ATL1103 200 mg administered three times in the first week (Days 1, 4 and 7) then 200 mg once weekly (Day 4 each week) in Week 2 through to Week 13 for a total of 15 doses.	
Reporting group title	Regimen 2
Reporting group description:	
ATL1103 200 mg administered three times in the first week (Days 1, 4 and 7), then 200 mg twice weekly (Days 4 and 7 each week) in Weeks 2 through to Week 13 for a total of 27 doses.	
Subject analysis set title	Regimen 1
Subject analysis set type	Safety analysis
Subject analysis set description:	
200mg per week group	
Subject analysis set title	Regimen 2
Subject analysis set type	Safety analysis
Subject analysis set description:	
400 mg per week	

Primary: To evaluate the safety and tolerability of ATL1103 in patients with acromegaly

End point title	To evaluate the safety and tolerability of ATL1103 in patients with acromegaly[1]
End point description:	
Safety and Tolerability: Physical examinations Adverse event recording and assessment Safety laboratory evaluations (biochemistry, haematology, urinalysis) Coagulation; Complement Bb Vital signs 12-lead ECGs Pituitary tumour size changes Injection site monitoring	
End point type	Primary
End point timeframe:	
One or more from screen, baseline, or all other days during treatment , W1, 2, 4, 6, 8, 10, 12, 13, and post completion of treatment follow up period D4, W14 , 16, 21.	

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: Only observations needed to be captured on the safety parameter in the 2 regimens. See publication referenced in the More Information section for safety & tolerability data.

End point values	Regimen 1	Regimen 2	Regimen 1	Regimen 2
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	13	13	13	13
Units: number				
number (not applicable)	13	13	13	13

Statistical analyses

No statistical analyses for this end point

Primary: To evaluate the single dose and multiple dose pharmacokinetic profiles of ATL1103 via the subcutaneous route in patients with acromegaly

End point title	To evaluate the single dose and multiple dose pharmacokinetic profiles of ATL1103 via the subcutaneous route in patients with acromegaly[2]

End point description:

AUC (0-6 hours) (ng.h/mL) ; Cmax (ng/mL); Tmax (h); T½=Terminal elimination half life.
The mean and standard deviation and Coefficient of variation. Median and range.

End point type	Primary

End point timeframe:

At Baseline and Week 13, PK samples were collected at pre-dose, then 1, 2, 3, 4, and 6 hours post dose. For all other PK days, W1, 2, 4, 8, 12, 13 on D4, W14 (D4 R2 or D7 R1), 16, 21 - samples were collected pre-dose only.

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: The statistical analysis performed was the median and range.

End point values	Regimen 1	Regimen 2	Regimen 1	Regimen 2
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	13	13	13	13
Units: ng.h/mL				
number (not applicable)	13	13	13	13

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were captured from the time of informed consent until the final study visit, or 28 days after the last dose of study drug, whichever was longer.

Adverse event reporting additional description:

All SAEs will be recorded in the patient records and the CRF. ATL or designee are responsible for informing the regulatory authorities of the SAE as appropriate.

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Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	Regimen 1 & 2

Reporting group description:

Both dosing arms

Serious adverse events	Regimen 1 & 2		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Regimen 1 & 2		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 26 (84.62%)		
General disorders and administration site conditions			
Injection Site Reaction	Additional description: The majority of patients in the safety set (84.6%) had ISRs; amongst these, injection site erythema, pain, swelling, bruising, pruritus, rash, haematoma, mass, irritation, warmth and in duration.		
subjects affected / exposed	22 / 26 (84.62%)		
occurrences (all)	22		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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/29789410