



## 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       |
| <b>Arm title</b>             | 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.

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 1</b> | Regimen 1 | Regimen 2 |
|---------------------------------------|-----------|-----------|
| Started                               | 13        | 13        |
| Completed                             | 13        | 13        |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                                       |           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Reporting group title                                                                                                                                                                                                 | Regimen 1 |
| Reporting group description:<br>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:<br>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<br>Regimen 2 Median Age 49 and age range 32-80 |           |           |       |
| Units: Subjects                                                                            |           |           |       |
| In utero                                                                                   | 0         | 0         | 0     |
| Preterm newborn infants<br>(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<br>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:<br>200mg per week group |                 |
| Subject analysis set title                                | Regimen 2       |
| Subject analysis set type                                 | Safety analysis |
| Subject analysis set description:<br>400 mg per week      |                 |

| <b>Reporting group values</b>                                                              | Regimen 1 | Regimen 2 |  |
|--------------------------------------------------------------------------------------------|-----------|-----------|--|
| Number of subjects                                                                         | 13        | 13        |  |
| Age categorical                                                                            |           |           |  |
| Regimen 1 Median Age 49 and age range 26-72<br>Regimen 2 Median Age 49 and age range 32-80 |           |           |  |
| Units: Subjects                                                                            |           |           |  |
| In utero                                                                                   | 0         | 0         |  |
| Preterm newborn infants<br>(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<br>Regimen 2 - 6 males & 7 females                         |           |           |  |
| Units: Subjects                                                                            |           |           |  |
| Female                                                                                     |           |           |  |
| Male                                                                                       |           |           |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                       |                 |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| Reporting group title                                                                                                                                                                                                 | Regimen 1       |
| Reporting group description:<br>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:<br>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:<br>200mg per week group                                                                                                                                                             |                 |
| Subject analysis set title                                                                                                                                                                                            | Regimen 2       |
| Subject analysis set type                                                                                                                                                                                             | Safety analysis |
| Subject analysis set description:<br>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 <sup>[1]</sup> |
| End point description:<br>Safety and Tolerability:<br>Physical examinations<br>Adverse event recording and assessment<br>Safety laboratory evaluations (biochemistry, haematology, urinalysis)<br>Coagulation; Complement Bb<br>Vital signs<br>12-lead ECGs<br>Pituitary tumour size changes<br>Injection site monitoring |                                                                                               |
| End point type                                                                                                                                                                                                                                                                                                            | Primary                                                                                       |
| End point timeframe:<br>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

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

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

End point description:

AUC (0-6 hours) (ng.h/mL) ; Cmax (ng/mL); Tmax (h); T<sub>1/2</sub>=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                   |

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**Statistical analyses**

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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.

|                 |            |
|-----------------|------------|
| 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

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29789410>