



Clinical trial results:

A phase II, open label, non-randomised, single centre, clinical trial of ANX776 in Healthy Volunteers and patients with Glaucoma, Age-Related Macular Degeneration, and Optic Neuritis and Down's Syndrome

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2016-002531-15 |
| Trial protocol | GB |
| Global end of trial date | 07 June 2018 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 22 August 2019 |
| First version publication date | 22 August 2019 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | 15/0959 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|----------------|
| ISRCTN number | ISRCTN10751859 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Comprehensive Clinical Trials Unit at UCL |
| Sponsor organisation address | Institute of Clinical Trials and Methodology, 90 High Holborn, London, United Kingdom, WC1V 6LJ |
| Public contact | CCTU Enquiry Desk, Comprehensive Clinical Trials Unit at UCL, CCTU-enquiries@ucl.ac.uk |
| Scientific contact | CCTU Enquiry Desk, Comprehensive Clinical Trials Unit at UCL, CCTU-enquiries@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 | 02 July 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 07 June 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 07 June 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary outcome is the efficacy of the intervention ascertained by the DARC Count, which is the number of apoptosing retinal cells visualised 4 hours after the ANX776 injection in patients with Glaucoma, Age-related Macular Degeneration (AMD), Optic Neuritis (ON), Down's syndrome and in Healthy volunteers.

Protection of trial subjects:

The trial was conducted in compliance with the approved protocol, UCL CCTU Standard Operating Procedures, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the Human Tissue (Quality and Safety for Human Application) Regulations 2007, the UK Data Protection Act, and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF).

The following protocol pre-defined reasons for stopping the trial early for a participant were in place: unacceptable toxicity or adverse event; inter-current illness that prevents further treatment; any change in the participant's condition that in the clinician's opinion justifies the discontinuation of the trial.

Participants were under no obligation to enter the trial and they could withdraw consent or assent / withdrawal of consent by the legal representative for Down's syndrome participants at any time during the trial, without having to give a reason, and without their clinical care being affected.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 08 February 2017 |
| 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: 113 |
| Worldwide total number of subjects | 113 |
| EEA total number of subjects | 113 |

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) | 78 |
| From 65 to 84 years | 31 |
| 85 years and over | 4 |

Subject disposition

Recruitment

Recruitment details:

Participants for the glaucoma, AMD, optic neuritis and healthy volunteer groups were recruited through designated participant identification centres and REC approved advertisements. Participants in the Down's syndrome arm were recruited from two pre-existing cohorts in the Cambridge Intellectual and Developmental Disabilities Research Group.

Pre-assignment

Screening details:

Eligibility criteria for all groups were those aged 18 years or above, with clear optical media in the studied eye, refractive error not higher than spherical equivalent of 10 D and women of childbearing potential identified as not pregnant. Each subgroup was enrolled into the study in accordance with group-specific inclusion/ exclusion criteria.

Period 1

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

Arms

| | |
|------------------------------|----------|
| Are arms mutually exclusive? | Yes |
| Arm title | Glaucoma |

Arm description:

Subjects with at least one eye with a diagnosis of Glaucoma.

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | ANX776 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

0.4mg

| | |
|------------------|----------------------------------|
| Arm title | Age-related Macular Degeneration |
|------------------|----------------------------------|

Arm description:

Subjects with Age-related Macular Degeneration (AMD).

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | ANX776 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

0.4mg

| | |
|------------------|----------------|
| Arm title | Optic Neuritis |
|------------------|----------------|

Arm description:

Subjects with clinical diagnosis of Optic neuritis (ON) affecting one eye within two years. All results including baseline data are based on the 14 eligible patients.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|-----------------|
| Investigational medicinal product name | ANX776 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 0.4mg | |
| Arm title | Down's Syndrome |

Arm description:

Subjects with confirmation of Down's Syndrome.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | ANX776 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 0.4mg | |
| Arm title | Healthy Volunteers |

Arm description:

Subjects with no evidence of any eye disease. All results including baseline data are based on the 39 eligible patients.

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | ANX776 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 0.4mg | |

| Number of subjects in period 1 | Glaucoma | Age-related Macular Degeneration | Optic Neuritis |
|---------------------------------------|----------|----------------------------------|----------------|
| Started | 20 | 19 | 18 |
| Completed | 20 | 19 | 14 |
| Not completed | 0 | 0 | 4 |
| Ineligible | - | - | 4 |
| Missing baseline spot count | - | - | - |

| Number of subjects in period 1 | Down's Syndrome | Healthy Volunteers |
|---------------------------------------|-----------------|--------------------|
| Started | 16 | 40 |
| Completed | 15 | 39 |
| Not completed | 1 | 1 |
| Ineligible | - | 1 |
| Missing baseline spot count | 1 | - |

Baseline characteristics

Reporting groups

| | |
|--|----------------------------------|
| Reporting group title | Glaucoma |
| Reporting group description: | |
| Subjects with at least one eye with a diagnosis of Glaucoma. | |
| Reporting group title | Age-related Macular Degeneration |
| Reporting group description: | |
| Subjects with Age-related Macular Degeneration (AMD). | |
| Reporting group title | Optic Neuritis |
| Reporting group description: | |
| Subjects with clinical diagnosis of Optic neuritis (ON) affecting one eye within two years. All results including baseline data are based on the 14 eligible patients. | |
| Reporting group title | Down's Syndrome |
| Reporting group description: | |
| Subjects with confirmation of Down's Syndrome. | |
| Reporting group title | Healthy Volunteers |
| Reporting group description: | |
| Subjects with no evidence of any eye disease. All results including baseline data are based on the 39 eligible patients. | |

| Reporting group values | Glaucoma | Age-related Macular Degeneration | Optic Neuritis |
|------------------------|----------|----------------------------------|----------------|
| Number of subjects | 20 | 19 | 18 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 12 | 1 | 13 |
| From 65-84 years | 8 | 14 | 1 |
| 85 years and over | 0 | 4 | 0 |
| Ineligible participant | 0 | 0 | 4 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 61.1 | 79.9 | 45.3 |
| standard deviation | ± 13.7 | ± 7.4 | ± 12.1 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 6 | 9 | 11 |
| Male | 14 | 10 | 3 |
| Ineligible participant | 0 | 0 | 4 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Caucasian | 16 | 15 | 10 |
| Black | 3 | 0 | 1 |
| Asian | 0 | 4 | 1 |
| Hispanic | 0 | 0 | 1 |
| Other | 1 | 0 | 1 |
| Ineligible participant | 0 | 0 | 4 |
| AMD type | | | |
| Units: Subjects | | | |
| Early AMD & Late AMD | 0 | 1 | 0 |

| | | | |
|---|--------|--------|--------|
| Early AMD & Neovascular AMD | 0 | 1 | 0 |
| Late AMD | 0 | 3 | 0 |
| Neovascular AMD | 0 | 12 | 0 |
| Early AMD | 0 | 2 | 0 |
| Not applicable | 20 | 0 | 18 |
| Glaucoma category | | | |
| Units: Subjects | | | |
| Glaucoma | 8 | 0 | 0 |
| Glaucoma suspect | 12 | 0 | 0 |
| Not applicable | 0 | 19 | 18 |
| Weight | | | |
| Units: Kg | | | |
| arithmetic mean | 81.3 | 65.8 | 74.8 |
| standard deviation | ± 17.5 | ± 9.9 | ± 14.3 |
| BMI | | | |
| Units: kg/m ² | | | |
| arithmetic mean | 26.8 | 24.9 | 26.1 |
| standard deviation | ± 4.6 | ± 3.1 | ± 4.7 |
| SBP | | | |
| Systolic Blood Pressure | | | |
| Units: mmHg | | | |
| arithmetic mean | 140 | 142 | 132 |
| standard deviation | ± 17.0 | ± 17.5 | ± 18.7 |
| DBP | | | |
| Diastolic Blood Pressure | | | |
| Units: mmHg | | | |
| arithmetic mean | 77.9 | 71.4 | 73.6 |
| standard deviation | ± 10.3 | ± 9.6 | ± 18.7 |
| Heart rate | | | |
| Units: beat/min | | | |
| arithmetic mean | 69.5 | 64.9 | 69.0 |
| standard deviation | ± 14.0 | ± 9.7 | ± 11.3 |
| Respiratory rate | | | |
| Units: breaths/min | | | |
| arithmetic mean | 17.0 | 16.6 | 16.9 |
| standard deviation | ± 2.6 | ± 1.4 | ± 1.9 |
| Autofluorescence spot count | | | |
| Units: Baseline spot count | | | |
| geometric mean | 30.2 | 67.5 | 30.8 |
| standard deviation | ± 1.62 | ± 1.71 | ± 1.39 |
| IOP | | | |
| Mean intraocular pressure of eligible eyes. | | | |
| Units: mmHg | | | |
| arithmetic mean | 18.9 | 13.5 | 13.9 |
| standard deviation | ± 2.6 | ± 3.5 | ± 2.0 |
| Corneal pachymetry | | | |
| Units: micrometer | | | |
| arithmetic mean | 555 | 541 | 528 |
| standard deviation | ± 33.6 | ± 37.2 | ± 40.3 |
| VF mean deviation | | | |
| Visual field mean deviation | | | |
| Units: dB | | | |

| | | | |
|--------------------|--------|-------|-------------|
| arithmetic mean | -1.7 | 0 | -4.7 |
| standard deviation | ± 2.1 | ± 0 | ± 5.7 |
| Visual acuity | | | |
| Units: logmar | | | |
| arithmetic mean | 0.01 | 0.45 | -0.00000001 |
| standard deviation | ± 0.08 | ± 0.9 | ± 0.28 |

| Reporting group values | Down's Syndrome | Healthy Volunteers | Total |
|-----------------------------|-----------------|--------------------|-------|
| Number of subjects | 16 | 40 | 113 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 16 | 31 | 73 |
| From 65-84 years | 0 | 8 | 31 |
| 85 years and over | 0 | 0 | 4 |
| Ineligible participant | 0 | 1 | 5 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 39.7 | 47.6 | - |
| standard deviation | ± 7.7 | ± 17.1 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 4 | 21 | 51 |
| Male | 12 | 18 | 57 |
| Ineligible participant | 0 | 1 | 5 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Caucasian | 16 | 28 | 85 |
| Black | 0 | 3 | 7 |
| Asian | 0 | 6 | 11 |
| Hispanic | 0 | 2 | 3 |
| Other | 0 | 0 | 2 |
| Ineligible participant | 0 | 1 | 5 |
| AMD type | | | |
| Units: Subjects | | | |
| Early AMD & Late AMD | 0 | 0 | 1 |
| Early AMD & Neovascular AMD | 0 | 0 | 1 |
| Late AMD | 0 | 0 | 3 |
| Neovascular AMD | 0 | 0 | 12 |
| Early AMD | 0 | 0 | 2 |
| Not applicable | 16 | 40 | 94 |
| Glaucoma category | | | |
| Units: Subjects | | | |
| Glaucoma | 0 | 0 | 8 |
| Glaucoma suspect | 0 | 0 | 12 |
| Not applicable | 16 | 40 | 93 |
| Weight | | | |
| Units: Kg | | | |
| arithmetic mean | 71.8 | 70.0 | - |
| standard deviation | ± 18.7 | ± 11.6 | - |
| BMI | | | |
| Units: kg/m^2 | | | |

| | | | |
|---|--------|--------|---|
| arithmetic mean | 29.7 | 24.0 | |
| standard deviation | ± 5.7 | ± 3.3 | - |
| SBP | | | |
| Systolic Blood Pressure | | | |
| Units: mmHg | | | |
| arithmetic mean | 119 | 129 | |
| standard deviation | ± 15.3 | ± 14.5 | - |
| DBP | | | |
| Diastolic Blood Pressure | | | |
| Units: mmHg | | | |
| arithmetic mean | 70.4 | 75.8 | |
| standard deviation | ± 8.9 | ± 9.0 | - |
| Heart rate | | | |
| Units: beat/min | | | |
| arithmetic mean | 65.3 | 69.7 | |
| standard deviation | ± 11.1 | ± 9.9 | - |
| Respiratory rate | | | |
| Units: breaths/min | | | |
| arithmetic mean | 17.3 | 16.7 | |
| standard deviation | ± 1.2 | ± 1.9 | - |
| Autofluorescence spot count | | | |
| Units: Baseline spot count | | | |
| geometric mean | 22.6 | 30.2 | |
| standard deviation | ± 1.32 | ± 1.34 | - |
| IOP | | | |
| Mean intraocular pressure of eligible eyes. | | | |
| Units: mmHg | | | |
| arithmetic mean | 0 | 13.6 | |
| standard deviation | ± 0 | ± 2.5 | - |
| Corneal pachymetry | | | |
| Units: micrometer | | | |
| arithmetic mean | 0 | 530 | |
| standard deviation | ± 0 | ± 25.8 | - |
| VF mean deviation | | | |
| Visual field mean deviation | | | |
| Units: dB | | | |
| arithmetic mean | 0 | -0.3 | |
| standard deviation | ± 0 | ± 1.1 | - |
| Visual acuity | | | |
| Units: logmar | | | |
| arithmetic mean | 0 | -0.03 | |
| standard deviation | ± 0 | ± 0.1 | - |

End points

End points reporting groups

| | |
|--|----------------------------------|
| Reporting group title | Glaucoma |
| Reporting group description: Subjects with at least one eye with a diagnosis of Glaucoma. | |
| Reporting group title | Age-related Macular Degeneration |
| Reporting group description: Subjects with Age-related Macular Degeneration (AMD). | |
| Reporting group title | Optic Neuritis |
| Reporting group description: Subjects with clinical diagnosis of Optic neuritis (ON) affecting one eye within two years. All results including baseline data are based on the 14 eligible patients. | |
| Reporting group title | Down's Syndrome |
| Reporting group description: Subjects with confirmation of Down's Syndrome. | |
| Reporting group title | Healthy Volunteers |
| Reporting group description: Subjects with no evidence of any eye disease. All results including baseline data are based on the 39 eligible patients. | |
| Subject analysis set title | Per protocol |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Only those participants who met the eligibility criteria and were not recruited by mistake are included in the analyses. | |

Primary: Primary outcome

| | |
|---|-----------------|
| End point title | Primary outcome |
| End point description: Raw DARC counts are taken from imaging of each eligible eye using an automated process built on an algorithm which was developed blind to disease group to ensure an objective measure which is comparable across groups. The cSLO images were background subtracted and standardised before a template matching approach was applied using a 50*50 pixel 'ideal spot' template to identify spot candidates. Once identified, spot candidates will be extracted from each cSLO image and spot morphology recorded. An exploratory technique was undertaken to validate an algorithm for differentiating 'true' DARC spots amongst candidates. The resulting DARC spots were summed for each eye to yield a 'weighted' DARC count. Analysis will be repeated using the 'weighted' DARC count produced using the algorithm as exploratory outcome. | |
| End point type | Primary |
| End point timeframe: 4 hours post injection. | |

| End point values | Glaucoma | Age-related Macular Degeneration | Optic Neuritis | Down's Syndrome |
|--------------------------------------|-------------------|----------------------------------|-------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 20 ^[1] | 19 ^[2] | 14 ^[3] | 15 ^[4] |
| Units: raw DARC counts | | | | |
| geometric mean (confidence interval) | 42.0 (38.4 to | 76.0 (63.5 to | 37.1 (29.2 to | 30.0 (26.2 to |

| | | | | |
|------|-------|-------|-------|-------|
| 95%) | 45.9) | 91.0) | 47.1) | 34.2) |
|------|-------|-------|-------|-------|

Notes:

[1] - Analysis based on the 38 eligible eyes.

[2] - Analysis based on the 32 eligible eyes.

[3] - Analysis based on the 22 eligible eyes.

[4] - Analysis based on the 30 eligible eyes.

| End point values | Healthy Volunteers | | | |
|--|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 39 ^[5] | | | |
| Units: raw DARC counts | | | | |
| geometric mean (confidence interval 95%) | 46.3 (41.7 to 51.4) | | | |

Notes:

[5] - Analysis based on the 75 eligible eyes.

Statistical analyses

| Statistical analysis title | Glaucoma and Healthy Volunteers |
|--|---------------------------------|
| Statistical analysis description: | |
| Comparison of raw DARC counts between Glaucoma group and healthy volunteers at 4 hours post injection. | |
| Comparison groups | Glaucoma v Healthy Volunteers |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Mixed models analysis |
| Parameter estimate | Geometric Mean Ratio |
| Point estimate | 0.91 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.75 |
| upper limit | 1.1 |

| Statistical analysis title | AMD and Healthy Volunteers |
|--|---|
| Statistical analysis description: | |
| Comparison of raw DARC counts between AMD participants and Healthy volunteers at 4 hours post injection. | |
| Comparison groups | Age-related Macular Degeneration v Healthy Volunteers |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Mixed models analysis |
| Parameter estimate | Geometric Mean Ratio |
| Point estimate | 1.1 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.96 |
| upper limit | 1.27 |

| | |
|-----------------------------------|---------------------------|
| Statistical analysis title | ON and Healthy Volunteers |
|-----------------------------------|---------------------------|

Statistical analysis description:

Comparison of raw DARC counts between ON participants and Healthy volunteers at 4 hours post injection.

| | |
|---|-------------------------------------|
| Comparison groups | Optic Neuritis v Healthy Volunteers |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Mixed models analysis |
| Parameter estimate | Geometric Mean Ratio |
| Point estimate | 0.93 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.85 |
| upper limit | 1.02 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Down's syndrome and Healthy Volunteers |
|-----------------------------------|--|

Statistical analysis description:

Comparison of raw DARC counts between Down's syndrome participants and Healthy volunteers at 4 hours post injection.

| | |
|---|--------------------------------------|
| Comparison groups | Down's Syndrome v Healthy Volunteers |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Mixed models analysis |
| Parameter estimate | Geometric Mean Ratio |
| Point estimate | 0.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.87 |
| upper limit | 0.98 |

Secondary: Secondary outcome - 2 hours post injection

| | |
|-----------------|--|
| End point title | Secondary outcome - 2 hours post injection |
|-----------------|--|

End point description:

Comparison of raw DARC counts between each of the study groups and Healthy volunteers at 2 hours post injection.

| | |
|-------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 2 hours post injection. | |

| End point values | Glaucoma | Age-related Macular Degeneration | Optic Neuritis | Down's Syndrome |
|--|---------------------|----------------------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 20 ^[6] | 19 ^[7] | 14 ^[8] | 15 ^[9] |
| Units: Raw DARC count | | | | |
| geometric mean (confidence interval 95%) | 41.3 (36.6 to 46.5) | 72.9 (59.9 to 88.8) | 48.4 (41.4 to 56.5) | 29.9 (26.5 to 33.8) |

Notes:

[6] - Analysis based on the 38 eligible eyes.

[7] - Analysis based on the 32 eligible eyes.

[8] - Analysis based on the 22 eligible eyes.

[9] - Analysis based on the 30 eligible eyes.

| End point values | Healthy Volunteers | | | |
|--|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 39 ^[10] | | | |
| Units: Raw DARC count | | | | |
| geometric mean (confidence interval 95%) | 47.0 (42.6 to 52.0) | | | |

Notes:

[10] - Analysis based on the 75 eligible eyes.

Statistical analyses

| Statistical analysis title | Glaucoma and Healthy Volunteers |
|----------------------------|---------------------------------|
|----------------------------|---------------------------------|

Statistical analysis description:

Comparison of raw DARC counts between Glaucoma group and healthy volunteers at 2 hours post injection.

| | |
|---|-------------------------------|
| Comparison groups | Glaucoma v Healthy Volunteers |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Mixed models analysis |
| Parameter estimate | Geometric Mean Ratio |
| Point estimate | 0.87 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 1.06 |

| Statistical analysis title | AMD and Healthy Volunteers |
|----------------------------|----------------------------|
|----------------------------|----------------------------|

Statistical analysis description:

Comparison of raw DARC counts between AMD group and healthy volunteers at 2 hours post injection.

| | |
|---|---|
| Comparison groups | Age-related Macular Degeneration v Healthy Volunteers |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Mixed models analysis |
| Parameter estimate | Geometric Mean Ratio |
| Point estimate | 1.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.96 |
| upper limit | 1.27 |

Statistical analysis title

ON and Healthy Volunteers

Statistical analysis description:

Comparison of raw DARC counts between ON group and healthy volunteers at 2 hours post injection.

| | |
|---|-------------------------------------|
| Comparison groups | Optic Neuritis v Healthy Volunteers |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Mixed models analysis |
| Parameter estimate | Geometric Mean Ratio |
| Point estimate | 1.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.93 |
| upper limit | 1.09 |

Statistical analysis title

Down's syndrome and Healthy Volunteers

Statistical analysis description:

Comparison of raw DARC counts between Down's syndrome group and healthy volunteers at 2 hours post injection.

| | |
|---|--------------------------------------|
| Comparison groups | Down's Syndrome v Healthy Volunteers |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Mixed models analysis |
| Parameter estimate | Geometric Mean Ratio |
| Point estimate | 0.91 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.86 |
| upper limit | 0.96 |

Secondary: Secondary outcome - 15 minutes post injection

| | |
|---|---|
| End point title | Secondary outcome - 15 minutes post injection |
| End point description: Comparison of raw DARC counts between each study group and healthy volunteers at 15 minutes post injection. | |
| End point type | Secondary |
| End point timeframe: 15 minutes post injection. | |

| End point values | Glaucoma | Age-related Macular Degeneration | Optic Neuritis | Down's Syndrome |
|--|---------------------|----------------------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 20 ^[11] | 19 ^[12] | 14 ^[13] | 15 ^[14] |
| Units: raw DARC count | | | | |
| geometric mean (confidence interval 95%) | 33.3 (29.9 to 37.1) | 67.9 (57.2 to 80.6) | 35.9 (30.7 to 42.0) | 27.6 (24.8 to 30.7) |

Notes:

[11] - Analysis based on the 38 eligible eyes.

[12] - Analysis based on the 32 eligible eyes.

[13] - Analysis based on the 22 eligible eyes.

[14] - Analysis based on the 30 eligible eyes.

| End point values | Healthy Volunteers | | | |
|--|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 39 ^[15] | | | |
| Units: raw DARC count | | | | |
| geometric mean (confidence interval 95%) | 32.3 (28.9 to 36.1) | | | |

Notes:

[15] - Analysis based on the 75 eligible eyes.

Statistical analyses

| | |
|--|---------------------------------|
| Statistical analysis title | Glaucoma and Healthy Volunteers |
| Statistical analysis description: Comparison of raw DARC counts between Glaucoma group and healthy volunteers at 15 minutes post injection. | |
| Comparison groups | Glaucoma v Healthy Volunteers |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Mixed models analysis |
| Parameter estimate | Geometric Mean Ratio |
| Point estimate | 1.06 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.82 |
| upper limit | 1.38 |

| | |
|-----------------------------------|----------------------------|
| Statistical analysis title | AMD and Healthy Volunteers |
|-----------------------------------|----------------------------|

Statistical analysis description:

Comparison of raw DARC counts between AMD group and healthy volunteers at 15 minutes post injection

| | |
|---|---|
| Comparison groups | Age-related Macular Degeneration v Healthy Volunteers |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Mixed models analysis |
| Parameter estimate | Geometric Mean Ratio |
| Point estimate | 1.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.09 |
| upper limit | 1.49 |

| | |
|-----------------------------------|---------------------------|
| Statistical analysis title | ON and Healthy Volunteers |
|-----------------------------------|---------------------------|

Statistical analysis description:

Comparison of raw DARC counts between ON group and healthy volunteers at 15 minutes post injection

| | |
|---|-------------------------------------|
| Comparison groups | Optic Neuritis v Healthy Volunteers |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Mixed models analysis |
| Parameter estimate | Geometric Mean Ratio |
| Point estimate | 1.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.94 |
| upper limit | 1.15 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Down's syndrome and Healthy Volunteers |
|-----------------------------------|--|

Statistical analysis description:

Comparison of raw DARC counts between Down's syndrome group and healthy volunteers at 15 minutes post injection.

| | |
|-------------------|--------------------------------------|
| Comparison groups | Down's Syndrome v Healthy Volunteers |
|-------------------|--------------------------------------|

| | |
|---|-----------------------|
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Mixed models analysis |
| Parameter estimate | Geometric Mean Ratio |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.92 |
| upper limit | 1.07 |

Other pre-specified: Exploratory analysis - weighted DARC counts

| | |
|-----------------|---|
| End point title | Exploratory analysis - weighted DARC counts ^[16] |
|-----------------|---|

End point description:

An exploratory technique was undertaken to validate an algorithm for differentiating 'true' DARC spots amongst candidates. Spot candidate populations were gated to exclude non-DARC spot objects and artefacts based on spot area (> 10 pixels and < 1000 pixels in size), standard deviation (standardised intensity units > 0.5) and solidity (measure of roundness/ overall concavity) < 0.75). The resulting DARC spots were summed for each eye to yield a 'weighted' DARC count.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

2 hours post injection

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: At present, data are available for the Glaucoma participants and Healthy volunteers only. The same technique will be used to obtain the weighted DARC counts in all the other groups.

| End point values | Glaucoma | Healthy Volunteers | | |
|--|-----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 ^[17] | 22 ^[18] | | |
| Units: weighted DARC count | | | | |
| geometric mean (confidence interval 95%) | 131.4 (97.0 to 177.9) | 98.3 (78.6 to 123.1) | | |

Notes:

[17] - Analysis based on images of 32 eligible eyes having clear quality for intensity measurements.

[18] - Analysis based on images of 41 eligible eyes having clear quality for intensity measurements.

Statistical analyses

| | |
|----------------------------|---------------------------------|
| Statistical analysis title | Glaucoma and Healthy Volunteers |
|----------------------------|---------------------------------|

Statistical analysis description:

Comparison of weighted DARC counts between Glaucoma group and healthy volunteers at 2 hours post injection.

| | |
|-------------------|-------------------------------|
| Comparison groups | Glaucoma v Healthy Volunteers |
|-------------------|-------------------------------|

| | |
|---|-----------------------|
| Number of subjects included in analysis | 40 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Mixed models analysis |
| Parameter estimate | Geometric Mean Ratio |
| Point estimate | 1.32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.86 |
| upper limit | 2.02 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Participants (or carer for Down's syndrome participants) were followed up via telephone call 30 days after administration of IMP to check for any symptoms and/or adverse events.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|-------|
| Dictionary name | CTCAE |
|-----------------|-------|

| | |
|--------------------|-----|
| Dictionary version | 4.0 |
|--------------------|-----|

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | Glaucoma |
|-----------------------|----------|

Reporting group description:

Subjects with at least one eye with a diagnosis of Glaucoma.

| | |
|-----------------------|----------------------------------|
| Reporting group title | Age-related Macular Degeneration |
|-----------------------|----------------------------------|

Reporting group description:

Subjects with Age-related Macular Degeneration (AMD).

| | |
|-----------------------|----------------|
| Reporting group title | Optic Neuritis |
|-----------------------|----------------|

Reporting group description:

Subjects with clinical diagnosis of Optic neuritis (ON) affecting one eye within two years. All results including baseline data are based on the 14 eligible patients.

| | |
|-----------------------|-----------------|
| Reporting group title | Down's Syndrome |
|-----------------------|-----------------|

Reporting group description:

Subjects with confirmation of Down's Syndrome. All results including baseline data are based on the 15 patients with complete baseline data.

| | |
|-----------------------|--------------------|
| Reporting group title | Healthy Volunteers |
|-----------------------|--------------------|

Reporting group description:

Subjects with no evidence of any eye disease. All results including baseline data are based on the 39 eligible patients.

| Serious adverse events | Glaucoma | Age-related Macular Degeneration | Optic Neuritis |
|---|----------------|----------------------------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 19 (0.00%) | 0 / 18 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

| Serious adverse events | Down's Syndrome | Healthy Volunteers | |
|---|-----------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 40 (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 | Glaucoma | Age-related Macular Degeneration | Optic Neuritis |
|---|-----------------|----------------------------------|-----------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 2 / 20 (10.00%) | 1 / 19 (5.26%) | 4 / 18 (22.22%) |
| Nervous system disorders | | | |
| Feeling disorientated | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 19 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Headache | | | |
| subjects affected / exposed | 2 / 20 (10.00%) | 0 / 19 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 3 | 0 | 1 |
| General disorders and administration site conditions | | | |
| Exhaustion/ Lethargy | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 19 (0.00%) | 3 / 18 (16.67%) |
| occurrences (all) | 0 | 0 | 3 |
| Rash on canula site | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 19 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sore throat | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 19 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear and labyrinth disorders | | | |
| Problems with balance | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 19 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Eye disorders | | | |
| Deteriorating eyesight | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 19 (5.26%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Difficulty seeing objects in motion | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 19 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Sensitivity to light | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 19 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|--|---------------------|---------------------|---------------------|
| Tired eyes subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 0 / 19 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 0 / 19 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 0 / 19 (0.00%) 0 | 1 / 18 (5.56%) 1 |
| Musculoskeletal and connective tissue disorders Swollen feet subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 0 / 19 (0.00%) 0 | 1 / 18 (5.56%) 1 |

| Non-serious adverse events | Down's Syndrome | Healthy Volunteers | |
|--|---|---|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 0 / 16 (0.00%) | 3 / 40 (7.50%) | |
| Nervous system disorders Feeling disorientated subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 0 / 16 (0.00%) 0 | 0 / 40 (0.00%) 0 1 / 40 (2.50%) 1 | |
| General disorders and administration site conditions Exhaustion/ Lethargy subjects affected / exposed occurrences (all) Rash on canula site subjects affected / exposed occurrences (all) Sore throat subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 0 / 16 (0.00%) 0 0 / 16 (0.00%) 0 | 0 / 40 (0.00%) 0 1 / 40 (2.50%) 1 1 / 40 (2.50%) 0 | |
| Ear and labyrinth disorders | | | |

| | | | |
|---|---------------------|---------------------|--|
| Problems with balance subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 40 (0.00%) 0 | |
| Eye disorders | | | |
| Deteriorating eyesight subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 40 (0.00%) 0 | |
| Difficulty seeing objects in motion subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 40 (0.00%) 0 | |
| Sensitivity to light subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 40 (2.50%) 1 | |
| Tired eyes subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 40 (2.50%) 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 40 (2.50%) 1 | |
| Psychiatric disorders | | | |
| Anxiety subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 40 (2.50%) 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Swollen feet subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 40 (0.00%) 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 30 November 2016 | Protocol updated to v3.0 with the following: removal of the Down's syndrome group and a reduction of the sample size accordingly by 20; general participant exclusion criterion in relation to contraception and pregnancy amended for consistency; inclusion of a table of additional pre-clinical data for DARC; clarifications throughout. |
| 03 January 2017 | Extension of the expiry date of the IMP (ANX776) until 30 June 2017 based on new stability testing data. Updated IMPD. |
| 20 April 2017 | Protocol updated to v4.0 with the following: re-inclusion of a subgroup of 20 participants with Down's syndrome. This subgroup was originally approved by the MHRA but was removed as the REC requested further scientific and ethical rationale for the inclusion of this subgroup. The rationale is provided in the protocol. |
| 01 June 2017 | Details: Protocol updated to v9.0 with the following: REC requested changes in relation to the inclusion of the participants with Down's syndrome subgroup; general inclusion criteria edited to remove requirement for best corrected visual acuity equal to 6/24 or better at qualification and to state women of childbearing potential must agree to a pregnancy test instead of consent; removal of the exclusion criteria for age-related macular degeneration subgroup relating to the presence of ocular conditions with increased risk of choroidal neovascularisation. Only those with choroidal neovascularisation will be excluded; removal of the single exclusion criteria for the optic neuritis subgroup; clarifications throughout. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported