



Clinical trial results:

Low-dose Atropine for the Prevention of Childhood Myopia Progression in Danish Children (APP-study)

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2018-001286-16 |
| Trial protocol | DK |
| Global end of trial date | 30 April 2024 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 04 May 2025 |
| First version publication date | 04 May 2025 |

Trial information

Trial identification

| | |
|-----------------------|-------------------------------------|
| Sponsor protocol code | The trial adhered to good APP-study |
|-----------------------|-------------------------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03911271 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Rigshospitalet |
| Sponsor organisation address | Valdemar Hansens vej 1, Glostrup, Denmark, 2600 |
| Public contact | Department of Ophthalmology, Department of Ophthalmology, +45 38634132, line.kessel.01@regionh.dk |
| Scientific contact | Department of Ophthalmology, Department of Ophthalmology, +45 38634132, line.kessel.01@regionh.dk |

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 | 23 April 2024 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 23 April 2024 |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 April 2024 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Myopia (nearsightedness) is increasing in prevalence throughout the world. It is associated with a risk of potentially blinding complications such as retinal detachment and myopic maculopathy. There is a direct association between the degree of myopia and the risk of complications. Myopia develops in childhood and during adolescence. In order to prevent higher degrees of myopia, we need to halt disease progression in children and teenagers. Low-dose atropine eye drops have been shown to reduce myopia progression by 50% in Asian populations but its effect in non-Asian populations is unknown. The aim of this study is to investigate if low-dose atropine can reduce myopia progression in Danish children and teenagers. The study is an investigator initiated randomized clinical trial conducted as a collaboration between three Danish Eye Departments covering all of Denmark.

Protection of trial subjects:

The trial adhered to good clinical practice (GCP) guidelines for clinical trials. Serious adverse events were reported to the principal investigator. Low-dose atropine eye drops are widely used outside of Europe with few side effects mainly related to the effect.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 01 January 2019 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Denmark: 97 |
| Worldwide total number of subjects | 97 |
| EEA total number of subjects | 97 |

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) | 66 |
| Adolescents (12-17 years) | 31 |

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

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from private practitioners of Ophthalmology and optometry. Recruitment and follow-up took place between May 2019 and May 2024. Participants were recruited across the geography of Denmark.

Pre-assignment

Screening details:

Children between 6 and 9 years of age with at least one negative spherical diopter in one eye and children between 9 and 12 years of age with at least two negative spherical diopters in one eye were included. In total 124 children were screened. Of these, 21 did not meet inclusion criteria, 4 declined to participate.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

Eye drops were manufactured and given a randomized id by the producer. Participants were allocated randomly to each intervention group and paired with a randomized trial medication id.

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Participants receiving placebo eye drops for 24 months, then followed by 12-months washout

| | |
|--|-------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo eye drops |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Eye drops |
| Routes of administration | Ocular use |

Dosage and administration details:

One eye drop in each eye before bedtime for two years then one year without treatment (wash-out)

| | |
|------------------|-------|
| Arm title | 0.01% |
|------------------|-------|

Arm description:

Participants who received 0.01% low dose atropine for 24 months, then followed by 12-months washout

| | |
|--|-------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | 0.01% low dose atropine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Eye drops |
| Routes of administration | Ocular use |

Dosage and administration details:

1 eye drop in each eye before bedtime

| | |
|------------------|-------------------|
| Arm title | 0.1% loading dose |
|------------------|-------------------|

Arm description:

Children who received 0.1% loading dose for the initial six months followed by 0.01% for 18 months, then followed by 12-months washout

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | 0.1% low dose atropine and 0.01% low dose atropine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Eye drops |
| Routes of administration | Ocular use |

Dosage and administration details:

0.1% for six months followed by 0.01% for 18 months followed by 12 months washout

| Number of subjects in period 1 | Placebo | 0.01% | 0.1% loading dose |
|---------------------------------------|---------|-------|-------------------|
| Started | 32 | 32 | 33 |
| Completed | 29 | 31 | 31 |
| Not completed | 3 | 1 | 2 |
| Consent withdrawn by subject | 2 | - | 1 |
| Lost to follow-up | 1 | 1 | 1 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|---------------|
| Reporting group title | Overall trial |
| Reporting group description: - | |

| Reporting group values | Overall trial | Total | |
|---|---------------|-------|--|
| Number of subjects | 97 | 97 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | | 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) | | 0 | |
| From 65-84 years | | 0 | |
| 85 years and over | | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 9.4 | | |
| full range (min-max) | 6 to 12 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 55 | 55 | |
| Male | 42 | 42 | |
| Spherical equivalent refraction | | | |
| SER in diopters | | | |
| Units: diopters | | | |
| arithmetic mean | -2.99 | | |
| standard deviation | ± 1.27 | - | |
| Axial length | | | |
| Axial length in mm | | | |
| Units: mm | | | |
| arithmetic mean | 24.6 | | |
| standard deviation | ± 0.84 | - | |

End points

End points reporting groups

| | |
|--|-------------------|
| Reporting group title | Placebo |
| Reporting group description: Participants receiving placebo eye drops for 24 months, then followed by 12-months washout | |
| Reporting group title | 0.01% |
| Reporting group description: Participants who received 0.01% low dose atropine for 24 months, then followed by 12-months washout | |
| Reporting group title | 0.1% loading dose |
| Reporting group description: Children who received 0.1% loading dose for the initial six months followed by 0.01% for 18 months, then followed by 12-months washout | |

Primary: Axial length

| | |
|--|--------------|
| End point title | Axial length |
| End point description: | |
| End point type | Primary |
| End point timeframe: 0 to 36 months | |

| End point values | Placebo | 0.01% | 0.1% loading dose | |
|----------------------------------|-----------------|-----------------|-------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 29 | 31 | 31 | |
| Units: mm | | | | |
| arithmetic mean (standard error) | 25.33 (± 0.11) | 25.25 (± 0.11) | 25.28 (± 0.11) | |

Statistical analyses

| | |
|---|-------------------------------------|
| Statistical analysis title | Linear |
| Comparison groups | Placebo v 0.01% v 0.1% loading dose |
| Number of subjects included in analysis | 91 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Mixed models analysis |

Secondary: Spherical equivalent refraction

| | |
|-----------------|---------------------------------|
| End point title | Spherical equivalent refraction |
|-----------------|---------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

0 to 36 months

| End point values | Placebo | 0.01% | 0.1% loading dose | |
|----------------------------------|-----------------|-----------------|-------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 29 | 31 | 31 | |
| Units: diopters | | | | |
| arithmetic mean (standard error) | -4.43 (± 0.20) | 4.26 (± 0.20) | -4.45 (± 0.20) | |

Statistical analyses

| | |
|---|-------------------------------------|
| Statistical analysis title | Linear mixed model |
| Comparison groups | Placebo v 0.01% v 0.1% loading dose |
| Number of subjects included in analysis | 91 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

0 to 36 months

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|----|
| Dictionary version | 28 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Participants receiving placebo eye drops for 24 months, then followed by 12-months washout

| | |
|-----------------------|-------|
| Reporting group title | 0.01% |
|-----------------------|-------|

Reporting group description:

Participants who received 0.01% low dose atropine for 24 months, then followed by 12-months washout

| | |
|-----------------------|-------------------|
| Reporting group title | 0.1% loading dose |
|-----------------------|-------------------|

Reporting group description:

Children who received 0.1% loading dose for the initial six months followed by 0.01% for 18 months, then followed by 12-months washout

| Serious adverse events | Placebo | 0.01% | 0.1% loading dose |
|---|---|----------------|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 32 (9.38%) | 0 / 32 (0.00%) | 0 / 33 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Suspected meningitis | Additional description: Suspicion of meningitis which was rejected at hospital stay | | |
| subjects affected / exposed | 3 / 32 (9.38%) | 0 / 32 (0.00%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 32 (0.00%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Appendicitis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 32 (0.00%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Placebo | 0.01% | 0.1% loading dose |
|---|------------------|------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 18 / 32 (56.25%) | 18 / 32 (56.25%) | 33 / 33 (100.00%) |
| Eye disorders | | | |
| Photophobia | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 4 / 32 (12.50%) | 30 / 33 (90.91%) |
| occurrences (all) | 1 | 4 | 30 |
| Eye redness/irritation | | | |
| subjects affected / exposed | 6 / 32 (18.75%) | 6 / 32 (18.75%) | 8 / 33 (24.24%) |
| occurrences (all) | 6 | 6 | 8 |
| Other | | | |
| subjects affected / exposed | 11 / 32 (34.38%) | 8 / 32 (25.00%) | 18 / 33 (54.55%) |
| occurrences (all) | 11 | 8 | 18 |

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

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|---|
| Moderate sample size, limited follow-up time (3 years), lack of documentation of other factors influencing myopia progression (parental myopia, myopia progression prior to enrollment) |
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Notes: