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.

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)

Notes: