Clinical trial results:
Intravenous hypertonic saline to lower intraocular pressure in ocular hypertension, primary open-angle glaucoma and exfoliation glaucoma

Summary

EudraCT number	2012-001247-51
Trial protocol	FI
Global end of trial date	28 January 2014

Results information

Result version number	v1 (current)
This version publication date	24 March 2021
First version publication date	24 March 2021

Trial information

Trial identification

Sponsor protocol code	v.1/040312

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Helsinki University Hospital
Sponsor organisation address	Haartmaninkatu 4 C, Helsinki, Finland, 00029
Public contact	Glaucoma department, Helsinki University Hospital, Eyeclinic, pia.inborr@helsinki.fi
Scientific contact	Glaucoma department, Helsinki University Hospital, Eyeclinic, pia.inborr@helsinki.fi

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	28 January 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 January 2014
Global end of trial reached?	Yes
Global end of trial date	28 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The amount of intraocular pressure reduction 16 minutes after a bolus of intravenous hypertonic saline

Protection of trial subjects:

The study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board. We required written informed consent from all participants. Patients on oral acetazolamide or with heart or kidney failure, dementia, any other condition that remarkably decreased the patients' physical performance, ocular surgery within six months, laser cyclophotogoagulation within one week, goniopuncture of Descemet´s membrane, or needling of a filtrating bleb on the same day as IVHTS were ineligible for safety reasons.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 August 2012
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	Finland: 44
Worldwide total number of subjects	44
EEA total number of subjects	44

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)	19
From 65 to 84 years	25
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from the Helsinki University Hospital Glaucoma Department between 1.10.2012 - 28.1.2014.

Pre-assignment

Screening details:

Eligible to this study were patients with OHT, POAG, and ExG with IOP of 24-30 mmHg who were 25-80 years old. A total of 44 patients gave their consent and completed the study.

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	Ocular hypertension

Arm description:

Eligible to this study were patients with ocular hypertension (OHT) with IOP of 24-30 mmHg who were 25-80 years old. OHT patients had no optic nerve head (ONH), retinal nerve fiber layer (RNFL), or visual field (VF) damage, and their untreated IOP was 24-30 mmHg.

Arm type	Active comparator
Investigational medicinal product name	23.4% sodium chloride; Natriumklorid Braun 234 mg/ml, B. Braun Medical Oy, Helsinki, Finland
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

We injected IVHTS (23.4% sodium chloride; Natriumklorid Braun 234 mg/ml, B. Braun Medical Oy, Helsinki, Finland) through a cannulated antecubital vein in the right or left arm. We confirmed the correct intravenous placement of the cannula by injecting 3 ml of physiologic saline. The dosage of IVHTS was 1 mmol/kg sodium chloride in all patients. For a patient who weighed 80 kg, the amount of 23.4% saline was 20 ml, and the infusion rate was 1 ml/s. Thereafter we rinsed the cannula and vein with 5 ml of physiologic saline.

Arm title	Primary open angle glaucoma

Arm description:

Eligible to this study were patients with primary open angle glaucoma (POAG) with IOP of 24-30 mmHg who were 25-80 years old. POAG patients had glaucomatous thinning of the ONH rim or thinning of the RNFL with corresponding VF defect.

Arm type	Active comparator
Investigational medicinal product name	23.4% sodium chloride; Natriumklorid Braun 234 mg/ml, B. Braun Medical Oy, Helsinki, Finland
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

We injected IVHTS (23.4% sodium chloride; Natriumklorid Braun 234 mg/ml, B. Braun Medical Oy, Helsinki, Finland) through a cannulated antecubital vein in the right or left arm. We confirmed the correct intravenous placement of the cannula by injecting 3 ml of physiologic saline. The dosage of IVHTS was 1 mmol/kg sodium chloride in all patients. For a patient who weighed 80 kg, the amount of

23.4% saline was 20 ml, and the infusion rate was 1 ml/s. Thereafter we rinsed the cannula and vein with 5 ml of physiologic saline.

Arm title	Exfoliation glaucoma

Arm description:

Eligible to this study were patients with exfoliation glaucoma (ExG) with IOP of 24-30 mmHg who were 25-80 years old. ExG patients had glaucomatous thinning of the ONH rim or thinning of the RNFL with corresponding VF defect. Patients with ExG had exfoliation material on the lens or pupil margin when examined with biomicroscopy through a dilated pupil.

Arm type	Active comparator
Investigational medicinal product name	23.4% sodium chloride; Natriumklorid Braun 234 mg/ml, B. Braun Medical Oy, Helsinki, Finland
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

We injected IVHTS (23.4% sodium chloride; Natriumklorid Braun 234 mg/ml, B. Braun Medical Oy, Helsinki, Finland) through a cannulated antecubital vein in the right or left arm. We confirmed the correct intravenous placement of the cannula by injecting 3 ml of physiologic saline. The dosage of IVHTS was 1 mmol/kg sodium chloride in all patients. For a patient who weighed 80 kg, the amount of 23.4% saline was 20 ml, and the infusion rate was 1 ml/s. Thereafter we rinsed the cannula and vein with 5 ml of physiologic saline.

Number of subjects in period 1	Ocular hypertension	Primary open angle glaucoma	Exfoliation glaucoma
Started	13	14	17
Completed	13	14	17

Baseline characteristics

Reporting groups	
Reporting group title	Ocular hypertension
Reporting group description:	
Eligible to this study were patients with ocular hypertension (OHT) with IOP of 24-30 mmHg who were 25-80 years old. OHT patients had no optic nerve head (ONH), retinal nerve fiber layer (RNFL), or visual field (VF) damage, and their untreated IOP was 24-30 mmHg.	
Reporting group title	Primary open angle glaucoma
Reporting group description:	
Eligible to this study were patients with primary open angle glaucoma (POAG) with IOP of 24-30 mmHg who were 25-80 years old. POAG patients had glaucomatous thinning of the ONH rim or thinning of the RNFL with corresponding VF defect.	
Reporting group title	Exfoliation glaucoma
Reporting group description:	
Eligible to this study were patients with exfoliation glaucoma (ExG) with IOP of 24-30 mmHg who were 25-80 years old. ExG patients had glaucomatous thinning of the ONH rim or thinning of the RNFL with corresponding VF defect. Patients with ExG had exfoliation material on the lens or pupil margin when examined with biomicroscopy through a dilated pupil.	

Reporting group values	Ocular hypertension	Primary open angle glaucoma	Exfoliation glaucoma
Number of subjects	13	14	17
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	12	5	2
From 65-84 years	1	9	15
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	5	8	12
Male	8	6	5

Reporting group values	Total		
Number of subjects	44		
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)	19		
From 65-84 years	25		
85 years and over	0		
Gender categorical Units: Subjects			
Female	25		
Male	19		

Subject analysis sets

Subject analysis set title	Gender
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All women and men patients were analysed separately.

Reporting group values	Gender		
Number of subjects	44		
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)	19		
From 65-84 years	25		
85 years and over	0		
Gender categorical Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Ocular hypertension
Reporting group description:	
Eligible to this study were patients with ocular hypertension (OHT) with IOP of 24-30 mmHg who were 25-80 years old. OHT patients had no optic nerve head (ONH), retinal nerve fiber layer (RNFL), or visual field (VF) damage, and their untreated IOP was 24-30 mmHg.	
Reporting group title	Primary open angle glaucoma
Reporting group description:	
Eligible to this study were patients with primary open angle glaucoma (POAG) with IOP of 24-30 mmHg who were 25-80 years old. POAG patients had glaucomatous thinning of the ONH rim or thinning of the RNFL with corresponding VF defect.	
Reporting group title	Exfoliation glaucoma
Reporting group description:	
Eligible to this study were patients with exfoliation glaucoma (ExG) with IOP of 24-30 mmHg who were 25-80 years old. ExG patients had glaucomatous thinning of the ONH rim or thinning of the RNFL with corresponding VF defect. Patients with ExG had exfoliation material on the lens or pupil margin when examined with biomicroscopy through a dilated pupil.	
Subject analysis set title	Gender
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All women and men patients were analysed separately.	

Primary: IOP 16 minutes after IVHTS

End point title	IOP 16 minutes after IVHTS
End point description:	
In our previous study the mean IOP reduction reached its maximum of 9 (SD, 4) mmHg 16 minutes after a 1.0 mmol/kg bolus of 23.4% IVHTS.8 This was used for sample size calculations for this study, and the amount of IOP reduction 16 minutes after the IVHTS bolus was set as the primary outcome measure.	
End point type	Primary
End point timeframe:	
We measured IOP before giving the IVHTS bolus (baseline), and then every minute for 10 minutes, and at 13, 16, 20, 30, 60, and 120 minutes after the bolus. We measured IOP with a Goldmann applanation tonometer.	

End point values	Ocular hypertension	Primary open angle glaucoma	Exfoliation glaucoma	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	14	17	
Units: mmHg				
median (full range (min-max))	16 (13 to 22)	18 (14 to 20)	16 (12 to 26)	

Attachments (see zip file)	Table 2.docx

Statistical analyses

Statistical analysis title	16 min

Statistical analysis description:

Our data were not normally distributed according to histograms. For comparison of three groups we used the Kruskal-Wallis test, and for paired comparisons the Mann-Whitney U-test. We applied the Bonferroni correction to adjust for multiple testing. For paired data (baseline vs after IVHTS) we used the Wilcoxon signed rank test. Significance was set at P < 0.05. P-values were two-tailed. For statistical analyses we used Stata version 13 (Stata Corp, College Station, TX).

Comparison groups	Ocular hypertension v Primary open angle glaucoma v Exfoliation glaucoma
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05 [1]
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - Significance was set at P < 0.05. P-values were two-tailed.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

We followed patients 2 hours time. Thereafter patients could report significant adverse events by e-mail or phone.

Adverse event reporting additional description:

The patients were prompted to report if they felt any pain or other sensations during or after the injection, and they graded the amount of pain from 0 to 10; from no pain to the most intolerable pain.

Assessment type	Systematic

Dictionary used

Dictionary name	symptoms
Dictionary version	1

Reporting groups

Reporting group title	Ocular hypertension

Reporting group description:

Eligible to this study were patients with ocular hypertension (OHT) with IOP of 24-30 mmHg who were 25-80 years old. OHT patients had no optic nerve head (ONH), retinal nerve fiber layer (RNFL), or visual field (VF) damage, and their untreated IOP was 24-30 mmHg.

Reporting group title	Primary open angle glaucoma

Reporting group description:

Eligible to this study were patients with primary open angle glaucoma (POAG) with IOP of 24-30 mmHg who were 25-80 years old. POAG patients had glaucomatous thinning of the ONH rim or thinning of the RNFL with corresponding VF defect.

Reporting group title	Exfoliation glaucoma

Reporting group description:

Eligible to this study were patients with exfoliation glaucoma (ExG) with IOP of 24-30 mmHg who were 25-80 years old. ExG patients had glaucomatous thinning of the ONH rim or thinning of the RNFL with corresponding VF defect. Patients with ExG had exfoliation material on the lens or pupil margin when examined with biomicroscopy through a dilated pupil.

Serious adverse events	Ocular hypertension	Primary open angle glaucoma	Exfoliation glaucoma
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	0 / 17 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Ocular hypertension	Primary open angle glaucoma	Exfoliation glaucoma
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 13 (92.31%)	14 / 14 (100.00%)	17 / 17 (100.00%)

General disorders and administration site conditions			
pain			
subjects affected / exposed	10 / 13 (76.92%)	11 / 14 (78.57%)	14 / 17 (82.35%)
occurrences (all)	10	11	14
facial heath			
subjects affected / exposed	10 / 13 (76.92%)	8 / 14 (57.14%)	11 / 17 (64.71%)
occurrences (all)	10	8	11
Dizziness			
subjects affected / exposed	0 / 13 (0.00%)	2 / 14 (14.29%)	2 / 17 (11.76%)
occurrences (all)	0	2	2
Headache			
subjects affected / exposed	0 / 13 (0.00%)	2 / 14 (14.29%)	2 / 17 (11.76%)
occurrences (all)	0	2	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/22834976