Clinical trial results:
Optic neuritis and early treatment with methylprednisolone.

Summary

EudraCT number	2012-002628-34
Trial protocol	DK
Global end of trial date	30 September 2015

Results information

Result version number	v1 (current)
This version publication date	18 February 2020
First version publication date	18 February 2020
Summary attachment (see zip file)	Time to steroid treatment in severe acute optic neuritis (Time to steroid treatment... (Dale, 2018).pdf)

Trial information

Trial identification

Sponsor protocol code	thorp8617-1

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Department of Neurology, Aarhus University Hospital
Sponsor organisation address	Palle Juul-Jensens Boulevard 99, Aarhus, Denmark,
Public contact	Sclerosis Clinic (Gro H. Dale), Department of Neurology, Aarhus University Hospital, grodale@gmail.com
Scientific contact	Sclerosis Clinic (Gro H. Dale), Department of Neurology, Aarhus University Hospital, grodale@gmail.com

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 February 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2015
Global end of trial reached?	Yes
Global end of trial date	30 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To see if early treatment of acute optic neuritis with high-dosis intravenous Solu-medrol, has effect on visual function at follow-up 6 months and 12 months later.

Protection of trial subjects:

To decrease the risk of side-effects, oral treatment with a proton pump inhibitor (Pantoprazol 20 mg × 1 daily) and a 400 mg calcium
and 19 µg (760 E) vitamin D combination (1 tablet × 2 daily) was added to the steroid treatment for the 3–5 days. If the patient
reported severe side-effects, the treatment would be terminated prematurely (n = 0).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 September 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 49
Worldwide total number of subjects	49
EEA total number of subjects	49

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)	49

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Ninety consecutive patients suspected of having ON that were referred to three neurological and two ophthalmological departments,
and private ophthalmologists, in the Central Region of Denmark (population nearly 1.3 million citizens) between December 1st 2012
and May 31st 2014, were considered for inclusion in this study.

Pre-assignment

Screening details:

Inclusion criteria: Age above 18 years, duration of symptoms less than 30 days, confirmation of optic neuritis (ON) by an ophthalmologist, previous ON and/or demyelinating disease, new ON.
Exclusion criteria: A refractive error >8 from emmetropia, known previous retinal disease, pregnancy, inability to give informed consent, etc.

Period 1

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

Blinding implementation details:

Blinding was not used.

Arms

Are arms mutually exclusive?	Yes
Arm title	Patients with severe optic neuritis

Arm description:

Twenty-eight patients with severe ON, defined as BCVA ≤ 0.5 decimal (0.30 logMAR) or BCVA >0.5 but severe amblyopia in the nonaffected eye (only one patient), were offered treatment with high-dose intravenous methylprednisolone (Solu-Medrol), 1 gram per day for 3–5 days.
22 patients accepted treatment, 6 patients declined the offer.

Arm type	Intervention (steroid treatment)
Investigational medicinal product name	Methylprednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

1 gram Methylprednisolone (Solu-Medrol) intravenously per day for 3-5 days.

Arm title	Patients with mild/moderate optic neuritis.

Arm description:

Twenty-one patients with mild/moderate ON were not offered treatment since the risk of side-effects from the treatment was considered to be higher than the possible benefits.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Patients with severe optic neuritis	Patients with mild/moderate optic neuritis.
Started	28	21
Completed	25	21
Not completed	3	0
Consent withdrawn by subject	2	-
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial
Reporting group description:	
49 patients with acute ON enrolled in the study.	

Reporting group values	Overall trial	Total	
Number of subjects	49	49	
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	34.9		
full range (min-max)	18 to 60	-	
Gender categorical Units: Subjects			
Female	32	32	
Male	17	17	

Subject analysis sets	
Subject analysis set title	Treated within 1 week
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with severe optic neuritis treated with steroids within 1 week after symptom presentation.	
Subject analysis set title	Treated later than 1 week
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with severe optic neuritis treated with steroids later than 1 week after symptom presentation.	
Subject analysis set title	Non-treated
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with severe optic neuritis who declined the offer of steroid treatment.	

Reporting group values	Treated within 1 week	Treated later than 1 week	Non-treated
Number of subjects	9	13	6
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	35.6	35.5	35.7
full range (min-max)	25 to 48	23 to 54	18 to 45
Gender categorical			
Units: Subjects			
Female	4	9	5
Male	5	4	1

End points

End points reporting groups

Reporting group title	Patients with severe optic neuritis
Reporting group description:	
Twenty-eight patients with severe ON, defined as BCVA ≤ 0.5 decimal (0.30 logMAR) or BCVA >0.5 but severe amblyopia in the nonaffected eye (only one patient), were offered treatment with high-dose intravenous methylprednisolone (Solu-Medrol), 1 gram per day for 3–5 days. 22 patients accepted treatment, 6 patients declined the offer.	
Reporting group title	Patients with mild/moderate optic neuritis.
Reporting group description:	
Twenty-one patients with mild/moderate ON were not offered treatment since the risk of side-effects from the treatment was considered to be higher than the possible benefits.	
Subject analysis set title	Treated within 1 week
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with severe optic neuritis treated with steroids within 1 week after symptom presentation.	
Subject analysis set title	Treated later than 1 week
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with severe optic neuritis treated with steroids later than 1 week after symptom presentation.	
Subject analysis set title	Non-treated
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with severe optic neuritis who declined the offer of steroid treatment.	

Primary: BCVA

End point title	BCVA
End point description:	
End point type	Primary
End point timeframe:	
Best corrected visual acuity (BCVA) was measured at baseline, 6 months and 12 months.	

End point values	Patients with severe optic neuritis	Patients with mild/moderate optic neuritis.	Treated within 1 week	Treated later than 1 week
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	28	21	9	13
Units: logMAR				
number (not applicable)	28	21	9	13

End point values	Non-treated			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: logMAR				

number (not applicable)	6			

Statistical analyses

Statistical analysis title	Repeated measurements of continuous data

Statistical analysis description:

Continuous data were analyzed in a mixed model with nested effects and an unstructured covariance matrix for repeated measurement analysis of variance (ANOVA). An inspection of residuals and fitted values supported the validity of the model. Post hoc overall likelihood ratio tests and marginal Wald tests were calculated.

Comparison groups	Treated within 1 week v Treated later than 1 week v Non-treated
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)

Primary: Inter-eye thickness difference in GCIP layer

End point title	Inter-eye thickness difference in GCIP layer

End point description:

End point type	Primary

End point timeframe:

The inter-eye thickness difference (i.e. affected eye - fellow eye) of the ganglion cell + inner plexiform (GCIP) layer was measured at baseline, 6 months and 12 months.

End point values	Patients with severe optic neuritis	Patients with mild/moderate optic neuritis.	Treated within 1 week	Treated later than 1 week
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	28	21	9	13
Units: µm				
number (not applicable)	28	21	9	13

End point values	Non-treated			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: µm				
number (not applicable)	6			

Statistical analyses

Statistical analysis title	Repeated measurements of continuous data

Statistical analysis description:

Continuous data were analyzed in a mixed model with nested effects and an unstructured covariance matrix for repeated measurement analysis of variance (ANOVA). An inspection of residuals and fitted values supported the validity of the model. Post hoc overall likelihood ratio tests and marginal Wald tests were calculated.

Comparison groups	Treated within 1 week v Treated later than 1 week v Non-treated
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first day of treatment and for up to four days after terminated treatment.

Adverse event reporting additional description:

The SAR/SAE are registered in the CRF, and an initial reporting at CIOSM-I form to the sponsor. A final reporting will be done when the patient has recovered or is not expected to recover any further. SAR/SAE will be noted on a list, which is sent yearly to the Danish Health Authorities and the Committees on Health Research Ethics.

Assessment type	Systematic

Dictionary used

Dictionary name	None
Dictionary version	0

Reporting groups

Reporting group title	Treated patients

Reporting group description:

Patients with severe optic neuritis who were treated with iv. steroids.

Serious adverse events	Treated patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 22 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Treated patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 22 (90.91%)		
Cardiac disorders			
Palpitations			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	4		
Nervous system disorders			
Sleep disorder			
subjects affected / exposed	10 / 22 (45.45%)		
occurrences (all)	10		
General disorders and administration site conditions			

General discomfort subjects affected / exposed occurrences (all) Tiredness subjects affected / exposed occurrences (all) Metallic taste in the mouth subjects affected / exposed occurrences (all)	6 / 22 (27.27%) 6 3 / 22 (13.64%) 3 3 / 22 (13.64%) 3		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 3		
Skin and subcutaneous tissue disorders Skin rash subjects affected / exposed occurrences (all)	5 / 22 (22.73%) 5		
Psychiatric disorders Euphoric mood subjects affected / exposed occurrences (all)	4 / 22 (18.18%) 4		
Infections and infestations Infections subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 3		

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/29931830