Clinical trial results:
Lyme borreliosis; a scientific approach to reduce diagnostic and therapeutic uncertainties (BorrSci)

WP2; SIX VERSUS TWO WEEKS TREATMENT WITH DOXYCYCLINE IN LYME NEUROBORRELIOSIS; A MULTICENTER, NON-INFERIORITY, PENTA-BLIND, RANDOMIZED TRIAL

Summary

EudraCT number	2015-001481-25
Trial protocol	NO
Global end of trial date	21 March 2021
Results information	
Result version number	v1 (current)
This version publication date	22 October 2022
First version publication date	22 October 2022
Summary attachment (see zip file)	Six versus 2 weeks treatment with doxycycline in European Lyme neuroborreliosis: a multicentre, non-inferiority, double-blinded, randomised and placebo-controlled trial (Solheim six versus two.pdf) BorrSci Primary endpoint (BorrSci primary endpoint.xlsx)

Trial information

Trial identification	
Sponsor protocol code	BorrSciWP2
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Sørlandet Hospital HF
Sponsor organisation address	Egsveien 100, Kristiansand, Norway,
Public contact	Coordinating investigator, Sørlandet Sykehus HF, 47 41208824, unn.ljostad@sshf.no
Scientific contact	Coordinating investigator, Sørlandet Sykehus HF, 47 41208824, unn.ljostad@sshf.no

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	07 March 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 February 2021
Global end of trial reached?	Yes
Global end of trial date	21 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To answer the question "is two weeks of doxycycline treatment (currently suggested treatment) at least as effective as six weeks doxycycline treatment in Lyme Neuroborreliosis?"

Protection of trial subjects:

The patients were followed closely during and after treatment to monitor safety. They were contacted by phone 1 week after start of treatment and questioned about symptom severity and possible side effects. Blood sampling with a status of haematology, liver and kidney function to monitor potential side effects takes place at 2 and 4 weeks after start of treatment. The patients were also asked to fill out a patient diary on symptoms and possible side effects once a week for 10 weeks. In cases of possible disease progression, the patients were evaluated by a physician.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 November 2015
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	Norway: 121
Worldwide total number of subjects	121
EEA total number of subjects	121

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)	88
From 65 to 84 years	32
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

One hundred and twenty-one patients were included from 8 Norwegian hospitals. Fifty-two treated for 2 weeks and 53 for 6 weeks were included in the intention-to-treat analyses, and 52 and 51 in per-protocol analysis.

Pre-assignment

Screening details:

Patients with definite or possible neuroborreliosis according to EFNS guidelines were screened for eligibility to include. At least 144 patients were screened in the inclusion period. We have a complete screening log from the primary inclusion site and 23 patients were considered ineligible for different reasons, including exclusion criteria.

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	Investigator, Monitor, Data analyst, Carer, Assessor, Subject

Blinding implementation details:

Patients were randomised into two treatment arms: oral doxycycline 200 mg once daily for 2 weeks, followed by 4 weeks of placebo, or doxycycline 200 mg once daily for 6 weeks. All patients received identically designed tablets and capsules for 6 weeks. The blinding was retained until all patients had completed the 6 months visit, the content of all tables and figures were fixed, and the statistical procedures were performed with the two treatment arms marked as groups A and B.

Arms

Are arms mutually exclusive?	Yes
Arm title	2 weeks treatment

Arm description:

2 weeks of unblinded doxycyline, followed by 4 weeks of placebo

Arm type	Placebo
Investigational medicinal product name	Doxycycline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

200 mg daily, orally for 14 days

Arm title	6 weeks treatment

Arm description:

2 weeks unblinded treatment with doxycycline, followed by 4 weeks treatment with doxycycline

Arm type	Active comparator

Investigational medicinal product name	Doxycycline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

200 mg of doxycycline daily for 6 weeks orally

Number of subjects in period 1	2 weeks treatment	6 weeks treatment
Started	60	61
Completed	55	54
Not completed	5	7
Consent withdrawn by subject	2	4
Other diagnosis discovered after inclusion	2	2
Protocol deviation	1	1

Baseline characteristics

Reporting groups	
Reporting group title	2 weeks treatment
Reporting group description:	
2 weeks of unblinded doxycyline, followed by 4 weeks of placebo	
Reporting group title	6 weeks treatment
Reporting group description:	
2 weeks unblinded treatment with doxycycline, followed by 4 weeks treatment with doxycycline	

Reporting group values	2 weeks treatment	6 weeks treatment	Total
Number of subjects	60	61	121
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			
Age, years 2 weeks group: 58 (12) 6 weeks group: 55 (15)			
Units: years			
geometric mean	58	55	
standard deviation	± 12	± 15	-
Gender categorical			
Sex Female in 2 weeks group: 21 (40%) 6 weeks group: 25 (47%) Male in 2 weeks groups: 31 (60%) 6 weeks group: 28 (53%)			
Units: Subjects			
Female	25	29	54
Male	35	32	67

End points

End points reporting groups

Reporting group title	2 weeks treatment
Reporting group description:	
2 weeks of unblinded doxycyline, followed by 4 weeks of placebo	
Reporting group title	6 weeks treatment
Reporting group description:	
2 weeks unblinded treatment with doxycycline, followed by 4 weeks treatment with doxycycline	

Primary: determine if treatment duration of 2 weeks doxycycline is as effective as a prolonged regimen of 6 weeks

End point title	determine if treatment duration of 2 weeks doxycycline is as effective as a prolonged regimen of 6 weeks
End point description:	
The CSS measures 10 subjective symptoms and 22 objective neurological findings. Each of the 32 items is scored as 0=none, 1=mild (without influence on daily life) or 2=severe (with influence on daily life), and the sum score range from 0 to 64.	
End point type	Primary
End point timeframe:	
The primary endpoint was clinical improvement 6 months after treatment start as measured by difference in CCS sum score from baseline to 6 months.	

End point values	2 weeks treatment	6 weeks treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	51		
Units: Composite Clinical Score				
geometric mean (confidence interval 95%)	6.3 (5.6 to 7.1)	6.7 (6.0 to 7.4)		

Statistical analyses

Statistical analysis title	Primary endpoint
Statistical analysis description:	
General linear model with treatment group as a factor, and adjustment for duration of symptoms, baseline score, gender and age.	
Comparison groups	2 weeks treatment v 6 weeks treatment
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	General linear model

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

For each patient the standard time period for collecting and recording AE and SAEs will begin at start of study treatment and will continue during follow up period for at least four weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: All registered side effects from the study medication were known from the doxycycline SPC. No serious adverse events were registered.

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