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

Protocol Identification Number: BorrSciWP2
EudraCT Number: 2015-001481-25

SPONSOR:

Frode Gallefoss
Research department, Sørlandet Hospital HF, Servicebox 416, 4604 Kristansand, Norway
Tel : +47 38 07 30 00
E-mail: frode.gallefoss@sshf.no

COORDINATING INVESTIGATORS :

Åse Mygland and Unn Ljøstad
Department of Neurology, Sørlandet Hospital HF, Servicebox 416, 4604 Kristansand, Norway
Tel : +47 38 07 39 10
E-mail:
aase.mygland@sshf.no
unn.ljostad@sshf.no

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CONTACT DETAILS

Sponsor:	**Frode Gallefoss,** **MD, Professor, PhD, leader of research department** Sørlandet Hospital HF**,** Servicebox 416, 4604 Kristiansand Tel : +47 38 07 30 00 E-mail: frode.gallefoss@sshf.no
Coordinating Investigators	**Unn Ljøstad, MD, Professor, PhD** Department of Neurology, Sørlandet Hospital HF, Servicebox 416, 4604 Kristansand Tel : +47 38 07 39 10 E-mail: unn.ljostad@sshf.no **Åse Mygland, MD, Professor PhD** Department of Neurology, Sørlandet Hospital HF, Servicebox 416, 4604 Kristansand Tel : +47 38 07 39 10 E-mail: aase.mygland@sshf.no
Principal investigator (at each participating site or if single site study):	**Name and title** Address Tel : E-mail:
Participating Departments:	**Name and title** Address Tel : E-mail:
Participating Departments:	**Name and title** Address Tel : E-mail:
Monitor:	**Department of Clinical Research Support, Marta Colban** Oslo University Hospital, Postbox 4956 Nydalen 0424 Oslo E-mail: Marcol@ous-hf.no

SIGNATURE PAGE

Title	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**
Protocol ID no:	BorrSciWP2
EudraCT no:	2015-001481-25

I hereby declare that I will conduct the study in compliance with the Protocol, ICH GCP and the applicable regulatory requirements:

Name	Title	Role	Signature	Date

PROTOCOL SYNOPSIS

Protocol title	Six versus two weeks treatment with doxycycline in Lyme Neuroborreliosis; a multicenter, non-inferiority, penta-blind, randomized trial
Sponsor	Sørlandet Hospital HF
Phase and study type	Phase III, interventional
Investigational Medical Product (IMP) (including active comparator and placebo) :	Doxycycline 200 mg once daily for six weeks versus Doxycycline 200 mg once daily for two weeks + placebo for four weeks
Centers:	Sørlandet Hospital + 5-10 other Norwegian hospitals
Study Period:	Estimated date of first patient enrolled: 01.10.15 Anticipated recruitment period: 01.10.15- 31.12.19 Estimated date of last patient completed: 31.12.20
Treatment Duration:	Six weeks
Follow-up:	13 months
Objectives	<u>Primary objective</u> To answer the question "is two weeks doxycycline treatment (currently suggested treatment) at least as effective as six weeks doxycycline treatment in Lyme Neuroborreliosis?" <u>Key secondary objectives</u> To provide a better understanding of the pathogenesis and long-term complaints, and to search for new biomarkers in LNB To collect clinical data, blood, and CSF in a biobank for future research
Endpoints:	<u>Primary endpoint:</u> Improvement in composite clinical score defined as clinical score at inclusion minus clinical score at 6 months. <u>Secondary endpoints:</u> Fatigue Severity Scale (FSS) Patient Health Questionnaire (PHQ-15) Short Form 36 (SF-36) Blood and CSF findings MRI, and neuropsychological assessments in a subset of patients Adverse events
Study Design:	Multicenter, non-inferiority, randomized, penta-blind, placebo-controlled trial
Main Inclusion Criteria:	1. Neurological symptoms suggestive of LNB without other obvious reasons and one or both of a. Cerebrospinal fluid pleocytosis ($\geq$5 leukocytes/mm^3) b. Intrathecal *Bb* antibody production 2. Signed informed consent
Main Exclusion Criteria	– Age less than 18 years – Pregnancy, breast-feeding – Adverse reaction to tetracyclines – Treatment with cephalosporin, penicillin, or tetracycline the last 14 days – Serious liver or kidney disease that contraindicates use of doxycyline – Lactose intolerance – Need to use medications contraindicated according to SmPC of the IMP
Sample Size:	120 patients
Efficacy Assessments:	Comparison of clinical outcome six months after end of treatment between the two treatment groups.
Safety Assessments:	Subjective experiences and blood tests including hematology and biochemistry for four weeks after ended treatment.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or special term	Explanation
AE	Adverse Event
AR	Adverse Reactions
Bb	Borrelia burgdorferi
CIOMS	Council for International Organizations of Medical Sciences
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form (electronic/paper)
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Event
CTU	Clinical Trial Unit
DAE	Discontinuation due to Adverse Event
DMC	Disease Monitoring Commitee
EC	Ethics Committee
FSS	Fatigue Severity Scale
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product (includes active comparator and placebo)
ISF	Investigator's Study File
ITT	Intention to treat
LNB	Lyme Neuroborreliosis
MRI	Magnetic Resonance Imaging
NMA	Norwegian Medical Agency
NTNU	Norwegian University of Science and Technology
OUS	Oslo Universitetssykehus
PHQ-15	Patient Health Questionnaire
PNS	Peripheral Nervous System
SAE	Serious Adverse Event
SDV	Source document verification
SF-36	Short Form 36
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SSHF	Sørlandet Sykehus HF
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
WP	Work Package

1 INTRODUCTION

1.1 Background – Lyme Neuroborreliosis (LNB)

Lyme borreliosis is a multisystem infectious disease, caused by the tick-borne spirochete *Borrelia burgdorferi (Bb)*, which frequently affects the nervous system. The most common clinical manifestations of European Lyme Neuroborreliosis (LNB) are painful radiculitis and cranial neuropathy (most often the facial nerve). Rarer manifestations are myelitis, encephalitis, and peripheral neuropathies. The diagnosis of LNB is based on a combination of clinical neurological findings, lymphocytic pleocytosis and intrathecal *Bb* antibody production (1).

Most patients recover well within weeks to a few months after standard antibiotic treatment, but 25-50% of LNB patients report residual complaints often labelled post-Lyme syndrome (2-9). The most common remaining complaints are subjective symptoms as fatigue, pain, concentration and memory problems. Remaining objective findings as facial palsy and radiculopathy are rarer.

The impact and prevalence of post-Lyme syndrome are debated, as similar symptoms are common in the general population. It is also questioned if the complaints are more common after LNB than after other infections in the nervous system. There are few controlled studies on the issue, but one previous study found more fatigue and lower mean scores on health related quality of life among 50 well-characterized LNB patients 30 months after treatment for LNB than among 50 matched healthy controls (3).

The underlying mechanism of post-Lyme syndrome is also debated and largely unresolved. Theories as ongoing chronic *Bb* infection (10), dysregulated immune responses (11, 12), genetic predisposition (13), co-infection with multiple tick-borne pathogens (14), structural changes in the Central Nervous System (CNS) (15), and personal traits (16, 17), have been suggested.

In the current trial, we will address the persistent infection hypothesis by assessing long-term prognosis after extended antibiotic treatment. Further, the trial is a part of the compound and large BorrSci study (Lyme borreliosis; a scientific approach to reduce diagnostic and therapeutic uncertainties) which also aims to address the other hypotheses mentioned above. These approaches are further described in the protocols for the other workpackages (WP) of BorrSci (Appendix A). The blood and cerebrospinal fluid (CSF) specimens along with comprehensive clinical information collected from the patients included in the current treatment trial is an important contribution to the biobank that will be established for these purposes.

1.2 Background - Therapeutic Information

Standard treatment for Lyme Neuroborreliosis (LNB) is intravenous ceftriaxone or penicillin, or oral doxycycline for two to four weeks (1). Previous studies have shown that two weeks of oral doxycycline and intravenous ceftriaxone are equally effective for LNB with painful radiculitis or cranial neuritis (5, 18). However, evidence about the optimal duration of treatment is currently lacking. There are a few studies of prolonged antibiotic treatment in LNB, but they are hampered with poorly-characterized patients, insufficient statistical power, lack of matched controls, and ambiguous results (19-23). A case series reported excellent or good response in 90% of patients with disseminated Lyme (including some with neuroborreliosis) after treatment with oral cefixime or IV ceftriaxone for 14 days followed by oral amoxicillin for 100 days (24). A controlled study of 152 patients with disseminated Lyme disease (including 62 with neuroborreliosis) (20), however, found similar outcome in patients treated with 3 weeks with IV ceftriaxone followed by oral amoxicillin for 100 days and patients treated with 3 weeks IV ceftriaxone followed by placebo for 100 days. An American openlabel randomized comparison of 14-days versus 28-days treatment with ceftriaxone for late Lyme borreliosis (143 patients, of whom a third with neurological symptoms), showed more treatment failures in the 14-day group than in the 28-day group, but did not have the power to determine if a clinical subset of patients may benefit from 28 days of therapy. There were more discontinuations because of adverse events in the 28- days group (25). Another series of late LNB showed disappearance of symptoms in 87% after 100 days regimens with various antibiotics, whereas 14 days with ceftriaxone cured 31% (26).

The possibility that a longer treatment with doxycycline, such as six weeks, is superior to the current standard treatment of two weeks in LNB has not been properly addressed in a randomized controlled trial.

1.3 Pre-Clinical & Clinical Experience with Investigational Medicinal Product (IMP)

Doxycycline is a well-known drug with a good safety profile used for several infectious diseases worldwide.

1.4 Rationale for the Study and Purpose

The main purpose of the trial is to answer the “is two weeks doxycycline treatment (currently suggested treatment) at least as effective as six weeks doxycycline treatment in LNB?” The benefits of a positive answer to this question would

be a reduced frequency of persisting complaints after treatment. The benefits of a negative answer would be avoidance of unnecessarily prolonged treatment with antibiotics and thereby reduced antibiotic resistance.
Doxycycline 200 mg daily for 2 weeks is recommended for LNB, and half of the study patients will receive this standard treatment (and additional four weeks of placebo). The other half will receive doxycycline 200 mg daily for six weeks. Possible disadvantages for the trial participants are more adverse advents as nausea and diarrhea, disturbances in leukocyte and thrombocyte count, and skin reactions (mostly photosensitivity). Longer antibiotic treatment may also lead to higher prevalence of resistant bacteria in patients and the general society. We regard these possible disadvantages as minor as the patients' subjective experiences and blood cell count will be closely monitored during the study, and both groups of patients will be discouraged sunbathing during treatment and up to two weeks after drug intake. In our opinion, the benefit of determination of preferred duration of treatment for the future eliminates the disadvantage of exposing. Besides this, several spin off effects strengthens the rationale for conducting the study. The collected clinical data and specimens (blood and CSF) from well-characterized LNB patients may enable us to address other hypotheses regarding long-term complaints as immune dysregulation, genetic predisposition, co-infections and structural changes in CNS, and it facilitates search for new biomarkers of LNB which could be used in diagnostics.

2 STUDY OBJECTIVES AND RELATED ENDPOINTS

	Objectives	Endpoints	Assessments
Primary	To answer the question "is two weeks doxycycline treatment (currently suggested treatment) at least as effective as six weeks doxycycline treatment in LNB?"	– Primary endpoint: Improvement of clinical score six months after ended treatment – Secondary endpoints: Fatigue, subjective somatic symptoms, health related quality of life, cognitive function, safety, inflammation.	- Composite clinical score. See section: 2.1 - FSS, PHQ-15, SF-36, adverse events inflammatory parameters in CSF. See section 2.2
Secondary	1. To provide a better understanding of the pathogenesis of LNB and long-term complaints 2. To search for new biomarkers in LNB	– Antibody and inflammatory profiles – Genomic profiles – Brain MRI – Neuropsychological profiles	Described in WP4 of BorrSci. See appendix A
Exploratory	To collect clinical data, blood, and CSF from well-characterized LNB patients in a biobank	– Further search for biomarkers, co-infections and other factors involved in LNB	Described in WP3 of BorrSci. See appendix A

Table 1. Summary of objectives, endpoints, and assessments

2.1 Primary Endpoint

The primary endpoint is improvement on a composite clinical score (Table 2) from inclusion to six months after ended treatment defined as clinical score at inclusion minus clinical score at six months.

Subjective symptoms	
Subjective symptoms related* by the patient to the current/recent LNB	Score
Malaise (sykdomsfølelse, redusert almentilstand)	
Fatigue (trøtthet, utmattelse)	
Headache (hodepine)	
Neck and/or back pain (nakke og/eller ryggsmerte)	
Abdominal and/or breast pain (smerter i bryst og/eller mageregion)	
Arm pain (smerter i armer)	
Leg pain (smerter i ben)	
Generalized pain located to joints and/or muscles (smerter i "hele kroppen" (ledd og muskler))	
Memory and/or concentration problems (hukommelse og/eller konsentrasjonsproblemer)	
Other (annet)	
Objective findings, PNS	
Findings related* to the current/recent LNB	Score
Facial palsy (facialisparese)	
Paresis of eye muscles (øyemuskelparese)	
Reduced hearing (redusert hørsel)	
Other cranial neuropathies (andre hjernenerveutfall)	
Cervical radicular sensory findings[a] (cervikale radikulære sensoriske funn)	
Cervical radicular paresis[b] (cervikal radikulær parese)	
Thoracal radicular sensory findings[a] (thoracale radikulære sensoriske funn)	
Lumbal radicular sensory findings[a] (lumbale radikulære sensoriske funn)	
Lumbal radicular paresis[b] (lumbal radikulær parese)	
Non-radicular sensory findings[c] (ikke-radikulære sensoriske funn)	
Non-radicular paresis[d] (ikke-radikulær nevropati med pareser)	
Other (annet)	
Objective findings, CNS	
Findings related* to the current/recent LNB	Score
Central findings[e] in one extremity (sentralnervøse funn i en ekstremitet)	
Central findings[e] in a hemi pattern (sentralnervøse funn i en kroppshalvdel)	
Central findings[e] in both legs (sentralnervøse funn i begge ben)	
Central findings[e] in all extremities (sentralnervøse funn i alle ekstremiteter)	
Gait ataxia (gangataksi, ustøhet)	
Dysphasi/aphasi (talevansker)	
Nystagmus (nystagmus)	
Involuntary movements including tremor (ufrivillige bevegelser inkl. skjelving)	
Cognitive impairment (kognitiv svikt/forvirring)	
Other (annet)	
Total score	

Table 2. Composite clinical score.

Each item is scored 0=none, 1=mild, without influence on daily life, or 2=severe, with influence on daily life.

Maximum total score=64 (sum of subjective symptoms and objective findings)

** Temporally and otherwise related to current LNB*

[a] Abnormal sensory findings in a radicular pattern

[b] Paresis in a radicular pattern

[c] Abnormal sensory findings in a non- radicular pattern (matching with peripheral nerve or plexus)

[d] Paresis in a non- radicular pattern (matching with peripheral nerve or plexus)

[e] Central weakness and/or spasticity (central paresis, spasticity and/or impairment in pace or fine motor skills)

2.2 Secondary Endpoints

Improvement of composite clinical score from inclusion to 12 months after end of treatment defined as clinical score at inclusion minus clinical score at 12 months. (Table1)

Fatigue Severity Scale (FSS) at six and 12 months after end of treatment. FSS is translated and validated for Norwegian purposes (12). It measures level of agreement (1– 7) with nine statements. The final score represents the mean value of the nine items. Severe fatigue is defined as a score >5 in a Norwegian population. Reported mean score in 20 American

healthy adults is 2.3 (13), and reported mean score in 50 Norwegian patients treated for LNB is 3.5 versus 2.1 in the control group (3).

Patient Health Questionnaire (PHQ-15) at six months**.** PHQ-15 is a brief, validated questionnaire, which consists of 13 questions concerning severity of different subjective somatic symptoms the last 4 weeks, and 2 questions concerning sleep and tiredness. Each item is scored from 0 to 2, and sum score ranges from 0 to 30. Sum scores of 5, 10, and 15 represent cutpoints for low, medium, and high symptom severity, respectively (27).

Short Form-36 (SF-36): SF-36 is a valid and reliable questionnaire assessing health related quality of life. It consists of 36 questions concerning general health perceptions, physical functioning, physical role functioning, emotional role functioning, social role functioning, bodily pain, vitality and mental health. A Norwegian normal material exist (28).

CSF findings at six and 12 months: Cell count, IgG index, OCB's, and *Bb* antibodies

Other laboratory tests, MRI, and neuropsychological assessments: In a subset of patients at inclusion and six months after end of treatment (WP4 of BorrSci).

Safety as measured by serious adverse events and less serious side effects of treatment (Table 3)

Table 3. Safety measures

Treatmentweek	0	1	2	3	4	5	6	7-10
Nausea		x	x	x	x	x	x	x
Vomiting		x	x	x	x	x	x	x
Diarrhea		x	x	x	x	x	x	x
Skin reactions		x	x	x	x	x	x	x
Vaginitis		x	x	x	x	x	x	x
Blodtests (Hb, Hb, white blood cell count with differential, platelet count, ASAT, ALAT, GT, ALP, Creatinine)	x		x		x			
Other AE or complications		x	x	x	x	x	x	x

Secondary and exploratory objectives and their endpoints and assessments are detailed in WP 3 and 4 (Appendix A)

3 OVERALL STUDY DESIGN

The study is a phase Phase III, randomized, penta-blind, placebo-controlled, multicenter trial with a non-inferiority design. The trial will be conducted and reported according to the CONSORT statement (Consolidated Standards of Reporting Trials), the SPIRIT initiative (Standard Protocol Items: Recommendations for Interventional Trials), and Good Clinical Practice (GCP) standards, and registered in ClinicalTrials.gov

Study Period	Estimated date of first patient enrolled: 01.10.15 (startup at Sørlandet Hospital 2015, recruitment from other centres gradually during 2016) Anticipated recruitment period: 01.10.15 - 31.12.19 Estimated date of last patient completed: 31.12.20
Treatment Duration:	Six weeks
Follow-up:	13 months

4 STUDY POPULATION

4.1 Selection of Study Population

The study will be headed from Sørlandet Hospital HF (SSHF). Selected hospitals throughout Norway (5-10) will recruit consecutive patients diagnosed with LNB. A contact person, familiar with diagnosis and treatment of LNB, at each study site will be trained in the current study and in general GCP.

4.2 Number of Patients

We plan to enroll 120 patients, 60 in each treatment arm.

4.3 Inclusion Criteria

In everyday clinical practice, patients with suspected LNB are routinely examined neurologically and their CSF is analyzed regarding cell count, protein level, IgG index, oligoclonal bands (OCB's) and *Bb* antibodies (including

calculations whether there are intrathecal production of *Bb* antibodies). Diagnostics may be somewhat uncertain in subacute cases as antibiotic treatment is often initiated before *Bb* antibody results are available, and *Bb* antibody production may be absent in early phases of LNB. In this trial, we will therefore use the following inclusion criteria:

1. **Neurological symptoms suggestive of LNB without other obvious reasons, and one or both of**
    a. **CSF pleocytosis (leucocytes ≥5/mm^3)**
    b. **Intrathecal *Bb* antibodyproduction**
2. **Signed informed consent**

During the course of the disease, the patients will be classified as either definite or possible LNB according to European diagnostic criteria (Table 4) (1).

Table 4. European diagnostic criteria

[a]If criterion 3 is lacking after a duration of six weeks, there have to be found Bb-specific antibodies in serum.

Definite LNB All three criteria fulfilled	Possible LNB[a] Two criteria fulfilled
1. Neurological symptoms suggestive of LNB without other obvious reasons 2. Cerebrospinal fluid pleocytosis 3. Intrathecal *Bb* antibody production	

4.4 Exclusion Criteria

Patients will be excluded from the study if they meet any of the following criteria:

- **Age less than 18 years**
- **Pregnancy, breast-feeding and/or women of childbearing potential not using adequate contraception. Adequate contraception include oral, injected or implanted hormonal methods of contraception, placement of an intrauterine device or system, vasectomized partner, or sexual abstinence imposed during treatment.**
- **Adverse reaction to tetracyclines**
- **Treatment with cephalosporin, penicillin, or tetracycline macrolide during the last 14 days before start of doxycycline treatment ***
- **Serious liver or kidney disease that contraindicates use of doxycyline**
- **Lactose intolerance**
- **Need to use medications contraindicated according to SmPC of the IMP (Antacid drugs, Didanosin, Probenecide, Phenobarbital, Phenytoin, Carbamazepine, Rifamphicin)**

*If used for other conditions than LNB, or if the active LNB has been treated with antibiotic drugs or dosage deviating from the protocol

5 TREATMENT

For this study, doxycycline and placebo are defined as Investigational Medicinal Product (IMP).

Included patients will be randomized to two weeks treatment with oral doxycycline (200 mg once daily) followed by four weeks placebo or six weeks treatment with oral doxycycline (200 mg once daily).

5.1 Drug Identity, Supply and Storage

IMPs (active drug and placebo) will be produced at Kragerø Tablettproduksjon. Production documentation is described in a separate document (Appendix B). All included patients will receive active drug (doxycyline) for 14 days, thereafter half of them will receive placebo and the other half will receive active drug (doxycyline) for four weeks.

5.2 Dosage and Drug Administration

Both active drug and placebo will be admistered per os as capsules every 24 hours. IMPs should be taken together with abundant water and a small meal. Iron tablets, calcium preparations youghurt, milk and food/ beverages that contain calcium may weaken the effect of doxycycline, and should not be taken less than three hours before or after intake of IMP.

5.3 Duration of Therapy

The patients will be treated for six weeks unless disease progression (see section 8.3) or unacceptable toxicity.

5.4 Concomitant Medication

The following medications are not allowed while the patient is in the treatment phase of the study:

- Antacid drugs (single use)
- Didanosin (single use)
- Probenecide (chronic use)
- Phenobarbital (chronic use)
- Phenytoin (chronic use)
- Carbamazepine (chronic use)
- Rifamphicin (chronic use)

All concomitant medication (incl. vitamins, herbal preparation and other "over-the-counter" drugs) used by the patient will be recorded in the patient's file and CRF.

5.5 Subject Compliance

Pillcount and patients compliance diary will be used to determine adherence to treatment.

5.6 Drug Accountability

The responsible site personnel will confirm receipt of study drug and will use the study drug only within the framework of this clinical study and in accordance with this protocol. Distribution and return of the study drug will be documented in the drug accountability log and in the CRFs.

If patients are included in the study after already having started doxyxycline 200 mg per day, the responsible site personnel will ensure that the appropriate amount of capsules, depending on the number of days already treated, are removed from the study drug packaging before distribution to the patients. The amount of study drug delievered to the patients will be documented in the CRF.

5.7 Drug Labeling

The IMPs will have a label permanently affixed to the outside and will be labeled according with GCP and national regulations (29, 30), stating that the material is for clinical trial/investigational use only and should be kept out of reach of children.The labeling will be prepared by Kragerø Tablettproduksjon. All text will be in Norwegian. Labeling details are described in separate document attatched (Appendix C).

Labels will also include blank lines for:

- Patient's initials
- Patient's enrolment code
- Date dispensed
- Name of prescribing doctor

5.8 Subject Numbering

Each subject is identified in the study by a unique subject number that is assigned when the subject is entered into the eCRF for the first time, after signing the Informed Consent Form. Once assigned the subject number cannot be reused for any other subject. The study treatment will be dispensed to the subject by authorized site personnel only.

6 STUDY PROCEDURES

6.1 Flow Chart

	Baseline	**Treatment and post-treatment Period Week 1-10**				**Follow-up Period**	
Time	**Before treatment**	**Once weekly**	**Week 2 - 4**	**Day 6-8 after start of treatment**	**End of week 10**	**6 months after end of treatment**	**12 months after end of treatment**
Enrollment and Infprmed consent	x						
Basic demographics	x						
Medical History	x						
Concomitant medications	x					x	x

	Baseline	Treatment and post-treatment Period Week 1-10				Follow-up Period	
Time	**Before treatment**	**Once weekly**	**Week 2 - 4**	**Day 6-8 after start of treatment**	**End of week 10**	**6 months after end of treatment**	**12 months after end of treatment**
Telephone to check for reasons to discontinue IMP (treatment failure, toxicity, and so on)				x			
Composite clinical score (Table 2)	x				x	x	x
FSS	x				x	x	x
PHQ-15						x	x
SF-36						x	
CSF sampling	X**					x	x
Blood sampling	X**					x	x
IMP delivery	x						
Patientregistration of compliance, concomitant medication, and adverse events (Table 3)		x					
Bloodtests to check toxicity of treatment	x		xx				
Pill count and collection of patients diaries					x		
Cerebral MRI*			x			x	
Neuropsychological screening tests*			x				
Neuropsychological testing*						x	

Table 5. Trial flow chart
**a subset of patients (WP4)*
*** obtained by clinican before inclusion*

6.2 By Visit

Clinical data will be collected in a clinical research e-database at Department of clinical research support at Oslo University Hospital (OUS).

Informed consent

Informed consent must have been given voluntarily by each subject before any study specific procedures are initiated.

6.2.1 Screening Visit

- Evaluate patient eligibility based on symptoms, findings and CSF findings
- Demographic data: Age, sex, education, occupational status, civil status
- Medical history: Comorbidity, medication, tick bite (ever and last six months), Erythema Migrans (ever and last six months), earlier treatment for Lyme borreliosis
- Clinical picture: Symptom description, symptom duration
- Physical examination: General clinical and neurological examination including composite clinical score
- Concomitant medication: All concomitant medication (incl. vitamins, herbal preparation and other "over-the-counter" drugs) used by the subject within 28 days of treatment start will be recorded in the CRF.
- Laboratory analysis from samples obtained before inclusion
    - Blood: Hb, white blood cell count with differential, platelet count, ASAT, ALAT, GT, ALP, Creatinine, CRP, electrophoresis, *Bb* antibodies, TBE antibodies. Pregnancy test should have been taken within the last 14 days before inclusion in fertile women.
    - CSF: Cellcount, protein level, Oligoclonal bands, *Bb* antibodies, PCR for Herpes Simplex Virus (HSV), Varicella Zoster Virus (VZV) and Enterovirus
- In addition aliquots of specimens will be transferred for biobank storage after inclusion

- FSS

6.2.2 During Treatment

- Adverse events: Diary (on paper or electronic - optional) every week until four weeks after ended treatment
- Registration of concomitant medications
- Blood analyses 2 and 4 weeks after treatment start (Hb, white blood cell count with differential, platelet count, ASAT, ALAT, GT, ALP, Creatinine)
- Talk (meeting or telephone, optional) 1 week after treatment start to uncover reasons for discontinuation of IMP (deterioration, progression or other - see 6.3)
- Non-scheduled visit in case of disease progression SAE or SUSAR
- Cerebral MRI and neuropsychological screening in a subset of patients (see APPENDIX A)

6.2.3 End of Treatment Visit (four weeks after ended treatment)

- Counting and relinquishment of remaining pills
- Collection of patients diary
- Registration of symptoms, concomitant medication, and adverse events
- Composite clinical score
- FSS

6.2.4 Withdrawal Visit (desirable but voluntary)

- Interview about medical history, symptom description, concomitant medication, reason for withdrawal, and adverse events
- Composite clinical score

6.2.5 Six months After End of Treatment (Follow-up)

- Interview about symptom description, concomitant medication, and sick leave attributable to LNB
- Composite clinical score
- FSS, PHQ-15, SF-36
- Laboratory analyses
    - Blood: Hb, white blood cell count with differential, platelet count, ASAT, ALAT, GT, ALP, Creatinine, CRP, electrophoresis, *Bb* antibodies, TBE antibodies
    - CSF: Cellcount, protein level, Oligoclonal bands, Bb antibodies,
    - In addition aliquots of specimens will be transferred for biobank storage
- Cerebral MRI and neuropsychological testing in a subset of patients (Appendix A)

6.2.6 Twelve months After End of Treatment (Follow-up)

- Interview about symptom description, concomitant medication, and sick leave attributable to LNB
- Composite clinical score
- FSS, PHQ-15
- Laboratory analyses
    - Blood: Hb, white blood cell count with differential, platelet count, ASAT, ALAT, GT, ALP, Creatinine, CRP, electrophoresis, Bb antibodies, TBE antibodies
    - CSF: Cellcount, protein level, Oligoclonal bands, Bb antibodies,
    - In addition aliquots of specimens will be transferred for biobank storage

6.3 Criteria for Patient Discontinuation

Patients may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a patient for this study are:

- Voluntary discontinuation by the patient who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment.
- Safety reason as judged by the coordinating investigators
- Major protocol deviation

- Incorrect enrolment ie, the patient does not meet the required inclusion/exclusion criteria for the study
- Patient lost to follow-up
- A female patient becoming pregnant during treatment
- Disease progression
- Deterioration in the patient's condition which in the opinion of the coordinatingl investigators warrants study medication discontinuation (to be recorded as an AE or under Investigator Discretion)
- Patient's non-compliance to study treatment and/or procedures

6.4 Procedures for Discontinuation

6.4.1 Patient Discontinuation

Patients who withdraw or are withdrawn from the study, will either stop further treatment or receive another antibiotic therapy. If possible, a final assessment shall be made (withdrawal visit and/or follow-up visits). The reason for discontinuation will be recorded, and the investigator will follow up any significant adverse events until the outcome is either recovered or resolved. Patients who withdraw or are withdrawn from the study before start of treatment, will be replaced.

6.4.2 Trial Discontinuation

The whole trial may be discontinued in the event of any of the following:

- Occurrence of AEs unknown to date in respect of their nature, severity and duration
- Medical or ethical reasons affecting the continued performance of the trial
- Difficulties in the recruitment of patients

The coordinating investigators will inform all investigators, the relevant Competent Authorities and Ethics Committees of the termination of the trial along with the reasons for such action. If the study is terminated early on grounds of safety, the Competent Authorities and Ethics Committees will be informed within 15 days.

6.5 Laboratory Tests

Blood and CSF samples will be analyzed at the local laboratories for registration of side effects of treatment and for diagnostic purposes according to existing routines. In addition, aliquots of specimens will be transferred for biobank storage and applied for genetic and immunologic purposes. Details regarding collection, handling, storage, packaging, shipment and destruction will be described in WP3 and WP4 in BorrSci (Appendix A).

7 ASSESSMENTS

7.1 Assessment of Efficacy

The treatment efficacy will be assessed by measuring symptoms and signs six months after ended treatment and summarized on a composite clinical score which reports subjective symptoms and objective findings in a clinical neurological examination. . The primary endpoint is improvement in the composite clinical score. The score is a modified version of a score used in an earlier treatment trial in LNB (5). Even if the score is not validated it is, in our opinion, the best way to assess outcome after LNB as it addresses and grades the most commonly reported remaining symptoms and signs. Our experience with the previous score was that it worked well, but some points were not entirely clear or somewhat overlapping. We therefore find it appropriate and more accurate to simplify it to reduce interrater disagreement and scala biases.

To support treatment effect assessment we have chosen several secondary endpoints; inflammatory findings in CSF as measured by cellcount, protein level and oligoclonal bands, fatigue as measured by FSS, burden of somatic symptoms as measured by PHQ-15, and health related quality of life as measured by SF-36. We will also apply proportion of patients with full recovery (score zero on the composite clinical score) as a secondary endpoint. In a subset of patients, MRI findings and neuropsychological profile will be a secondary endpoint.

7.2 Safety and Tolerability Assessments

Significant findings that are present prior to the signing of informed consent will be included in the relevant medical history/ current medical condition page of the CRF. For the assessment of safety and tolerability, refer to Flow chart in Section 6 and Table 3.

8 SAFETY MONITORING AND REPORTING

The site invetigators and the coordinating investigators are responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE). Each patient will be instructed to contact the site investigator immediately should they manifest any signs or symptoms they perceive as serious.

8.1 Definitions

8.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. The term AE is used to include both serious and non-serious AEs. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

8.1.2 Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

Medical and scientific judgment is to be exercised in deciding on the seriousness of a case. Important medical events may not be immediately life threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the listed outcomes in the definitions above. In such situations, or in doubtful cases, the case should be considered as serious. Hospitalization for administrative reason (for observation or social reasons) is allowed at the investigator's discretion, and will not qualify as serious unless there is an associated adverse event warranting hospitalization.

8.1.1 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Adverse Reaction: all untoward and unintended responses to an investigational medicinal product related to any dose administered.

Unexpected Adverse Reaction: an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

Suspected Unexpected Serious Adverse Reaction: SAE (see section 8.1.2) that is unexpected as defined in section 8.2 and possibly related to the IMP.

8.2 Expected Adverse Events

Nausea, vomiting, diarrhea, vaginitis, skin reactions, disturbancies in bloodtests are all expected AE. The manufactorers SmPC will be used as reference document. All AE will be recorded in the CRF.

8.3 Disease Progression

Disease progression in this trial is defined as worsening of the patient's condition attributable to LNB despite treatment for 14 days with doxycycline, or serious progression of neurological signs from CNS (myelitis or encephalitis) during treatment. Events that are definitely due to disease progression will not be reported as an AE/SAE unless the investigator considers there is a causal relationship between treatment with IMP or protocol design/procedures and the disease progression/recurrence. Death due to progressive disease is to be recorded on a specific from in the CRF but not as an SAE.

8.4 Time Period for Reporting AE and SAE

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

During the course of the study all AEs and SAEs will be proactively followed up for each patient; events should be followed up to resolution, unless the event is considered by the investigator to be unlikely to resolve due to the underlying

disease. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

8.5 Recording of Adverse Events

If the patient has experienced adverse event(s), the investigator will record the following information in the CRF:

- The nature of the event(s) will be described by the investigator in precise standard medical terminology (i.e. not necessarily the exact words used by the patient).
- The duration of the event will be described in terms of event onset date and event ended data.
- The intensity of the adverse event: Mild/Moderate/Severe according to Common Terminology Criteria for Adverse Events version 4.0 (CTCAE).
- The Causal relationship of the event to the study medication will be assessed as one of the following:

  Unrelated:

  There is not a temporal relationship to investigational product administration (too early, or late, or investigational product not taken), or there is a reasonable causal relationship between non-investigational product, concurrent disease, or circumstance and the AE.

  Unlikely:

  There is a temporal relationship to investigational product administration, but there is not a reasonable causal relationship between the investigational product and the AE.

  Possible:

  There is reasonable causal relationship between the investigational product and the AE. Dechallenge information is lacking or unclear.

  Probable:

  There is a reasonable causal relationship between the investigational product and the AE. The event responds to dechallenge. Rechallenge is not required.

  Definite:

  There is a reasonable causal relationship between the investigational product and the AE.
- Action taken
- The outcome of the adverse event – whether the event is resolved or still ongoing.

8.6 Reporting Procedure

8.6.1 AEs and SAEs

All adverse events and serious adverse events that should be reported as defined in section 8.1.1 will be recorded in the patient's CRF.

SAEs must be reported by the site investigator to the sponsor represented by the coordinating investigators within 24 hours after the site has gained knowledge of the SAE. Every SAE must be documented by the investigator on the SAE pages (to be found as part of the CRF). The Serious Adverse Event Report Form must be completed and signed. The initial report shall promptly be followed by detailed, written reports if necessary. The initial and follow-up reports shall identify the trial subjects by unique code numbers assigned to the latter.

The coordinating investigators keep detailed records of all SAEs reported and perform an evaluation with respect to seriousness, causality and expectedness.

8.6.2 SUSARs

SUSARs will be reportd to the Competent Authority according to national regulation. The following timelines should be followed:

On suspicion of SUSAR the site investigator report to the sponsor represented by the coordinating investigators. If the coordinating investigators consider the event as a SUSAR they report it to the Department of clinical research support. Personell at the department of clinical research support, not otherwise involved in the trial, will unblind the treatment and ensure that all relevant information about SUSARs that are fatal or life-threatening is recorded and reported unblinded as soon as possible to the Competent Authority, no later than seven days after knowledge of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

All other SUSARs will be reported to the Competent Authority concerned and to the Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge.

SUSARs will be reported using the CIOMS form.

8.6.3 Annual Safety Report

Once a year throughout the clinical trial, the sponsor will provide the Competent Authority with an annual safety report. The format will comply with national requirements.

8.6.4 Clinical Study Report

The adverse events and serious adverse events occurring during the study will be discussed in the safety evaluation part of the Clinical Study Report.

8.7 Procedures in Case of Emergency

The site investigators are responsible for assuring that there are procedures and expertise available to cope with emergencies during the study. Code break may be relevant in case of toxicity and other events were knowledge of treatmentarm matters for further management of the patient. Envelopes with randomization codes are available in such cases.

9 DATA MANAGEMENT AND MONITORING

9.1 Case Report Forms (CRFs)

The designated investigator staff will enter the data required by the protocol into an electronic Case Report Form (CRF). The site investigators are responsible for assuring that data entered into the CRF is complete, accurate, and that entry is performed in a timely manner. The signature of the investigator will attest the accuracy of the data on each CRF. If any assessments are omitted, the reason for such omissions will be noted on the CRFs. Corrections, with the reason for the corrections will also be recorded.

9.2 Source Data

The medical records for each patient should contain information which is important for the patient's safety and continued care, and to fulfill the requirement that critical study data should be verifiable.

To achieve this, the medical records of each patient should clearly describe:

- That the patient is participating in the study, e.g. by including the enrollment number and the study code or other study identification;
- Date when Informed Consent was obtained from the patient and statement that patient received a copy of the signed and dated Informed Consent;
- Results of all assessments confirming a patient's eligibility for the study;
- Diseases (past and current; both the disease studied and others, as relevant);
- Treatments withdrawn/withheld due to participation in the study;
- Results of assessments performed during the study;
- Treatments given, changes in treatments during the study and the time points for the changes;
- Visits to the clinic / telephone contacts during the study, including those for study purposes only;
- Non-Serious Adverse Events and Serious Adverse Events (if any) including causality assessments;
- Date of, and reason for, discontinuation from study treatment;
- Date of, and reason for, withdrawal from study;
- Date of death and cause of death, if available;
- Additional information according to local regulations and practice.

9.3 Study Monitoring

We plan a strategic monitoring with focus on the most critical data, such as primary endpoint data and key safety data, including adverse events and a higher source document verification (SDV) coverage on the first one or two subjects enrolled at each site in order to establish an early data quality "yardstick" for each site. A risk-based monitoring plan will be made.

Monitors, and/or competent authorities will be allowed access to source data for SDV in which case a review of those parts of the hospital records relevant to the study may be required.

9.4 Confidentiality

The investigator shall arrange for the secure retention of the patient identification and the code list. Patient files shall be kept for the maximum period of time permitted by each hospital. The study documentation (CRFs, Site File etc) shall be retained and stored during the study and for 15 years after study closure. All information concerning the study will be stored in a safe place inaccessible to unauthorized personnel.

9.5 Database management

The Department of clinical research support, OUS, will perform data management in accordance with ICH guidelines, CRS SOPs, and described in the trial specific Data Handling Plan. The plan will describe the processes and documentation related to data capture and data quality control. The data will be captured in an electronic CRF (eCRF). The eCRF will ensure security (to prevent unauthorized access to, or loss of data) and storage during trial. After database lock, the trial will be archived by sponsor and removed from the eCRF.

10 STATISTICAL METHODS AND DATA ANALYSIS

10.1 Determination of Sample Size ** Manuela?

In a previous trial on well-characterized LNB patients, 102 patients were treated with either oral doxycyline or IV cephtriaxone for two weeks. From this trial we have available outcome scores at 12 months from 93 patients, measured on a slightly different composite clinical scale, but with the same max score of 64. We consider the scales as so similar that the results from the former trial can be used in power analyses in the current planned trial. The mean score in the former trial was 1.7 with a standard deviation (SD) of 2.6.

10.2 Randomization

10.2.1 Allocation- sequence generation

Computerized allocation to two or six weeks doxycycline (1:1) will be performed at Department of clinical research support, OUS by an internet based solution. Automatic e-mails with the result of the randomization will be sent to the involved hospitals.

10.2.2 Blinding and emergency unblinding

To achieve maximum objective performance and reporting of the study we will use the "penta blind" approach. First, we use the traditional double blind design with blinding of participants and investigators (first and second blinding). The staff evaluating end-points and adverse effects is blinded to all other study information (third blinding). Then the content of all tables and figures are fixed before any study data are available (fourth blinding) and then the statistical procedures are performed with treatment groups marked as group A and B. First, when all the tables and figures are filled out, the randomization code is broken. Unblinding for the investigator will be done when all patients have completed the six month visit (primary and several secondary end-points answered), and for the patients after the 12 month registration.
Emergency unblinding is permissible as described in section 8.7. Unblindingprocedure in case of SUSAR is described in section 8.6.2.

10.3 Population for Analysis

The following populations will be considered for the analyses:

- Intention to treat (ITT) population: All randomized participant, regardless of protocol adherence.
- Per-protocol population (PP): Includes all without significant protocol deviation
- Safety population: Includes all subjects who have received at least one dose of study medication. Subjects who withdraw from the study will be included in the safety analysis. A list of withdrawn subjects, preferably with the reasons for withdrawal, will be made.

10.4 Planned analyses

The main statistical analysis is planned when all patients have completed the six months visit. Deviation from the original statistical plan will be described and justified in the Clinical Study Report. Amendments to plan can be done until day of database lock.

10.5 Statistical Analysis **Manuela?

Results will be reported as mean scores with standard deviation or proportions as appropriate.

To compare the two groups on the primary outcome, we will use a general linear model with treatment group was factor and adjust for duration of symptoms, gender and age. The analysis will be conducted according to the intention to treat principle.
For other analysis, comparison between groups will be done with e.g. independent samples t-test, nonparametric Mann-Whitney-U test or Pearsons chi-square test for crosstabs as appropritate.
P-values <0.05 are considered statistically significant.

11 STUDY MANAGEMENT

11.1 Investigator Delegation Procedure

The coordinating investigators are responsible for making and updating a "delegation of tasks" listing all the involved co-workers and their role in the project. They will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

11.2 Protocol Adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations.
All significant protocol deviations will be recorded and reported in the Clinical Study Report (CSR).

11.3 Study Amendments

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol (Amended Protocol) must be notified to and approved by the Competent Authority and the Ethics Committee according national regulations.

11.4 Audit and Inspections

Authorized representatives of a Competent Authority and Ethics Committee may visit the centre to perform inspections, including source data verification. Likewise the representatives from sponsor may visit the center to perform an audit. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, and any applicable regulatory requirements. The principal investigators will ensure that the inspectors and auditors will be provided with access to source data/documents.

12 ETHICAL AND REGULATORY REQUIREMENTS

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and applicable regulatory requirements. Registration of patient data will be carried out in accordance with national personal data laws.

12.1 Ethics Committee Approval

The study protocol, including the patient information and informed consent form to be used, must be approved by the regional ethics committee before enrolment of any patients into the study.
The investigator is responsible for informing the ethics committee of any serious and unexpected adverse events and/or major amendments to the protocol as per national requirements.

12.2 Other Regulatory Approvals

The protocol will be submitted and approved by the applicable competent authorities before commencement of the study. The protocol will also be registered in www.clinicaltrials.gov before inclusion of the first patient.

12.3 Informed Consent Procedure

The investigator is responsible for giving the patients full and adequate verbal and written information about the nature, purpose, possible risk and benefit of the study. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician.
It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever she/he wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered in the study. This will be done in

accordance with the national and local regulatory requirements. The investigator is responsible for obtaining signed informed consent.

A copy of the patient information and consent will be given to the patients. The signed and dated patient consent forms will be filed in the Investigator Site File binder and also scanned to be part of the patient's electronic medical record at the hospital.

12.4 Subject Identification

The investigator is responsible for keeping a list of all patients (who have received study treatment or undergone any study specific procedure) including patient's date of birth and personal number, full names and last known addresses.

The patients will be identified in the CRFs by patient number, initials and date of birth.

13 TRIAL SPONSORSHIP AND FINANCING

The study is sponsored by HELSEFORSK funds from the Research Counsil of Norway administered by Sørlandet Hospital HF. The funds are assigned the composite project BorrSci.

14 TRIAL INSURANCE

The coordinating investigators will obtain insurance coverage through membership of the Drug Liability Association.

15 PUBLICATION POLICY

Upon study completion, the results of this study will be submitted for publication. The results of this study will also be submitted to the Competent Authority and the Ethics Committee according to national regulations. All personnel who have contributed significantly with the planning and performance of the study (Vancouver convention 1988) may be included in the list of authors.

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17 LIST OF APPENDICES

A Protocoll for work packages 3, 4, and 5 in BorrSci
B Chemical and pharmacological documentation of IMPs
C Details of labeling of IMPs
D Informed consent