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Six versus two weeks treatment with doxycycline in Lyme Neuroborreliosis: a multicenter, non-inferiority, pentablinde and randomized controlled trial.

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Keywords:	Infectious disease/HIV < NEUROLOGY, Adult neurology < NEUROLOGY, INFECTIOUS DISEASES

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Title:

Six versus two weeks treatment with doxycycline in Lyme Neuroborreliosis: a multicenter, non-inferiority, penta-blinded and randomized controlled trial.

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UL and ÅM have contributed equally to the manuscript and should be listed as last author.

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Keywords

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Abstract

Introduction

Current treatment guidelines for European Lyme neuroborreliosis (LNB) recommend cephalosporins, penicillin or doxycycline for 14 to 28 days but evidence for optimal treatment length is poor. Treatment lengths in clinical practice tend to exceed the recommendations. Most patients experience a rapid improvement of symptoms and neurological findings within days of treatment, but some report long-term complaints. The underlying mechanisms of remaining complaints are debated, and theories as ongoing chronic infection with *Borrelia burgdorferi*, dysregulated immune responses, genetic predisposition, co-infection with multiple tick-borne pathogens, structural changes in CNS, and personal traits have been suggested.

The main purpose of our trial is to address the hypothesis of persistent infection as cause of remaining symptoms, by comparing efficacy of treatment with two and six weeks courses of doxycycline in LNB

Methods and analysis

The trial has a multi-center, non-inferiority, penta-blinded design. One hundred and twenty patients diagnosed with LNB according to EFNS guidelines will be randomized to six or two weeks treatment with oral doxycycline. The patients will be followed for 12 months. The primary endpoint is improvement on a composite clinical score (CCS) from baseline to 6 months after inclusion. Secondary endpoints are improvements in the CCS 12 months after inclusion, fatigue scored on FSS, subjective symptoms on the PHQ-15 scale, health related quality of life scored on RAND 36- Item Short Form Health Survey, and safety as measured by side effects of the two treatment arms. Blood and CSF are collected from inclusion and through-out the follow-up and a biobank will be established. The study started including patients in November 2015 and will continue throughout December 2019.

Strengths and limitations of this study

Strengths:

- Penta-blinded design
- Inclusion criteria for LNB according to EFNS guidelines
- Well-defined endpoints
- Long follow-up

Weaknesses

- The composite clinical score is not validated

Ethics and dissemination

The study is approved by the Norwegian regional committees for medical and health research ethics (REC) and the Norwegian Medicines Agency (SLV).

Funding

This work is supported by the Norwegian Multiregional Health Authorities through the BorrSci project (Lyme borreliosis; a scientific approach to reduce diagnostic and therapeutic uncertainties, project 2015113), letter dated April 17th 2015 with case reference 14/01152-4.

Trial registration number

EudraCT number 2015-001481-5. The trial is registered on Clinicaltrials.org.

Introduction

European Lyme neuroborreliosis (LNB) is caused by the tick-borne spirochete *Borrelia burgdorferi* (*Bb*). LNB can manifest weeks or months after a tick bite that only half of the patients remember. The most common clinical manifestations are subacute painful radiculitis and cranial neuropathy (most often the facial nerve). More rare manifestations are myelitis, encephalitis, and peripheral neuropathies.

Patients diagnosed with LNB should be treated with antibiotics as early as possible to relieve symptoms and prevent sequelae (1-3). Most patients experience a rapid improvement within days of treatment, but some report long-term complaints (4). The most common long-term complaints are fatigue, pain, concentration and memory problems. Some patients may also have neurological sequela such as sensory disturbances, unsteadiness/vertigo, facial paresis and other paresis (5). The underlying mechanisms of remaining complaints are debated. Theories suggested are ongoing chronic *Bb* infection, dysregulated immune responses, genetic predisposition, co-infection with multiple tick-borne pathogens, structural changes in CNS, and personal traits.

Standard treatment for LNB is intravenous ceftriaxone or penicillin, or oral doxycycline for two to four weeks (6). Previous studies have shown that two weeks of oral doxycycline and intravenous ceftriaxone are equally effective for LNB with painful radiculitis or cranial neuritis and probably also for LNB with symptoms from the central nervous system (myelitis and encephalitis) (7-9). Arguments for choosing oral doxycycline are that it is inexpensive and convenient and effective against co-infections with other tick-borne agents (10, 11).

We lack evidence about the optimal duration of antibiotic treatment. Most guidelines recommend treatment for 14 to 28 days. (6, 12, 13) In Norway, the site for the current study, the guidelines recommend 14 days of treatment. A recent Cochrane review of six randomized treatment studies of adult patients with acute LNB reported improvement in the majority of patients after the initial course of antibiotics and no consistent evidence of treatment failure or need of retreatment (14). In another systematic review, the authors conclude that there is insufficient evidence to determine if extended antibiotic treatment is beneficial to outcome (15). Despite this, and perhaps because of

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uncertainties surrounding LNB, there are varying treatment regimes in clinical practice, generally with more extensive treatment strategies than recommended in current guidelines. A recent study of the treatment practice of 253 Norwegian LNB patients showed that adherence to guidelines was poor and that two-thirds of the patients received more than two weeks of antibiotic treatment (16). In a time with increasing knowledge and awareness of microbial resistance and other complications of long-term antibiotic treatment these findings seem like a paradox. The present study therefore seeks to increase the evidence of the current treatment advice by evaluating if treatment with 14 days of doxycycline is as effective as a longer course of treatment or if a longer course may improve the course and long-term prognosis of LNB. By doing this the hypothesis of persistent infection will also be addressed.

Method

Study design and interventions

The study is a randomized, penta-blinded, placebo-controlled, multicenter trial with a non-inferiority design. We plan to recruit 120 patients diagnosed with definite or probable LNB according to EFNS guidelines (6) at six different hospitals in the southern part of Norway as shown in figure 1. The study is coordinated from Sørlandet hospital in Kristiansand, Agder County by neurologists connected to the large BorrSci study (Lyme borreliosis; a scientific approach to reduce diagnostic and therapeutic uncertainties). The inclusion and exclusion criteria are shown in Table 1. Inclusion started in 2015 and will continue through December 2019 or until the necessary sample size is obtained. Eligibility before inclusion is assessed by, or discussed with, a physician connected to the study and accustomed to evaluating patients with neurological symptoms. The patients are randomized into two treatment arms: A) doxycycline 200 mg daily for 2 weeks, followed by four weeks of placebo; B) doxycycline 200 mg daily for six weeks (Figure 2).

Table 1: Inclusion and exclusion criteria

INCLUSION CRITERIA	
1	Neurological symptoms suggestive of LNB without other obvious reasons, and one or both of
	A) CSF pleocytosis (leucocytes $\geq 5/\text{mm}^3$)
	B) Intrathecal <i>Bb</i> antibodyproduction
2	Signed informed consent
EXCLUSION CRITERIA	
1	Age less than 18 years
2	Treatment with cephalosporin, penicillin, or tetracycline macrolide during the last 14 days before start of doxycycline treatment
3	Pregnancy, breast-feeding and/or women of childbearing potential not using adequate contraception.
4	Adverse reaction to tetracyclines
5	Serious liver or kidney disease that contraindicates use of doxycycline
6	Lactose intolerance
7	Need to use medications contraindicated according to SmPC of the IMP (Antacid drugs, Didanosin, Probenecide, Phenobarbital, Phenytoin, Carbamazepine, Rifampicin)

Allocation and blinding

Computerized allocation is performed at Department of clinical research support, Oslo University Hospital, by an internet-based solution. Maximum objective performance and reporting of the study is achieved by applying a “penta-blinded” approach. The first and second blinding is the traditional double blind design with blinding of participants and investigators. Thirdly, the staff evaluating endpoints and adverse effects is blinded to all other study information. Further, the content of all tables and figures will be fixed before any study data are available. Lastly, the statistical procedures will be performed with the two treatment arms marked as group A and B. Revealing the study arms for the investigators will not take place until all patients have completed the six-month visit, and for the patients after the 12 month visit.

Monitoring and data collection

The study is monitored independently according to Good Clinical Practice (GCP) by the Department of clinical research. The coordinating investigators at Sørlandet hospital and investigators at cooperating centers are certified according to GCP. The investigators will enter the data required by protocol into an electronic Case Report Form (Viedoc), also designed by the Department of clinical research. The same protocol for data management and monitoring is applied to all collected data.

Outcome measures

A composite clinical score (CCS) based on subjective symptoms and objective neurological findings from the peripheral and central nervous system (Table 2) is registered at baseline, 10 weeks, 6 months, and 12 months. Each of the 62 items of the CCS is scored 0=none, 1=mild (without influence on daily life), or 2=severe (with influence on daily life). Maximum total score is 64. The primary endpoint of the study is the difference in CCS sum score at baseline and six months after inclusion. Secondary endpoints are the difference in CCS at baseline and 12 months after inclusion, fatigue scored according to the questionnaire FSS (Fatigue Severity Scale) at six and 12 months, subjective somatic symptoms scores according to the questionnaire PHQ-15 (Patient Health Questionnaire) at six and 12 months and health related quality of life according to RAND 36 item short form health survey at six months, and side effects of the treatment.

FSS measures level of agreement (1-7) with nine statements with the final score representing the mean value of nine items. Scores >5 are regarded as severe fatigue. The FSS has been translated into Norwegian, validated in the general Norwegian population, and normative Norwegian data are available (17).

PHQ-15 charts prevalence and intensity of 13 somatic symptoms; fatigue/lack of energy, and difficulty sleeping during the last 4 weeks. Sum score ranges from 0-28 for men and from 0-30 for women (only women are asked about menstrual symptoms). The following cut-off values for sum score have been stated for load of somatic symptom, 0-4 points: normal, 5-9 points: mild, 10-14 points: moderate, 15-30 points: severe. The PHQ-15 has been validated in several studies and languages, and normative Swedish data are available (18).

RAND 36 item short form health survey consists of 36 questions about different aspects of health-related quality of life. The answer to each question is transformed into a score ranging from 0 to 100, where a higher score indicates better health. The questionnaire is validated in Norwegian, and Norwegian normative data are available (19).

Systemic and CSF inflammation will be assessed with lumbar punctures and blood samples at six and 12 months after treatment. There will be established a biobank from this material. Figure 3 depicts a flow chart of the study procedures.

Table 2: Composite clinical score

Subjective symptoms related by the patient to the current LNB

Malaise
 Fatigue
 Headache
 Neck and/or back pain
 Abdominal and/or breast pain
 Arm pain
 Leg pain
 Generalized pain located to joints and/or muscles
 Memory and/or concentration problems
 Other

Peripheral findings related to the current LNB

Facial palsy
 Paresis of the eye muscles
 Reduced hearing
 Other cranial neuropathies
 Cervical radicular sensory findings*
 Cervical radicular paresis**
 Thoracic radicular sensory findings*
 Lumbar radicular sensory findings*
 Lumbar radicular paresis**
 Non-radicular sensory findings***
 Non-radicular paresis****
 Other

Central findings related to the current LNB

Central findings in one extremity#
 Central findings in a hemi pattern
 Central findings in both legs
 Central findings in all extremities
 Gait ataxia
 Dysphasia/aphasia
 Nystagmus
 Involuntary movement including tremor
 Cognitive impairment
 Other

*Abnormal sensory pattern in a radicular pattern. **Paresis in a radicular pattern. ***Sensory findings matching with a peripheral nerve or plexus. ****Paresis matching a peripheral nerve or plexus #Central weakness and/or spasticity, impairment in pace or fine motor skills.

Safety

The patients are followed closely during and after treatment to monitor safety. They are contacted by phone one week after start of treatment and questioned about symptom severity and possible side effects. Blood sampling in regard to side effects takes place at two and four weeks after start of treatment. The patients are also asked to fill out a patient diary on symptoms and possible side effects once a week for 10 weeks. .

In cases of disease progression the patients will be evaluated by a physician and adequate intervention initiated. Disease progression is, in this trial, defined as worsening of the patient's condition attributed to LNB, despite treatment for 14 days with doxycycline, or serious progression of neurological signs from CNS during treatment.

Sample size

We used data from our previous treatment trial on 102 LNB patients treated with either oral doxycycline or IV cephtriaxone for two weeks and scored with an almost similar clinical scale as the CCS in the power analyses (7).

From a clinical point of view, a mean group difference of $\Delta=0.5$ in disfavor of two weeks treatment compared to six weeks treatment was regarded as an appropriate non-inferiority margin. This non-inferiority margin corresponds to a Cohen's d effect size of $\Delta/\sigma = 0.5/1.0 = 0.5$, which is a small and clinical acceptable effect size. With a one-sided test and significance level of 0.05, 50 patients in each treatment group was found to be needed to claim non-inferiority with a non-inferiority margin on mean group difference of 0.5 and a SD of 1.0 with 80% power. To compensate for up to 20% dropouts and non-evaluable patients 120 (i.e. 60 in each group) patients will be enrolled.

Statistical analysis

The main statistical analysis is planned when all patients have completed the six months visit. Results will be reported as mean scores with standard deviation or proportions as appropriate.

To compare the primary outcome in the two groups we will use a general linear model with treatment group as factor, and adjustment for clinical presentation and baseline score. 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 Pearson's chi-square test for crosstabs as appropriate.

P-values <0.05 will be considered statistically significant.

Ethics and dissemination

The Norwegian regional committees for medical and health research ethics (REC) and the Norwegian Medicines Agency (SLV) have approved the study. EudraCT number 2015-001481-5. The trial is registered on Clinicaltrials.org.

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.

Each patient in the trial is submitted to extensive follow-up as previously described in terms of disease, effect of treatment and side effects to outweigh potential harms. The benefits are considered to outweigh the cons of this trial in the long term, with a potentially more evidence-based treatment of LNB and less extensive use of antibiotics.

Patient and Public involvement

Representatives from the Norwegian patient organization for Lyme borreliosis (Norsk Lyme Borreliose Forening, NLBF) were invited and participated in the early stages of planning of the BorrSci project's design and gave feedback on the drafts of the application for funding. They were also invited to continue work with the project. Inclusion to the study, implications of the intervention and

time required to participate is discussed with each individual patient. Local newspapers and other media have been involved in making the project known to the public in different parts of Norway.

Authors' contributions

AMS contributed in drafting this manuscript, has participated in revisions of the original protocol, includes patients to the study and coordinates the study at Sørlandet hospital and at the other centers of recruitment. UL and ÅM drafted the original protocol, worked on applications for funding, contributed in drafting this manuscript and include patients to the study.

Statement of competing interests

The authors have no competing interests to declare.

Figure 1: Map of Norway with the active centers of recruitment per August 2018 marked in red.

Figure 2: Inclusion procedures

Figure 3: Flow chart of the study procedures

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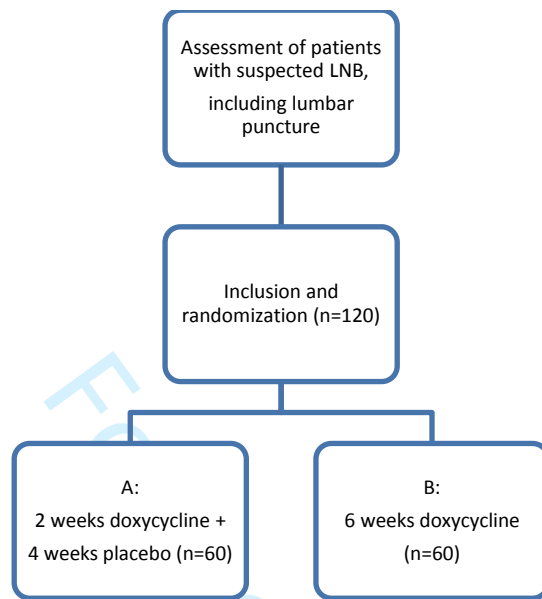
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Figure 1: Map of Norway with the active centers of recruitment per August 2018 marked in red.

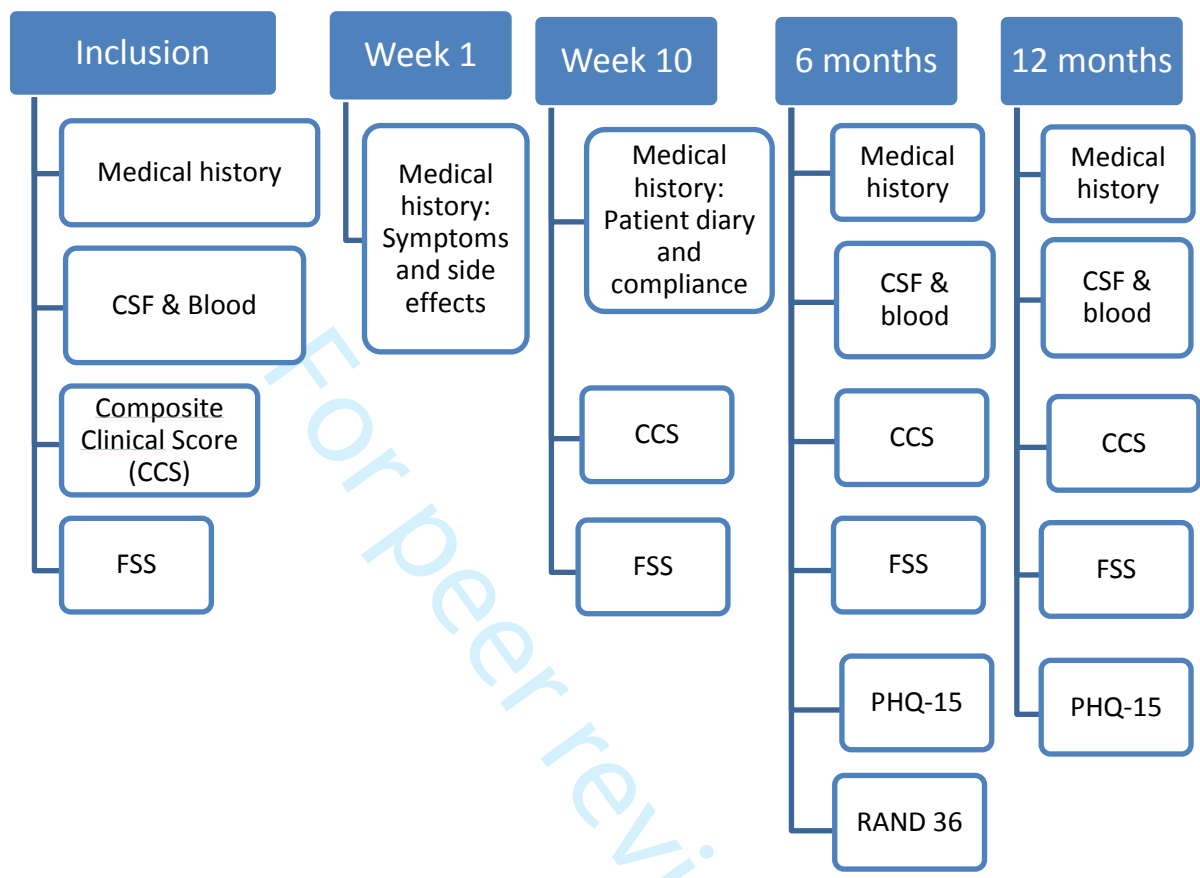
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Figure 2: Inclusion procedures



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Figure 3: Flow chart of the study procedures



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Six versus two weeks treatment with doxycycline in Lyme Neuroborreliosis: the protocol of a multicenter, non-inferiority, double-blinded and randomized controlled trial.

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8 4 Anne Marit Solheim^{1,2}, Unn Ljøstad^{1,2}, Åse Mygland^{1,2}

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14 7 UL and ÅM have contributed equally to the manuscript and should be listed as last author.
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Abstract

Introduction

Current treatment guidelines for European Lyme neuroborreliosis (LNB) recommend cephalosporins, penicillin or doxycycline for 14 to 28 days but evidence for optimal treatment length is poor.

Treatment lengths in clinical practice tend to exceed the recommendations. Most patients experience a rapid improvement of symptoms and neurological findings within days of treatment, but some report long-term complaints. The underlying mechanisms of remaining complaints are debated, and theories as ongoing chronic infection with *Borrelia burgdorferi*, dysregulated immune responses, genetic predisposition, co-infection with multiple tick-borne pathogens, structural changes in CNS, and personal traits have been suggested.

The main purpose of our trial is to address the hypothesis of improved outcome after long-term antibiotic treatment of LNB, by comparing efficacy of treatment with two and six weeks courses of doxycycline

Methods and analysis

The trial has a multi-center, non-inferiority, double-blinded design. One hundred and twenty patients diagnosed with LNB according to EFNS guidelines will be randomized to six or two weeks treatment with oral doxycycline. The patients will be followed for 12 months. The primary endpoint is improvement on a composite clinical score (CCS) from baseline to 6 months after inclusion.

Secondary endpoints are improvements in the CCS 12 months after inclusion, fatigue scored on FSS, subjective symptoms on the PHQ-15 scale, health related quality of life scored on RAND 36- Item Short Form Health Survey, and safety as measured by side effects of the two treatment arms. Blood and CSF are collected from inclusion and through-out the follow-up and a biobank will be established. The study started including patients in November 2015 and will continue throughout December 2019.

Ethics and dissemination

The study is approved by the Norwegian regional committees for medical and health research ethics (REC) and the Norwegian Medicines Agency (SLV).

Strengths and limitations of this study

The strengths of the trial are

- The double-blinded design
- Inclusion criteria for LNB according to the EFNS guidelines
- Well-defined endpoints
- Long period of follow-up of the included patients with registered symptoms, signs and potential side effects.

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5 67 - The primary scoring tool, the composite clinical score, is not validated.
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9 69 **Funding**

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11 70 This work is supported by the Norwegian Multiregional Health Authorities through the BorrSci
12 71 project (Lyme borreliosis; a scientific approach to reduce diagnostic and therapeutic uncertainties,
13 72 project 2015113), letter dated April 17th 2015 with case reference 14/01152-4.
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17 74 **Trial registration number**

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19 75 EudraCT number 2015-001481-25. The trial is registered on Clinicaltrials.org.
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23 77 **Introduction**

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25 78 European Lyme neuroborreliosis (LNB) is caused by the tick-borne spirochete *Borrelia burgdorferi*
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28 80 The most common clinical manifestations are subacute painful radiculitis and cranial neuropathy
29 81 (most often the facial nerve). More rare manifestations are myelitis, encephalitis, and peripheral
30 82 neuropathies.

31
32 83 Patients diagnosed with LNB should be treated with antibiotics as early as possible to relieve
33 84 symptoms and prevent sequelae (1-3). Most patients experience a rapid improvement within days of
34 85 treatment, but some report long-term complaints (4). The most common long-term complaints are
35 86 fatigue, pain, concentration and memory problems. Some patients may also have neurological
36 87 sequela such as sensory disturbances, unsteadiness/vertigo, facial paresis and other paresis (5). The
37 88 underlying mechanisms of remaining complaints are debated. Theories suggested are ongoing
38 89 chronic *Bb* infection, dysregulated immune responses, genetic predisposition, co-infection with
39 90 multiple tick-borne pathogens, structural changes in CNS, and personal traits.

40
41 91 Standard treatment for LNB is intravenous ceftriaxone or penicillin, or oral doxycycline for two to
42 92 four weeks (6). Previous studies have shown that two weeks of oral doxycycline and intravenous
43 93 ceftriaxone are equally effective for LNB with painful radiculitis or cranial neuritis and probably also
44 94 for LNB with symptoms from the central nervous system (myelitis and encephalitis) (7-9). Arguments
45 95 for choosing oral doxycycline are that it is inexpensive and convenient, is found to penetrate the
46 96 blood-brain-barrier and give adequate concentrations in the CSF and is effective against co-
47 97 infections with other tick-borne agents (10, 11).

48
49 98 We lack evidence about the optimal duration of antibiotic treatment. Most guidelines recommend
50 99 treatment for 14 to 28 days. (6, 12, 13) In Norway, the site for the current study, the guidelines
51 100 recommend 14 days of treatment. A recent Cochrane review of six randomized treatment studies of
52 101 adult patients with acute LNB reported improvement in the majority of patients after the initial
53 102 course of antibiotics and no consistent evidence of treatment failure or need of retreatment (14). In

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3 103 another systematic review, the authors conclude that there is insufficient evidence to determine if
4 104 extended antibiotic treatment is beneficial to outcome (15). Despite this, and perhaps because of
5 105 uncertainties surrounding LNB, there are varying treatment regimes in clinical practice, generally
6 106 with more extensive treatment strategies than recommended in current guidelines. A recent study of
7 107 the treatment practice of 253 Norwegian LNB patients showed that adherence to guidelines was
8 108 poor and that two-thirds of the patients received more than two weeks of antibiotic treatment (16).
9 109 In a time with increasing knowledge and awareness of microbial resistance and other complications
10 110 of long-term antibiotic treatment these findings seem like a paradox. The present study therefore
11 111 seeks to increase the evidence of the current treatment advice by evaluating if treatment with
12 112 doxycycline in 14 days is inferior or not to treatment for six weeks with respect to long-term
13 113 prognosis of LNB.
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115 **Method**

116 **Study design and interventions**

117 The study is a randomized, double-blinded, placebo-controlled, multicenter trial with a non-
118 inferiority design. We plan to recruit 120 patients diagnosed with definite or probable LNB according
119 to EFNS guidelines (6) at six different hospitals in the southern part of Norway as shown in figure 1.
120 The study is coordinated from Sørlandet hospital in Kristiansand, Agder County by neurologists
121 connected to the large BorrSci study (Lyme borreliosis; a scientific approach to reduce diagnostic and
122 therapeutic uncertainties). The inclusion and exclusion criteria are shown in Table 1. Inclusion started
123 in 2015 and will continue through December 2019 or until the necessary sample size is obtained.
124 Eligibility before inclusion is assessed by, or discussed with, a physician connected to the study and
125 accustomed to evaluating patients with neurological symptoms. The patients are randomized into
126 two treatment arms: A) doxycycline 200 mg daily for 2 weeks, followed by four weeks of placebo; B)
127 doxycycline 200 mg daily for six weeks (Figure 2).
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141 **Table 1: Inclusion and exclusion criteria**

INCLUSION CRITERIA

- 1 Neurological symptoms suggestive of LNB without other obvious reasons, and one or both of
 - A) CSF pleocytosis (leucocytes $\geq 5/mm^3$)
 - B) Intrathecal *Bb* antibodyproduction
- 2 Signed informed consent

EXCLUSION CRITERIA

- 1 Age less than 18 years
- 2 Treatment with cephalosporin, penicillin, or tetracycline macrolide during the last 14 days before start of doxycycline treatment
- 3 Pregnancy, breast-feeding and/or women of childbearing potential not using adequate contraception.
- 4 Adverse reaction to tetracyclines
- 5 Serious liver or kidney disease that contraindicates use of doxycycline
- 6 Lactose intolerance
- 7 Need to use medications contraindicated according to SmPC of the IMP (Antacid drugs, Didanosin, Probenecide, Phenobarbital, Phenytoin, Carbamazepine, Rifampicin)

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143

144 **Allocation and blinding**

145 Computerized allocation (stratified according to hospital) is performed at Department of clinical
 146 research support, Oslo University Hospital, by an internet-based solution . Maximum objective
 147 performance and reporting of the study is achieved by applying a “penta-blinded” approach. The first
 148 and second blinding is the traditional double blind design with blinding of participants and
 149 investigators. Thirdly, the staff evaluating endpoints and adverse effects is blinded to all other study
 150 information. Further, the content of all tables and figures will be fixed before any study data are
 151 available. Lastly, the statistical procedures will be performed with the two treatment arms marked as
 152 group A and B. Revealing the study arms for the investigators will not take place until all patients
 153 have completed the six-month visit, and for the patients after the 12 month visit.

154

155 **Monitoring and data collection**

156
 157 The study is monitored independently according to Good Clinical Practice (GCP) by the Department
 158 of clinical research. The coordinating investigators at Sørlandet hospital and investigators at
 159 cooperating centers are certified according to GCP. The investigators will enter the data required by
 160 protocol into an electronic Case Report Form (Viedoc), also designed by the Department of clinical
 161 research. The same protocol for data management and monitoring is applied to all collected data.

162

163 Outcome measures

164 A composite clinical score (CCS) based on subjective symptoms and objective neurological findings
 165 from the peripheral and central nervous system (Table 2) is registered at baseline, 10 weeks, 6
 166 months, and 12 months. Each of the 32 items of the CCS is scored 0=none, 1=mild (without influence
 167 on daily life), or 2=severe (with influence on daily life). Maximum total score is 64. The primary
 168 endpoint of the study is the difference in CCS sum score at baseline and six months after inclusion.

169 Secondary endpoints are the difference in CCS at baseline and 12 months after inclusion, fatigue
 170 scored according to the questionnaire FSS (Fatigue Severity Scale) at six and 12 months, subjective
 171 somatic symptoms scores according to the questionnaire PHQ-15 (Patient Health Questionnaire) at
 172 six and 12 months and health related quality of life according to RAND 36 item short form health
 173 survey at six months, and side effects of the treatment.

174 FSS measures level of agreement (1-7) with nine statements with the final score representing the
 175 mean value of nine items. Scores >5 are regarded as severe fatigue. The FSS has been translated into
 176 Norwegian, validated in the general Norwegian population, and normative Norwegian data are
 177 available (17).

178 PHQ-15 charts prevalence and intensity of 13 somatic symptoms; fatigue/lack of energy, and
 179 difficulty sleeping during the last 4 weeks. Sum score ranges from 0-28 for men and from 0-30 for
 180 women (only women are asked about menstrual symptoms). The following cut-off values for sum
 181 score have been stated for load of somatic symptom, 0-4 points: normal, 5-9 points: mild, 10-14
 182 points: moderate, 15-30 points: severe. The PHQ-15 has been validated in several studies and
 183 languages, and normative Swedish data are available (18).

184 RAND 36 item short form health survey consists of 36 questions about different aspects of health-
 185 related quality of life. The answer to each question is transformed into a score ranging from 0 to 100,
 186 where a higher score indicates better health. The questionnaire is validated in Norwegian, and
 187 Norwegian normative data are available (19).

188 The patient reported outcome measures (PROM) were included as secondary endpoints to evaluate
 189 the potential impact of residual symptoms on patients' daily life.

190

191 Systemic and CSF inflammation will be assessed with lumbar punctures and blood samples at six and
 192 12 months after treatment. There will be established a biobank from this material. Figure 3 depicts a
 193 flow chart of the study procedures.

194

195

196 Table 2: Composite clinical score

197

198

Subjective symptoms related by the patient to the current LNB

Malaise

Fatigue

Headache

Neck and/or back pain

Abdominal and/or breast pain

Arm pain

Leg pain

Generalized pain located to joints and/or muscles

1
2
3 Memory and/or concentration problems

4 Other

7 **Peripheral findings related to the current LNB**

8 Facial palsy

9 Paresis of the eye muscles

10 Reduced hearing

11 Other cranial neuropathies

12 Cervical radicular sensory findings*

13 Cervical radicular paresis**

14 Thoracic radicular sensory findings*

15 Lumbar radicular sensory findings*

16 Lumbar radicular paresis**

17 Non-radicular sensory findings***

18 Non-radicular paresis****

19 Other

24 **Central findings related to the current LNB**

25 Central findings in one extremity#

26 Central findings in a hemi pattern

27 Central findings in both legs

28 Central findings in all extremities

29 Gait ataxia

30 Dysphasia/aphasia

31 Nystagmus

32 Involuntary movement including tremor

33 Cognitive impairment

34 Other

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40 199

41 200

42 201 *Abnormal sensory pattern in a radicular pattern. **Paresis in a radicular pattern. ***Sensory

43 202 findings matching with a peripheral nerve or plexus. ****Paresis matching a peripheral nerve or

44 203 plexus #Central weakness and/or spasticity, impairment in pace or fine motor skills.

45 204

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48 **205 Safety**

49 206

50 207 The patients are followed closely during and after treatment to monitor safety. They are contacted

51 208 by phone one week after start of treatment and questioned about symptom severity and possible

52 209 side effects. Blood sampling with a status of hematology, liver and kidney function to monitor

53 210 potential side effects takes place at two and four weeks after start of treatment. The patients are

54 211 also asked to fill out a patient diary on symptoms and possible side effects once a week for 10 weeks.

55 212 .

56 213

57 214 In cases of disease progression the patients will be evaluated by a physician and adequate

58 215 intervention initiated. Disease progression is, in this trial, defined as worsening of the patient's

216 condition attributed to LNB, despite treatment for 14 days with doxycycline, or serious progression
217 of neurological signs from CNS during treatment.

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222 **Sample size**

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224 We used data including the SD from our previous treatment trial on 102 LNB patients treated with
225 either oral doxycycline or IV cephtriaxone for two weeks and scored with an almost similar clinical
226 scale as the CCS in the power analyses (7).

227 From a clinical point of view, a mean group difference of $\Delta=0.5$ in disfavor of two weeks treatment
228 compared to six weeks treatment was regarded as an appropriate non-inferiority margin. This non-
229 inferiority margin corresponds to a Cohen's d effect size of $\Delta/\sigma = 0.5/1.0 = 0.5$, which is a small and
230 clinical acceptable effect size. With a one-sided test and significance level of 0.05, 50 patients in each
231 treatment group was found to be needed to claim non-inferiority with a non-inferiority margin on
232 mean group difference of 0.5 and a SD of 1.0 with 80% power. To compensate for up to 20%
233 dropouts and non-evaluable patients 120 (i.e. 60 in each group) patients will be enrolled.

234

235 **Statistical analysis**

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237 The main statistical analysis is planned when all patients have completed the six months visit. Results
238 will be reported as mean scores with standard deviation or proportions as appropriate.

239 To compare the primary outcome in the two groups we will use a general linear model with
240 treatment group as a factor, and adjustment for duration of symptoms, gender and age. The analysis
241 will be conducted according to the intention to treat principle.

242 For other analysis, comparison between groups will be done with e.g. independent samples t-test,
243 nonparametric Mann-Whitney-U test or Pearson's chi-square test for crosstabs as appropriate.

244 Results from the FSS and PHQ-15 questionnaires will be dichotomized according to predefined
245 cutoffs recommended for case definition and statistically treated as categorical outcomes.

246 P-values <0.05 will be considered statistically significant.

247

248 **Ethics and dissemination**

249 The Norwegian regional committees for medical and health research ethics (REC) and the Norwegian
250 Medicines Agency (SLV) have approved the study. EudraCT number 2015-001481-5. The trial is
251 registered on Clinicaltrials.org.

252 The study will be conducted in accordance with ethical principles that have their origin in the
253 Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and applicable regulatory
254 requirements.

255 Each patient in the trial is submitted to extensive follow-up as previously described in terms of
256 disease, effect of treatment and side effects to outweigh potential harms. The benefits are
257 considered to outweigh the cons of this trial in the long term, with a potentially more evidence-
258 based treatment of LNB and less extensive use of antibiotics.

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260 **Patient and Public involvement**

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4 262 Representatives from the Norwegian patient organization for Lyme borreliosis (Norsk Lyme
5 263 Borreliose Forening, NLBF) were invited and participated in the early stages of planning of the BorrSci
6 264 project's design and gave feedback on the drafts of the application for funding. They were also
7 265 invited to continue work with the project. Inclusion to the study, implications of the intervention and
8 266 time required to participate is discussed with each individual patient. Local newspapers and other
9 267 media have been involved in making the project known to the public in different parts of Norway.

12 268

14 269 **Authors' contributions**

15 270

17 271 AMS contributed in drafting this manuscript, has participated in revisions of the original protocol,
18 272 includes patients to the study and coordinates the study at Sørlandet hospital and at the other
19 273 centers of recruitment. UL and ÅM drafted the original protocol, worked on applications for funding,
20 274 contributed in drafting this manuscript and include patients to the study.

22 275

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24 277 **Statement of competing interests**

25 278

27 279 The authors have no competing interests to declare.

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31 282 **Figure 1: Map of Norway with the active centers of recruitment per August 2018 marked in red.**

32 283 **Figure 2: Inclusion procedures**

33 284 **Figure 3: Flow chart of the study procedures**

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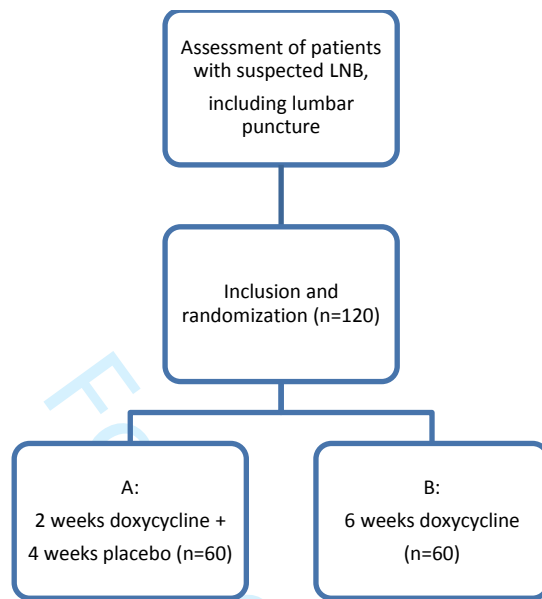


Figure 1: Map of Norway with the active centers of recruitment per August 2018 marked in red.

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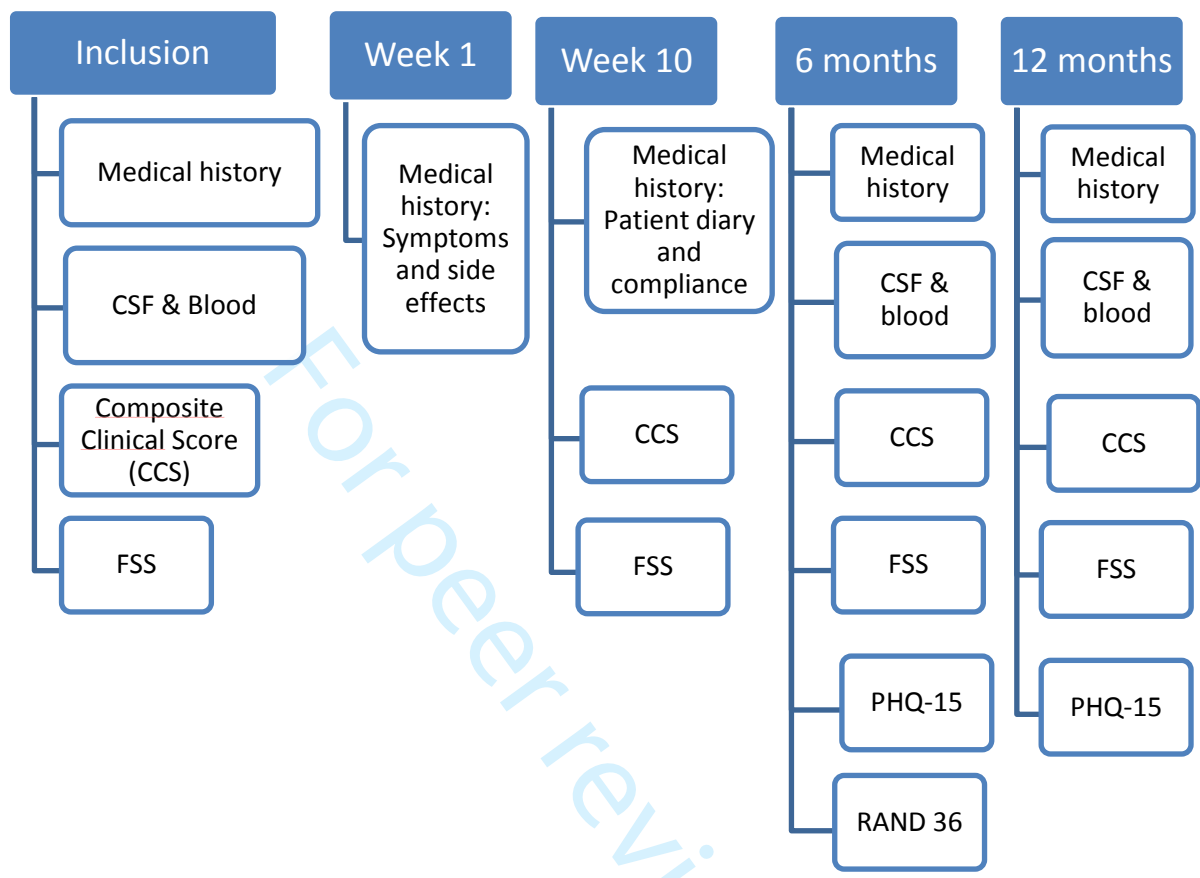
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Figure 2: Inclusion procedures



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Figure 3: Flow chart of the study procedures



BMJ Open

Six versus two weeks treatment with doxycycline in Lyme Neuroborreliosis: the protocol of a multicenter, non-inferiority, double-blinded and randomized controlled trial.

Journal:	<i>BMJ Open</i>
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Keywords:	Infectious disease/HIV < NEUROLOGY, Adult neurology < NEUROLOGY, INFECTIOUS DISEASES

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3 1 **Title:**
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5 2 **Six versus two weeks treatment with doxycycline in Lyme Neuroborreliosis: the protocol of a**
6 3 **multicenter, non-inferiority, double-blinded and randomized controlled trial.**
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8 4 Anne Marit Solheim^{1,2}, Unn Ljøstad^{1,2}, Åse Mygland^{1,2}
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25 12
26 13 **Keywords**

27 14 Neurology

28 15 Infectious diseases

29 16 Lyme Neuroborreliosis
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18 **Word count** 2704 words

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Abstract

Introduction

Current treatment guidelines for European Lyme neuroborreliosis (LNB) recommend cephalosporins, penicillin or doxycycline for 14 to 28 days but evidence for optimal treatment length is poor.

Treatment lengths in clinical practice tend to exceed the recommendations. Most patients experience a rapid improvement of symptoms and neurological findings within days of treatment, but some report long-term complaints. The underlying mechanisms of remaining complaints are debated, and theories as ongoing chronic infection with *Borrelia burgdorferi*, dysregulated immune responses, genetic predisposition, co-infection with multiple tick-borne pathogens, structural changes in CNS, and personal traits have been suggested.

The main purpose of our trial is to address the hypothesis of improved outcome after long-term antibiotic treatment of LNB, by comparing efficacy of treatment with two and six weeks courses of doxycycline

Methods and analysis

The trial has a multi-center, non-inferiority, double-blinded design. One hundred and twenty patients diagnosed with LNB according to EFNS guidelines will be randomized to six or two weeks treatment with oral doxycycline. The patients will be followed for 12 months. The primary endpoint is improvement on a composite clinical score (CCS) from baseline to 6 months after inclusion.

Secondary endpoints are improvements in the CCS 12 months after inclusion, fatigue scored on FSS, subjective symptoms on the PHQ-15 scale, health related quality of life scored on RAND 36- Item Short Form Health Survey, and safety as measured by side effects of the two treatment arms. Blood and CSF are collected from inclusion and through-out the follow-up and a biobank will be established. The study started including patients in November 2015 and will continue throughout December 2019.

Ethics and dissemination

The study is approved by the Norwegian regional committees for medical and health research ethics (REC) and the Norwegian Medicines Agency (SLV). Data from the study will be published in peer-reviewed medical journals.

Strengths and limitations of this study

- The trial has a double-blinded design
- The inclusion criteria for LNB are according to the EFNS guidelines
- The endpoints of the trial are well-defined.

65 - The follow-up period of the included patients is long with registered symptoms, signs and
66 potential side effects.

67
68 - A weakness of the study is that the primary scoring tool, the composite clinical score, is not
69 validated.
70

71 **Funding**

72 This work is supported by the Norwegian Multiregional Health Authorities through the BorrSci
73 project (Lyme borreliosis; a scientific approach to reduce diagnostic and therapeutic uncertainties,
74 project 2015113), letter dated April 17th 2015 with case reference 14/01152-4.
75

76 **Trial registration number**

77 EudraCT number 2015-001481-25. The trial is registered on Clinicaltrials.org.
78

79 **Introduction**

80 European Lyme neuroborreliosis (LNB) is caused by the tick-borne spirochete *Borrelia burgdorferi*
81 (*Bb*). LNB can manifest weeks or months after a tick bite that only half of the patients remember.
82 The most common clinical manifestations are subacute painful radiculitis and cranial neuropathy
83 (most often the facial nerve). More rare manifestations are myelitis, encephalitis, and peripheral
84 neuropathies.

85 Patients diagnosed with LNB should be treated with antibiotics as early as possible to relieve
86 symptoms and prevent sequelae (1-3). Most patients experience a rapid improvement within days of
87 treatment, but some report long-term complaints (4). The most common long-term complaints are
88 fatigue, pain, concentration and memory problems. Some patients may also have neurological
89 sequela such as sensory disturbances, unsteadiness/vertigo, facial paresis and other paresis (5). The
90 underlying mechanisms of remaining complaints are debated. Theories suggested are ongoing
91 chronic *Bb* infection, dysregulated immune responses, genetic predisposition, co-infection with
92 multiple tick-borne pathogens, structural changes in CNS, and personal traits.

93 Standard treatment for LNB is intravenous ceftriaxone or penicillin, or oral doxycycline for two to
94 four weeks (6). Previous studies have shown that two weeks of oral doxycycline and intravenous
95 ceftriaxone are equally effective for LNB with painful radiculitis or cranial neuritis and probably also
96 for LNB with symptoms from the central nervous system (myelitis and encephalitis) (7-9). Arguments
97 for choosing oral doxycycline are that it is inexpensive and convenient, is found to penetrate the
98 blood-brain-barrier and give adequate concentrations in the CSF and is effective against co-
99 infections with other tick-borne agents (10, 11).

100 We lack evidence about the optimal duration of antibiotic treatment. Most guidelines recommend
101 treatment for 14 to 28 days. (6, 12, 13) In Norway, the site for the current study, the guidelines
102 recommend 14 days of treatment. A recent Cochrane review of six randomized treatment studies of

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3 103 adult patients with acute LNB reported improvement in the majority of patients after the initial
4 104 course of antibiotics and no consistent evidence of treatment failure or need of retreatment (14). In
5 105 another systematic review, the authors conclude that there is insufficient evidence to determine if
6 106 extended antibiotic treatment is beneficial to outcome (15). Despite this, and perhaps because of
7 107 uncertainties surrounding LNB, there are varying treatment regimes in clinical practice, generally
8 108 with more extensive treatment strategies than recommended in current guidelines. A recent study of
9 109 the treatment practice of 253 Norwegian LNB patients showed that adherence to guidelines was
10 110 poor and that two-thirds of the patients received more than two weeks of antibiotic treatment (16).
11 111 In a time with increasing knowledge and awareness of microbial resistance and other complications
12 112 of long-term antibiotic treatment these findings seem like a paradox. The present study therefore
13 113 seeks to increase the evidence of the current treatment advice by evaluating if treatment with
14 114 doxycycline in 14 days is inferior or not to treatment for six weeks with respect to long-term
15 115 prognosis of LNB.

116

117 **Method**

118 **Study design and interventions**

119 The study is a randomized, double-blinded, placebo-controlled, multicenter trial with a non-
120 inferiority design. We plan to recruit 120 patients diagnosed with definite or probable LNB according
121 to EFNS guidelines (6) at six different hospitals in the southern part of Norway as shown in figure 1.
122 The study is coordinated from Sørlandet hospital in Kristiansand, Agder County by neurologists
123 connected to the large BorrSci study (Lyme borreliosis; a scientific approach to reduce diagnostic and
124 therapeutic uncertainties). The inclusion and exclusion criteria are shown in Table 1. Inclusion started
125 in 2015 and will continue through December 2019 or until the necessary sample size is obtained.
126 Eligibility before inclusion is assessed by, or discussed with, a physician connected to the study and
127 accustomed to evaluating patients with neurological symptoms. The patients are randomized into
128 two treatment arms: A) doxycycline 200 mg daily for 2 weeks, followed by four weeks of placebo; B)
129 doxycycline 200 mg daily for six weeks (Figure 2).

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INCLUSION CRITERIA

- 1 Neurological symptoms suggestive of LNB without other obvious reasons, and one or both of
 - A) CSF pleocytosis (leucocytes $\geq 5/mm^3$)
 - B) Intrathecal *Bb* antibodyproduction
- 2 Signed informed consent

EXCLUSION CRITERIA

- 1 Age less than 18 years
- 2 Treatment with cephalosporin, penicillin, or tetracycline macrolide during the last 14 days before start of doxycycline treatment
- 3 Pregnancy, breast-feeding and/or women of childbearing potential not using adequate contraception.
- 4 Adverse reaction to tetracyclines
- 5 Serious liver or kidney disease that contraindicates use of doxycycline
- 6 Lactose intolerance
- 7 Need to use medications contraindicated according to SmPC of the IMP (Antacid drugs, Didanosin, Probenecide, Phenobarbital, Phenytoin, Carbamazepine, Rifampicin)

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143 **Table 1: Inclusion and exclusion criteria**

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Allocation and blinding

147 Computerized allocation (stratified according to hospital) is performed at Department of clinical
 148 research support, Oslo University Hospital, by an internet-based solution . Maximum objective
 149 performance and reporting of the study is achieved by applying a “penta-blinded” approach. The first
 150 and second blinding is the traditional double blind design with blinding of participants and
 151 investigators. Thirdly, the staff evaluating endpoints and adverse effects is blinded to all other study
 152 information. Further, the content of all tables and figures will be fixed before any study data are
 153 available. Lastly, the statistical procedures will be performed with the two treatment arms marked as
 154 group A and B. Revealing the study arms for the investigators will not take place until all patients
 155 have completed the six-month visit, and for the patients after the 12 month visit.

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Monitoring and data collection

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3 159 The study is monitored independently according to Good Clinical Practice (GCP) by the Department
4 160 of clinical research. The coordinating investigators at Sørlandet hospital and investigators at
5 161 cooperating centers are certified according to GCP. The investigators will enter the data required by
6 162 protocol into an electronic Case Report Form (Viedoc), also designed by the Department of clinical
7 163 research. The same protocol for data management and monitoring is applied to all collected data.
8
9 164

11 165 **Outcome measures**

13 166 A composite clinical score (CCS) based on subjective symptoms and objective neurological findings
14 167 from the peripheral and central nervous system (Table 2) is registered at baseline, 10 weeks, 6
15 168 months, and 12 months. Each of the 32 items of the CCS is scored 0=none, 1=mild (without influence
16 169 on daily life), or 2=severe (with influence on daily life). Maximum total score is 64. The primary
17 170 endpoint of the study is the difference in CCS sum score at baseline and six months after inclusion.
18 171 Secondary endpoints are the difference in CCS at baseline and 12 months after inclusion, fatigue
19 172 scored according to the questionnaire FSS (Fatigue Severity Scale) at six and 12 months, subjective
20 173 somatic symptoms scores according to the questionnaire PHQ-15 (Patient Health Questionnaire) at
21 174 six and 12 months and health related quality of life according to RAND 36 item short form health
22 175 survey at six months, and side effects of the treatment.

23 176 FSS measures level of agreement (1-7) with nine statements with the final score representing the
24 177 mean value of nine items. Scores >5 are regarded as severe fatigue. The FSS has been translated into
25 178 Norwegian, validated in the general Norwegian population, and normative Norwegian data are
26 179 available (17).

27 180 PHQ-15 charts prevalence and intensity of 13 somatic symptoms; fatigue/lack of energy, and
28 181 difficulty sleeping during the last 4 weeks. Sum score ranges from 0-28 for men and from 0-30 for
29 182 women (only women are asked about menstrual symptoms). The following cut-off values for sum
30 183 score have been stated for load of somatic symptom, 0-4 points: normal, 5-9 points: mild, 10-14
31 184 points: moderate, 15-30 points: severe. The PHQ-15 has been validated in several studies and
32 185 languages, and normative Swedish data are available (18).

33 186 RAND 36 item short form health survey consists of 36 questions about different aspects of health-
34 187 related quality of life. The answer to each question is transformed into a score ranging from 0 to 100,
35 188 where a higher score indicates better health. The questionnaire is validated in Norwegian, and
36 189 Norwegian normative data are available (19).

37 190 Three patient reported outcome measures (PROM) were included as secondary endpoints to evaluate
38 191 the potential impact of residual symptoms on patients daily life.
39 192

40 193 Systemic and CSF inflammation will be assessed with lumbar punctures and blood samples at six and
41 194 12 months after treatment. There will be established a biobank from this material. Figure 3 depicts a
42 195 flow chart of the study procedures.
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45 198 **Table 2: Composite clinical score**

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48 199 **Subjective symptoms related by the patient to the current LNB**

49 200 Malaise

50 Fatigue

51 Headache

52 Neck and/or back pain

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3 Abdominal and/or breast pain
4 Arm pain
5 Leg pain
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7 Generalized pain located to joints and/or muscles
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9 Memory and/or concentration problems
10 Other
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13 **Peripheral findings related to the current LNB**

14 Facial palsy
15 Paresis of the eye muscles
16 Reduced hearing
17 Other cranial neuropathies
18 Cervical radicular sensory findings*
19 Cervical radicular paresis**
20 Thoracic radicular sensory findings*
21 Lumbar radicular sensory findings*
22 Lumbar radicular paresis**
23 Non-radicular sensory findings***
24 Non-radicular paresis****
25 Other
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30 **Central findings related to the current LNB**

31 Central findings in one extremity#
32 Central findings in a hemi pattern
33 Central findings in both legs
34 Central findings in all extremities
35 Gait ataxia
36 Dysphasia/aphasia
37 Nystagmus
38 Involuntary movement including tremor
39 Cognitive impairment
40 Other
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*Abnormal sensory pattern in a radicular pattern. **Paresis in a radicular pattern. ***Sensory findings matching with a peripheral nerve or plexus. ****Paresis matching a peripheral nerve or plexus #Central weakness and/or spasticity, impairment in pace or fine motor skills.

207 **Safety**

209 The patients are followed closely during and after treatment to monitor safety. They are contacted
210 by phone one week after start of treatment and questioned about symptom severity and possible
211 side effects. Blood sampling with a status of hematology, liver and kidney function to monitor
212 potential side effects takes place at two and four weeks after start of treatment. The patients are

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3 213 also asked to fill out a patient diary on symptoms and possible side effects once a week for 10 weeks.
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6 216 In cases of disease progression the patients will be evaluated by a physician and adequate
7 217 intervention initiated. Disease progression is, in this trial, defined as worsening of the patient's
8 218 condition attributed to LNB, despite treatment for 14 days with doxycycline, or serious progression
9 219 of neurological signs from CNS during treatment.
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224 **Sample size**

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19 226 We used data including the SD from our previous treatment trial on 102 LNB patients treated with
20 227 either oral doxycycline or IV cephtriaxone for two weeks and scored with an almost similar clinical
21 228 scale as the CCS in the power analyses (7).

22 229 From a clinical point of view, a mean group difference of $\Delta=0.5$ in disfavor of two weeks treatment
23 230 compared to six weeks treatment was regarded as an appropriate non-inferiority margin. This non-
24 231 inferiority margin corresponds to a Cohen's d effect size of $\Delta/\sigma = 0.5/1.0 = 0.5$, which is a small and
25 232 clinical acceptable effect size. With a one-sided test and significance level of 0.05, 50 patients in each
26 233 treatment group was found to be needed to claim non-inferiority with a non-inferiority margin on
27 234 mean group difference of 0.5 and a SD of 1.0 with 80% power. To compensate for up to 20%
28 235 dropouts and non-evaluable patients 120 (i.e. 60 in each group) patients will be enrolled.
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30 236

31 237 **Statistical analysis**

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34 239 The main statistical analysis is planned when all patients have completed the six months visit. Results
35 240 will be reported as mean scores with standard deviation or proportions as appropriate.

36 241 To compare the primary outcome in the two groups we will use a general linear model with
37 242 treatment group as a factor, and adjustment for duration of symptoms, gender and age. The analysis
38 243 will be conducted according to the intention to treat principle.

39 244 For other analysis, comparison between groups will be done with e.g. independent samples t-test,
40 245 nonparametric Mann-Whitney-U test or Pearson's chi-square test for crosstabs as appropriate.

41 246 Results from the FSS and PHQ-15 questionnaires will be dichotomized according to predefined
42 247 cutoffs recommended for case definition and statistically treated as categorical outcomes.

43 248 P-values <0.05 will be considered statistically significant.
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46 250 **Ethics and dissemination**

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49 251 The Norwegian regional committees for medical and health research ethics (REC) and the Norwegian
50 252 Medicines Agency (SLV) have approved the study. EudraCT number 2015-001481-5. The trial is
51 253 registered on Clinicaltrials.org.
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54 254 The study will be conducted in accordance with ethical principles that have their origin in the
55 255 Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and applicable regulatory
56 256 requirements.
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3 257 Each patient in the trial is submitted to extensive follow-up as previously described in terms of
4 258 disease, effect of treatment and side effects to outweigh potential harms. The benefits are
5 259 considered to outweigh the cons of this trial in the long term, with a potentially more evidence-
6 260 based treatment of LNB and less extensive use of antibiotics.
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10 262 Data from the study will be published in peer-reviewed medical journals.
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12 263

13 264 **Patient and Public involvement**

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15 266 Representatives from the Norwegian patient organization for Lyme borreliosis (Norsk Lyme
16 267 Borreliose Forening, NLBF) were invited and participated in the early stages of planning of the BorrSci
17 268 project's design and gave feedback on the drafts of the application for funding. They were also
18 269 invited to continue work with the project. Inclusion to the study, implications of the intervention and
19 270 time required to participate is discussed with each individual patient. Local newspapers and other
20 271 media have been involved in making the project known to the public in different parts of Norway.
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25 272 **Authors' contributions**

26 273
27 274
28 275 AMS contributed in drafting this manuscript, has participated in revisions of the original protocol,
29 276 includes patients to the study and coordinates the study at Sørlandet hospital and at the other
30 277 centers of recruitment. UL and ÅM drafted the original protocol, worked on applications for funding,
31 278 contributed in drafting this manuscript and include patients to the study.
32
33 279
34 280

35 281 **Statement of competing interests**

36 282
37 283 The authors have no competing interests to declare.
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43 286 **Figure 1: Map of Norway with the active centers of recruitment per August 2018 marked in red.**

44 287 **Figure 2: Inclusion procedures**

45 288 **Figure 3: Flow chart of the study procedures**
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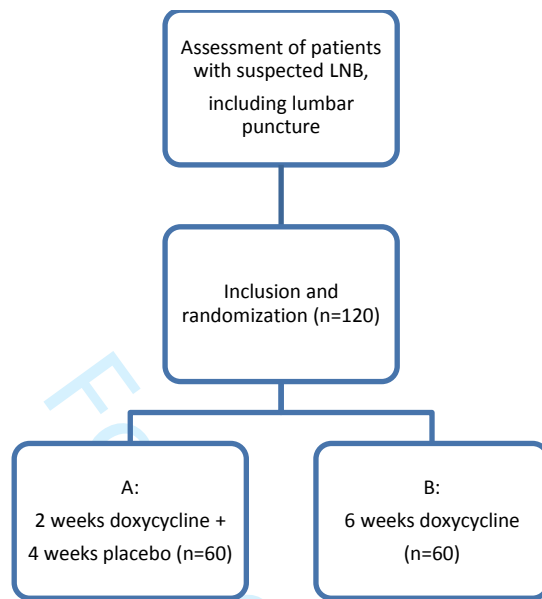
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Figure 1: Map of Norway with the active centers of recruitment per August 2018 marked in red.

1488x891mm (96 x 96 DPI)

Figure 2: Inclusion procedures



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Figure 3: Flow chart of the study procedures

