NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	209844
Priority or Standard	Standard
Submit Date(s)	August 18, 2017
Received Date(s)	August 18, 2017
PDUFA Goal Date	June 18, 2018
Division/Office	DAIP/OAP
Review Completion Date	See DARRTS electronic signature page
Established Name	Doxycycline Hyclate
(Proposed) Trade Name	LYMEPAK
Pharmacologic Class	Tetracycline
Applicant	Chartwell Pharma NDA B2 Holdings, LLC
Formulation(s)	Oral tablet
Dosing Regimen	100 mg twice daily for 21 days
Applicant Proposed Indication(s)/Population(s)	Treatment of early Lyme disease, as evidenced by erythema migrans in adults and pediatric patients 8 years of age or older
Recommendation on Regulatory Action	Approval

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OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

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Glossary

AC	Advisory Committee
ACA	Acrodermatitis Chronica Atrophicans
AE	Adverse Event
ANA	Antinuclear Antibody
ANDA	Abbreviated New Drug Application
AR	Adverse Reaction
AV	Atrioventricular
BID	Bis In Die (twice a day)
BLA	Biologics License Application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBC	Complete Blood Count
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	Chemistry, Manufacturing, and Controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	Case Report Form
CRO	Contract Research Organization
CRT	Clinical Review Template
CSR	Clinical Study Report
CSS	Controlled Substance Staff
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCTD	Electronic Common Technical Document
EM	Erythema Migrans
ESR	Erythrocyte Sedimentation Rate
ETASU	Elements To Assure Safe Use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	Good Clinical Practice
GRMP	Good Review Management Practice
HGA	Human Granulocytic Anaplasmosis
ICH	International Council for Harmonization
IDSA	Infectious Disease Society of America
IND	Investigational New Drug Application

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iPSP	Initial Pediatric Study Plan
ISE	Integrated Summary Of Effectiveness
ISS	Integrated Summary Of Safety
ITT	Intent To Treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent To Treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	New Drug Application
NME	New Molecular Entity
NSS	Non-Specific Symptoms
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Pharmacodynamics
PI	Prescribing Information or Package Insert
PIND	Pre-Investigational New Drug
PK	Pharmacokinetics
PLLR	Pregnancy Lactation Labeling Rule
PMC	Postmarketing Commitment
PMR	Postmarketing Requirement
PO	Per Oral
PP	Per Protocol
PPI	Patient Package Insert
PREA	Pediatric Research Equity Act
PRO	Patient Reported Outcome
PSUR	Periodic Safety Update report
QD	Quaque Die (daily)
REMS	Risk Evaluation and Mitigation Strategy
RLD	Reference Listed Drug
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGE	Special Government Employee
SOC	Standard of Care
TEAE	Treatment Emergent Adverse Event
TID	Ter In Die (three times a day)

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1 Executive Summary

1.1. Product Introduction

Doxycycline is a tetracycline-class antibacterial drug that was approved in 1967 for multiple indications. Doxycycline hyclate, USP is the hyclate salt form of doxycycline, which is synthetically derived from oxytetracycline. It inhibits protein synthesis by binding to the 30S ribosome and has activity against a wide range of gram-positive and gram-negative bacteria, (b) (4).[1] Doxycycline also has *in vitro* activity against *Borrelia burgdorferi* (*B. burgdorferi*), the prevailing causative agent of Lyme disease in the United States (US). The Applicant, Chartwell Pharma NDA B2 Holdings LLC, submitted NDA 209844 for LYMEPAK (doxycycline hyclate) tablets for the treatment of early Lyme disease, as evidenced by erythema migrans (EM). Chartwell is relying upon the published scientific literature for efficacy of various formulations of doxycycline products and approved labeling of Vibra-Tabs® (NDA 50533, Pfizer) for the findings of safety in support of this indication. Chartwell markets 100 mg immediate release doxycycline hyclate tablets (ANDA 062505). The proposed dosing is doxycycline hyclate 100 mg twice daily for 21 days in adults and pediatric patients, ages 8 years and older. The proposed trade name is LYMEPAK.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommendation for the approval of LYMEPAK, per 21 Code of Federal Regulations (CFR) 314.126(a)(b), is primarily based on the efficacy data from three randomized, prospective studies of doxycycline 100 mg BID for 20-21 days, conducted in 131 US patients with early Lyme disease. Primary evidence for efficacy was derived by comparing the doxycycline treatment effect in 3 US studies of the BID regimen (Dattwyler 1990 and 1997, Massaroti 1992) with no treatment in two natural history studies (Steere 1979 and 1980). Early Lyme disease, as evidenced by erythema migrans and associated non-specific symptoms (NSS), such as malaise, fatigue, arthralgia, and myalgias, was the initial presentation in all studies. The Dattwyler 1997 study included a greater proportion of patients (14%) with early disseminated disease (joint swelling, facial palsy, and carditis). The primary efficacy endpoint was the absence of objective manifestations of Lyme disease, specifically those related to the musculoskeletal, nervous, and cardiac systems at 6 months after initial presentation. The 6-month timepoint was chosen since both natural history studies and the 3 US BID treatment studies reported outcomes at 6 months.

As EM and associated symptoms can resolve spontaneously and the natural history studies did not describe the timing of their resolution in sufficient detail, endpoint assessing resolution of

[1] Vibra-Tabs (doxycycline hyclate tablets, USP). New York, NY: Pfizer Labs; Approved labeling. 2017

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the initial clinical manifestations was not considered in the efficacy evaluation. Doxycycline treatment effect in the three aforementioned BID studies was demonstrated when compared to no treatment in the two natural history studies. The treatment effect of doxycycline over no treatment was at least 4.4% when all 3 studies were pooled, using a conservative estimate of efficacy (i.e., a comparison of the largest likely rate of absence of manifestations of Lyme disease for no treatment with the lowest likely rate of absence of objective manifestations of Lyme disease for doxycycline). When the Dattwyler 1997 study (which had patients with early disseminated disease) was excluded, the treatment effect of doxycycline was conservatively estimated at 17.1% as compared to no treatment. The indication for approval of LYMEPAK is early Lyme disease, as evidenced by erythema migrans (in the absence of specific neurologic and cardiac manifestations which may require parenteral antibacterial drugs).

The safety of LYMEPAK was based on the approved labeling of Vibra-Tabs®. The Jarisch-Herxheimer reaction was identified in up to 30% of patients with early Lyme disease treated with doxycycline in the studies reviewed for safety. The safety profile of LYMEPAK is acceptable for the intended population. No disciplines identified outstanding issues that precluded approval. In summary, for the treatment of early Lyme disease in adults and pediatric patients over 8 years of age (weighing over 45 kilograms), LYMEPAK demonstrates a favorable benefit-risk profile with sufficient evidence to recommend approval.

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1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Doxycycline hyclate (LYMEPAK) is a tetracycline-class antibacterial drug, indicated for the treatment of early Lyme disease, as evidenced by erythema migrans, due to *B. burgdorferi* in adults and pediatric patients 8 years of age and older.

Lyme disease is a spirochetal infection, transmitted by a bite of infected Ixodid ticks. It is caused primarily by *B. burgdorferi sensu stricto* in the US. The clinical manifestations of Lyme disease can generally be divided into three phases: early localized, early disseminated, and late disease. In all parts of the world with endemic Lyme disease, EM, often accompanied by non-specific findings that resemble a viral syndrome, is a hallmark of early localized disease. EM occurs in approximately 80% of patients usually within one month following a tick bite. Early disseminated Lyme disease with acute neurologic or cardiac involvement usually occurs weeks to several months after a tick bite, but can be the first manifestation of Lyme disease in some patients. Late Lyme disease occurs months to a few years after the onset of infection, and in the US, arthritis in one or a few joints is the most common feature. The goal of antibacterial treatment is to resolve early signs and symptoms, and prevent late complications.

Ceftin (cefuroxime axetil) is the only FDA-approved drug for the treatment of adult and pediatric patients (aged 13 and older) with early Lyme disease (erythema migrans). It was approved in 1996 based on noninferiority to doxycycline 100 mg TID for 20 days. Doxycycline is used widely off-label in clinical practice for the treatment of early Lyme disease.

The Applicant searched published literature and identified 31 studies in which doxycycline treatment was used for the treatment of Lyme disease. Of these 31, three randomized studies evaluating doxycycline treatment in patients with erythema migrans and associated symptoms, were identified as appropriate for efficacy analyses based on the assessment of the baseline characteristics, degree of missing data, and other confounding factors. In addition, two natural history studies of Lyme disease evaluated disease progression in patients presenting with erythema migrans and associated symptoms. Over 200 patients from Lyme-disease hyperendemic areas were enrolled in these five studies, and more than 100 received doxycycline. The incidence of disseminated disease at presentation in the US natural history studies was 0-8.8%. In one treatment study (Dattwyler 1997), 14% of doxycycline treated patients had disseminated disease (joint swelling, facial palsy, or carditis) at presentation. The other treatment studies did not have patients with disseminated disease at baseline.

Evidence of efficacy was derived by comparing doxycycline treatment in studies using doxycycline 100 mg twice daily for 20-21 days with no treatment in the natural history studies. Clinical resolution of symptoms was defined as absence of objective later manifestations of Lyme disease, i.e. arthritis, neurologic disease, and carditis at 6 months. In comparison to untreated patients, doxycycline-treated patients had a higher response rate at 6 months. Doxycycline-treated patients had a response rate of 75-95% compared to 56-66% in the untreated patients.

There was a modest treatment benefit of at least 4.4% using the 95% Exact confidence interval when comparing the three studies (Dattwyler 1990 and 1997, and Massaroti 1992) with no treatment. When excluding the Dattwyler study (which enrolled 14% patients with early disseminated disease), the estimate of efficacy increased to 17.1% using the 95% Exact confidence interval. Although the treatment benefit appears small, the estimates consider the variability of both the untreated cure rate and the doxycycline cure rate and the actual number of treatment failures in each of the doxycycline treatment studies was ≤ 1. Patients lost to follow up or those taking concurrent antibacterial drugs were considered failures in the analyses.

The safety profile of doxycycline is well-established. Common adverse reactions noted in the submitted studies are included in the approved labeling of Vibra-Tabs®, the RLD for LYMEPAK. Mild to moderate Jarisch-Herxheimer reactions were noted in up to 30% of patients in the submitted studies. The Jarisch-Herxheimer reaction will be added to the Warnings and Precautions section of the proposed product's updated label, as it is not currently in the approved labeling for the RLD.

Overall, the benefit-risk profile for LYMEPAK is favorable for patients with early Lyme disease, as evidenced by erythema migrans. The benefit of LYMEPAK in treatment of early disseminated disease (Lyme disease spread to the musculoskeletal, cardiac, or nervous system) could not be assessed fully as there were limited numbers of patients with early disseminated disease in the studies evaluated.

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Dimension	Evidence and Uncertainties	• Conclusions and Reasons
Analysis of Condition	• Lyme disease, caused by *B. burgdorferi*, is the most common tickborne infection in both US and Europe. In 2014, Lyme disease was the fifth most common reportable disease in the US. • Each year, approximately 30,000 cases of Lyme disease are reported to CDC. The estimated number of people diagnosed annually, is closer to 300,000 based on epidemiological studies. • Lyme disease occurs in stages, typically beginning with erythema migrans rash in about 80% of patients.	• If left untreated, infection can spread to the musculoskeletal, cardiac, and nervous system, leading to significant complications, such as arthritis, carditis, and meningitis. • Early diagnosis and prompt treatment can alleviate early Lyme disease symptoms and signs, and prevent late complications.
Current Treatment Options	• Ceftin is the only FDA-approved antibacterial drug for early Lyme disease. • Doxycycline and amoxicillin are the preferred oral antibacterial drugs used off-label to treat early Lyme disease.	• There is an unmet medical need for other FDA-approved antibacterial drugs for early Lyme disease • Doxycycline, although widely used in clinical practice, does not have an FDA-approved indication for any stage of Lyme disease, which can lead to inappropriate dosing, and lack of awareness for drug-disease interactions.
Benefit	• Based on the assessment of the baseline characteristics, degree of missing data, and other confounding factors (e.g. use of intercurrent antibacterial drugs), 2 US natural history studies and 3 US studies of the 100 mg BID regimen formed the basis for the review of doxycycline efficacy in early localized and early disseminated Lyme disease. • Primary evidence for efficacy was derived by comparing the doxycycline treatment effect in the US studies of the BID	• Doxycycline 100 mg BID for 21 days was the only treatment regimen for which a treatment benefit versus no treatment could be shown. • The studies using a shorter duration were either confounded by intercurrent antibacterial drugs, or did not demonstrate a treatment benefit when

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Dimension	Evidence and Uncertainties	• Conclusions and Reasons
	regimen with no treatment in the natural history studies. • The primary efficacy endpoint was the absence of objective manifestations of Lyme disease, involving the musculoskeletal, cardiac, and nervous system at 6 months after initial presentation (EM and associated symptoms). • A positive treatment effect of doxycycline treatment versus no treatment at 6 months was identified (4.4%). • The conservative treatment effect of doxycycline versus no treatment at 6 months increased to 17.1% when Dattwyler 1997 study with greater number of early disseminated disease patients was excluded.	compared to no treatment (European studies). • The efficacy of doxycycline was greatest in patients who presented with early Lyme disease, evidenced by EM and associated non-specific symptoms (uncomplicated disease). • Only a few patients with early disseminated Lyme disease enrolled in these studies, and thus conclusions on efficacy of doxycycline in patients with early disseminated disease is limited.
Risk	• The safety profile of doxycycline is well-established in adults and pediatric patients over 8 years of age. • Most adverse reactions noted in the submitted studies are described in the approved labeling for Vibra-Tabs®. • Mild to moderate Jarisch-Herxheimer reactions were noted in up to 30% of patients in the submitted studies, and did not require patient discontinuation of doxycycline.	• LYMEPAK is contraindicated in pediatric patients < 8 years of age due to known adverse safety profile of doxycycline. • The safety profile of LYMEPAK is acceptable for the intended population. • The Jarisch-Herxheimer reaction will be added to the Warnings and Precautions section of the product labeling.
Risk Management	• Lyme disease should be treated by providers who can accurately diagnose early Lyme disease, and differentiate symptoms from those with more advanced disease. • Lyme disease treatment might be performed in consultation with or by an infectious disease specialist. • Early disseminated disease may require serologic confirmation of the disease, and procedures to exclude certain	• LYMEPAK is intended for use in early Lyme disease, as evidenced by erythema migrans. • Appropriate (21-day) presentation was requested from the Applicant to be congruent with the recommended dosing regimen.

Dimension	Evidence and Uncertainties	• Conclusions and Reasons
	manifestations of Lyme disease that may require parenteral antibacterial drugs. • Applicant's proposed dosage form is 100 mg tablet presented as a 7-day (b) (4). Recommended duration of treatment for early Lyme disease is 21 days. • 100 mg (b) (4) tablet dosage form allows for dosing of pediatric patients aged 8 years and older weighing 45 kg or more.	• PeRC recommended a PMR to develop appropriate changes to the current dosage form of 100 mg tablet, (b) (4) to allow dosing of pediatric patient 8 years and older who weigh less than 45 kg • No REMS is indicated.

1.4. Patient Experience Data

Not Applicable.

2 Therapeutic Context

2.1. Analysis of Condition

Introduction

Lyme disease is a spirochetal infection, which is transmitted by the bite of infected Ixodid ticks[2]. Lyme disease is caused by *B. burgdorferi* sensu stricto in the US, and *B. burgdorferi* sensu lato (*B. afzelii, B. garinii, B. burgdorferi*) in Europe. It is the most common tick-borne infection in the US and Europe. In endemic regions, the peak months of disease onset are June and July. Early localized disease is characterized by EM, often accompanied by influenza-like symptoms. Most often, EM is sufficiently distinctive to allow clinical diagnosis in the absence of laboratory confirmation. Although the basic features of Lyme disease are similar worldwide, there are regional variations between the US and Europe[3]. Table 1 below provides a comparison of clinical manifestations between the two regions.

Lyme disease in the US

In the US, the age distribution is typically bimodal, with peaks among children 5-15 and adults 45-55, years of age. The incidence is higher among men than women (53 vs. 47%), in those < 60 years of age. Since its discovery in the 1970s, the incidence has been steadily increasing in the US with approximately 300,000 people diagnosed annually[4]. In North America, over 90% of cases are reported from the Northeast, mid-Atlantic and North-Central region. Because the ticks that transmit Lyme disease are frequently encountered in backyards and outdoor recreational areas, a high degree of public health awareness of Lyme disease must be maintained wherever the disease is known to occur.

Without antibacterial drug therapy, the clinical manifestations occur in three stages: early localized, early disseminated, and late; however, there is some overlap among the stages. While EM can be isolated, many experience additional nonspecific symptoms (NSS), such as

[2] Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steere AC, Klempner MS et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2006; 43(9):1089-1134.
[3] Stanek G, Strle F. Lyme Disease – European Perspective. Infect Clin Dis N Am. 2008(22):227-339.
[4] Beard CB. Epidemiology of Lyme disease. In: Steere, AC, ed. UpToDate. Waltham, Mass: UpToDate; 2017. www.uptodate.com. Accessed October 27, 2017.

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fatigue, headache, arthralgia, myalgia, and less often, fever. In the US, EM is the presenting manifestation in about 80% of patients, while 18% have NSS during summer without recognition of EM and the remaining 2-3% initially present with a manifestation of early or late disseminated infection. EM begins as a small erythematous papule or macule that appears at the site of a tick bite 1 to 2 weeks later (range 3 to 32 days) and subsequently enlarges. The CDC case definition for surveillance maintains that a single primary lesion must reach at least 5 cm in size across its largest diameter. Even without antibacterial drug treatment, EM typically improves or resolves within an average of 3-4 weeks[5].

Early disseminated disease is caused by hematogenous spread of the spirochete to other skin sites causing multiple EM lesions, or to other organs, usually to the peripheral or central nervous system, heart, or joints. The most common clinical feature is lymphocytic meningitis with episodic headaches, mild neck stiffness, cranial neuropathy (particularly facial palsy), or radiculoneuritis[6]. Acute cardiac involvement usually manifests as atrioventricular nodal (AV) block, myo-pericarditis, and rarely cardiomegaly or pancarditis. Even without antibacterial drugs, acute carditis usually resolves, but a rare number of fatal cases has been reported.

Late Lyme disease may develop months to a few years after the initial infection. It is typically associated with intermittent or persistent arthritis involving one or a few large joints, especially the knee. A subtle encephalopathy or sensory polyneuropathy can occur.

Lyme Disease in Europe

The highest prevalence is noted in forested regions, such as Austria, Estonia, Lithuania, the Netherlands, and Slovenia. The prevalence of Lyme disease in Europe has increased, possibly secondary to climate change which has brought about an increased density and broader geographic distribution of Ixodes ticks.

Clinically, European Lyme disease typically begins with EM, but its characteristics are distinct. *B. afzelii* does not disseminate as often as *B. burgdorferi* and can persist in the skin for months to years. Arthritis is less frequent, occurs earlier in the disease course, and rarely becomes chronic.

Despite differences in genospecies between the US and Europe and absence of studies that directly compare treatment outcomes, the overall results of antibacterial drug treatment appear to be similar in decreasing the duration of early symptoms and halting the progression of the disease[7]. The most comprehensive 2006 treatment guidelines for Lyme disease from Infectious Disease Society of America (IDSA) were authored by both US and European

[5] Shapiro ED. Lyme Disease. N Engl J Med. 2014; 370(18): 1724-1731
[6] Hu, L. Clinical manifestations of Lyme Disease. In: Steere, AC, ed. UpToDate. Waltham, Mass: UpToDate; 2017. www.uptodate.com. Accessed October 27, 2017.
[7] Steere AC, Strle FDA, Wormser G. Lyme Borreliosis. Nat Rev Dis Primers. 2016(2): 16090

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professional societies.

Although most patients with Lyme disease respond well to antibacterial drug therapy and experience a complete recovery, about 10% of patients do not return to pre-Lyme health status, and these post-infectious sequelae can affect their quality of life. The etiology and frequency of these sequelae, termed post-Lyme disease syndrome remain an area of uncertainty.

Table 1: A Comparison of Clinical Features of Lyme Disease by Region

	GEOGRAPHIC LOCATION	
CLINICAL FEATURE	**US**	**EUROPE**
Species	*B. burgdorferi* sensu stricto	*B. burgdorferi* sensu lato: *B. afzelii, B. garinii, B. burgdorferi*
Early localized		
Erythema migrans (EM)	Faster spreading, more intensely inflamed, present for briefer duration	Slower spreading, less intensely inflamed, present for longer duration
Dissemination	More hematogenous	More regional
Non-specific symptoms	Greater frequency	Lower frequency
Early disseminated		
Cardiac disease	Atrioventricular block, mild myopericarditis disease or cardiomyopathy	Atrioventricular block, subtle myopericarditis
Neurologic disease	Meningitis, pleocytosis, cranial or peripheral neuropathy, less radiculoneuritis, less intrathecal antibody production against Borrelia (*B. burgdorferi* sensu stricto*)*	Meningoradiculoneuritis, severe radicular pain (Bannworth syndrome), pleocytosis, intrathecal antibody production against Borrelia (primarily *B. garinii*)
Musculoskeletal disease	Oligoarthritis: more frequent, more intense joint inflammation	Oligoarthritis: less frequent, less intense joint inflammation
Skin involvement	Multiple EM	Borrelial lymphocytoma
Late or chronic disease		
Arthritis	Intermittent mono- or oligoarthritis (usually knee)	Persistent arthritis: rare
CNS disease	Subtle sensory neuropathy, cognitive disturbance	Subtle sensory neuropathy: often within areas of acrodermatitis chronica atrophicans (ACA); severe encephalomyelitis; spasticity,

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	GEOGRAPHIC LOCATION	
CLINICAL FEATURE	**US**	**EUROPE**
		cognitive abnormalities
Skin involvement	ACA: rare	ACA: frequent
Source: Stanek 2008		

2.2. Analysis of Current Treatment Options

There is only one FDA-approved antibacterial drug, cefuroxime axetil (Ceftin), for the treatment of Lyme disease. It was approved in 1996 based on noninferiority to doxycycline 100 mg given TID for 20 days. There are alternative treatments that are used off-label in the treatment of Lyme disease which are listed in Table 2.

Table 2: Currently Available Oral Regimens for Early Lyme Disease in the US*

Product Name	Relevant Indication	Year of Approval	Dose/Duration	Efficacy Information	Safety and Tolerability Issues	Other Comments
FDA Approved Treatments						
Ceftin (cefuroxime axetil)	Early Lyme Disease	1996	(b) (4) mg po BID for 20 days	355 patients with EM randomized to Ceftin or doxycycline. Satisfactory outcome at 12 months - 84% with Ceftin	GI-related adverse reactions were similar. Diarrhea: 11% with Ceftin vs. 3% with doxycycline	For adults and pediatric patients ≥13
Unapproved (Off label Use) Treatments						
Doxycycline	N/A	1967	100 mg po BID for 10-21 days	Refer to section 7	Refer to section 8.4	See label for specific populations
Amoxicillin	N/A	1974	500 mg po TID for 14-21 days	Refer to IDSA guidelines[2]	Refer to IDSA guidelines	Can be taken by children <8 years old, pregnant women
Azithromycin (and selected macrolides^) 1991	N/A	1991	500 mg po QD for 7-10 days	Refer to IDSA guidelines	Refer to IDSA guidelines	For those who are intolerant of doxycycline, penicillins, & cephalosporins

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Product Name	Relevant Indication	Year of Approval	Dose/Duration	Efficacy Information	Safety and Tolerability Issues	Other Comments
*In the absence of specific neurologic or cardiac manifestations of early Lyme disease ^ Macrolides are not recommended as first-line therapy for early Lyme disease due to decreased efficacy						

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

No formulation of doxycycline has been previously marketed for Lyme disease. Doxycycline is approved for multiple indications including infections due to susceptible *Rickettsia, Chlamydia, Mycoplasma*, and certain gram-negative and gram-positive bacteria.

3.2. Summary of Presubmission/Submission Regulatory Activity

Chartwell Pharma B2 Holdings, LLC will be referred to as the Applicant and The Food and Drug Administration will be referred to as the Agency throughout this review.

On March 3, 2015, in a Type B Pre-IND meeting (PIND 125184) for doxycycline hyclate tablets, USP, 100 mg for the proposed indication of Lyme disease, the following was discussed:

- a 505(b)(2) pathway as a reasonable regulatory approach for the NDA;

(b) (4)

On June 29, 2016, the Agency provided written responses to the Pre-NDA background package for PIND 125184:

- The Applicant could rely on Vibramycin (doxycycline hyclate) as an RLD for the safety of LYMEPAK if the dose and duration of treatment fell within that described in the Vibramycin labeling.
- need for identification of the salt form or comparative PK data between the salt forms

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for each publication being relied on for efficacy;

- agreement to a waiver of pediatric studies (iPSP) for pediatric patients < 8 years of age based on doxycycline's known safety profile in adversely affecting bone and tooth growth, and plans to extrapolate efficacy of doxycycline from adults to pediatric patients ≥ 8 years.

3.3. Foreign Regulatory Actions and Marketing History

The European studies reviewed were conducted in Slovenia, Croatia, Netherlands, and Sweden. The regulatory authorities of these countries were contacted about marketing status of

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No clinical site inspections were requested for this literature based NDA.

4.2. Product Quality

Novel excipients: No
Any impurity of concern: No
Sufficient controls to insure safety and efficacy of the commercial product: Yes

Doxycycline hyclate, USP is the hyclate salt form of doxycycline, a tetracycline class antibacterial drug, synthetically derived from oxytetracycline. The chemical name of doxycycline hyclate is 4-(Dimethylamino)-1,4,4α,5,5α,6,11,12α-octahydro-3,5,10,12,12α-pentahydroxy-6-methyl-1,11-dioxo-2- naphthacenecarboxamide monohydrochloride, compound with ethyl alcohol (2:1), monohydrate. The molecular formula for doxycycline hyclate is (C22H24N2O8·HCl)2·C2H6O·H2O and the molecular weight is 1025.8 (b) (4) The chemical structure of doxycycline hyclate is provided in Figure 1 below.

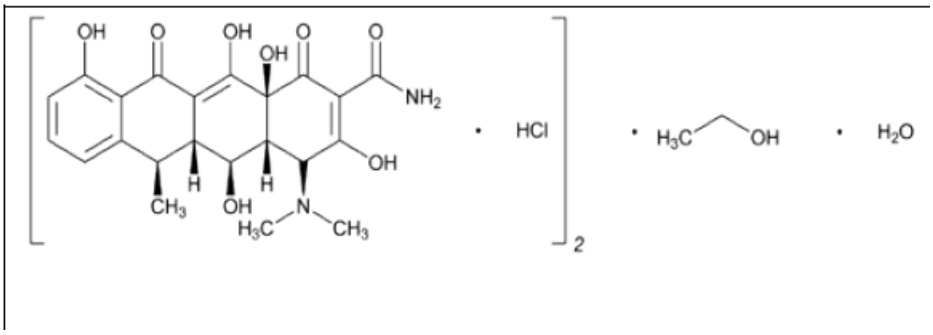

Figure 1 Structure of Doxycycline Hyclate

CAS No: 24390-14-5
USP Catalog No: 1226003
Table 3 provides detailed information regarding drug product composition

Table 3: Quantitative Composition of LYMEPAK (doxycycline hyclate) Drug Product

Component	Function	Quantity per unit (mg/tab)	% w/w per tablet
Doxycycline as Doxycycline Hyclate, USP	Active Pharmaceutical Ingredient	(b) (4)	(b) (4)
Lactose Anhydrous, NF (b) (4)	(b) (4)		
Microcrystalline Cellulose, NF (b) (4)			
Polyethylene Glycol, NF (b) (4)			

Component	Function	Quantity per unit (mg/tab)	% w/w per tablet
Methylcellulose, USP (b) (4)			(b) (4)
Sodium Starch Glycolate, NF (b) (4)			
Stearic Acid, NF			
Colloidal Silicon Dioxide, NF			
Magnesium Stearate, NF			
(b) (4)			
(b) (4) */hypromellose (USP, Pheur, JP)*			(b) (4)
D&C yellow #10 (b) (4)			
Titanium Dioxide (USP,FCC, Pheur, JP)			
(b) (4) *(NF, FCC, Pheur,JECFA, JP)*			
FD&C blue #1/ (b) (4) (b) (4) *(JECFA, JSFA, JP Mo)*			
FD&C Yellow #6/ (b) (4) (b) (4) *(JECFA, JSFA, JP Mo)*			
Coating Sub-total			
Final Tablet Total			

Adapted from the applicant's product summary.

For details of product quality assessment refer to the multidisciplinary quality assessment review by the Office of Product Quality (OPQ). A summary of the review findings is presented below.

Doxycycline hyclate drug substance is described as yellow, crystalline powder soluble in water and in solutions of alkali hydroxides and carbonates, slightly soluble in alcohol, and practically insoluble in chloroform and in ether.

The drug product is a round green film-coated tablet engraved with "LP1" on one side and plain on the other, packaged in a unit dose blister pack of 14 (7 x 2). The formulation is the same as doxycycline hyclate tablets currently marketed under ANDA 62505 held by the Applicant,

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Chartwell Pharma, except for the orange film coat and the engraving. The excipients are conventional for a product of this type. Apart from the (b) (4) the excipients are compendial.

The proposed specification generally matches the USP specification for doxycycline hyclate tablets, and is appropriate given the observed stability data. The acceptance criteria for impurities/degradation products are reasonable and supported by the data. The absence of routine microbial limits testing in the drug product specification was found adequately justified in the course of the manufacturing process review. The analytical methods are described in reasonable detail and have been validated.

Based on the stability data provided, the proposed expiration dating period of 12 months with the storage statement: "Store at 20°C to 25°C (68° to 77°F) [See USP Controlled Room temperature]" can be assigned for the drug product packaged in blisters, the proposed commercial container closure system.

Dissolution method and dissolution acceptance criterion were found to be acceptable. Based on the information provided in the NDA (which included comparative dissolution profiles), the bridge has been established between the proposed LYMEPAK tablets and the drug products used in the three pivotal/key literature publications as well as the LD products.

(b) (4)

The OPQ review team concluded that NDA contains sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug product, doxycycline hyclate tablets. The manufacturing and testing facilities for this NDA are deemed acceptable. From a Product Quality perspective, the NDA is recommended for approval.

4.3. Devices and Companion Diagnostic Issues

Not applicable.

4.4. Biopharmaceutics

The Applicant proposed that LYMEPAK tablets are bioequivalent to the relied-upon listed drug, Vibra-Tabs® (doxycycline hyclate tablets USP) (NDA 50533, Pfizer, Inc). The proposed drug

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product (LymePak, NDA 209844) and doxycycline hyclate tablets approved under ANDA 62505 (for which the applicant provided a letter of authorization to reference) have the same formulation except for the color of the film coat and are bridged by comparative dissolution data. Doxycycline hyclate tablets approved under ANDA 62505 are bioequivalent to Vibra-Tabs.

The studies reviewed for efficacy and safety in this NDA (listed in

Table **5** and
Table 6) used various formulations of doxycycline for treatment of early Lyme disease. Most often, the doxycycline salt form was not specified, and only the active moiety "doxycycline" was noted. The relied upon literature describes products that contain the same active moiety (doxycycline) administered at the same dose (100 mg BID) and duration (21 days), and for the same indication, as that proposed for LYMEPAK.

Based on the information provided in the NDA (which included comparative dissolution profiles), the bridge has been established between the proposed LYMEPAK tablets and the drug products used in the three pivotal/key literature publications as well as the relied-upon listed drug product.

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5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Applicant did not submit any new Pharmacology/Toxicology information in the NDA. No Pharmacology/Toxicology information was reviewed to support this NDA. The Applicant relies upon labeling information of the RLD, as well as published literature for the safety and efficacy of doxycycline. The Applicant proposes that LYMEPAK (doxycycline hyclate, USP) tablets are therapeutically equivalent to the RLD. (b) (4)

Table 4 Dose of Colorants in 100 mg Tablet Calculated Relative to the Listed IID Levels

(b) (4)

The limits for impurities in the drug product are similar to the Applicant's currently marketed doxycycline products (doxycycline hyclate tablets, USP ANDA 062505 and doxycycline hyclate capsules ANDA 062500, both approved 1984). It is noted that the limit set for total impurities (NMT (b) (4)%) for the Applicant's currently marketed products and LYMEPAK exceed the USP limit

(2%). After discussion with the CMC reviewer Dr. George Lunn, it was determined that the impurities mentioned in the current application are a combination of degradants and non-degradation impurities, whereas the USP only includes limits for degradants. Dr. Lunn confirmed that the proposed total impurity limit of NMT (b)(4)% is acceptable. Overall, there were no novel excipients or impurities at levels that warranted any new nonclinical studies. The Applicant's proposed addition of colorant levels and the overall impurity profile in LYMEPAK are acceptable from a Pharmacology/Toxicology perspective. (For details of product quality assessment refer to Office of Product Quality review by Dr. George Lunn – briefly summarized in Section 4.2).

Labeling: Relevant nonclinical information from the "Warnings and Precautions" section has been removed and placed under "Animal Data" in Section 8.1. No other changes were made to any of the Pharmacology/Toxicology relevant sections in the proposed label.

From a Pharmacology/Toxicology perspective, the NDA is recommended for approval.

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6 Clinical Pharmacology Executive Summary

6.1. Executive Summary

No new clinical pharmacology information was provided in this application. This application relied on in vitro dissolution comparison between the proposed product and the RLD.

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7 Statistical and Clinical Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Trials

Table **5** summarizes all the US studies submitted by the Applicant for review of efficacy and safety of LYMEPAK in the treatment of early Lyme disease. Studies 1 and 2 are natural history studies, and 3-8 are doxycycline treatment studies. Studies 3-6 used the 100 mg BID regimen, and Studies 7-8 used the TID regimen.
Table 6 lists the European studies reviewed for efficacy and safety of LYMEPAK. Study 9, a European natural history study, was found in the literature search conducted by the Medical Reviewer. All studies except for Study 9 were referenced by the Applicant.

Table 5: **US Studies Early Lyme Disease**

#	AUTHOR/ PUBLICATION	STUDY DESIGN	REGIMEN/DOSE	TREATMENT DURATION	N	STUDY ENDPOINTS	STUDY POPULATION	FOLLOW-UP	NUMBER OF CENTERS
Studies to Support Efficacy									
1	Steere 1979	Natural History	None	N/A	48	Absence of disease progression (joint, neurologic)	EM/NSS	6 and 18 months	1
2	Steere 1980	Natural History	None	N/A	55	Absence of disease progression (joint, neurologic, cardiac)	EM/NSS	6, 12, and 18 months	1
			Penicillin 250K U QID	7-10 days	42				
			Erythromycin 250 mg QID	7-10 days	9				

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#	AUTHOR/ PUBLICATION	STUDY DESIGN	REGIMEN/DOSE	TREATMENT DURATION	N	STUDY ENDPOINTS	STUDY POPULATION	FOLLOW-UP	NUMBER OF CENTERS
			Tetracycline 250 mg QID	7-10 days	7				
Studies to Support Efficacy and Safety									
3	Dattwyler 1990	Randomized Open-label	Doxycycline 100 mg BID	21 days	37	Development of disease progression	EM/NSS	Day 21 and 6 months	1
			Amoxicillin + probenecid 500 mg TID	21 days	38				
4	Massaroti 1992	Randomized Open-label	Doxycycline 100 mg BID	10 days	22	Resolution of early symptoms and development of disease progression	EM/NSS	Day 10 and 6 months	7
			Amoxicillin + probenecid 500 mg TID	10 days	17				
			Azithromycin 500 mg x 1, then 250 mg x 4 days	5 days	16				
5	Dattwyler 1997	Randomized Open-label	Doxycycline100 mg BID	21 days	72	Clinical cure or failure	EM/NSS; 14% with early disseminated disease	3, 6, and 9 months	9
			Ceftriaxone 2 gm QD	14 days	68				
6	Wormser 2003	Randomized Double-blind	2 g Ceftriaxone + Doxy 100 mg BID	10 days	60	Complete response, partial response, and failure	EM/NSS	Day 20, 3, 12, and 30 months	1
			Doxycycline 100 mg BID	10 days	61				
			Doxycycline 100 mg BID	20 days	59				
7	Nadelman	Randomized	Doxycycline 100 mg	20 days	60	Early resolution	EM/NSS	Day 30	4

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#	AUTHOR/ PUBLICATION	STUDY DESIGN	REGIMEN/DOSE	TREATMENT DURATION	N	STUDY ENDPOINTS	STUDY POPULATION	FOLLOW-UP	NUMBER OF CENTERS
	1992	Single-blind	TID			of EM & other clinical signs/symptoms, no disease progression		and 12 months	
			Cefuroxime 500 mg BID	20 days	63				
8	Luger 1995	Randomized Single-blind	Doxycycline 100 mg TID	20 days	113	Early resolution of EM & other clinical signs/symptoms, no disease progression	EM/NSS	Day 30 and 12 months	5
			Cefuroxime 500 mg BID	20 days	119				

Table 6: European Studies Early Lyme Disease

#	AUTHOR/ YEAR	STUDY DESIGN	REGIMEN/DOSE	TREAT-MENT DURATION	N	STUDY ENDPOINTS	STUDY POPULATION	FOLLOW UP	NUMBER OF COUNTRIES AND CENTERS
Studies to Support Efficacy									
9	Asbrink 1986	Natural History	None	N/A	16	Absence of disease progression (EM recurrence, joint or	EM/NSS	6 and 12 months	Sweden: 1
			Penicillin 2 g QD, Tetracycline 1 g QD or Erythromycin 1 g	10 days	215				

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#	AUTHOR/ YEAR	STUDY DESIGN	REGIMEN/DOSE	TREAT-MENT DURATION	N	STUDY ENDPOINTS	STUDY POPULATION	FOLLOW UP	NUMBER OF COUNTRIES AND CENTERS
			QD			neurologic disease)			
Studies to Support Efficacy and Safety									
10	Barsic 2000	Randomized Open-label	Doxycycline hyclate 100 mg BID	14 days	40	Resolution of EM/NSS, improvement, or failure	EM/NSS	Day 14, 6 and12 months	Croatia: 2
			Azithromycin 500 mg BID x 1 d, then 500 mg x 5 days	6 days	48				
11	Strle 1992	Randomized	Doxycycline 100 mg BID	14 days	23	Time to resolution of EM/NSS & development of disease progression	EM/NSS	Day 7, 14; 2, 6, 12, 18, 24 months	Slovenia: 1
			Phenoxymethyl-penicillin 1 million IU TID	14 days	21				
			Azithromycin 250 mg BIDx2 d, 250 mg x 10 days	12 days	20				
12	Strle 1993	Randomized	Doxycycline 100 mg BID	14 days	52	Development of disease progression	EM/NSS	Day 7, 14 2, 6, 12, 18, 24 months	Slovenia: 1
			Azithromycin 500 mg BID x 1, 500 mg x 5 days	6 days	55				
13	Stupica 2012	Randomized	Doxycycline 100 mg BID	10 days	108	Early complete or partial response &	Solitary EM/NSS	Day 14; 2, 6, 12 months	Slovenia: 1
			Doxycycline 100 mg BID	15 days	117				

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#	AUTHOR/ YEAR	STUDY DESIGN	REGIMEN/DOSE	TREAT-MENT DURATION	N	STUDY ENDPOINTS	STUDY POPULATION	FOLLOW UP	NUMBER OF COUNTRIES AND CENTERS
						late complete response, partial response or failure			
14	Kuiper 1994	Prospective, Non-randomized	Doxycycline 100 mg BID	10-14 days	24	Development of disease progression	Solitary EM/NSS	Week 6; By tele-phone at 6-31 months	Netherlands : 1
			Tetracycline 250 mg QID	10-14 days	52				
			Penicillin	Not specified	1				
15	Strle 1996	Prospective, Non-randomized	Doxycycline 100 mg BID	14 days	42	Development of disease progression	Solitary EM/NSS	Day 14; 2, 6, 12 months	Slovenia: 1
			Azithromycin 500 mg BID x 1, 500 mg x 5 days	6 days	58				
16	Cerar 2010	Prospective, Non-randomized	Doxycycline 100 mg BID	15 days	145	Complete or incomplete response (partial response & failure)	Solitary EM/NSS	Day 14; 2, 6, 12 months	Slovenia: 1
			Cefuroxime axetil 500 mg BID	15 days	140				
			Cefuroxime axetil 500 mg BID	15 days	124				

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7.1.2. Review Strategy

The Applicant submitted publications for 34 studies of which 31 evaluated doxycycline for the treatment of Lyme disease and two evaluated the natural history of Lyme disease. One study was not applicable to the efficacy analysis since clinical outcomes were presented by culture results rather than treatment group. Of the 31 studies, 4 US (3, 4, 5, 6) and 7 European (10-16) studies assessed the efficacy of doxycycline for early Lyme disease, as evidenced by EM. Based on the assessment of the baseline characteristics and degree of missing data and other confounding factors, e.g. use of intercurrent antibacterial drugs, we focused on 2 US natural history studies (1,2) and 3 US studies (3, 4, 5) of the 100 mg BID regimen as the basis for the assessment of doxycycline efficacy in early localized and early disseminated Lyme disease. Two additional studies using doxycycline 100 mg TID for 20 days (7, 8) were also reviewed given that these studies were the basis for the approval of cefuroxime axetil for treatment of early Lyme disease (erythema migrans) caused by susceptible strains of *B. burgdorferi*. Twenty studies that examined the efficacy of doxycycline treatment in late disseminated Lyme disease, including neuroborreliosis, for the prevention of EM, and retrospective studies were considered supportive.

The US and European studies were analyzed separately as the disease is milder in Europe and is caused by distinct Borrelia species. One additional natural history study from Europe (9) was identified in a literature search and was compared to the European treatment studies.

No placebo-controlled studies were identified, likely because these studies are considered unethical/non-feasible. Primary evidence for efficacy was derived by comparing the doxycycline treatment effect in the 3 US studies of the BID regimen with no treatment in the 2 natural history studies. The primary efficacy endpoint was the absence of objective Lyme disease manifestations, specifically, arthritis, carditis, or neurologic disease at 6 months.

7.2. Review of Relevant Individual Trials Used to Support Efficacy

Data and Analysis Quality

There were no case report forms or patient data to review for this NDA, a 505(b)(2) application, where the published literature and RLD labeling served as sources for safety and efficacy data. The Applicant was unable to obtain subject level data for any of the studies in this submission. Clinical studies were reviewed by the medical reviewer individually for data quality (see individual study reports in Section 7.2).

Compliance with Good Clinical Practices

The applicant states that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act do not apply because the application/submission which this certification

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accompanies does not reference any clinical trial. Most of the studies reviewed noted that informed consent was obtained and study protocol was approved by the institutional review board. However, because this review was based on the published literature, only minimal information could be obtained regarding whether the study sponsors/investigators adhered to Good Clinical Practices (GCP). This applies to all studies in section 7.2.

Financial Disclosure

Please refer to the section on Financial Disclosures.

Statistical Analysis Plan

In this review, the efficacy of doxycycline will be compared to no treatment using the results seen in the natural history studies. The statistical plan for such an analysis is discussed in section **Error! Reference source not found.**.

Protocol Amendments

For each study discussed in section 7.2, protocol amendments will not be discussed.

Studies discussed below will be identified either by author and year or by the study number (#) assigned in

Table **5** and
Table 6.

7.2.1. US Natural History Studies

Two natural history studies were conducted in the US by Dr. Allen Steere to assess the natural progression of Lyme disease after onset of EM. The study design and endpoints for each study will be summarized in
Table 7.

7.2.1.1 Study Design and Endpoints

1. Study 1 - Steere 1979

In 1976-77, a surveillance system identified patients in Southeastern Connecticut with a recent onset of EM. Patients were examined when EM was present and after its disappearance. Those who developed joint or neurologic involvement were seen at 1-4 week intervals and after recovery. A CBC, ESR, rheumatoid factor, cryoglobulins, immunoglobulins, and complement levels were obtained. If arthritis developed, antistreptolysin O and antinuclear antibodies were obtained. For data analysis, patients were divided into 2 groups:

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- EM with neurologic +/- joint involvement
- EM without any late features

For patients seen multiple times, only one value was used for each system affected (the one that coincided with the greatest clinical activity). Patients with onset of disease in 1976 were followed for 18 months, and those with onset in 1977 were followed for 6 months.

2. Study 2 - Steere 1980

A prospective study of 135 patients with active EM was conducted from 1976 to 1979. When EM was active, patients were examined at least every other week, and during later manifestations, examined every 1 to 4 weeks. Patients were asked to keep a record of symptoms between visits, and telephoned yearly to confirm remission since they were last seen. With a few exceptions, during the summers of 1976 and 1978, patients were untreated, and during 1977 and 1979, they were treated with antibacterial drugs as noted in

Table **5**. Depending on which summer the patient entered the study, the follow-up was between 6 to 29 months. The cut-off time of the study was 1 January 1980. The primary endpoint in the study was the development of later manifestations such as neurologic abnormalities (meningoencephalitis – headache, stiff neck, CSF pleocytosis, abnormal electroencephalogram or facial palsy), cardiac abnormalities (AV block or EKG changes compatible with myocarditis), or arthritis, defined as pain on motion, swelling, or warmth of affected joints. Arthralgia and periarticular pain were excluded.

Key Inclusion and Exclusion Criteria

1. Steere 1979 - recent onset of EM was the only inclusion criteria.
2. Steere 1980 - active EM was the only inclusion criteria.

Table 7: Primary Endpoints for Untreated Patients in US Natural History Studies

AUTHOR/ PERIOD	N	CLINICAL ASSESSMENTS		PRIMARY OBJECTIVES
		Early	Late	
Steere 1976-1977	48	Time to resolution of EM and NSS	6 - 18 months	• Assess clinical course of Lyme disease beginning with EM • Absence of disease progression (neurologic or joint)
Steere 1976-1979	55	Time to resolution of EM and NSS	6 – 29 months	• Evaluate outcomes of treated and untreated patients • Absence of disease progression (neurologic, joint, cardiac)

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Medical Reviewer Comment: The two natural history studies shared similar characteristics (same investigators, study site, and study period between 1976 and 1977), but the Applicant was unable to determine if there was any overlap among patients. Based on our assessment, there may have been an overlap of 8 patients at the 6-month time point in both studies at the most. For purposes of the efficacy analysis, it will be assumed that the patients in each study are unique.

These studies had limitations as they were conducted at a time when the diagnosis and clinical characteristics of Lyme disease had not been fully described, and not treating with antibacterial drugs was still feasible. Lyme disease was known to affect both children and adults with a characteristic skin lesion (EM), followed weeks to months later by involvement of the joints, nervous system, and heart. The etiology of Lyme disease was unknown, but the disease was hypothesized to be transmitted by a tick vector. Patients were enrolled through a surveillance system in southeastern CT, and the diagnosis of Lyme disease was made by identification of patients with EM (described as a red, expanding macule or papule that formed a large annular lesion, usually with a bright red border and partial central clearing). The authors did not measure the EM lesion, test for other tick borne infections, such as Southeastern Tick-Associated Rash Illness (STARI) or for co-infections such as human granulocytic anaplasmosis (HGA), or report the history of a tick bite. Diagnostic testing for Lyme disease was also unavailable at the time.

Both studies were observational and non-randomized. Cardiac evaluation was not conducted and carditis was not evaluated in Study # 1. In Study # 2, cardiac abnormalities were reported. In Study # 2, the untreated and treated groups were not randomized or blinded. As it was unknown whether the disease will respond to antibacterial drugs, patients were either treated or left untreated during a given year based on clinical responses to antibacterial drugs during the preceding year. On occasion, patients were treated or untreated based on the severity of symptoms regardless of which year they entered the study. This may have led to selection bias. Patients were asked to keep a symptom diary between visits.

As far as clinical outcomes, both studies measured the time to resolution of EM and NSS (early clinical assessment). However, the timing of this early assessment was not the same for each patient. Thus, an early endpoint of resolution of EM and NSS could be not used in the efficacy analysis.

7.2.1.2. Study Results

Patient Disposition

1. **Steere 1979** – no discontinuations or dropouts were reported.

2. **Steere 1980** – From 1976 to 1979, 135 patients were enrolled with active EM. Twenty-

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two were excluded from the analysis: 13 patients did not take antibacterial drugs as prescribed, and 9 were lost to follow-up.

Protocol Violations/Deviations

Not applicable to the natural history studies.

Demographic Characteristics

The demographic parameters were similar in both natural history studies. Both genders were represented. The range of ages for the patients enrolled was available for both studies, and included pediatric patients. In Study 2, 29% of the untreated patients were under 11 years of age. The race and ethnicity was not reported. The studies were conducted in Southeastern Connecticut where Lyme disease is hyperendemic.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

All untreated patients presented with EM, but whether it was single or multiple EM was not specified. The number of patients with associated NSS was not specified. No patients had arthritis at baseline in either study. In Study 2, two patients had cardiac abnormalities in the untreated group and 6 patients had neurologic abnormalities (meningoencephalitis and facial palsy) at baseline in the entire cohort (untreated and treated groups combined). Table 8 shows the demographics and baseline clinical characteristics in each study.

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Table 8: Demographic and Baseline Characteristics of Patients in US Natural History Studies

PARAMETERS	**Study 1 STEERE 1979 Untreated N = 48**	**Study 2 STEERE 1980 N = 113**			
		Untreated N = 55	**Penicillin N = 42**	**Erythromycin N = 9**	**Tetracycline N = 7**
Demographic parameter					
Sex					
Male n (%) Female n (%)	28 (58) 20 (42)	28 (51) 27 (49)	23 (55) 19(45)	5 (55) 4 (45)	6 (86) 1 (14)
Age					
Mean years Median (years) Range (years)	ns ns 2-67	26 25.5 2-61	ns 24 2-67	ns 27 6-41	ns 32 18-59
Age Group					
<11 years 12-25 years 26-37 years > 37 years		16 (29) 11 (20) 14 (25) 14 (25)	10 (24) 12 (28) 13 (31) 7 (17)		
Race	ns	ns			
Region (US)	Connecticut	Connecticut			
Baseline Characteristics					
Any EM	48 (100)	55 (100)	42 (100)	9 (100)	7 (100)
Single EM	ns	66 (58)			
Multiple EM	ns	47 (42)			
NSS	present	present			
Arthritis	0	0			
Neurologic disease	0	6 (5)			
Cardiac disease	0	2 (4)	2 (5)	0	0

ns = not specified; NSS = Non-specific symptoms: malaise, fatigue, chills, fever, headache, stiff neck, myalgia, nausea, vomiting, migratory arthralgia, backache, lymphadenopathy, or sore throat.

Medical Reviewer Comment: The number of males and females differed between Tables 1 and 2 in the publication by Steere 1980 (study 2). Table 1 reported 29 males, 26 females in the untreated group, and 21 males and 21 females in the penicillin group. The numbers reported above in Table 8 above correspond to the gender reported in Table 2 of the publication.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Not applicable to the natural history studies.

Reference ID: 4276904

Efficacy Results – Primary Endpoint

The primary efficacy endpoint for the natural history studies was the absence of objective Lyme disease manifestations at 6 months, shown in bold in Table 9. Overall results of the entire study period and at specific time points are also included. Time to resolution, duration, and characteristics of specific clinical manifestations are provided below under the subheadings for each study.

Table 9: Objective Lyme Disease Manifestations in Natural History Studies

PARAMETERS	STUDY 1 STEERE 1979 UNTREATED N = 48	STUDY 2 STEERE 1980 N = 113			
		UNTREATED N = 55	PENICILLIN N= 42	ERYTHRO-MYCIN N = 9	TETRA-CYCLINE N=7
Overall results n (%)					
No objective manifestations	26 (54.2)	21 (38.1)	ns	ns	ns
Arthritis	22 (45.8)	34 (61.8)	12 (28.6)	2 (22)	1 (14)
Neurologic disease	9 (18.8)	4 (7.3)	5 (11.9)	1 (11.1)	0
No arthritis at specific time points n (%)					
6 months	**23/35 (65.7)[a]**	**31/55 (56.4)**	**33/42 (78.6)**	**ns**	**ns**
12 months	ns	15/42 (35.7)	ns	ns	ns
18 months	3/13 (23.1)[b]	(26.0)	(65.0)	ns	ns

[a] Based only on cohort with onset in 1977
[b] Based only on cohort with onset in 1976

1. Study 1 - Steere 1979

Thirteen patients with onset in 1976 and 35 with onset in 1977 were studied prospectively for 18 and 6 months, respectively. All patients presented with EM, and many had NSS (malaise, fatigue, chills, fever, headache, stiff neck, myalgia, nausea, vomiting, migratory arthralgia, or sore throat). The first phase of illness lasted a median of 4 weeks (range 2 days-10 weeks). Twenty-six patients (54%) had no later symptoms, while 22 (46%) developed arthritis, and 9 (19%) of them also developed neurologic disease. Neurologic abnormalities began at a median of 7 weeks (range 0.5-10) after the onset of EM, and included meningoencephalitis in 8, with superimposed brachial or lumbar neuritis in 2, sensory radiculoneuritis in 1, mononeuritis multiplex in 1, and cerebellar ataxia in 1. The ninth patient had facial palsy alone. Neurologic symptoms were most severe at onset, and recurred intermittently for 2-9 months. Intermittent attacks of mono- or oligoarticular arthritis, especially of the knee, were most common.

2. Study 2 - Steere 1980

Reference ID: 4276904

From 1976 to 1979, 135 patients with active EM were studied. Twenty-two were excluded from the analysis for non-adherence to medication or follow-up. Of the remaining 113, 55 were untreated and 58 were treated with an antibacterial drug listed in

Table **5**. Most patients received antibacterial drugs during the summers of 1977 and 1979 with the following exceptions: 21 patients were not treated: 11 were seen prior to the decision to treat, 9 had fading lesions and mild symptoms, and 1 refused therapy. Most patients received no antibacterial drugs during the summers of 1976 and 1978 with the following exceptions: 3 patients received antibacterial drugs due to the discretion of their treating physician in 1978. The number untreated in each subsequent year of the study was: 11, 8, 23, and 13.

All untreated patients presented with EM, and many of them had NSS (frequency was not specified). In untreated patients, EM and NSS resolved within a median of 10 days (range 1-46) after the first visit. Significantly fewer antibacterial drug-treated patients developed recurrence (5) than did untreated patients (17). The recurrences occurred usually within 1 year, but in one case, a recurrence was documented after 4 years. When data from all 4 years are combined, 34 untreated patients (62%) developed arthritis, and 4 (7%) developed neurologic disease (either meningoencephalitis or facial palsy). None developed carditis during the study. For the 11 untreated patients with arthritis who were followed at least 29 months (1976 and 1977 patients), the median total duration of joint involvement (all attacks added together) was 17 weeks (range 4-80). For untreated patients, the median duration of neurologic involvement was 10 weeks (range 1-40) with a time to onset of 4 weeks (range 2-12). The percentage of patients who remained free of arthritis from the time from first visit is noted in Figure 2. Seventy-nine percent of patients who received penicillin were still free of arthritis after 6 months compared to 56% of untreated ones; after 18 months, the disparity was even greater (65% compared to 26%, $p < 0.01$) for patients in 1976-1978 cohorts followed beyond 6 months.

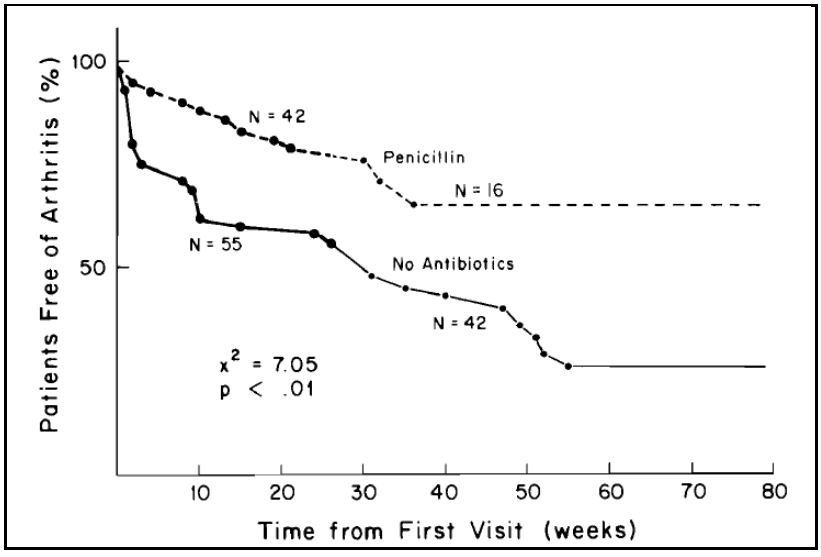

Figure 2: Percentage of Patients Free from Arthritis (Study 2)
Source: Steere 1980

A longitudinal study was conducted by Steere et al. in the same 55 untreated patients, who were then followed for a mean duration of 6 years (range 3-8) for the development of arthritis[8]. The time to onset of arthritis was the following: from 4 days to 2 years (mean of 6 months) in 28 patients (51%) who developed one or intermittent attacks of frank arthritis; 4 months to 4 years (mean of 12 months) in 6 patients (11%) who developed chronic synovitis in one to three large joints for ≥ 1 year. Of the remaining patients, 11 (20%) had no subsequent manifestation of Lyme disease and 10 (18%) had only arthralgias.

Medical Reviewer Comments: At the time of study 1, the clinical spectrum and diagnosis of Lyme disease was not yet fully discovered. Over 50% of patients had no disease progression. EM and NSS can resolve spontaneously, so this is biologically plausible. However, it is also possible that the patients and the providers did not fully recognize all features of Lyme disease. The subsequent failures reported were true failures, with objective manifestations (arthritis and neurologic disease). Cardiac outcomes were not assessed systematically. The Applicant reported the frequency of disease progression, which is the inverse ratio of the primary efficacy endpoint. As for disease progression, thirty-five patients were followed for only 6 months on study; their outcomes could have become worse by 18 months. Among 13 patients who were followed through 18 months, nearly 75% developed arthritis. However, the exact timing of the late manifestations could not be determined from the publication and it is possible that some of the events could have occurred during the first 6 months. Nevertheless, it appears that the longer the patients are followed, the greater the number who develop arthritis (34% by 6 months, and 77% by 18 months).

In Study 2, the length of follow-up may have influenced the results as well. The frequency of arthritis in untreated patients increased the longer that they were followed (44 and 74% at 6 and 18 months, respectively). However, there were fewer patients available for evaluation at 12 months than at 6 months, and the number available for evaluation at 18 months could not be determined. Specifically, in Figure 2, the solid line representing the percentage of patients free of arthritis plateaus at 26% at 18 months, and the denominator (number of patients) cannot be determined.

Nonetheless, as most treatment studies using the doxycycline BID regimen reported clinical outcome at 6 months, the outcome at 6 months in both natural history studies was used as the primary endpoint to compare doxycycline treatment with no treatment. Penicillin treatment decreased the frequency of arthritis at both 6 and 18 months by about 50%. The frequency of arthritis was lower in the tetracycline group as compared to the untreated group, but the difference was not statistically significant. Unfortunately, there are no studies in early Lyme disease comparing doxycycline treatment to no treatment.

[8] Steere Ac, Schoen Rt, Taylor E. The Clinical Evolution of Lyme Arthritis. Ann Intern Med. 1987;107:725–731.

Reference ID: 4276904

There were greater numbers of recurrences in the untreated group (17/55) compared to the penicillin-treated group (4/42) (p=0.013). In the treatment studies, recurrences were usually considered as clinical failures. Since the number of recurrences occurring at 6 months was unknown in the natural history studies, recurrence of EM could not be used as an endpoint to estimate the treatment failure rate. Also, since it was noted that recurrences usually occur within 1 year, and in one instance, 4 years, it is difficult to exclude the possibility of a new tick bite causing re-infection.

Efficacy Results – Secondary and other relevant endpoints
Other endpoints not used in the efficacy determination, such as early resolution of EM/NSS and recurrence, were discussed above.

Findings in Special/Subgroup Populations or Additional Analyses Conducted on the Individual Trials

No differences in clinical outcomes between adult and pediatric patients were reported in either study. In Study 2, the authors concluded that more men developed arthritis among patients given penicillin, but no reason for this distribution was given. This gender difference was not observed among untreated patients.

Gender, Race, Age, Weight, Baseline Disease Severity

Study 1 did not report any differences in gender, race, age, weight, or baseline disease severity in the untreated patients. In Study 2, all groups were equivalent with regards to age and gender, except that most patients in the tetracycline group were adult men. In Studies 1 and 2, 0% and 8.8% of all patients had evidence of early disseminated Lyme disease at baseline, respectively. Race and weight were not reported.

Geographic location (country)

The natural history studies were conducted in Southeastern Connecticut, a hyperendemic area of the Northeastern US for Lyme disease.

7.2.2. US Doxycycline Treatment Studies using BID Regimen

Four US studies assessed the efficacy of doxycycline (100 mg BID for 10, 20, or 21 days) compared to other antibacterial drugs (as noted in

Table **5**) in the treatment of early Lyme disease, as evidenced by EM. The major objective in the studies was to assess the resolution of acute symptoms (EM and NSS) and to evaluate disease progression despite antibacterial therapy. The primary efficacy endpoint of interest was the absence of objective manifestations of Lyme disease at 6 months. Objective manifestations were advanced manifestations of Lyme disease involving musculoskeletal, cardiac, and nervous

Reference ID: 4276904

system, as defined by the CDC clinical case definition of Lyme disease (see 15.3 Appendix A). The study design and clinical endpoints of each study are summarized below:

7.2.2.1 Study Design and Endpoints

1. Study 3 - Dattwyler 1990

A randomized, open-label, prospective study was conducted in patients with early Lyme disease at Stony Brook Lyme Disease Clinic in NY. Patients were enrolled between June 1988 to August 1989, and were given doxycycline 100 mg BID for 21 days or an active comparator. At presentation, EM was classified as uncomplicated (single lesion with no or very mild malaise) or complicated (single lesion with accompanying systemic signs and symptoms). Multiple disease was defined as having two or more EM lesions. At presentation, serology for *B. burgdorferi* was recorded.

All patients were evaluated at 2 weeks, 3 and 6 months after treatment. The clinical features of Lyme disease were described to each patient, and they were to notify the clinic immediately if signs or symptoms of progression developed. The primary endpoint was the development of late features, classified as major, minor, or none. Major features were defined as active neurologic infection: meningitis, or meningoencephalitis (severe headache, stiff neck on physical examination, and CSF pleocytosis); myocarditis (AV nodal block or left ventricular dysfunction); or recurrent attacks of arthritis (pain on movement and swelling of at least one joint). Minor features were cranial neuropathy, brief arthritis (one episode for less than 2 weeks); severe unremitting fatigue (interfering with daily findings); or arthralgia (joint pain without abnormal physical findings). Patients with no signs or symptoms other than mild fatigue were considered free of late disease. For purposes of this review, arthritis, carditis, and neurologic disease, signs of disseminated and late disease, will be referred to as objective Lyme disease manifestations.

Key Inclusion and Exclusion Criteria

Inclusion Criteria

- Adults with EM

Exclusion Criteria

- History of nervous system, cardiac, or collagen vascular disease
- History of arthritis
- Pregnancy or lactation
- Acute objective neurologic or cardiac features secondary to *B. burgdorferi* infection.

Medical Reviewer Comments: The limitations of this study included the following: the diagnosis of Lyme disease was based only on the appearance of EM. The size of the EM lesion was not

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reported, so it is unclear if it met the CDC surveillance definition (≥ 5 cm in diameter). Laboratory data were not obtained to exclude other diseases that can mimic Lyme disease. Testing for co-infections such as HGA or Babesiosis was not performed in any of the four studies conducted in the US. For this reviewer's efficacy analysis, the endpoint of 'no late disease' was categorized as a 'satisfactory outcome' and the development of any major or minor feature (which could include brief attacks of arthritis and neurologic disease) was considered treatment failure.

2. Study 4 - Massaroti 1992

A randomized, open-label, prospective study was conducted in patients with early Lyme disease in the early 1990s at multiple study sites in MA, MN, and CT. For data analysis, the patients were divided into three groups according to sites of dissemination: 1) localized infection was defined as EM accompanied by no more than regional lymphadenopathy, fatigue, or minor headache; 2) dissemination to non-neurologic sites was defined by the presence of secondary annular skin lesions, arthralgia, abdominal pain, or generalized lymphadenopathy; 3) dissemination to nervous system was defined by presence of headache, neck stiffness, facial palsy, or dysethesias. Headache alone was not considered sufficient for inclusion in this group. Patients were randomized to receive doxycycline 100 mg BID for 10 days or an active comparator.

Ten days after study entry, the patients were re-evaluated. If symptoms were still present, except for fatigue, patients who received amoxicillin/probenecid or doxycycline were given either antibacterial drug for an additional 10 days. Patients were re-evaluated again 30 days after study entry. If all symptoms had disappeared, patients were asked to call if they had recurrent symptoms or if they developed joint, cardiac, or neurologic symptoms. A final evaluation was done 6 months after study entry. At each visit, a history and physical examination was performed, and a CBC, UA, ESR, liver function tests, BUN, creatinine, and ELISA testing for *B. burgdorferi* was obtained. Women of childbearing potential were required to have a negative pregnancy test at entry, and to use contraception for 3 months thereafter.

Key Inclusion and Exclusion Criteria

Inclusion Criteria

- Adults over 16 years of age with EM or with flu-like symptoms AND elevated IgM or IgG antibody response to *B. burgdorferi* at study entry or a fourfold change in titer between acute and convalescent sera 4 weeks later

Exclusion Criteria

- Radiculopathy or CSF pleocytosis (but not facial palsy alone)
- Pregnancy

Medical Reviewer Comments: The authors defined EM by CDC criteria as an expanding annular skin lesion of at least 5 cm in diameter, usually with central clearing and a bright red outer

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border. Generally, having flu-like symptoms with only positive IgG would not necessarily confirm a diagnosis of Lyme disease. In the doxycycline arm, all evaluable patients had EM at baseline. Although the patients were randomized to receive 10 days of antibacterial drugs, a few patients who were randomized to the doxycycline arm, were given an additional 10 days of doxycycline. So essentially, these patients received a 20-day course of doxycycline. Thus, for the purposes of this review the duration of doxycycline in this study was considered 20 days rather than 10 days.

3. Study 5 - Dattwyler 1997

A randomized, open-label, prospective study was conducted in patients with early Lyme disease at multiple study sites in NY, CT, WI, PA, and NJ between May 1990 and June 1994. Patients were randomized to receive doxycycline 100 mg BID for 21 days or an active comparator. Patients with signs of meningitis or neurologic involvement underwent lumbar punctures at the investigator's discretion. EM lesions were photographed and evaluated by the same investigator. CBC, chemistry panel, VDRL, ANA, RF, and ELISA and Western blot testing for *B. burgdorferi* antibody reactivity were obtained at baseline.

Examinations were performed weekly during the therapy, and three, six, and nine months after completion of therapy. Clinical cure was defined as resolution of objective clinical findings of Lyme disease, while treatment failure was indicated by objective signs compatible with clinically active Lyme disease, including evidence of arthritis or neurologic disease. Outcome was not assessable if antibacterial drug was administered at improper dose or duration, concomitant antibacterial drugs were used, patient failed to meet entry criteria, withdrew from the study because of severe adverse events, or death.

Key Inclusion and Exclusion Criteria

Inclusion Criteria

- Patients eight years of age or older with EM, defined as an expanding, erythematous skin lesion at least 5 cm in diameter
- Acute disseminated Lyme disease (defined as 1 or more of the following):
    - more than one EM
    - carditis manifested by heart block
    - neurologic manifestations - seventh-cranial nerve palsy or radiculitis of less than three months' duration
    - acute large-joint arthritis

Exclusion Criteria

- Pregnancy or lactation

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- Evidence of syphilis, meningitis, encephalitis, collagen vascular disease, gallbladder disease
- Current symptoms of Lyme disease for which previous treatment had been given
- Serious underlying disease that precluded evaluation of a response to treatment
- Hypersensitivity to ceftriaxone or doxycycline.
- Those treated with antibacterial drugs effective in Lyme disease 48 hours prior to entry or an investigational compound within 2 weeks of entry were excluded.

Concurrent treatment with other antimicrobial agents or steroids during the treatment period was not permitted. Investigators were instructed to not prescribe antibacterial drugs with known effectiveness in Lyme disease until after the patients had been evaluated three months after study treatment.

Medical Reviewer Comments: This study enrolled patients with more disseminated Lyme disease at baseline as compared to Studies 3 and 4. The strengths of this study included more robust diagnostic criteria (CDC definition of EM, photographic evaluation of EM and testing for other conditions that can mimic Lyme disease) and classification of patients who were given intercurrent antibacterial drugs as 'not assessable.' The authors stated that intercurrent antibacterial drugs were not be given until the patient had been evaluated 3 months after study treatment. Data on intercurrent antibacterial drugs past 3 months were unavailable. This potential use of intercurrent antibacterial drugs may have led to confounding in this study.

4. Study 6 – Wormser 2003

A randomized, placebo-matched, double-blinded study was conducted between 1992 and 1994. The study was performed at Westchester Medical Center in NY. Patients were randomly assigned to one of three treatment groups as noted in

Table **5**, including a doxycycline 100 mg BID regimen given for 10 days and the same regimen given for 20 days. Matching placebo was given in each treatment arm. Block randomization and stratification by whether patients were symptomatic (defined as having any systemic symptoms or multiple EM) or asymptomatic (defined as having a single EM, and no systemic symptoms) were used. This was done to ensure equal representation of disseminated disease in each group.

Key Inclusion and Exclusion Criteria

Inclusion Criteria

- 16 years of age or older with EM (defined by the CDC surveillance definition of Lyme disease)

Exclusion Criteria

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- Pregnancy or lactation
- Allergy to a tetracycline or β-lactam antibacterial drug
- Receipt of antibacterial drug treatment for Lyme disease for more than 48 hours before enrollment
- Meningitis or advanced heart block
- Any underlying condition that might interfere with evaluability or follow-up

A history and physical examination was performed at baseline, day 10, day 20, and 3, 6, 12, 24, and 30 months after initiation of therapy. Complete neurologic examinations and neurocognitive evaluations using healthy volunteers as controls were performed at several time points. Patients were interviewed by telephone if appointments were missed. CBC, serum chemistry, ELISA for *B. burgdorferi*, and EKG was obtained at baseline. Patients were considered unevaluable if they did not adhere to study medication. Nonadherence was defined by taking fewer than 90% of prescribed capsules or not returning pill containers at the 10 and 20-day visit, receiving an intercurrent antibacterial drug within the first 20 days, not meeting study inclusion criteria, or not attending follow-up visits. Patients who had an intercurrent EM due to re-infection were considered unevaluable from that point onward. Outcome was characterized as a complete response, partial response, or failure at 20 days, and 3, 12, and 30 months. The definitions of these outcomes are noted below:

Clinical Assessment at Day 20:

- Complete response: Resolution of EM and associated symptoms and return to pre-Lyme disease health status
- Partial response: Resolution of EM but incomplete resolution of development of subjective symptoms
- Failure: Occurrence of any one of the following during the first 20 days: no clinical improvement by day 10, recurrence of EM, recurrence of fever attributed by the study physician to Lyme disease, development of new objective rheumatologic, cardiac, or neurologic manifestations of Lyme disease that were not present with in the first 10 days, or the occurrence of meningitis, advanced heart block, or another objective manifestation of Lyme disease requiring intravenous therapy.

Clinical Assessment at 3, 12, and 30 months:

- Complete response: No recurrence of EM or associated symptoms and the continued absence of objective rheumatologic, cardiac, or neurologic manifestations of Lyme disease, with return to pre-Lyme disease health status
- Partial response: No recurrence of EM and the continued absence of objective manifestations of Lyme disease but incomplete resolution or development of subjective symptoms of uncertain cause
- Failure: Occurrence of objective manifestations of Lyme disease

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Medical Reviewer Comments: Six-month clinical outcome data were not available in this study to compare with the efficacy of no treatment at 6 months in the natural history studies. The major limitation in this study was that several patients received 1 or more courses of antibacterial drugs for unrelated conditions, such as sinusitis, during the 30-month follow-up period. These patients were not excluded from the analysis, and their outcomes were not reported separately, except at the last contact with the patient. Use of intercurrent antibacterial drugs may have led to confounding in this study (discussed further in study results under concomitant medications).

For the efficacy analysis, this reviewer included both complete and partial responses at month 12 as 'satisfactory' as this included resolution of EM and some improvement in associated symptoms with continued absence of objective manifestations of Lyme disease. Only objective evidence of treatment failure (arthritis, neurologic or cardiac manifestations) were considered true failures.

7.2.2.2 Study Results

In this section, study results pertaining only to the doxycycline treatment arm will be discussed.

Patient Disposition

Patient discontinuation was highest in Studies 5 and 6. The numbers of subjects who discontinued the studies and the reasons for discontinuation are listed in Table 10.

Study 5 – Dattwyler 1997 had 8 patient discontinuations (4 due to adverse events, 3 left due to administrative reasons, and 1 was judged to not have EM after treatment had begun).

Study 6 – Wormser 2003 had the highest number of discontinuations, post-randomization. In the 10-day arm, one patient each developed an intercurrent EM (likely due to reinfection) at 3, 12, and 30 months. In the 20-day arm, 1 and 4 patients developed intercurrent EM at 3 and 30 months, respectively. During the 30-month follow up period, 16 and 9 patients, in the 10- and 20-day arms, respectively, were not available for follow-up on one or more study visits. In the 10-day arm, 11 were non-adherent: 9 did not take the study drug as prescribed and 2 took intercurrent antibacterial drugs within the first 20 days. In the 20-day arm, 14 did not take the study drug as prescribed.

Reference ID: 4276904

Table 10: Summary of Subject Discontinuations from 4 US Studies of Doxycycline BID Regimen

#	Treatment duration	Study Duration	N	Discontinued N (%)	Reason Given for Discontinuation				
					Adverse event	Intercurrent EM (reinfection)	Lost to Follow-up	Non-adherence	Other
3	21 days	6 months	37	2 (5)	2 (5)				
4	20 days	6 months	22	0					
5	21 days	9 months	72	8 (12)	4 (6)				4 (6)
6	10 days	30 months	61	31 (51)	1 (2)	3 (5)	16 (26)	11 (18)	
6	20 days	30 months	59	28 (48)		5 (9)	9 (15)	14 (24)	

Reference ID: 4276904

Demographic Characteristics

The demographic characteristics are listed in Table 11. Both genders were represented in the studies, with a slight male predominance in most of the studies. The gender was not reported in two patients excluded for adverse reactions in Study 3. Study 5 recruited both adult and pediatric patients, and the other studies recruited only adults. The race and ethnicity was not specified except in Study 6, in which the majority were white.

Table 11: Demographic Characteristics of US Subjects Treated with Doxycycline BID

PARAMETER	STUDY 3 DATTWYLER 1990 N = 37	STUDY 4 MASSAROTI 1992 N = 22	STUDY 5 DATTWYLER 1997 N = 72	STUDY 6 WORMSER 2003	
				10 day N = 61	20 day N = 59
Sex					
Male n (%)	19 (54)	11 (50)	44 (61)	42 (69)	35 (59)
Female n (%)	16 (46)	11 (50)	28 (39)	19 (31)	24 (41)
Age (years)					
Mean (SD)	36.1	44 (16)	43 (18)	42 (13)	44 (14)
Median	ns	ns	ns	39	42
Range	ns	ns	7-84	16-73	20-74
Race n (%)	ns	ns	ns		
White				57 (93)	57 (97)
Black				1 (2)	1 (2)
Hispanic				2 (3)	1 (2)
Asian				1 (2)	0
Study site	NY	MA, CT, MN	NY, CT, WI, NJ, PA	NY	NY
ns = not specified; NY = New York; MA = Massachusetts, MN = Minnesota, CT = Connecticut, WI = Wisconsin, PA = Pennsylvania, NJ = New Jersey					

Medical Reviewer Comments: The higher enrollment of males in most studies and whites in the study in which race was specified, may reflect the higher incidence of Lyme disease in these populations (per US Surveillance for Lyme Disease 1992-2006). Overall, racial-, ethnic-, and gender-based differences in the epidemiology, clinical presentation, and immunologic response to Lyme disease remain unknown. Lyme disease has similar manifestations in adults and children, and the diagnostic and therapeutic approach is based on the methods used for adults. Although there is some variability in the patient demographics of the studies above, they were conducted in regions which are hyperendemic for Lyme disease and likely to be representative of those populations who are susceptible to Lyme disease.

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Other Baseline Characteristics

For comparison between the 4 doxycycline treatment studies, baseline clinical characteristics were categorized in a similar method: single or multiple EM, frequency of NSS, and evidence of early disseminated disease. This is shown in Table 12. Details are given below for each study.

Table 12: Baseline Clinical Characteristics in Doxycycline Studies using BID Regimen

PARAMETER	STUDY 3 DATTWYLER 1990 N=37	STUDY 4 MASSAROTI 1992 N=22	STUDY 5 DATTWYLER 1997 N=72	STUDY 6 WORMSER 2003	
				10 day N = 61	20 day N = 59
Clinical Feature					
Any EM n %	37 (100)	22 (100)	71 (99)	61 (100)	59(100)
Single EM n (%)	31 (84)	15 (68)	1 (1)	47 (77)	45 (76)
Multiple EM n (%)	6 (17)	7 (32) *	71 (99)	14 (23)	14 (24)
NSS n (%)	13 (35)	22 (100) *	61 (85) *	43 (71)	45 (76)
Onset of EM to treatment (d ± SD)	ns	7 ± 8	10 ± 14	3	5
Prior Lyme disease n (%)	ns	ns	ns	5 (8)	7 (12)
Evidence of early disseminated disease					
Joint swelling	0	0	5 (7)	0	0
Facial palsy	0	0	3 (4)	0	1
Carditis	0	0	2 (3)	0	0
* approximation derived from studies					

1. **Study 3 – Dattwyler 1990**

Thirty-seven patients with EM were treated with doxycycline. Two were excluded from the study due to adverse reactions (1 with gastrointestinal upset, and the other with photodermatitis). At presentation, 22 had uncomplicated disease (single lesion with no or very mild malaise), 7 had complicated disease (single lesion with NSS), and 6 had multiple lesions. Patients with complicated and multiple lesions had NSS such as malaise, profound fatigue, migratory musculoskeletal pain, headache, fever, chills, or regional lymphadenopathy. None had evidence of objective manifestations such as arthritis, cardiac or neurologic disease at baseline.

2. **Study 4 – Massaroti 1992**

Reference ID: 4276904

Twenty-two patients with EM were treated with doxycycline. At baseline, 4 had localized infection (EM with only fatigue, minor headache, or regional lymphadenopathy), 7 had non-neurologic symptoms (secondary EM, arthralgia, or abdominal pain), and 11 had neurologic symptoms (headache with neck stiffness and dysesthesia). Up to 7 patients may have had multiple EM based on the definitions above, and the remaining likely had single EM. The approximate numbers of single and multiple EM are noted in Table 12. All 3 groups, those with localized infection, non-neurologic symptoms, and neurologic symptoms had NSS, but the localized infection group may have had milder symptoms based on the definition above. None had evidence of objective manifestations such as arthritis, cardiac or neurologic disease at baseline.

3. Study 5 – Dattwyler 1997

Seventy-two patients with EM were treated with doxycycline. After treatment was begun, 1 patient was judged not to have had EM. Seventy-one (99%) had multiple EM at baseline. At baseline, 5 patients had joint swelling, 3 had seventh-cranial-nerve palsy, and 2 had carditis, manifested by heart block. Overall, 10/72 (14%) had early disseminated Lyme disease. Thirty patients had arthralgia, 47 had fever or chills, 61 had fatigue, 49 had headache, and 31 had stiff neck. Up to 61 patients (85%) had NSS, manifesting as fatigue. It is unknown which patients had overlapping symptoms.

4. Study 6 – Wormser 2003

Sixty-one and 59 patients were treated with doxycycline for 10 and 20 days, respectively. The number of patients with multiple EM and NSS in each arm are noted in Table 12. There was 1 patient in the 20-day doxycycline arm with facial nerve palsy at baseline. About 10% of the patients had a history of Lyme disease. The clinical significance of this history was not discussed in the study.

Medical Reviewer Comments: EM and associated symptoms were present in almost all patients, but given the lack of patient-level data, the severity of illness was difficult to assess. Patients had relatively more disseminated disease at baseline (multiple EM, NSS, and symptoms of early disseminated disease) in Study 5 than in the other studies. Study 6 enrolled patients with history of Lyme disease, but did not discuss possible antibacterial drug exposure prior to the study or during the study as compared to patients without history of Lyme disease. It is difficult to interpret how the clinical outcomes in these patients may have differed from patients with index Lyme disease episode.

The consistent clinical characteristic in all studies was early Lyme disease, as evidenced by EM, which is the indication being sought by the Applicant.

Treatment Compliance

Reference ID: 4276904

Discussed above under patient disposition.

Concomitant Medications

Concomitant antibacterial drugs were not allowed during the study period in most studies, with the following exceptions:

In Study 5, investigators were asked not to give antibacterial drugs that may have efficacy in treating Lyme disease until 3 months after doxycycline treatment. The number of patients receiving intercurrent antibacterial drugs was not provided. Please refer to 7.2.2.1 Study Design and Endpoints

In Study 6, the definition of nonadherence included the use of intercurrent antibacterial use within the first 20 days. However, the protocol did not preclude use of intercurrent antibacterial drugs for unrelated conditions, such as sinusitis, during the 30-month follow-up. A large proportion of patients received one or more courses of antibacterial drugs during the 30-month period: 24 of 50 (48%) patients in the 10-day doxycycline group and 22 of 45 (48.9%) patients in the 20-day doxycycline group. The authors reported that, at the last evaluation, the complete response rate of patients who did not take intercurrent antimicrobials was similar in each group (23 of 26 in the 10-day doxycycline group, 20 of 23 in the 20-day doxycycline group, $p>0.2$).

Medical Reviewer Comments: Nearly 50% of patients in the 10- and 20-day arms received other antibacterial drugs during study 6. The Applicant could not determine the number of patients who received intercurrent antibacterial drugs by the 12-month endpoint, which was the endpoint of interest in this study. Also, the type, duration, and number of courses taken of each antibacterial, and its indication were unknown. The authors mentioned that sinusitis was one of the unrelated conditions for which antibacterial drugs were given. As common treatments for sinusitis (e.g. amoxicillin, cefuroxime, or macrolides) can also treat early Lyme disease, this may have led to significant confounding in this study.

Rescue Medication Use

There was 1 doxycycline treatment failure in each of the 3 studies (4-6). Each patient who failed doxycycline therapy received intravenous ceftriaxone for 2-4 weeks and had a complete resolution of objective manifestations of Lyme disease.

Efficacy Endpoint – Primary Endpoint

The primary endpoint in the studies was the absence of objective manifestations of Lyme disease, such as arthritis, carditis or neurologic disease at long-term follow-up 3-30 months after initial presentation. The resolution of EM and NSS may have been an additional endpoint. However, as EM and NSS can resolve spontaneously and the natural history studies did not

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describe the timing of their resolution in sufficient detail, this earlier clinical endpoint was not used in the efficacy evaluation. The primary endpoint of interest for this review is the absence of objective manifestations of Lyme disease at 6-months post-treatment with doxycycline. A 6-month endpoint was chosen as the natural history studies and 3 of 4 US treatment studies using the BID regimen reported clinical outcome at 6 months. Study 6 reported long-term outcomes at 3, 12, and 30 months. The 12-month time point was chosen to compare with no treatment in Study 2 at 12 months (Study 1 had 6 & 18 month outcomes, Study 2 had 6 & 12 month outcomes). The specific results of each of the 4 studies will be outlined below.

1. Study 3 – Dattwyler 1990

Thirty five of thirty 37 patients had no objective symptoms of Lyme disease (meningitis, meningoencephalitis, myocarditis, or recurrent attacks of arthritis recurrences of EM), or needed additional antibacterial drug therapy at 6 months. Two patients were unevaluable due to adverse reactions. Minor symptoms of mild fatigue and/or arthralgia, which resolved during the 6-month follow-up, occurred in 2 patients. Overall, the satisfactory response with doxycycline was 94.6 (95% Exact CI 81.8, 99.3) at 6 months with the lower bound of the CI for this study greater than the upper bound of the no treatment CI (81.8-70.3 = 11.5). See Section 7.3.1 for a discussion of estimate of the no treatment response for the natural history studies pooled.

Medical Reviewer Comments: The Applicant and the authors of the publication reported that 33/35 (94%) had no late disease. The two patients not represented in the numerator were those with minor symptoms. Two patients who had adverse reactions were excluded from the analysis, and the number of clinically evaluable patients was used as the denominator. The resultant percentage for success of doxycycline was similar to the satisfactory response noted above.

This study enrolled patients with the least disseminated disease at baseline (mostly single EM and fewer NSS) as compared to the other studies. There were only 2 unevaluable patients. A combination of these factors may have led to the highest efficacy rate for doxycycline in this study. Study 3 demonstrated the largest treatment effect of the three US studies 3, 4, and 5 compared to the pooled estimate of the natural history study.

2. Study 4 – Massaroti 1992

In 15/22 patients, early symptoms resolved within 3 to 10 days. Treatment was extended for 10 more days in 7 patients: 6 were treated with doxycycline and 1 was treated with amoxicillin/ probenecid. The patient who received an additional 10 days of an alternate antibacterial drug (amoxicillin/probenecid) was considered unevaluable. One patient in the doxycycline arm had treatment failure at the 30-day follow-up visit. This was a 37-year-old female who initially presented with EM, headache, and dysethesias and was treated with 10 days of doxycycline. She had not received an additional 10 days of antibacterial drugs, presumably due to resolution

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of early symptoms by day 10. She developed facial palsy 23 days after study entry. The CSF was normal, Lyme IgM was 200, and IgG was 1600. Values above >200 are generally considered positive, but can vary depending on stage of Lyme disease[9]. She was treated with parenteral ceftriaxone and recovered during the 6-month follow-up.

Overall, 20/22 patients had no objective symptoms of Lyme disease at 6 months after 20 days of doxycycline treatment. The satisfactory response was 90.9% (95% Exact CI 70.8, 98.9). The lower bound of the 95% CI was just above the upper bound of the no treatment CI (70.8-70.3 = 0.5).

Medical Reviewer Comments: The Applicant proposed that 21/22 patients in the doxycycline arm were treated with doxycycline throughout the entire study. Of these 21 clinically evaluable patients, 20 had no evidence of late disease at or after 30 days (95% had a satisfactory response). The analysis reported above that treats the unevaluable subject as a non-successful outcome is a more conservative estimate of efficacy. This more conservative analysis still leads to a positive treatment effect of 0.5% with doxycycline treatment as compared to no treatment. As compared to Study # 3, the treatment benefit may have been smaller due to wider confidence intervals as this study had a lower number of patients.

As stated above, although patients were randomized to receive 10 days of doxycycline, ten days after study entry, the patients were re-evaluated and treated for an additional 10 days if symptoms were still present. *Six of the patients received the additional 10 days of doxycycline for a 20-day course. We consider this treatment plan as essentially a 20-day course of doxycycline. In assessing efficacy, we can assume that those subjects receiving 10 days of doxycycline would have had similar or greater efficacy if they had received 10 additional days.*

Treatment failure occurred in a patient mentioned above who received 10 days of doxycycline. The authors reported that this patient had baseline symptoms suggesting neurologic dissemination (headache and facial dysethesias). However, the CSF was normal. Per IDSA guidelines, antibacterial drugs may not hasten the resolution of facial palsy, but are recommended to prevent further neurologic sequelae. Facial palsy in the absence of CSF pleocytosis, may be treated with a 14-day course of the same antibacterial drugs that are used to treat EM. Thus, if this patient had not been re-treated with an alternate agent (other than doxycycline), she may not have been a true failure. Also, it is plausible that this represents a true failure of a 10-day course of doxycycline, and that an initial course of 20 days may have prevented this neurologic manifestation.

3. Study 5 – Dattwyler 1997

[9] Craft JE, Grodzicki RL, Shrestha M, Fischer DK, Garcia-Blanco M, Steere AC. The antibody response in Lyme disease. Yale J Biol Med. 1984 Jul-Aug;57(4):561-5

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At 6 months, 54/72 patients had no objective signs of Lyme disease. One patient developed acute large-joint arthritis, fatigue, joint swelling, limitation of joint movement, arthralgia, and myalgia during treatment and seventeen patients were unevaluable. Overall, the satisfactory response of doxycycline treated patients at 6 months was 75% (95% Exact CI 63.4, 84.5) when considering those unevaluable as failures which is a conservative analysis. The lower bound of the CI was not greater than the upper bound of the no treatment CI (63.4-70.3 = -6.9).

Medical Reviewer Comments: *The Applicant submitted this study as a part of the NDA, but not as the primary evidence for efficacy. The authors of the publication reported a satisfactory response in 54/61 (89%) clinically evaluable patients at 6 months. The seven patients considered as not having a satisfactory response in the author's analysis were 'not-assessable' at the 6 months visit due to inadequate follow-up or withdrawal for adverse events. Eleven subjects were excluded from the author's analysis. The one failure discussed above does not appear to be considered a failure at 6 months in the author's analysis, possibly excluded due to being lost to follow-up. The satisfactory outcome using the ITT population in this study was lower as compared to Study 3 and 4. It is difficult to attribute low success rate to a greater number of patients with disseminated disease because there was only one treatment failure. The reviewers' conservative approach to efficacy evaluation and limitations of data in the literature based NDA likely underestimate the true satisfactory response in this study. One of the study limitations is that specific outcomes of those with more disseminated disease at baseline were not provided. For example, it is not specifically mentioned in the study that the patient who developed large-joint arthritis had joint swelling at presentation. This study alone does not provide sufficient evidence for efficacy of 21-day doxycycline regimen for the treatment of disseminated Lyme disease, specifically in patients presenting with frank arthritis, facial palsy, and carditis.*

4. Study 6 – Wormser 2003

Sixty-one patients were assigned to receive 10 days of doxycycline and 59 were assigned to receive 20 days of doxycycline. One patient in the 10-day arm developed meningitis at day 18. The patient developed low-grade fever, headache, nuchal rigidity, and the CSF showed pleocytosis. The patient's condition improved after ceftriaxone. The definition of both complete and partial response included resolution of objective manifestations of Lyme disease, which was the endpoint of interest in the efficacy analysis. Complete and partial response at 12 months were combined to achieve a 'satisfactory response'. In the 10- and 20-day groups, the satisfactory response was 50/61 (82%) and 50/59 (85%), respectively. The number of patients who received intercurrent antibacterial drugs was close to 50% in each group as discussed above (under Concomitant Medications). Satisfactory outcome at 12 months in the 10-day and 20-day arms were 42.6% and 47.4% when all patients who received intercurrent antibacterial drugs were assumed to have done so by 12 months and considered as failures, making this study uninterpretable in the efficacy analyses (See Integrated Review of Effectiveness).

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Medical Reviewer Comments: The authors and the Applicant performed an intention-to-treat analysis, but did not consider as failures patients given intercurrent antibacterial drugs during the 30-month follow-up. Upon FDA request, the Applicant was unable to clarify the number of patients who received antibacterial drugs by month 12, or any other information concerning their use such as type, dose, duration, and indication. This was one of only 2 studies that assessed a 10-day regimen of doxycycline 100 mg BID (the other was Study 2). A 10-day regimen is recommended by the IDSA guidelines. Effectiveness of 10-day doxycycline regimen cannot be established in this study due to confounding by intercurrent antibacterial drug use.

The following tables summarize the results of the 4 US Studies. Table 13 shows the clinical outcomes at both early and late assessments in all studies. The late assessment is shown in bold as it was used for the primary efficacy analysis. Table 14 summarizes the treatment effect in each individual study (in bold) as compared to the pooled estimate of no treatment in the natural history studies, see section 7.3.1.

Table 13: Early and Late Assessment in US Doxycycline Studies using BID Regimen

CLINICAL RESPONSE	**STUDY 3 DATTWYLER 1990**	**STUDY 4 MASSAROTI 1992**	**STUDY 5 DATTWYLER 1997**	**STUDY 6 WORMSER 2003**	
Treatment Duration	21 days	20 days	20 days	10 days	20 days
N	37	22	72	61	59
Early Assessment:	Post-treatment	Post-treatment	3 months	Day 20	
Satisfactory	35 (94.6)	20 (90.9)	63 (87.5)	51 (84)	57 (97)
Unsatisfactory	0	1 (4.5)	1 (1)	1 (2)	0
Unevaluable	2 (5.4)	1 (4.5)	8 (11)	9 (15)	2 (3)
Late Assessment:	**6 months**	**6 months**	**6 months**	**12 months**	
Satisfactory	**35 (94.6)**	**20 (90.9)**	**54 (75.0)**	**50 (82)** *	**50 (85)** *
Unsatisfactory	**0**	**1 (4.5)**	**1 (1)**	**1 (2)**	**0**
Unevaluable	**2 (5.4)**	**1 (4.5)**	**17 (24)**	**10 (16)**	**9 (15)**

Satisfactory: resolution of objective manifestations of Lyme disease (complete or partial)
Unsatisfactory: recurrence or failure (objective Lyme disease manifestations: arthritis, carditis, neurologic disease)
Unevaluable: discontinuation from study, or not assessable for any reason
*Study 6: Response does not account for possible intercurrent antibacterial drug use at 12 months. 24 and 22 patients in 10 and 20-day arm, respectively, given intercurrent antibacterial drugs during 30-month follow-up

Table 14: Estimate of Treatment Effect in US Doxycycline Studies of BID Regimen

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	ASSESSMENT	RESPONSE (%) [95% Exact CI]	ESTIMATE OF TREATMENT EFFECT*
STUDY 3 DATTWYLER 1990 (21 DAYS)	No late features through 6 months	35/37 (94.6) [81.8, 99.3]	81.8-70.3 = **11.5**
STUDY 4 MASSAROTI 1992 (20 DAYS)	No late features through 6 months	20/22 (90.9) [70.8, 98.9]	70.8-70.3 = **0.5**
STUDY 5 DATTWYLER 1997 (21 DAYS)	Clinical cure at 6 months	54/72 (75.0) [63.4, 84.5]	63.4-70.3 = **-6.9**
* Lower bound of the 95% CI in Study compared to upper bound of pooled no treatment 95% CI (70.3)			

7.2.3. US Doxycycline Treatment Studies using a TID Regimen

Studies 7 and 8 were submitted by the Applicant for review of clinical safety as the TID dosing regimen in these studies was higher than the proposed dosing for LYMEPAK. The Division chose to consider these studies in the assessment of efficacy as they were the basis for approval of cefuroxime axetil, in which the comparator drug was doxycycline 100 mg TID. However, the efficacy of doxycycline in these studies was uninterpretable due to a high number of unevaluable subjects in the ITT population. Thus, these studies were not included in the integrated review of effectiveness. A brief overview is provided below. As the study design and endpoints of each study was similar, section 7.2.3.1 will discuss both studies, with a few exceptions noted.

7.2.3.1 Study Design and Endpoints

Studies 7 and 8 were randomized, single-blinded, multicenter trials conducted in patients with EM (with or without NSS). Study 7 was conducted between June and September 1989 and Study 8 was conducted between May and November 1990. Both studies were conducted in CT, NJ, NY, and NC. The number of EM lesions was recorded and the primary lesion measured and (in nearly all cases) photographed. Patients were assigned to either cefuroxime 500 mg BID or doxycycline hyclate 100 mg TID for 20 days. A minimum of 12 days of therapy, with uninterrupted dosing in the first 5 days, was required for a patient to be considered evaluable.

A complete history and physical examination were done at the time of enrollment. A CBC, serum chemistry, EKG, UA, and Lyme IgM and IgG antibodies by ELISA and immunofluorescence assay were collected at the baseline visit. Repeat physical examinations were performed 1, 5, and 30 days post-treatment. Follow-up laboratory tests and EKGs were done at the first posttreatment visit. The clinical response of each patient at 1 and 12-months post-treatment was categorized as noted below. In each definition, 'other clinical signs and symptoms' were ranked by severity (mild, moderate, severe), and included splenomegaly, radiculopathy,

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regional and generalized lymphadenopathy, malaise, irritability, fatigue, jaw pain, headache, chills, stiff neck, paresthesia, myalgia, arthralgia, arthritis, pleuritis, backache, nausea, vomiting, diarrhea, sore throat, and fever.

At 1 month:

- Success: resolution of EM and other clinical signs and symptoms by the day 1 to day 5 post-treatment visit with a continued asymptomatic state through the 1 month post treatment follow-up period.
- Improvement: resolution of EM but incomplete resolution of any other clinical signs and symptoms of early Lyme disease by the day 1 to day 5 post-treatment visit with further improvement or complete resolution by the 1-month post-treatment follow-up visit
- Failure: no improvement in EM or other clinical signs and symptoms of early Lyme disease by day 1 to day 5 post-treatment visit
- Recurrence: initial success or improvement with recurrence of EM or other signs and symptoms of early Lyme disease by the 1 month post-treatment follow-up visit
- Unevaluable: receipt of less than 12 days of study drug, interruption of antimicrobial treatment in the first 5 days of therapy, violation of selection criteria, receipt of concomitant treatment with non-study antibacterial drug, failure to complete the post-treatment visits, withdrawal from the study because of an adverse event, or evidence of poor compliance with therapy.

At 12 months: Those who had success or improvement at 1 month were followed until 1 year post-treatment to determine whether they subsequently developed signs and symptoms of late Lyme disease.

- Success: no signs or symptoms of late Lyme disease (arthralgia, fatigue, arthritis, carditis, neurologic disease) throughout the 1-year follow-up period
- Improvement: some signs or symptoms consistent with Lyme disease but no objective evidence of active disease during the 1-year follow-up period
- Failure: signs or symptoms of late Lyme disease, including seropositivity to *B. burgdorferi* at the time of assessment during or at the completion of the 1-year follow-up period
- Unevaluable: lost to follow-up, development of evidence of early Lyme disease (EM) due to recurrence or reinfection during 1 year follow-up

Key Inclusion and Exclusion Criteria in both Study 7 and 8 (unless otherwise specified)

Inclusion Criteria

- Outpatients 12 years of age or older, weighing at least 45 kg
- Diagnosed with early Lyme disease confirmed by presence of physician-document EM (with or without systemic manifestations of infection)

Exclusion criteria

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- Pregnancy
- Lactation
- History of serious adverse reactions to any cephalosporin or tetracycline or an immediate hypersensitivity reaction to any penicillin
- Gastrointestinal disorders interfering with absorption of orally-administered antimicrobial agents
- Receipt of any systemic antimicrobial agent with known activity against *B. burgdorferi* within 10 days before enrollment
- Unstable comorbidity compromising the ability to respond to infection
- Advanced heart block or first degree block with PR interval of at least 0.3 seconds (Study 7 only)
- Neurologic illness requiring parenteral therapy (Study 7 only)

7.2.3.2 Study Results

Patient Disposition

Study 7 – Nadelman 1992

At 1-month post-treatment, 9 patients were unevaluable due to various reasons, including withdrawal due to an adverse event, failure to complete follow-up visits, and use of non-study antibacterial drugs. The early unevaluable patients at 1 month were carried over to the late assessment at 12 months. At the 12-month assessment, 7 additional patients were unevaluable. There were 16 out of 60 unevaluable patients at the end of the study.

Study 8 – Luger 1995

At 1-month post-treatment, 19 patients were unevaluable for various reasons, including deviation from the protocol, failure to complete follow-up visits, withdrawal because of adverse events, and enrollment in violation of selection criteria. These were carried over to the 12-month assessment. There were an additional 36 unevaluable patients at the 12-month assessment due to loss to follow-up, use of non-study antibacterial drugs, deviation from the protocol, and evidence of early Lyme disease (re-infection or recurrence). There were 55 out of 113 unevaluable patients at the end of the study.

Protocol violations/Deviations

See patient disposition above.

Demographic and Other Baseline Characteristics

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Table 15 shows the demographics and clinical characteristics of the patients in the studies evaluating the efficacy of doxycycline TID for 20 days.

Table 15: Demographic and Baseline Characteristics in Doxycycline Studies using TID Regimen

PARAMETER	STUDY 7 NADELMAN 1992 N= 60	STUDY 8 LUGER 1995 N = 113
Sex		
Male n (%) Female n (%)	35 (58) 25 (42)	68 (60) ^ 45 (40) ^
Age (years)		
Mean (SD) Range	45 (15) 19-83	ns 45-47
Race (%)		
White African-American Asian	96 2 2	97 ns ns
Study site	CT, NY, NJ, MN	CT, NY, NJ, MN
Clinical Characteristic		
EM n (%) Single EM n (%) Multiple EM n (%) NSS n (%) Onset of EM to treatment (median days)	59 (98) * 46 (76) 13 (22) 48 (80) 3	113 (100) 101 (89) 12 (11) 84 (74) 4
* 1 patient had a misdiagnosed skin disorder rather than EM ^ approximately 3/5 of all patients were male, exact number of male and female not specified		

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

In Study 7 and 8, patients who were non-compliant with treatment or used non-study antibacterial drugs, were considered unevaluable, as discussed under patient disposition. Rescue medication use for patients with unsatisfactory responses were discussed in *section 7.2.3.2 Study Results.*

Efficacy Results – Primary Endpoint

The absence of objective manifestations of Lyme disease, such as arthritis, carditis, or neurologic disease at 12 months was the primary efficacy endpoint in the US doxycycline TID studies. The estimate of treatment effect for this review will compare doxycycline to no treatment in Study 2, which had 12-month outcome data.

Reference ID: 4276904

1. Study 7 – Nadelman 1992

A satisfactory response was documented in 35/60 (58%) doxycycline patients at 12 months. Nine patients had an unsatisfactory response (failure or recurrence) by 12 months. Of these 9 patients, 2 had objective manifestations of Lyme disease: one patient had persistent EM and the other had arthritis at 1 month. The other 7 patients had NSS (e.g. myalgia, arthralgia, backache, headache, irritability, sore throat, stiff neck). However, the number of patients re-treated for failure or recurrence with alternate antibacterial drugs was not specified for the treatment arms separately. In the doxycycline treatment arm, 6/10 and 7/8 patients with unsatisfactory responses, were re-treated at 1 and 12 months, respectively. Thus, all 9 doxycycline patients were assumed to have had an unsatisfactory response due to the high probability of having been re-treated with alternate antibacterial drugs. The remaining patients were unevaluable as discussed under patient disposition. At 12 months, the lower bound of the point estimate of efficacy for doxycycline, 58% (46,71) was below the upper bound of the point estimate for no treatment, 35.7% (21,50) in Study 2. Thus, this study could not be used in the integrated review of effectiveness for LYMEPAK.

Medical Reviewer Comments: The authors used a clinically evaluable population for their efficacy analysis. A separate intent-to-treat analysis was also conducted by the authors in which all unevaluable patients were considered as having an unsatisfactory clinical response. The authors noted that there was an expected reduction in early satisfactory response rates to 75%, and the results were otherwise analogous to those presented for evaluable patients. This satisfactory response rate matched this reviewer's satisfactory response rate at day 30. The authors did not report the satisfactory response rate at 12 months, using the ITT population.

The approval of cefuroxime axetil in 1996 for early Lyme disease was based on the clinically evaluable population which used a "validated" subset of patients. The clinical diagnosis of early Lyme disease in these subjects was validated by 1) blinded expert reading of photographs, when available, of the pretreatment erythema migrans skin lesion, and 2) serologic confirmation (using enzyme-linked immunosorbent assay [ELISA] and immunoblot assay ["Western" blot]) of the presence of antibodies specific to *B. burgdorferi*, the etiologic agent of Lyme disease. *Currently, antibacterial drug approvals rely on an estimate of effectiveness using appropriately justified non-inferiority margin or superiority of an antibacterial drug to placebo or no treatment. To determine the efficacy of doxycycline compared to the cefuroxime arms in these studies, we would need a justified non-inferiority (NI) margin. This NI margin would need to consider the treatment effect of cefuroxime compared to no treatment. As this data is not available, we will instead directly compare the doxycycline results to the natural history studies as was done with the US BID studies in the previous section.*

2. Study 8 – Luger 1995

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There was a satisfactory response in 53/113 (46.9%) of the doxycycline patients at 12 months. Five patients on doxycycline arm had an unsatisfactory response at 1 month: 3 patients had objective manifestations of Lyme disease (1 had persistent EM, 1 had arthritis, and 1 had radiculopathy) and 2 patients had only NSS (e.g. arthralgia, fatigue, headache, backache, paresthesia). Of 15 patients with unsatisfactory responses between the two treatment arms, 2 received re-treatment with amoxicillin and two received re-treatment with doxycycline. However, it is unclear if the 2 patients who received amoxicillin (presumably randomized to doxycycline) had objective manifestations of Lyme disease or NSS alone. Nonetheless, the 5 patients with residual signs and symptoms at 1 month were assumed to have had an unsatisfactory response. No additional patients had an unsatisfactory response at 12 months in the doxycycline arm. At 12 months, due to the high unevaluable rate the efficacy of doxycycline (46.9%) was below the upper bound of the point estimate for no treatment 35.6% (21, 50) in Study 2. Thus, this study could not be used in the integrated review of effectiveness for LYMEPAK.

Table 16 summarizes early and late assessments of doxycycline efficacy in Study 7 and 8. Satisfactory response includes complete resolution of EM and absence of objective manifestations of Lyme disease. Unsatisfactory response includes any failures and recurrences, as was defined by the author.

Table 16: Early and Late Assessment in Doxycycline Studies using TID Regimen

PARAMETER	**STUDY 7 NADELMAN 1992 N= 60**	**STUDY 8 LUGER 1995 N= 113**
Early Assessment:	Day 30	Day 30
Satisfactory	45 (75.0)	89 (78.8)
Unsatisfactory	6 (10.0)	5 (4.4)
Unevaluable	9 (15.0)	19 (16.8)
Late Assessment:	**12 months**	**12 months**
Satisfactory	**35 (58.3)**	**53 (46.9)**
Unsatisfactory (total)	**9 (15.0)**	**5 (4.4)**
Unevaluable (total)	**16 (26.7)**	**55 (48.7)**

7.2.4. European Studies

The Applicant submitted 8 European studies to support efficacy; one study was not applicable to the efficacy analysis since clinical outcomes were presented by culture results rather than treatment group. Seven studies were considered in the evaluation of efficacy (Table 6). As European Lyme disease has distinct clinical features and different causative Borrelia species than in the US, as noted in Table 1, this reviewer compared the European treatment studies with a European natural history study (Study 9). The primary endpoint in the

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natural history and treatment studies using doxycycline BID for 10, 14, or 15 days was the absence of objective manifestations of Lyme disease at 12 months. The European doxycycline treatment studies did not demonstrate a treatment effect when compared to no treatment in Study 9. Thus, this section on the European studies will be brief, and data will be presented in tabular format when feasible.

7.2.4.1 Study Design and Endpoints

1. Study 9 – Asbrink 1986

A prospective, natural history study in patients with EM was conducted in Sweden from 1978 to 1984. EM was diagnosed by gross appearance and course. Patients were treated with phenoxymethyl penicillin, or in case of a penicillin allergy, tetracycline or erythromycin. The patients who declined antibacterial drug therapy were followed until spontaneous healing of the skin lesion occurred. Patients were examined at presentation, then at 2-4 weeks after treatment. Untreated patients were interviewed at 2-4 weeks by phone. A questionnaire regarding recurrences and symptoms related to the joints, nervous system, and heart was sent to all patients with EM. Patients with symptoms at any point were interviewed by telephone and/or examined by the authors. Medical records were scrutinized, and sera were drawn for determination of antibodies against Borrelia using indirect immunofluorescence assay and with ELISA. EKG was performed in less than half of the total number of patients.

The primary endpoint was absence of objective manifestations (arthritis, carditis, or neurologic disease) in the untreated group at 12 months.

Medical Reviewer Comments: The timing of the clinical assessments for the untreated patients was not specifically noted; however, the late outcomes were reported until the lesion healed, which was up to 12 months. The limitations of the study were that patients were not randomized to placebo, rather this was an observational study of patients who declined antibacterial drugs. Since these patients had declined treatment, they may have had milder disease at presentation, and may have been less likely to report symptoms in the questionnaire. Patient recall of symptoms may have been incomplete as well.

2. Study 10 - Barsic 2000

A randomized, open-label, multicenter study was conducted in Croatia, in patients 12 years of age or older with physician-documented EM, with or without systemic manifestations. The number of EM lesions was recorded, and the primary lesion was measured. Subjective symptoms such as fatigue, joint pain, headache, muscle symptoms, stiff neck, fever, paresthesia, nausea and vomiting were recorded. Exclusion criteria were the following: pregnancy; lactation; history of adverse reactions to tetracyclines or azithromycin; receipt of systemic antimicrobial agents with known activity against *B. burgdorferi* within 10 days before enrollment; antibacterial drug treatment of Lyme disease during the preceding 12 months;

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gastrointestinal or hepatic disorders that would interfere with the pharmacokinetics of orally administered antimicrobial agents; any major manifestation of disseminated Lyme disease (frank arthritis, evidence of neurologic or cardiac involvement at time of presentation).

Patients were randomly assigned to doxycycline (Hiramicin or doxycycline hyclate) for 14 days or an active comparator. A complete history, physical examination, CBC, serum chemistry, EKG, UA, serologies for Lyme disease (IgM and IgG by ELISA, and confirmation by WB) were done at enrollment. The response to therapy was based on EM remission and eventual subsequent appearance of major manifestations (arthritis, carditis, radiculopathy, meningitis) as the primary endpoints. The secondary endpoints were remission of NSS and new onset of minor manifestations. Repeat examinations were performed at day 14 and 56, and month 6 and 12 after treatment. Exclusion from the study because of an adverse event, interrupted antimicrobial treatment and failure to complete the post-treatment visit were considered as treatment failure.

The clinical response of each patient was categorized by the author as follows:

- Success: Resolution of EM rash and other clinical signs and symptoms in a period of 14 days after the start of therapy and absence of major manifestations during the follow-up period
- Improvement: Incomplete resolution of EM and/or incomplete resolution of other clinical signs and symptoms of early Lyme disease in a period of 14 days after the start of therapy with further improvement or complete resolution during follow-up
- Failure: No improvement in EM rash or other clinical signs and symptoms, recurrence or new onset of EM and other signs and symptoms, new onset of the major clinical manifestations of Lyme disease during the follow-up period, or withdrawal because of adverse drug events that necessitated a change of antimicrobial therapy

Medical Reviewer Comments: In the 'improvement' category, it is unclear whether EM was fully resolved during the follow-up period of 12 months. If EM had not resolved, it is difficult to categorize the clinical response as 'satisfactory'. Thus, this reviewer categorized the clinical response of 'improvement' and any objective manifestations of Lyme disease as 'failures.' Patients with adverse events prompting a change in therapy and those who did not complete post-treatment visits were considered 'unevaluable,' rather than as failure.

The clinical response definitions set forth by the author were modified to separate the true treatment failure (incomplete resolution of EM, development of objective manifestations of Lyme disease with those who were unevaluable for various reasons (lost to follow-up or adverse events prompting change in therapy). Although this reviewer could replicate the response rates in the Applicant analysis, the modification of the successful outcome definition had to be performed to maintain consistency in analyses across all studies.

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3. Study 11 - Strle 1992

A randomized, prospective study of patients 15 years of age and older with EM was conducted in Slovenia between September and December 1988. Patients were excluded if they were receiving antibacterial drugs or had evidence of late manifestations of Lyme disease at the time of examination.

The patients were randomized, based on the order of their visit, to either doxycycline for 14 days or the active comparators. Basic demographic data and information about the course of the illness were obtained by means of a questionnaire, and all patients were followed for up to 24 months. They were seen at baseline, and at day 7, 14, 56, and at month 6, 12, 18, and 24. A medical history, physical examination, CBC, serum chemistry, serological testing for Lyme disease, UA, and EKG was obtained at baseline. The diagnosis of Lyme disease was confirmed serologically (*B. burgdorferi* IgM and/or IgG titers ≥ 1:256). Patients were asked to record the time when their skin lesions and localized symptoms began to resolve, and the time of complete resolution (after a symptom-free interval of at least 14 days). They were asked to return to the clinic if an exacerbation or development of new symptoms has occurred.

The primary endpoint was the absence of objective manifestations of Lyme disease (arthritis, carditis, or neurologic disease) at 12 months.

Medical Reviewer Comments: The author and Applicant reported the absence of major manifestations of Lyme disease at 24 months, rather than at 12 months. The 12-month outcome data were evaluated to compare with no treatment in the natural history study.

4. Study 12 - Strle 1993

A randomized, prospective study of patients 18 years of age or older with EM was conducted in Slovenia between May and July 1990, and in summer of 1991. Patients received doxycycline for 14 days or an active comparator. This study was similar in design to Study # 10 with the following additions: 1) Pregnant women were excluded; 2) Patients were seen at day 7, 14, 56 and at month 6 and 12; 3) Only patients who underwent a skin biopsy procedure for *B. burgdorferi* culture were enrolled. In patients with positive skin culture for *B. burgdorferi*, skin biopsy was repeated approximately 3 months later. If the repeat culture was positive after treatment, antibacterial drug resistance was determined, and further testing for immunodeficiency was performed. Also, in case of a positive skin culture for *B. burgdorferi*, therapy with an alternate antibacterial drug was instituted, and another skin biopsy performed 3 months later. Development of objective manifestations of Lyme disease were categorized as failures. If alternate antimicrobials were used for a positive skin culture, the clinical response was categorized as unevaluable.

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Medical Reviewer Comments: Even if the patient with a positive skin biopsy did not have the presence of objective manifestations of Lyme disease (true treatment failure), he/she was still treated with alternate antimicrobials in this study. This reviewer considered these patients unevaluable since re-treatment was at 3 months, and the true outcome of these patients at 12 months is unknown. The Applicant did not consider those re-treated with alternate antimicrobials as unevaluable or as failures.

5. Study 13 - Stupica 2012

A non-randomized, non-inferiority, prospective study was conducted in Slovenia between June and October 2009 in patients with solitary EM. Patients with EM < 5 cm in diameter were allowed into the study with the same clinical characteristics as in Study 15. Exclusion criteria were the following: prior antibacterial drug therapy, history of Lyme disease, multiple EM, immunocompromising condition, pregnancy, lactation, meningitis, or a serious adverse reaction to tetracycline. Developing an intercurrent episode of Lyme disease during follow-up rendered ineligibility for evaluation.

Patients received doxycycline for 10 or 15 days, and the treatment duration option changed on a weekly basis. At baseline, day 14, and month 2, 6, and 12, patients were examined and asked about NSS. They were asked to complete a questionnaire that included 14 NSS (fatigue, malaise, arthralgia, myalgias, headache, paresthesias, dizziness, nausea, insomnia, sleepiness, forgetfulness, concentration difficulties, irritability, or backache). Spouses or other family members served as controls and were given the same 14-symptom questionnaire at 6 months. The purpose of these controls was to compare the frequency of NSS in uninfected individuals. A CBC, serum chemistry, Lyme serologies (IgM and IgG by immunofluorescence assay), and skin biopsy was obtained at baseline. Biopsy was repeated at 2-3 months in patients who had a positive culture for *Borrelia* species.

Response to treatment at Day 14 was defined by the author as:

- Complete response: Resolution of erythema migrans (the interval was calculated as the number of days from starting antibacterial drug treatment until erythema migrans could no longer be seen in daylight at room temperature), with return to pre-Lyme borreliosis health status
- Partial response: Either incomplete resolution of erythema migrans or the presence of NSS

Response to treatment at 2, 6, and 12 months was defined by the author as:

- Complete response: Continued absence of any manifestations of Lyme borreliosis, with return to pre-Lyme borreliosis health status
- Partial response: The presence of NSS

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- Failure: The occurrence of new objective manifestations of Lyme borreliosis or the persistence of *B. burgdorferi* sensu lato in skin at the site of the previous erythema migrans (Failure was considered a rare event. The authors did not analyze it separately, but grouped partial responses and failures together in the incomplete response category.)

Medical Reviewer Comments: This reviewer categorized patients with a complete or partial response at 12 months (both with absence of objective manifestations of Lyme disease) as having a 'satisfactory outcome.' As in Study 6, there was a proportion of patients who received 1 or more courses of intercurrent antibacterial drugs for unrelated conditions. It was not specified when these were given. Those who were lost to follow-up or given intercurrent antibacterial drugs (when assumed to be given at 12 months) were considered unevaluable at 12 months.

The Applicant reported the complete response at 6 and 12 months without including those patients who had a partial response only (presence of NSS). The clinically evaluable population, rather than the ITT population was analyzed.

6. Study 14 - Kuiper 1994

A non-randomized, prospective study of patients 2 years of age or older with EM was conducted in the Netherlands between August 1987 and December 1992. Only patients with solitary EM were included, and EM was defined by CDC criteria. Patients who were treated with antibacterial drugs after the onset of EM, and patients with obvious clinical manifestations of disseminated disease, were excluded.

A complete physical and neurologic examination was performed, as were antibody testing for *B. burgdorferi* by ELISA and a skin biopsy from the EM site. As doxycycline became standard of care in the Netherlands after 1990, patients enrolled before 1990 received tetracycline, and after 1990, received doxycycline for 10-14 days. Patients were examined 6 weeks after treatment. All patients were informed about the manifestations of early disseminated Lyme disease, and were asked to return if these occurred. Long-term follow was by telephone interview at 1-4 years after treatment. The clinical response of those who were unable to be contacted by telephone after 6-31 months (in doxycycline arm) were considered unevaluable.

Medical Reviewer Comments: The clinical evaluable population rather than ITT was used in the Applicant's analysis of efficacy. Thus, those unavailable for telephone follow-up were excluded from the Applicant's analysis.

7. Study 15 - Strle 1996

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A non-randomized, prospective study of patients 18 years of age or older with solitary EM was conducted in Slovenia. Doxycycline for 14 days or an active comparator were given. The methodology in this study was similar to Study 11 above.

Medical Reviewer Comments: In contrast to Study 11, the authors did not re-treat patients with alternate antibacterial drugs in the setting of a positive skin biopsy at 2 months after treatment with a study drug.

8. Study 16 - Cerar 2010

A non-randomized, prospective study of patients 15 years of age or older with solitary EM was conducted between June and September 2006 in Slovenia. EM was defined by CDC criteria, but patients with skin lesions < 5 cm in diameter were allowed into the study if they recalled a recent tick bite at the site of the skin lesion, had a symptom-free interval between the bite and the onset of the lesion, and reported an expanding skin lesion before diagnosis. Exclusion criteria were a history of Lyme disease, pregnancy, lactation, immunocompromising condition, serious adverse reaction to a beta-lactam or tetracycline drug, receipt of an antibacterial drug with known activity against *Borrelia* within 10 days, multiple EM lesion or an extracutaneous manifestation of Lyme disease.

The treatment option (doxycycline for 15 days or a comparator) changed on a weekly basis. Patients were evaluated at baseline, day 14, and 2, 6, and 12 months after treatment. A skin biopsy was obtained and repeated at the site after 2-3 months in patients with an initial positive culture. Each patient was asked to refer a spouse or other family member as a control. Patients and the control subjects completed a symptom questionnaire for new or increased symptoms (NSS: fatigue, arthralgia, myalgias, headache, paresthesias, dizziness, irritability, or nausea) at baseline, and month 12. The purpose of these controls was to compare the frequency of NSS in any group, uninfected with Lyme disease.

At day 14, patients were asked about medication compliance and adverse events. Responses to treatment was defined by the author as follows:

- Complete response: Resolution of erythema migrans with return to pre-Lyme borreliosis health status
- Partial response: Incomplete resolution of erythema migrans or the presence of NSS.
- Failure: Persistence of erythema migrans or occurrence of new objective signs of Lyme disease.

At 2, 6, and 12-months post-enrollment, responses to treatment were defined by the author as follows:

- Complete response: Continued absence of objective manifestations of Lyme borreliosis, with return to pre-Lyme borreliosis health status

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- Partial response: The presence of NSS without an objective manifestation of Lyme disease
- Failure: Occurrence of objective manifestations of Lyme disease or persistence of *B. burgdorferi* sensu lato in skin at the site of the previous erythema migrans

Medical Reviewer Comments: This reviewer combined complete and partial responses at 12 months as 'satisfactory,' as these responses included the absence of objective manifestations of Lyme disease. Patients who were re-treated with antibacterial drugs for a persistently positive skin culture at 2 months after treatment with the study drug were considered 'unevaluable,' rather than failure. The Applicant analyzed the clinical evaluable population at the 6 and 12 month endpoints rather than the ITT population. With a high number of unevaluable patients, the efficacy of doxycycline was reduced significantly using the ITT population (see Section 7.2.4.2 Study Results.

7.2.4.2 Study Results

Patient Disposition

Studies 13 (Stupica) and 16 (Cerar) had a high number of patient discontinuations due to loss of follow-up. Table 17 shows a summary of discontinuations in the European Studies.

Table 17: Summary of Discontinuations in European Studies of Doxycycline BID Regimen

#	TREATMENT DURATION	FOLLOW-UP	N	DISCONTINUED N (%)	REASON GIVEN FOR DISCONTINUATION		
					ADVERSE EVENT	LOST TO FOLLOW-UP	OTHER
10	14 days	12 months	40	5 (13)	1 (3)	4 (10)	
11	14 days	24 months	23	0			
12	14 days	12 months	52	0			
13	10 days	12 months	108	22 (20)		22 (20)	
13	15 days	12 months	117	26 (22)		26 (22)	
14	10-14 days	31 months	24	0			
15	14 days	12 months	42	0			
16	15 days	12 months	145	29 (20)		29 (20)	

Protocol Violations/Deviations

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None

Demographics and Baseline Characteristics

1. Study 9 – Asbrink 1986 (Natural History Study)

The demographics and baseline characteristics are shown in Table 18. These parameters were not stratified by treatment. Nearly 75% of the patients were female and the median age was 52. Race and ethnicity were not available, but the study was conducted in an endemic area for Lyme disease (Stockholm, Sweden). Most of the patients had single EM with associated symptoms. Of 231 patients, 84 had baseline cardiac testing. Of these 84, 3 patients who received antibacterial drugs had baseline EKG changes, such as T-wave inversions, suggesting cardiac involvement. The untreated patients did not have evidence of joint, cardiac, or neurologic dissemination.

Table 18: Demographics and Baseline Characteristics in European Natural History Study

PARAMETER	ASBRINK 1986	
Treatment	Untreated N= 16	PCN/Tetracycline/Erythromycin N = 215
Sex		
Male n (%) Female n (%)	61 (26) 170 (74)	
Age (years)		
Median Range	52 0.5–84	
Study site	Sweden	
Clinical Characteristics		
Single EM n (%)	212 (92)	
Multiple EM n (%)	18 (8)	
NSS n (%) with EM of duration: ≤ 3 weeks > 3 weeks	 40/78 (51) 36/144 (25)	

2. European Treatment Studies using Doxycycline BID Regimen

The demographics and baseline clinical characteristics in the 7 doxycycline treatment studies conducted in Europe are noted in Table 19. The baseline variables were similar to the natural history study. There was a female predominance, a similar median age, the studies were conducted in hyperendemic areas for Lyme disease, and enrollment of mostly patients with single EM with NSS. Studies 13-16 enrolled patients with solitary EM +/-NSS. None of the

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studies reported race, ethnicity, and history of Lyme disease. None of the patients in the studies had baseline dissemination to the joints, cardiac, or nervous system.

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Table 19: Demographic and Baseline Characteristics in European Studies of BID Regimen

PARAMETER	STUDY 10 BARSIC 2000 N = 40	STUDY 11 STRLE 1992 N=23	STUDY 12 STRLE 1993 N=52	STUDY 13 STUPICA 2012		STUDY 14 KUIPER 1994 N=77*	STUDY 15 STRLE 1996 N =42	STUDY 16 CERAR 2000 N=145
				10 day N=108	15 day N=117			
Sex n (%)								
Male	19 (48)	10 (43)	29 (56)	46 (43)	54 (43)	32 (42)	21 (50)	61 (42)
Female	21 (52)	13 (57)	23 (44)	62 (57)	63 (54)	45 (58)	21 (50)	84 (58)
Age (years)								
Mean (SD)	49 (12)	40 (11)	45 (12)	ns	ns	ns	44 (11)	54
Median	ns	39	42	54	51	48	50	ns
Range	ns	17-64	19-71	44-62^	38-60^	2-78	34-62	17-85
Study site	Croatia	Slovenia	Slovenia	Slovenia		Netherlands	Slovenia	Slovenia
Clinical Characteristics n (%)								
Single EM	36 (90)	21 (91)	46 (85)	108 (100)	117 (100)	77 (100)	42 (100)	145 (100)
Multiple EM	4 (10)	2 (9)	6 (12)	0	0	0	0	0
NSS	18 (45)	11 (48)	24 (46)	34 (32)	35 (30)	18 (23)	20 (48)	50 (35)
Duration of EM to treatment median days	10	27	8.5	14	12	ns	15	7

* Demographics available for entire cohort, not stratified by treatment group
^ interquartile range

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Treatment Compliance, Concomitant Medications, and Rescue Medication Use

This information will be discussed below under "Efficacy Results."

Efficacy Results – Primary Endpoint

The primary endpoint in the European studies was the absence of objective manifestations of Lyme disease, such as arthritis, cardiac or neurologic disease at 12 months. Treatment effect at 12 months was measured by comparison of doxycycline efficacy in the treatment studies to no treatment in the natural history study. The estimate of the treatment effect will be discussed in section **Error! Reference source not found. Error! Reference source not found.**. Table 20 shows the clinical outcomes at 12 months in these studies. Each individual study is discussed below.

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Table 20: Clinical Outcomes at 12 months in European Studies of Doxycycline BID

PARAMETER	STUDY 10 BARSIC 2000 N = 40	STUDY 11 STRLE 1992 N=23	STUDY 12 STRLE 1993 N=52	STUDY 13 STUPICA 2012		STUDY 14 KUIPER 1994 N=24	STUDY 15 STRLE 1996 N =42	STUDY 16 CERAR 2000 N=145
				N=108	N=117			
Treatment duration, days	14	14	14	10	15	10-14	15	14
Response n (%)								
Satisfactory	29 (72.5)	22 (95.7)	45 (86.5)	76 (70.4)	79 (67.5)	21 (87.5)	41 (97.6)	114 (78.6)
Unsatisfactory	6 (15)	1 (4.3)	3 (5.8)	0	0	0	1 (2.4)	1 (1.3)
Unevaluable	5 (12.5)	0	4 (7.7)	32* (29.6)	38* (32.4)	3 (12.5)	0	30 (20.7)
Treatment failure (Development of objective manifestations)								
Persistent EM	4+	0	0	0	0	0	0	1
Joint disease	0	0	2	0	0	0	1^	0
Neurologic disease	0	1	1	0	0	0	1^	0
Cardiac disease	2	0	0	0	0	0	0	0

+ 4 had either incomplete resolution of EM or other clinical signs/symptoms
* includes patients lost to follow-up and those given intercurrent antibacterial drugs during 12- month follow-up
^ same patient had joint and neurologic disease

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1. Study 10 - Barsic 2000

The satisfactory response was 72.5% which was the same as the Applicant's ITT analysis of clinical efficacy. There were 6 unsatisfactory responses: 4 patients had incomplete resolution of EM or other clinical signs and symptoms of early Lyme disease, and 1 developed premature ventricular beats at 6 months, and 1 developed a right bundle branch block at 12 months. Re-treatment for failures was not discussed. Treatment was switched from doxycycline to azithromycin due to diarrhea in one patient who was considered 'unevaluable.' Four additional patients who failed to complete post-treatment visits, were considered 'unevaluable.'

Medical Reviewer Comments: The unsatisfactory responses in this study were questionable. The authors defined improvement as incomplete resolution of EM or other clinical signs and symptoms in a period of 14 days with further improvement or complete resolution during follow-up. It is unclear if these 4 patients who 'improved,' had incomplete resolution of EM or other clinical signs/symptoms. It would be unusual for EM to persist for 12 months despite antimicrobial therapy, but individual patient outcomes are not available. The cardiac manifestations of premature ventricular beats and right bundle branch block at 6 months and 12 months, respectively, seem rather non-specific, and may have been unrelated to the initial episode of Lyme disease. In fact, palpitations, bradycardia, bundle branch block, or myocarditis alone do not meet the CDC clinical case definition for Lyme Disease (see section 15.3 Appendix A*). Rescue antibacterial drugs were not reported. It is possible that the cardiac manifestations resolved spontaneously. Thus, the less conservative efficacy rate for doxycycline in this study may be closer to 87.5% when all failures are counted as satisfactory outcomes.*

2. Study 11 – Strle 1992

The satisfactory response was 95.7% at 12 months. One patient developed facial palsy with positive CSF findings on day 6, post-treatment. Re-treatment with rescue antibacterial drugs was not reported for this patient.

Medical Reviewer comment: The Applicant reported that 21/23 (91%) had a satisfactory response using a 24- month endpoint. There was one additional failure at 20 months. This patient was a 36-year old male who initially developed arthralgia at 7 months, but knee effusions developed 20 months after EM had resolved. Arthralgia is considered a NSS whereas knee effusion is an objective manifestation of Lyme disease.

3. Study 12 Strle 1993

The satisfactory response was 86.5% at 12 months. Three patients had treatment failure by 12 months, and were re-treated with ceftriaxone. A 36-year old male presented with a solitary EM with local itching, mild headaches, arthralgia, and myalgias. Approximately 3 months later, he developed paresthesias and radiculopathy, followed by evidence of lymphocytic pleocytosis

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with intrathecal *B. burgdorferi* antibody production. A 49-year old female presented with a solitary EM with local itching, fatigue, and myalgias, followed by frank arthritis at 8 months. A 42-year old male presented with EM for 16 days, and developed facial palsy with an elevated CSF protein and lymphocytic pleocytosis at 6 weeks. Four patients had positive skin cultures 3 months after treatment with doxycycline and were re-treated with azithromycin. These 4 were considered 'unevaluable.'

Medical Reviewer Comments: The Applicant reported a satisfactory response in 49/52 (94%) of patients. The four patients who were re-treated with azithromycin for positive skin cultures were not considered as unevaluable or failure. If retreatment had not occurred, this reviewer would agree with the Applicant's analysis, especially since the patients who were re-treated did not actually have persistence of EM or other objective manifestations of Lyme disease by 12 months. In the US, skin cultures are rarely done in the setting of early Lyme disease, unless there is an atypical rash or uncertainty in the diagnosis. Also, a skin biopsy is usually not repeated in clinical practice, once there is clinical cure. The clinical significance of a persistent skin culture in the setting of a clinical cure may be limited. Thus, the less conservative efficacy rate for doxycycline in this study may be closer to 94% when re-treatment for a positive skin culture is not counted as 'unevaluable.'

4. Study 13 - Stupica 2012

The satisfactory response at 12 months in the 10- and 15-day doxycycline arms was 70.4 and 67.5%, respectively. There were no treatment failures. A large percentage of patients discontinued the study due to loss of follow-up. This study required 4 post-treatment visits, from 14 days to 12 months, and at each time point, there were patients lost to follow up. Also, 10 (9.3%) and 12 (10.3%) patients in the 10-day and 20-day doxycycline arm, respectively, received ≥ 1 course of antibacterial drugs for unrelated conditions during the 12-month study period. The timing of these was not reported. Thus, the patients who received intercurrent antibacterial drugs were assumed to be unevaluable at the 12-month endpoint.

Medical Reviewer Comments: The Applicant reported the author's analysis which used the clinically evaluable population at 12 months. The patients with intercurrent antibacterial drug use were not considered unevaluable. The Applicant reported an efficacy rate of over 90% in both treatment arms. Like Study 6, this study was confounded by intercurrent antibacterial drug use and a high number of unevaluable subjects. See section ***Error! Reference source not found. Error! Reference source not found.*** *for an estimate of treatment effect including and excluding this study.*

5. Study 14 – Kuiper 1994

The satisfactory response was 87.5% at 12 months with no treatment failures. Three patients were unevaluable for telephone interview from 6 to 12 months.

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Medical Reviewer Comments: The Applicant reported 100% efficacy of doxycycline while using the clinically evaluable population in their analysis. Also, a limitation of the study was that the exact duration of doxycycline treatment could not be ascertained. The range of treatment provided was 10-14 days.

6. Study 15 – Strle 1996

The satisfactory response was 97.6% at 12 months. One patient who presented with EM, headache, arthralgia, myalgia, and fatigue developed swollen knee joints and lymphocytic meningitis with intrathecal borrelial antibody production at 5 months, post-treatment. The patient received ceftriaxone with residual NSS at 28 months. One patient had a positive skin culture for *B. burgdorferi* on repeat biopsy at 2 months, post-treatment, but re-treatment was not reported. Thus, the patient was considered to have had a satisfactory response to treatment.

Medical Reviewer Comments: The Applicant also reported a satisfactory response rate of 98%. Strle et al. conducted Study 12 in which 4 patients were re-treated for repeat positive skin cultures. In this later study, the authors did not mention re-treatment. Perhaps it was decided that re-treatment was not indicated in the patients that had no subsequent clinical signs and symptoms for Lyme disease. In both studies, no overt cause such as non-adherence to therapy or immunological defects was found for persistently positive skin cultures.

7. Study 16 - Cerar 2010

The satisfactory response was 78.6% at 12 months. One patient developed treatment failure with multiple EM on the day 14 visit, and was re-treated with ceftriaxone. One patient who had a positive skin culture for *B. burgdorferi* 2-months post-treatment, was re-treated with cefuroxime axetil. This patient was considered 'unevaluable.' Another 29 patients were considered 'unevaluable' due to loss of follow-up at 12 months.

Medical Reviewer Comments: The author reported a complete response rate of 97.4% at 12 months using the clinically evaluable population (n=116). The Applicant used the last evaluable visit (n=145), which was at a mean of 313 days +/- 105 days, to determine a complete response rate of over 95%. Although this was the largest European study submitted in the NDA, it was limited by the high percentage of unevaluable patients (20%). There was only 1 true treatment failure, and the low satisfactory response in reviewers' analyses is driven by the number of missing patients. See section ***Error! Reference source not found. Error! Reference source not found.*** *for an estimate of treatment effect including and excluding this study.*

Efficacy Results – Secondary and other relevant endpoints

One difference between the US and European studies was that the European studies reported the rate of persistent NSS separately. Barsic et al. noted that "antimicrobials have little

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influence on minor symptoms which often results in overtreatment. The resolution of EM and incidence of major signs are the only relevant parameters for treatment success and should be separately reported." At 12 months, an average of approximately 13% of patients treated with 10-15 days of doxycycline BID had persistent NSS in all the European studies (excluding Study 14).

Findings in Special/Subgroup Populations Conducted on the Individual Trials

The natural history study and Study 14 enrolled pediatric patients, but did not report their outcome separately. In addition, there were studies in which patients over 65 were enrolled, but no differences in outcomes were reported by age. The age and gender of patients who had treatment failure were only noted in Study 13. Due to small number of treatment failures, with limited demographic information, no conclusions can be drawn in any specific populations.

Gender, Race, Age, Weight, and Baseline Severity

The race/ethnicity of patients was unknown in all European studies. The severity of early Lyme disease upon presentation was overall milder than in the US: less multiple EM, lower frequency of NSS, and absence of objective manifestations.

Geographic location

The European studies were conducted in hyperendemic areas for Lyme disease.

7.2.5. Assessment of Efficacy Across Trials

Since no randomized placebo controlled trials of doxycycline were identified in the literature, the primary assessment of efficacy is based on a comparison of a pooled estimate of the effect of doxycycline from the US studies of the BID regimen for 20-21 days to a pooled estimate of the effect of no treatment from the US natural history studies. The primary efficacy endpoint is the absence of objective manifestations of Lyme disease at 6 months follow-up. The 6 month timepoint was chosen since both natural history studies and 3 of the 4 US BID treatment studies reported outcomes at 6 months.

A meta-analytic approach (random effects analysis using the DerSimonian and Laird method) was used to estimate the pooled response rates and corresponding confidence intervals for no treatment and doxycycline, respectively. Two approaches were used to calculate an estimate of the treatment effect of doxycycline:

1. the difference of the lower bound of the doxycycline confidence interval and the upper bound of the no treatment confidence interval
2. the difference of the pooled point estimates with a corresponding confidence interval.

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Given the data come from separate sources, the first approach can be considered to provide a more conservative estimate of the treatment effect as compared to the second approach.

Table 21 summarizes the response rates of no treatment from the US natural history studies. The rate reported for Steere, 1979 is based only on the cohort with onset in 1977 since a 6-month rate could not be determined from the data presented in the publication for the cohort with onset in 1976. As previously mentioned, Steere, 1980 also reported subjects with an onset in 1977 (a total of 8 subjects). Since the study site was the same in both Steere publications it is possible that these subjects are not unique. However, given the relatively small number reported in Steere, 1980 as compared to Steere, 1979 (35 subjects), it will be assumed that the subjects in each study are unique.

Table 21: Absence of Objective Manifestations of Lyme Disease at 6 months Follow-up- Natural History (no treatment)

Study	**Response Rate [n/N (%)]**	**Notes**
Steere, 1979	23/35 (65.7)	12 subjects developed arthritis (± CNS disease)
Steere, 1980	31/55 (56.4)	24 subjects developed arthritis (± CNS disease)
Pooled	60.2 95% CI (50.1, **70.3**)	

The response rates of doxycycline from the US BID treatment studies for 20 to 21 days of treatment are summarized in Table 22. As previously mentioned, patients in Massaroti, 1992 were to receive 10 days of treatment with doxycycline. However, if symptoms were still present at day 10 the patient could receive an additional 10 days of treatment. Therefore, the study is being considered as a 20-day treatment for the efficacy assessment. Dattwyler, 1997 included patients with more disseminated Lyme disease at baseline and a high unevaluable rate as compared to the other two studies. Given this difference in baseline characteristics, a pooled estimate for doxycycline was calculated for all 3 studies as well as by excluding Dattwyler, 1997.

Table 22: Absence of Objective Manifestations of Lyme Disease at 6 months follow-up- Doxycycline US BID studies for 20-21 days

Study	**Response Rate [n/N (%)]**	**Notes**
Dattwyler, 1990	35/37 (94.6)	No true failure Two unevaluable
Massaroti, 1992	20/22 (90.9)	1 true failure (facial palsy) 1 unevaluable
Dattwyler, 1997	54/72 (75.0)	1 true failure (arthritis) 17 unevaluable
Pooled		

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Study	Response Rate [n/N (%)]	Notes
All 3	87.0 95% CI (**74.7**, 99.4)	
Excluding Dattwyler, 1997	93.6 95% CI (**87.4**, 99.8)	

From Table 21, the pooled estimate of the absence of objective manifestations of Lyme disease at 6-months follow-up for no treatment is 60.2% with an upper bound of the 95% confidence interval of 70.3%. From Table 22, the pooled estimate of the absence of objective manifestations of Lyme disease at 6-months follow-up for doxycycline is 87.0% with a lower bound of the 95% confidence interval of 74.7%. Thus, the treatment effect of doxycycline over no treatment can be estimated to be at least 4.4%. If one excludes Dattwyler, 1997 from the pooled estimate for doxycycline, the estimate is 93.6% with a lower bound of the 95% confidence interval of 87.4%. A conservative estimate of the treatment effect would then be 17.1%. When considering just the point estimates, the difference between doxycycline (all 3 studies) and no treatment is 26.8% with a 95% confidence interval of (10.9, 42.7) and the difference between doxycycline (excluding Dattwyler, 1997) and no treatment is 33.4% with a 95% confidence interval of (21.6, 45.2). Regardless of the approach taken to estimate the treatment effect, there appears to be a positive effect of treatment with doxycycline on the absence of objective manifestations of Lyme disease at 6 months follow-up as compared to no treatment. These results are summarized in Table 23.

Table 23: Estimate of Treatment Effect of Doxycycline 100 mg BID for 20-21 days

Approach	Estimate
Difference of lower bound of doxycycline 95% CI (3 studies) and upper bound of no treatment 95% CI	74.7-70.3= 4.4%
Difference of lower bound of doxycycline 95% CI (excluding Dattwyler, 1997) and upper bound of no treatment 95% CI	87.4 – 70.3= 17.1%
Difference of point estimates	
Between doxycycline (3 studies) and no treatment	87.0-60.2= 26.8% 95% CI (10.9, 42.7)
Between doxycycline (excluding Dattwyler, 1997) and no treatment	93.6-60.2=33.4% 95% CI (21.6, 45.2)

Similarly, a pooled estimate of the effect of doxycycline was calculated for the 7 European doxycycline studies. For the European studies, the endpoint of interest was the absence of objective manifestations of Lyme disease at 12-months follow-up. The twelve month timepoint was used for the European studies since all 7 of the European treatment studies as well as the single European natural history study reported outcomes at 12-months follow-up.

The response rates of doxycycline from the European BID treatment studies for 10 to 15 days of treatment are summarized in Table 24. Given the large number of unevaluable subjects

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observed in the Stupica and Cerar studies, a pooled rate was also calculated by excluding these studies.

Table 24: Absence of Objective Manifestations of Lyme Disease at 12-months follow-up-Doxycycline European BID studies for 10 to 15 days

Study	Duration	Response Rate [n/N (%)]	Notes
Barsic, 2000 (Croatia)	14 days	29/40 (72.5)	2 true failures
Strle, 1992 (Slovenia)	14 days	22/23 (95.7)	1 true failure
Strle, 1993 (Slovenia)	14 days	45/52 (86.5)	3 true failures
Stupica, 2012 (Slovenia)	10 days 15 days	76/108 (70.4) 79/117 (67.5)	No true failures-unevaluable or received intercurrent antibiotics
Kuiper, 1994 (Netherlands)	10 or 14 days	21/24 (87.5)	No true failures Unable to distinguish actual duration
Strle, 1996 (Slovenia)	14 days	41/42 (97.6)	1 true failure
Cerar, 2010 (Slovenia)	15 days	114/145 (78.6)	1 true failure
Pooled (rate and 95% CI) All 7 Excluding Stupica/Cerar		 82.3 (**73.2**, 91.4) 89.5 (**81.7**, 97.3)	

A single study (Asbrink, 1996) provides an estimate of a European natural history assessment of no treatment. In this study, 11 of 16 subjects (68.8%) had the absence of objective manifestations of Lyme disease at 12 months. The Exact 95% confidence interval about the rate is (41.3, 89.0). From Table 24, the pooled estimate of the absence of objective manifestations of Lyme disease at 12-months follow-up for doxycycline is 82.3% with a lower bound of the 95% confidence interval of 73.2%. If one excludes Stupica and Cerar, the estimate is 89.5% with a lower bound of the 95% confidence interval of 81.7%. Since the lower bound of the doxycycline confidence intervals are less than the upper bound of the no treatment confidence interval, a positive treatment effect of doxycycline in the European studies is not able to be demonstrated based on this assessment. This conclusion is in part due to the extremely limited amount of data available to estimate the response of no treatment and the resulting wide confidence interval. When considering just the point estimates, the difference between doxycycline (all 7 studies) and no treatment is 13.5% with a 95% confidence interval of (-11.0, 38.0) and the difference between doxycycline (excluding Stupica and Cerar) and no treatment is 20.7% with a 95% confidence interval of (-3.3, 44.7). Since the confidence intervals contain zero, one cannot rule out no effect of treatment with doxycycline in the European studies.

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7.3. Summary and Conclusions

7.3.1. Summary and Conclusions – Statistics and Clinical

No randomized placebo-controlled trials were submitted to support the efficacy of doxycycline for the proposed indication of the treatment of early Lyme disease. Assessment of the efficacy of doxycycline for the treatment of early Lyme disease is based primarily on a comparison of 3 trials conducted in the US that included a doxycycline treatment arm to a series of patients from two natural history studies. The assessment of these data indicates that there is a positive effect of treatment with doxycycline, when dosed as 100 mg BID for 20-21 days, on the absence of objective manifestations of Lyme disease at 6 months follow-up as compared to no treatment (Section 7.3).

Other supportive information on the efficacy of doxycycline comes from 2 additional US doxycycline treatment trials and 8 (7 treatment and 1 natural history) European studies. The supportive information these data provides is, however, limited.

The 2 additional US doxycycline studies (discussed in Section 7.2.3) used a dosing regimen of doxycycline 100 mg TID for 20 days which is higher than the proposed 100 mg BID dosing regimen. While these studies were used as the basis for approval of cefuroxime axetil, the interpretation of the efficacy from these studies is also limited due to a high number of unevaluable subjects in the ITT population.

The European studies (discussed in Section 7.2.4) can only provide limited supportive evidence of efficacy of doxycycline for many reasons. Lyme disease in Europe has distinct clinical features and different causative *Borrelia* species than in the US and therefore may not be fully comparable. In the European studies, doxycycline was dosed as 100 mg BID for 10, 14, or 15 days which is a shorter treatment duration than that used in the primary US studies. None of the European studies were randomized placebo controlled trials and a comparison of the pooled European treatment studies to a single European natural history study was unable to demonstrate a significant treatment effect (discussed in Section 7.3). Nonetheless, one of the European studies (Kuiper 1994) noted that doxycycline had become standard of care for treatment of early Lyme disease after 1990, and most of the European studies noted in this review appeared to have used doxycycline as a control for treatment in early Lyme disease.

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8 Clinical Microbiology Review

8.1. Nonclinical Microbiology

8.1.1. Mechanism of Action

Doxycycline is a member of the tetracycline class that inhibits bacterial protein synthesis by binding to bacterial 30s ribosomal subunits.

8.1.2. Antibacterial Activity

Doxycycline is bacteriostatic against gram-positive bacteria and gram-negative bacteria, and has activity against some protozoa. The list of specific organisms for which doxycycline is approved are listed in the approved labeling of the Listed Drug (RLD), Vibra-Tabs®. The Applicant has identified studies in the literature that assess the susceptibility of *B. burgdorferi* sensu lato species to doxycycline. The Applicant references studies examining in vitro susceptibility of *Borrelia* species with minimum inhibitory concentrations (MIC) ranging from 0.1 – 4 µg/mL, and MBC values ranging from 0.2-64 µg/mL. The current Vibramycin labeling includes *Borrelia recurrentis*; however, these bacteria are transmitted by the louse, and infection results in a relapsing fever. The mode of transmission of *Borrelia recurrentis* is different than other *Borrelia* species which are transmitted by ticks.

Clinical Microbiology Reviewer's Comment
The in vitro data provided by the Applicant as well as the clinical evidence from the literature, suggests that doxycycline is effective against B. burgdorferi. The MIC studies submitted by the Applicant demonstrated in vitro activity of doxycycline against some Borrelia species; however, there are no standardized methods for antimicrobial susceptibility testing (AST) of Borrelia spp. Thus, the doxycycline AST methods used by the authors of the 12 literature references on Borrelia spp. susceptibility varied, and inferences to clinical significance cannot be made.

8.1.3. Resistance and Cross-Resistance

Cross-resistance with other tetracyclines is common.
Sapi et al. (2011)[10] described three morphological forms of *Borrelia burgdorferi* (spirochetes, round-bodies, and biofilm-like colonies) based on culture methods. The study found that

[10] Sapi E, Kaur N, Anyanwu S, Luecke DF, Datar A, Patel S, Rossi M, Stricker RB. Evaluation of in-vitro antibiotic susceptibility of different morphological forms of *Borrelia burgdorferi*. Infect Drug Resist. 2011;4:97-113.

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doxycycline in vitro activity varied with different morphological forms of the organism, and that doxycycline significantly reduced the spirochete form of *B. burgdorferi* by approximately 90%, and increased the round body form two-fold. The authors discussed that "Persistence of viable organisms in round body forms and biofilm-like colonies may explain treatment failure and persistent symptoms".

8.1.4. Antibacterial Activity in Animal Models

The Applicant submitted the following key findings examining the efficacy of doxycycline in treating disease in animal models:

- Murine model of Lyme borreliosis-examined whether infectious spirochetes could persist after antibacterial drug treatment of disseminated infection (Bockenstedt, 2002 and Wormser, 2009)
- Immunosuppressed murine model of Lyme borreliosis-demonstrated that *B. burgdorferi* antigens, but not infectious spirochetes, can remain in the cartilage for extended periods after antibacterial drug treatment (Bockenstedt, 2012). The MIC and mean bactericidal concentrations (MBC) of doxycycline for spirochete strains was determined by serial dilution of antibacterial drugs in liquid cultures of *B. burgdorferi*. For laboratory strains of *B. burgdorferi* BbN40, the MIC and MBC for doxycycline were reported as 0.5 mcg/ml and 4 mcg/ml, respectively; for strain Bb914, the MIC and MBC for doxycycline were reported as 0.5 mcg/ml and 1.0 mcg/ml, respectively.
- Canine models of Lyme borreliosis-investigated the clinical manifestations, pathogenesis and effect of antibacterial drug treatment (Straubinger, 1998)
- Canine models of borreliosis-examined the effect of corticosteroids following antibacterial drug treatment (Straubinger, 2000)

Clinical Microbiology Reviewer's Comment
The nonclinical studies to examine the effect of doxycycline in animals infected with B. burgdorferi used healthy animals infected by tick bite. Successful infections were confirmed by serologic analysis and the treatment outcome was evaluated using several criteria including bacterial outgrowth assays, xenodiagnostic test (detection of B. burgdorferi in ticks), transplantation of tissues from infected animals, immunohistochemistry, and PCR of B. burgdorferi DNA. Only one study measured doxycycline MIC/MBC values. These studies were supportive of the use of doxycycline for the treatment of active infections of Lyme disease. However, there was evidence of persistence of B. burgdorferi infection following doxycycline treatment.

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8.2. Clinical Microbiology

8.2.1. Assay Descriptions and Methodologies

In the United States, the diagnosis of Lyme disease (most often EM) and the primary endpoints for studies (absence of objective clinical manifestations) are typically clinical in nature. Early disseminated disease may require serologic confirmation of the disease. In some studies referenced by the Applicant, ELISA and Western blot testing were done for *B. burgdorferi* antibody reactivity (e.g. Dattwyler, 1997). Susceptibility testing of *B. burgdorferi* has not been standardized. Some of the studies conducted in Europe included skin biopsy procedure for *B. burgdorferi* culture; however, skin biopsy is rarely done in the United States.

8.2.2. Clinical Microbiology Analyses of Efficacy

Since the primary efficacy endpoint was the absence of objective Lyme disease manifestations, and the study which had culture methods was excluded from analysis, clinical microbiology defers to the clinical team for the adequacy of the clinical endpoints in the Applicant's literature studies. The submitted information, from a clinical microbiology perspective, appears supportive of the inference that doxycycline demonstrates activity in vitro and in animal models against *B. burgdorferi*.

9 Review of Safety

There is extensive safety experience with doxycycline since the approval of doxycycline hyclate capsules in 1967. The proposed dose and duration for the treatment of early Lyme disease (100 mg BID for 21 days) are within the labeled dose ranges and durations. The applicant is relying on the safety for the approved labeling of Vibra-Tabs® (NDA 50533, Pfizer, Inc.). While the dosing regimen depends on the type of infection, most indications are treated with 100-200 mg daily for 7-28 days. The maximum length of dosing is 60 days (100 mg bid) for inhalational anthrax post-exposure, while the maximum daily dose is two-300 mg doses separated by 1 hour for the treatment of uncomplicated gonococcal infections in adults. The adverse event profile of doxycycline is well described within the approved product labeling for various doxycycline formulations. A new safety issue, the Jarisch-Herxheimer reaction, discussed in detail below does not appear in the current labeling for the RLD and will be added to the Applicant's proposed draft labeling.

9.1.1. Safety Review Approach

The adverse events sections in the published literature submitted by the Applicant were reviewed to determine if there were any new safety concerns, not previously addressed in the most recent labeling for Vibra-Tabs®. The adverse events reported in the studies supporting the efficacy of LYMEPAK (noted in

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Table **5** and
Table 6: Studies 3,4,5,6, 7, 8, 10-16) are described below.

Overall Exposure

In total, the number of patients exposed to doxycycline in the 36 submitted clinical studies was 2314. Most studies involved administration of doxycycline by the oral route. Doses in these clinical studies ranged from 100 mg to 400 mg daily and for duration of 1 day to 12 weeks. In the studies supporting the safety and efficacy of LYMEPAK, 975 patients were exposed to oral doxycycline 100 mg BID or TID for 10-21 days. There was a total of 94 patients exposed to doxycycline 100 mg BID for 21 days, the reviewer-recommended dosing regimen for LYMEPAK.

Relevant characteristics of the safety population:

Adverse events were considered relatively mild and similar across studies, regardless of patient demographics.

The age range of Lyme disease patients assessed for doxycycline safety was from 7 to 85 years. While most patients studied were adults, of studies that provided the age range of patients, 5 studies included patients treated with doxycycline under the age of 18, and 7 studies included patients treated with doxycycline over the age of 65 (see

Table **5** and
Table 6). Based on the current Vibra-Tabs® labeling, aside from adverse tooth and bone effects in children under age 8, no age-related safety issues are associated with doxycycline use. Insufficient information is available to determine any age-related adverse events in patients being treated with doxycycline for Lyme disease.

Gender distributions show nearly equal male/female ratios for clinical safety studies. No safety differences due to gender are expected with doxycycline treatment.

Race information was reported in 3 studies, where greater than 90% of patients were Caucasian. While most studies did not provide ethnicity information, the clinical safety studies were performed in hyperendemic regions of Lyme disease. Therefore, the clinical safety data provided in this summary would be largely representative of the race and ethnicity of patients that would be treated for early Lyme disease. A total of 4 studies were performed in the US, comprising 424 patients exposed to doxycycline. Seven studies were performed in Europe, comprising 551 patients exposed to doxycycline. No safety differences due to race or geographic location are expected with doxycycline treatment.

Adequacy of the safety database:

The overall number of patients exposed to doxycycline in the studies appears adequate to perform a safety evaluation. However, the number of patients exposed to the proposed dosing

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regimen of LYMEPAK (100 mg BID for 21 days) was limited to 94, and in most cases, only a brief description of the adverse events reported was noted. However, the safety profile of doxycycline is well established and described in the product labeling.

In special populations, such as pregnancy, patients with renal or hepatic insufficiency or with other underlying diseases, none of the clinical studies provided safety data on use of LYMEPAK. Although some elderly patients were included in these studies, safety and efficacy data were not provided separately by age. Additionally, most studies combined adult and pediatric patients, so conclusions regarding pediatric safety of LYMEPAK for pediatric patients, ages 8-18 years, could not be drawn.

9.1.2. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Not applicable.

Categorization of Adverse Events

Not applicable.

Routine Clinical Tests

Not applicable.

9.1.3. Safety Results

Deaths

No studies reported patient deaths.

Serious Adverse Events

The Applicant noted that there was one SAE of photosensitivity in Study 11 in a patient receiving doxycycline on the last day of therapy. It is unknown whether the event was life-threatening, resulted in hospitalization or persistent or significant disability.

Another SAE reported in Study 5 was gastrointestinal hemorrhage on day 6 of doxycycline treatment in a 77-year old female. The patient had had severe abdominal pain on days 4 and 5, and was found to have a duodenal ulcer, a hiatal hernia with reflux, and hepatic cysts. Doxycycline was discontinued on day 6. The approved labeling of the RLD contains esophagitis and esophageal ulcerations as adverse reactions reported with the use of drugs in the tetracycline class.

Medical Reviewer Comments: Details of this patient's medical history and concomitant medications was not provided. It is biologically plausible that doxycycline can cause mucosal

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erosions in the entire gastrointestinal tract. Thus, a causal relationship of this SAE with doxycycline to duodenal ulcer and gastrointestinal hemorrhage cannot be excluded.

Mercado, an Internal FDA Database for Regulatory Review, was utilized to determine which types of ulcer were reported with use of doxycycline in the post-market setting. Using the preferred term "ulcer" and "duodenal ulcer", 9 cases were retrieved. Only 1 case was associated with gastric polpys with superficial ulcers, and localized duodenal bulb erosion after doxycycline use for H. pylori, in a patient with celiac disease and reflux disease. The other cases did not specify an ulcer, or noted 'varicose', 'skin', or 'esophageal' ulcers.

Dropouts and/or Discontinuations Due to Adverse Effects

The number of patients that were withdrawn or required a change in doxycycline therapy and associated adverse event are shown in Table 25. Most of the adverse events that occurred are described in the approved labeling for the RLD. These include gastrointestinal upset, photosensitivity/dermatitis, headache, nausea, diarrhea, and vomiting. Chest pain/discomfort occurred in 2 patients, and dyspnea occurred in 1 patient in Study 8. No details about the medical history, concomitant medications, or history of dechallenge with doxycycline was provided for these patients, to determine if the adverse events were truly related to doxycycline.

Table 25: Discontinuations of Doxycycline Treatment Due to Adverse Events

STUDY	NUMBER OF PATIENTS WITHDRAWN/REQUIRING CHANGE IN THERAPY	ADVERSE EVENT
3	2	Gastrointestinal upset (1); photodermatitis (1)
5	4	Headache, nausea, vomiting, weight loss (1); unspecified events (2); abdominal pain, duodenal ulcer, hiatal hernia, reflux, hepatic cysts, and gastrointestinal hemorrhage (1)
7	1	Nausea and diarrhea (1)
8	5	Chest discomfort and burning (1); chest pain and shortness of breath (1); rash (1); abdominal pain (2)
6	1	Nausea, vomiting, and diarrhea (1)
10	1	Diarrhea (1)

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Significant Adverse Events

Not applicable.

Treatment Emergent Adverse Events and Adverse Reactions

The patient population, treatment regimen, and pertinent safety outcomes in the US and European doxycycline treatment studies are listed in Table 26 and

Table **27**, respectively. The highest drug-related adverse events were reported in 42-44% patients in two US doxycycline treatment studies using the BID regimen (Studies 5 and 6). The US studies using the TID regimen reported 28-32% drug-related adverse events. The most common adverse events reported were GI disturbances (including nausea, vomiting, (b) (4) , and diarrhea), phototoxicity, and rash. These adverse events are found within approved labeling of the RLD. Overall, the frequency of drug-related adverse events was reported to be higher in the US rather than in European studies. However, the system organ classes for the drug-related adverse events between the US and Europe were similar. The Jarisch-Herxheimer reaction is discussed in 9.1.4 Analysis of Submission-Specific Safety Issues.

Table 26: Summary of Treatment Emergent Adverse Events by Organ System in US Studies

PARAMETER	STUDY AUTHOR/NUMBER						
	DATTWYLER 3 N=37	MASSAROTI 4 N=22	DATTWYLER 5 N=72	WORMSER 6		NADELMAN 7 N=60	LUGER 8 N=113
				N=61	N=59		
Doxycycline frequency (100 mg)	BID	BID	BID	BID		TID	TID
Treatment duration, days	21	20	21	10	20	20	20
Deaths, n	0	0	0	0	0	0	0
SAE (n, %)	0	0	1 (1)	0	0	0	0
Adverse Events (%)	ns	ns	ns	ns	ns	ns	ns
Any Drug Related Adverse Event n (%)	ns	ns	31 (43)	27 (44)[+]	25 (42)[+]	19 (32)[+]	32 (28)[+]
Gastrointestinal	1 (3)	1 (5)	18 (25)	29 (48)	33 (56)	6 (10)	10 (9)
Skin	1 (3)	1 (5)	9 (12)	5 (8)	2 (3)	9 (15)	11 (10)
Other	0	0	0	1 (2)	1 (2)	3 (5)	5 (4.4)
Changes in laboratory assessments	ns	ns	4 (6)	ns	ns	1 (2)	ns
Jarisch-Herxheimer Reaction n %	3 (8)	7 (12) *	ns	ns	ns	5 (8)	13 (12)

* intensification in symptoms during first 24 hours of therapy, without fever, in all patient arms combined (7/57)
[+] may not be additive as the same patient may have had ≥ 1 event

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Table 27: Summary of Treatment Emergent Adverse Events by Organ System in European Studies

PARAMETER	STUDY AUTHOR/NUMBER						
	Barsic 10 N =40	Strle 11 N=23	Strle 12 N=52	Stupica 13 N= 108	Stupica 13 N=117	Strle 15 N=42	Cerar 16 N=145
Doxycycline Frequency (100 mg)	BID	BID	BID	BID		BID	BID
Duration, days	14	14	14	10	15	14	15
Deaths, n	0	0	0	0	0	0	0
SAE (n, %)	0	1 (4)	0	0	0	0	0
Any Drug Related Adverse Event n (%)	5 (13)	ns	ns	ns	ns	ns	22 (15)
Gastrointestinal	5 (13)	4 (17)	15 (29)	24 (22)	25 (21)	9 (21)	20 (14)
Skin	1 (3)	1 (4)	6 (12)	0	7 (6)	5 (12)	1 (1)
Other	1 (1)	0	0	5 (5)	9 (8)	0	5 (3)
Changes in Laboratory Assessments	0	4 (17)	3 (6)	76 (70) [α]	85 (73) [α]	3 (7)	ns
Jarisch-Herxheimer Reaction n (%)	ns	7 (30) [*]	9 (17) [×]	ns	ns	4 (10) [+]	ns

[*] Exacerbation of local and/or general symptoms, frequently with elevated body temperature
[×] 6 had exacerbation of local and/or general symptoms; 3 had more severe reaction with weakness, shivering, and fever over 38°C
[+] 4 had exacerbation of local and/or general symptoms
[α] Number of patients with >10% decrease in WBC or platelets, or >10% increase in bilirubin, AST, or ALT at 14 days compared with test results at enrollment.

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Laboratory Findings

Most of the laboratory findings were reported as minor, and no patient-level laboratory values were available. In Study 5, 4 patients receiving doxycycline had minor, transient abnormalities on unspecified laboratory testing. In Study 11, 4 patients receiving doxycycline had slightly abnormal liver enzymes at baseline. One patient continued to have slightly abnormal liver enzymes after treatment which resolved at the 24-month follow-up visit. The actual values were not reported. In Study 12, 8 patients had abnormal liver enzymes at baseline. Two weeks later, 4 patients continued to have abnormal liver enzymes. Three patients treated with doxycycline developed abnormal liver enzymes during treatment, which may have been interpreted as an adverse effect of therapy, per the author. Eight weeks after the first test, the results were normal. Other than the description above, no specific laboratory parameters and values were reported. In Study 13, the changes in WBC, platelets, and liver enzymes were quantified more than in other studies, and the results were still generally mild and similar between the 10- and 15-day treatment. In Study 15, 3 patients had mildly abnormal liver enzymes. It is unknown if these resolved. In Study 16, nonspecific laboratory values were mildly changed, and similar before and after treatment in the 10 and 15-day doxycycline regimens.

Medical Reviewer Comments: Abnormal liver enzymes can be associated with early Lyme disease, and usually improve or resolve after antibacterial therapy within 3 weeks[11]. Overall, the abnormal liver enzymes appeared to be mild and transient, mostly likely originating from the disease process itself, rather than from doxycycline. Hepatoxicity, although rare, is listed under adverse reactions in the RLD label.

[11] Horowitz H, Dworkin B, Forseter G et al. 1996. Liver function in early Lyme disease. Hepatology (23): 1412-17.

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Vital Signs

No safety-related vital signs were described in the studies.

Electrocardiograms (ECGs) and QT

ECG was obtained at baseline and at follow-up in most studies to evaluate cardiac manifestations of Lyme disease. No ECG or QT changes due to doxycycline treatment were described in the studies.

Immunogenicity

Not applicable.

9.1.4. Analysis of Submission-Specific Safety Issues

Most adverse events noted in the safety studies in (b) (4) APPEARS THIS WAY ON ORIGINAL ®. Adverse events noted in this submission that are not specifically listed within the approved labeling are chest pain/discomfort, shortness of breath, gastrointestinal hemorrhage secondary to duodenal ulcer (shown in Table 25), as well as the Jarisch-Herxheimer reaction (shown in Table 26 and Table 27). As chest pain/discomfort and shortness of breath are generally considered NSS, and were rarely reported with doxycycline treatment in the safety analysis (2/975 patients), it will not be added to the Applicant's proposed labeling. Rare instances of esophagitis and esophageal ulcerations have been reported in patients receiving tablet forms of tetracycline-class drugs. However, there is no known association with duodenal ulceration. Theoretically, pill-induced gastric injury leading to gastrointestinal hemorrhage can occur. While the patient with duodenal ulcer and gastrointestinal hemorrhage was considered to have a SAE, these adverse events do not warrant in a change in the proposed labeling. The Jarisch-Herxheimer reaction has been added to the proposed labeling and will be discussed further below.

Jarisch-Herxheimer Reaction

The Jarisch-Herxheimer reaction (JHR) has been reported after treatment with penicillins, tetracyclines, and erythromycin in spirochetal infections, most commonly in syphilis, but also in Lyme disease, leptospirosis, and relapsing fever. The Jarisch-Herxheimer reaction is a systemic reaction that begins one to two hours after initiation of therapy and disappears within 12 to 24 hours. It is characterized by fever, chills, myalgias, headache, exacerbation of cutaneous lesions, tachycardia, hyperventilation, vasodilation with flushing, and mild hypotension. The

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pathogenesis of the Jarisch-Herxheimer reaction is unknown, but is hypothesized to be due to the release from the spirochetes of heat-stable pyrogen. Antipyretics may reduce the severity of symptoms and the duration of the reaction. In published literature on the treatment of Lyme disease with doxycycline therapy, the range of JHR frequency was 7–30%, indicating a trend toward lower frequency than for syphilis (1-100%).[12] Furthermore, the reactions in Lyme disease with various antibacterial therapies were clinically milder than in the other diseases, without organ dysfunction or need for hospitalization.

In safety studies, relevant to this NDA, JHR occurred after the initiation of doxycycline therapy in up to 12% of US patients and 30% of European patients with early Lyme disease. Most of the studies discussed the "intensification of local and/or general symptoms, with or without fever," without referring to this reaction, specifically as JHR. However, this reviewer interpreted these descriptions as probable JHR or Jarisch-Herxheimer-like reactions. The frequency of JHR reported in the NDA safety studies and other published reports warrant an addition of a warning to the Applicant's proposed labeling. This is discussed further in section 12, Labeling Recommendations.

9.1.5. Safety Analyses by Demographic Subgroups

No specific safety concerns were identified in pediatric patients (see Pediatrics), elderly (over age 65), or other demographic subgroups such as race or gender.

9.1.6. Specific Safety Studies/Clinical Trials

[12] Butler T. The Jarisch–Herxheimer Reaction After Antibiotic Treatment of Spirochetal Infections: A Review of Recent Cases and Our Understanding of Pathogenesis. *Am J Trop Med Hygiene*. 2017;96(1):46-52.

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Not applicable.

9.1.7. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Not applicable.

Pediatrics and Assessment of Effects on Growth

Not applicable.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

9.1.8. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Mercado, an Internal FDA Database for Regulatory Review, was searched to identify the most commonly reported adverse events with use of doxycycline products using the FAERS completion dates from 1 January 2012 to 2018. When doxycycline was entered in the product active ingredient search, cases involving doxycycline (without specification of the salt formulation), doxycycline hyclate, doxycycline calcium, doxycycline hydrochloride were retrieved. A total of 6168 cases were retrieved, of which 3277 were from the US. In cases in which gender was reported, 56.7% cases were identified as female. In cases in which the indication was reported or known, Lyme disease was the third most common indication after acne and lower respiratory tract infection. One hundred and fifty-three cases (2.5%) reported Lyme disease as the reason for use. The preferred terms for AEs reported for all indications are listed in

Table 28.

Table 28: Case Count by MedDRA Event

Preferred Terms	Total Cases	% of Cases
Drug hypersensitivity	1,038	16.8%
Nausea	501	8.1%
Vomiting	444	7.2%
Headache	363	5.9%
Rash	325	5.3%
Malaise	280	4.5%
Drug ineffective	254	4.1%

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Preferred Terms	Total Cases	% of Cases
Diarrhoea	250	4.1%
Dyspnoea	209	3.4%
Pruritus	202	3.3%
Dizziness	200	3.2%
Drug interaction	186	3.0%
Jarisch-Herxheimer reaction	183	3.0%
Fatigue	163	2.6%
Abdominal discomfort	160	2.6%
Abdominal pain upper	157	2.5%
Anxiety	153	2.5%
Pyrexia	152	2.5%
Erythema	136	2.2%
Pain	136	2.2%
Urticaria	126	2.0%
Abdominal pain	122	2.0%
Arthralgia	117	1.9%
Condition aggravated	110	1.8%
Photosensitivity reaction	106	1.7%
Chest pain	105	1.7%
Oesophageal ulcer	100	1.6%

As noted above in Table 25, chest pain and dyspnea were adverse events leading to discontinuation of 2 patients out of 975 patients exposed to doxycycline 100 mg BID-TID for 10-21 days. From the Mercado Database search, above, chest pain occurred in 1.7% and dyspnea occurred in 3.4% of patients receiving doxycycline in the postmarket setting for any indication. To determine the causality of these cases, a few narratives were reviewed in which the preferred term contained either chest pain/discomfort or dyspnea. In most cases, chest pain appeared to be non-cardiac, resulting from (b) (4) or esophagitis, which is a known adverse reaction (labeled in the RLD). In most cases of dyspnea, the reports describe possible allergic reactions including throat swelling and difficulty swallowing. Hypersensitivity reactions including urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, serum sickness, pericarditis, exacerbation of systemic lupus erythematosus, and drug reaction with eosinophilia and systemic symptoms (DRESS) are listed under adverse reactions in the RLD's label.

Five FAERS cases revealed the following:

1. Case # 3948212 – patient had history of angina and was taking 9 other suspect medications in addition to doxycycline and experienced chest pain

2. Case # 8473549 – patient developed shortness of breath after taking doxycycline, and he had a documented hypersensitivity reaction to tetracyclines in the past

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3. Case # 8699253 – patient had chest pain related to esophagitis

4. Case # 8747309 – patient had symptoms of indigestion mimicking chest pain

5. Case # 9215094 – patient had chronic obstructive pulmonary disease, and had taken another antibacterial drug to which he may have had an allergy, and then experienced breathlessness after adding doxycycline

9.2. Integrated Assessment of Safety

See Section 9 Review of Safety

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10 Advisory Committee Meeting and Other External Consultation

This application was not presented to the Anti-Infective Drug Advisory Committee. On February 28, 2018, DAIP sought guidance from the CDER Medical Policy and Program Review Council (MPPRC) concerning whether the data presented from the Applicant, including the small number of studies, use of historic control, and lack of patient-level data provide sufficient evidence for the efficacy of doxycycline 100mg bid x (b) (4) 21 days for the treatment of early Lyme disease.

The Council stated support for approving this application based upon the strong literature evidence in concert with the prior Ceftin approval and lack of feasibility for the placebo controlled trials; however, seeking additional supporting data (real world evidence) if feasible, was recommended.

For labeling recommendations related to the PLLR section, the Division of Maternal and Pediatric Health was consulted for label review.

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11 Pediatrics

Clinical manifestations of Lyme disease, specifically localized EM, in the pediatric age group are generally like adults. The EM rash varies in appearance as in adults; however, small ring-shaped lesions in children are more commonly caused by insect bites rather than Lyme disease[13]. Also, one-half of EM lesions appear on the head and neck. Although some forms of disseminated Lyme disease may manifest somewhat differently in children compared to adults (e.g. increased intracranial pressure is more severe in pediatric neuroborreliosis), early localized Lyme disease presents in a similar manner regardless of the patient's age. Children are more likely to present with fever and joint complaints, possibly due to the lower threshold for seeking medical care for a child than for an adult with joint complaints and fever.

In this submission for LYMEPAK, there were limited data on disease progression or treatment outcomes in pediatric patients. There were a few studies of doxycycline that enrolled pediatric patients between 8-16. Studies 7, 8, and 10 allowed enrollment of patients 12 years or older, weighing at least 45 kg. None of these studies specifically stated that patients between the ages of 12 and 16 were enrolled or completed the study. Additionally, none of these studies stratified the results of doxycycline treatment by age or reported any other age-related outcomes; therefore, it is reasonable to assume the investigators discovered no age specific concerns. The US natural history studies included patients aged 2 to 67, but did not specify outcomes in pediatric patients.

On 3 March 2015, the Agency agreed to a waiver of pediatric studies (iPSP) for pediatric patients < 8 years of age based on doxycycline's known safety profile in adversely affecting bone and tooth growth, and plan for extrapolating efficacy of doxycycline from adults to pediatric patients ≥ 8 years. In pediatric patients age 0 to < 8 years of age, other antibacterial drugs are routinely prescribed for the treatment of early Lyme disease.

Based on similar clinical features of Lyme disease, response to treatment, and comparable systemic exposure, the Agency agreed with the Applicant that efficacy of doxycycline could be extrapolated from adult to pediatric patients 8 years of age and older, weighing 45 kilograms (kg) or more. The same fixed-dose tablet will be recommended for adults and pediatric patients 8 years of age and older, weighing 45 kg or more (b) (4)

The Review Division met with the FDA Pediatric Review Committee (PeRC) to discuss the pediatric plan for LYMEPAK. It was noted that the 100 mg tablet formulation can only be administered to pediatric patients who weigh 45 kg or greater (50th percentile for a 12-year-old child). Partial waiver for LYMEPAK covers pediatric patients ages 0 < 8 years. The proposed

[13] Sood, SK. Lyme disease in children. Infect Dis Clin North Am 2015 Jun;29(2):281-94

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formulation (b) (4) are deemed inadequate for certain pediatric patients (8 years and older who weigh < 45 kg). A postmarketing requirement (PMR) to develop a formulation (b) (4) for LYMEPAK that can be administered to pediatric patients age 8 years and older who weigh less than 45 kg will be recommended.

12 Labeling Recommendations

12.1. Prescribing Information

High-level changes to the proposed labeling are summarized in Table 29. **Error! Reference source not found.**These relate to changes in the duration (b) (4) 21 days only, removing (b) (4), adding the Jarisch-Herxheimer Reaction, and adding more detailed information to the PLLR sections.

Table 29: Summary of Significant Labeling Changes

Section	Proposed Labeling	Approved Labeling
2.1	(b) (4)	Adults and Pediatric Patients 8 years of age and older weighing 45 kg and above. Administer LYMEPAK (100 mg) tablet every 12 hours for 21 days.
2.1		

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Section	Proposed Labeling	Approved Labeling
5.6		The Jarisch-Herxheimer reaction is a self-limiting systemic reaction that has been reported after the initiation of doxycycline therapy in up to 30% of patients with early Lyme disease. The reaction begins one to two hours after initiation of therapy and disappears within 12 to 24 hours. It is characterized by fever, chills, myalgias, headache, exacerbation of cutaneous lesions, tachycardia, hyperventilation, vasodilation with flushing, and mild hypotension. The pathogenesis of the Jarisch-Herxheimer reaction is unknown, but thought to be due to the release of spirochetal heat-stable pyrogen. Advise the patient of this reaction before starting LYMEPAK. Administer fluids and antipyretics to alleviate symptoms and duration of the reaction if severe.
8.1	(b) (4)	LYMEPAK, like other tetracycline-class antibacterial drugs, may cause discoloration of deciduous teeth and reversible inhibition of bone growth when administered during the second and third trimester of pregnancy *[see Warnings and Precautions (5.1, 5.2), Data, Use in Specific Populations (8.4)].* Available data from published studies over decades have not shown a difference in major birth defect risk compared to unexposed pregnancies with doxycycline exposure in the first trimester of pregnancy *(see Data).* There are no available data on the risk of miscarriage following exposure to doxycycline in pregnancy.

Section	Proposed Labeling	Approved Labeling
		The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Summary of Significant Labeling Changes Pertaining to Clinical Microbiology

- Subsection 12.1: The mechanism of action should be removed from this section to subsection 12.4 Microbiology
- Subsection 12.4 Microbiology was updated throughout in accordance with the Clinical Microbiology guidance document titled, "Microbiology Data for Systemic Antibacterial Drugs; Development, Analysis and Presentation"
- The indications are specifically for treatment of *Borrelia burgdorferi*, (b) (4) should not be in subsection 12.4 of the labeling
- (b) (4) should not be included in subsection 12.4 of the labeling for the following reasons:

(b) (4)

12.2. Patient Labeling

Not applicable.

13 Risk Evaluation and Mitigation Strategies (REMS)

Not applicable.

13.1. Safety Issue(s) that Warrant Consideration of a REMS

Not applicable.

13.2. Conditions of Use to Address Safety Issue(s)

Not applicable.

13.3. Recommendations on REMS

Not applicable.

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14 Postmarketing Requirements and Commitments

On 27 April 2018, The Division of Anti-Infective Products (DAIP) met with the FDA Pediatric Review Committee (PeRC) to discuss the pediatric plan for LYMEPAK. DAIP and PeRC agree to grant a partial waiver for LYMEPAK that covers pediatric patients ages 0 to less than 8 years. However, it was noted that the 100-mg tablet formulation can only be administered to pediatric patients who weigh 45 kilograms or greater (50th percentile for a 12-year-old child). The proposed formulation (b) (4) is inadequate for certain pediatric patients (8 years and older who weigh < 45 kg). The Applicant has agreed to the following (PMR to develop a formulation/(b) (4) for your doxycycline hyclate product that can be administered to pediatric patients age 8 years and older who weigh less than 45 kg:

PREA PMR: Provide the title(s) of the clinical study and/or CMC study to address dosing and formulation of LYMEPAK for use in pediatric patients who are 8 years and older and weigh less than 45 kg.

On 22 May 2018, the Applicant accepted the Division recommendation and committed to the following title and dates for a CMC study to address dosing and formulation of LYMEPAK for use in pediatric patients who are 8 years and older and weigh less than 45 kg:

PREA PMR: An evaluation of (b) (4) LYMEPAK tablets to validate dosing and formulation for use in pediatric patients 8 years of age and older who weigh less than 45 kg.

Draft protocol submission date: **September 2018**
Final protocol submission date: **January 2019**
Study completion date: **June 2019**
Final study report submission date: **December 2019**

The Applicant will refer the recommended Guidance "(b) (4) Nomenclature, Labeling, and Data for Evaluation" (b) (4)

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15 Appendices

15.1. References

See footnotes within document

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15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number):

1. **Dattwyler 1990**
2. **Dattwyler 1997**
3. **Massaroti 1992**
4. **Antal 1975**

Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 3		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: ____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

The Applicant submitted studies sponsored by a firm or party other than the Applicant. The

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Applicant certifies that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (Dattwyler and Antal) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21CFR 54.2(a)); had no proprietary interest in this product of significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

15.3. Appendix A

A. CDC Clinical Case Definition for Lyme Disease

Definition: Erythema migrans, or at least one advanced manifestation, as defined below, and laboratory confirmation of infection

Advanced manifestations:

1. Musculoskeletal system

Recurrent, brief attacks (lasting weeks or months) of objective joint swelling in one or a few joints, sometimes followed by chronic arthritis in one or a few joints; manifestations not considered criteria for diagnosis include chronic progressive arthritis, not preceded by brief attacks, and chronic symmetrical polyarthritis; arthralgia, myalgia, or fibromyalgia syndromes alone are not criteria for musculoskeletal involvement

2. Nervous system

Any of the following, alone or in combination: lymphocytic meningitis; cranial neuritis, particularly facial palsy (may be bilateral); radiculoneuropathy; or, rarely, encephalomyelitis (must be confirmed by showing antibody production against Borrelia burgdorferi in the cerebrospinal fluid, demonstrated by a higher titer of antibody in cerebrospinal fluid than in serum); headache, fatigue, paresthesia, or mild stiff neck alone are not criteria for neurologic involvement

3. Cardiovascular system

Acute-onset, high-grade (2 or 3) atrioventricular conduction defects that resolve in days to weeks and are sometimes associated with myocarditis; palpitations, bradycardia, bundle branch block, or myocarditis are not criteria for cardiovascular involvement

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16 Division Director (Clinical)

Concur with review.

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/s/

KRISTINE E PARK
06/12/2018

SUMATHI NAMBIAR
06/12/2018