Early Lyme Disease as Manifested by Erythema Migrans: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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TABLE OF CONTENTS

Early Lyme Disease as Manifested by Erythema Migrans: Developing Drugs for Treatment Guidance for Industry[1]

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I. INTRODUCTION

The purpose of this guidance is to provide the Food and Drug Administration's (FDA's) current recommendations regarding the development of drugs[2] to support an indication for the treatment of early Lyme disease as manifested by erythema migrans (EM).[3]

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the International Council for Harmonisation guidances for industry *E9 Statistical Principles for Clinical Trials* (September 1998), *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (May 2021) and *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001).[4] This guidance also does not discuss general considerations (e.g., pharmacology/ toxicology or clinical pharmacology) of drug development because these considerations are similar to those for other indications for anti-infective drugs.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Division of Anti-Infectives in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products regulated by CDER unless otherwise specified.

[3] Sponsors that intend to develop drugs for patients with cardiac or neurologic manifestations of early Lyme disease, or for late Lyme disease, should discuss this with FDA before trial initiation.

[4] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

II. BACKGROUND

Lyme disease is a tick-borne infection, transmitted by the bite of infected Ixodid ticks. In North America, Lyme disease is primarily caused by the spirochete *Borrelia burgdorferi* and rarely by *B. mayonii,* which is an emerging pathogen for Lyme disease in the Upper Midwest of the United States.[5] In Europe and Asia, Lyme disease is caused by *B. afzelli* and *B. garinii*; *B. burgdorferi* is also reported in Europe. There are some differences in clinical manifestations of Lyme disease in the United States and in Europe and Asia with patients in the United States having higher rates of systemic symptoms as well as multiple and more rapidly expanding EM lesions (Strle et al. 1999; Jones et al. 2008).

Clinically, Lyme disease can be divided into early localized, early disseminated, and late disease. Early localized disease occurs within 1 month following the tick bite and is characterized by EM, a rash at the site of the tick bite that may be accompanied by nonspecific symptoms (e.g., fatigue, myalgias).[6] Diagnosis of early localized disease rests primarily on clinical findings because serology is often negative early in the infection. Early disseminated disease occurs days to months after the tick bite and is characterized by multiple EM lesions often distant from the bite site, and/or neurologic and/or cardiac findings. Late disease occurs months after the onset of infection, and arthritis in a large joint is the most common feature. The goal of antibacterial treatment is to resolve symptoms and prevent later complications.

III. DEVELOPMENT CONSIDERATIONS

A. Trial Population

The trial(s) should enroll subjects with early localized (i.e., a single EM lesion) or early disseminated (i.e., multiple EM lesions) disease, who reside in or traveled to a Lyme-endemic area. In general, sponsors should not enroll subjects with musculoskeletal, neurologic, or cardiac manifestations of Lyme disease (e.g., active arthritis, myocarditis, meningitis, cranial neuropathy). Also, sponsors should not enroll subjects with ongoing symptoms attributed to a history of Lyme disease or a concurrent tick-borne infection (e.g., babesiosis, ehrlichiosis, anaplasmosis).

B. Trial Design

Trials are expected to be randomized, double-blinded, and controlled. Subjects should not be left untreated; thus, placebo-controlled trials, unless of an add-on design, would not be appropriate. Superiority trials with a direct comparison to an approved drug or as an add-on design are

[5] See the Centers for Disease Control and Prevention (CDC) Lyme Disease web page at https://www.cdc.gov/lyme/index.html.

[6] Sponsors can refer to the CDC's clinical case definition on the web page Lyme Disease (*Borrelia burgdorferi*) 2017 Case Definition at https://ndc.services.cdc.gov/case-definitions/lyme-disease-2017/.

acceptable to support an indication of treatment for early Lyme disease. Noninferiority (NI) trials are also acceptable (see the Appendix regarding the justification of an NI margin).

Sponsors can consider stratification of randomization according to clinical manifestations (e.g., a single EM lesion versus multiple EM lesions) to ensure similar proportions of subjects with disseminated disease in each group. Sponsors can also consider additional stratification by age group (pediatric, adult) when enrollment is not limited to adult subjects.

C. Efficacy Considerations

Generally, two adequate and well controlled trials are necessary to provide evidence for drug effectiveness.[7] In some cases, such as development of a drug previously approved to treat a serious infection, a robust finding from a single, adequate, and well-controlled trial supported by other independent clinical and/or nonclinical data such as in vitro or animal models, may provide evidence of effectiveness (see section III., E., Other Considerations). If a single, adequate, and well-controlled trial is proposed, the sponsor should discuss with FDA the other independent evidence that could be used to support the findings from this single trial.

1. Choice of Comparators, Prior and Concomitant Antibacterial Drugs

For an NI trial, FDA recommends an active control with known activity in early Lyme disease. Sponsors can use oral doxycycline or other comparators if adequate evidence is available to justify an NI margin. We recommend that the sponsor discuss with FDA the choice of comparator before study initiation.

No antibacterial drug known to be active against *B. burgdorferi* or *B. mayonii* should be administered to subjects within 48 hours before enrollment or during the trial. If concomitant antibacterial drugs are administered, the sponsors should report the reason, dosing, and dates of administration.

2. Efficacy Endpoints

a. Primary efficacy endpoint

The primary efficacy endpoint should be a responder outcome at 6 months after randomization.

[7] See the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

Clinical success should be defined as resolution of EM and continued absence of objective manifestations of Lyme disease without need for additional antibacterial treatment for Lyme disease.[8]

Clinical failure should be defined as the presence of unresolving or recurrent EM, objective manifestations of Lyme disease, or the need for additional antibacterial treatment for Lyme disease.[9]

b. Secondary endpoints

Secondary endpoints should include the following:

- Clinical success or clinical failure (as defined above) through 30 days after randomization
- Clinical success or clinical failure (as defined above) through 12 months after randomization

3. Statistical Considerations

In general, sponsors should provide a detailed statistical analysis plan stating the trial hypotheses and the analysis methods before trial initiation. The primary efficacy analysis is usually based on the difference in the proportions of subjects achieving clinical success.

To improve the precision of treatment effect estimation and inference, sponsors should consider adjusting for prespecified baseline factors that are anticipated to be prognostic of the outcome. If randomization is stratified by baseline covariates, the analysis should account for the stratified randomization.[10]

a. Analysis populations

The following are definitions of various analysis populations. The primary analysis population for efficacy should be the intent-to-treat population.

Intent-to-treat (ITT) population: All randomized subjects

[8] Objective manifestations could include signs of advanced Lyme disease involving the musculoskeletal, cardiac, or nervous system as defined by CDC's clinical case definition on the web page Lyme Disease (*Borrelia burgdorferi*) 2017 Case Definition at https://ndc.services.cdc.gov/case-definitions/lyme-disease-2017/.

[9] Sponsors that intend to use a different endpoint for the assessment of the primary endpoint in early Lyme disease should discuss this with FDA. Sponsors should document the reasons for clinical failure and should plan for supplementary analyses to compare treatment groups with respect to proportions of subjects with objective manifestations of Lyme disease and need for additional antibacterial treatment for Lyme disease. Sponsors should also plan for supplementary analyses to compare treatment groups with respect to the proportions of subjects who received antibacterial drugs with activity against *B. burgdorferi* for infections other than Lyme disease during the trial period.

[10] See the draft guidance for industry *Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products* (May 2021). When final, this guidance will represent the FDA's current thinking on this topic.

Safety population: All subjects who received at least one dose of the investigational drug during the trial.

Per-protocol population: Subjects who are not lost to follow-up and adhere to trial procedures as specified in the protocol.

b. NI margins

There are some historical data available to help support the appropriateness of NI trials for the treatment of Lyme disease (see the Appendix for an example). Note that the NI justification used for any particular trial will depend on the active control used, trial population, and trial endpoints.

c. Subject follow-up/missing data

The protocol should include plans to minimize the amount of missing data. All subjects should be followed throughout the trial unless a subject withdraws consent, is lost to follow-up, or dies. The protocol should clearly outline how the sponsor will handle the outcomes of subjects with missing data in the primary analysis.

D. Safety Considerations

The size of the safety database may depend on several factors, such as the adverse event profile expected with the drug or drug class, and the duration of use. Sponsors should discuss the appropriate size of the premarketing safety database with FDA during development. A minimum size of 300 subjects treated at the proposed dose and duration is expected for drugs with no prior clinical experience. The required safety database may be larger depending on the safety signals identified during the development program.

E. Other Considerations

1. Clinical Microbiology Considerations

a. Serology

In general, confirmatory serological testing is not required in the presence of single or multiple lesions consistent with EM. Sponsors could use detection of antibodies to *B. burgdorferi* to confirm the infection in atypical EM presentations (antibody testing performed on an acute-phase serum sample followed by a convalescent-phase serum sample if the initial result is negative). FDA-cleared tests are recommended. If tests are not FDA-cleared, sponsors should submit performance characteristics (e.g., sensitivity and specificity) for FDA review.

b. Antimicrobial susceptibility testing

The in vitro activity of antibacterial drugs against some *Borrelia* species has been described in the literature; however, there are no standardized methods for antibacterial susceptibility testing (AST) of *Borrelia* species. The clinical relevance of *Borrelia* species susceptibility testing is unknown because of variability in testing methodology and the presence of different morphological forms of *B. burgdorferi* (Lantos et al. 2014). However, AST results (e.g., minimum inhibitory concentration (MIC)) and antibacterial activity determination may be useful for proof-of-concept studies when used with appropriate controls. To distinguish between isolates with the same MICs, genotypic testing may be useful.

c. Animal models of infection

Nonclinical studies to examine the effect of antibacterial drugs in animals infected with *B. burgdorferi* have included various methods, including the use of healthy animals infected by tick bite.[11] Successful infections in animal models have been confirmed by serologic analysis, and the treatment outcomes have been evaluated using several laboratory criteria including bacterial outgrowth assays, xenodiagnostic tests (detection of *B. burgdorferi* in ticks), transplantation of tissues from infected animals, immunohistochemistry, and polymerase chain reaction test for *B. burgdorferi* DNA. Activity in animal models of infection can be used as supportive evidence for the use of antibacterial drugs for the treatment of active *B. burgdorferi* infections in clinical trials; however, evidence of pathogen or *B. burgdorferi* antigen persistence and ongoing inflammatory responses following treatment have been observed in some animal models of *B. burgdorferi* infection (Brockenstedt et al. 2002; Brockenstedt et al. 2012; Hodzic et al. 2008; Straubinger et al 1998; Straubinger et al. 2000; Sapi et al. 2011). We recommend that sponsors discuss with FDA animal models of infection and the doses to be evaluated before study initiation.

2. Inclusion of Pediatric and Pregnant Subjects in Drug Development

It is important to conduct clinical studies in the pediatric population to inform dosing and assess the safety and effectiveness of anti-infective drugs. Sponsors should consider whether efficacy results from adequate and well-controlled clinical trials of an investigational drug in adult subjects could be extrapolated to a pediatric population.[12] In addition, inclusion of adolescent subjects in adult trials may be appropriate for some investigational drugs. FDA encourages sponsors to begin discussions about their pediatric clinical development plans as early as is feasible but no later than 60 days after an end-of-phase 2 meeting.[13]

[11] We support the principles of the 3Rs (reduce/refine/replace) for animal use in testing when feasible. We encourage sponsors to consult with review divisions when considering a nonanimal testing method believed to be suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

[12] See the guidance for industry *Development of Anti-Infective Drug Products for the Pediatric Population* (December 2021).

[13] See the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (July 2020).

As treatment options are limited for pregnant subjects with early Lyme disease, it may be appropriate to characterize safety and pharmacokinetics in pregnant subjects with early Lyme disease who have the potential to benefit from the investigational drug after completion of reproductive toxicology studies and phase 1 and 2 clinical trials in nonpregnant adult subjects. Sponsors should follow infants born to pregnant subjects who received the investigational drug for pregnancy outcome.[14]

3. Labeling Considerations

The labeled indication should reflect the patient population and *Borrelia* species evaluated in the clinical trials.

[14] See the draft guidance for industry *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials* (April 2018). When final, this guidance will represent the FDA's current thinking on this topic.

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APPENDIX:
JUSTIFICATION FOR NONINFERIORITY MARGIN FOR EARLY LYME DISEASE

This justification is for the use of doxycycline as an active control in a noninferiority (NI) trial. Because no randomized placebo-controlled trials of doxycycline in the treatment of early Lyme disease were identified to date in the literature, the assessment of the treatment effect of doxycycline is based on a comparison of a meta-analyzed estimate of the effect of doxycycline from U.S. studies with a twice-a-day (BID) regimen for 20 to 21 days to a meta-analyzed estimate of the effect of no treatment from U.S. natural history studies. The primary efficacy endpoint considered here is the absence of objective manifestations of Lyme disease (specifically, arthritis, carditis, or neurological disease) at a 6-month follow-up.

A review of the literature found two U.S. natural history studies of Lyme disease and three U.S. doxycycline treatment studies of early Lyme disease that reported outcomes at 6 months (see Table 1).

Table 1: U.S. Studies in Lyme Disease

#	Author/ Publication	Study Design	Regimen/Dose	Treatment Duration	N	Study Endpoints	Study Population	Follow-up	# of Centers
1	Steere et al. 1979[a]	Natural history	None	N/A	48	Absence of disease progression (joint, neurologic)	EM/NSS	6 and 18 months	1
2	Steere et al. 1980[b]	Natural history with inclusion of nonrandomized open label treatment arms	None	N/A	55	Absence of disease progression (joint, neurologic, cardiac)	EM/NSS	6, 12, and 18 months	1
			Penicillin 250,000 U QID	7-10 days	42				
			Erythromycin 250 mg QID	7-10 days	9				
			Tetracycline 250 mg QID	7-10 days	7				
3	Dattwyler et al. 1990[c]	Randomized, controlled, 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				

continued

#	Author/ Publication	Study Design	Regimen/Dose	Treatment Duration	N	Study Endpoints	Study Population	Follow-up	# of Centers
4	Massaroti et al. 1992[d]	Randomized, controlled, 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 day, then 250 mg x 4 days	5 days	16				
5	Dattwyler et al. 1997[e]	Randomized, controlled, open label	Doxycycline100 mg BID	21 days	72	Clinical cure or failure	EM/NSS; early disseminated Lyme disease (14%)	3, 6, and 9 months	9
			Ceftriaxone 2 g QD	14 days	68				

N/A – not available, EM – erythema migrans, NSS – non-specific symptoms, QID – four times a day, QD – daily, BID – twice a day, TID – three times a day, U – units, mg – milligrams, g – gram.

[a] Steere AC, Hardin JA, Ruddy S, Mummaw JG, and Malawista SE, 1979, Lyme Arthritis: Correlation of Serum and Cryoglobulin IgM with Activity, and Serum IgG with Remission, Arthritis Rheum, 22(5):471–483.
[b] Steere AC, Malawista SE, Newman JH, Spieler PN, and Bartenhagen NH, 1980, Antibiotic Therapy in Lyme Disease, Ann Intern Med, 93(1):1–8.
[c] Dattwyler RJ, Volkman DJ, Conaty SM, Platkin SP, and Luft BJ, 1990, Amoxycillin Plus Probenecid Versus Doxycycline for Treatment of Erythema Migrans Borreliosis, Lancet, 336(8728):1404–1406.
[d] Massarotti EM, Luger SW, Rahn DW, Messner RP, Wong JB, Johnson RC, and Steere AC, 1992, Treatment of Early Lyme Disease, Am J Med, 92(4):396–403.
[e] Dattwyler RJ, Luft BJ, Kunkel MJ, Finkel MF, Wormser GP, Rush TJ, Grunwaldt E, Agger WA, Franklin M, Oswald D, Cockey L, and Maladorno D, 1997, Ceftriaxone Compared with Doxycycline for the Treatment of Acute Disseminated Lyme Disease, N Engl J Med, 337(5):289–294.

A meta-analytic approach (random effects analysis using the DerSimonian and Laird method[1]) was used to estimate the pooled response rates and corresponding confidence intervals for no treatment and doxycycline, respectively. The following 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 meta-analytic point estimates with a corresponding confidence interval

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 2 summarizes the response rates of no treatment from the U.S. natural history studies. The response rate reported for the Steere et al. 1979[2] study 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. The

[1] DerSimonian R and Laird N, 1986, Meta-Analysis in Clinical Trials, Control Clin Trials, 7(3):177–188.

[2] Steere AC, Hardin JA, Ruddy S, Mummaw JG, and Malawista SE, 1979, Lyme Arthritis: Correlation of Serum and Cryoglobulin IgM with Activity, and Serum IgG with Remission, Arthritis Rheum, 22(5):471–483.

Steere et al. 1980[3] study also reported on subjects with an onset in 1977 (a total of eight subjects). Because 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 et al. 1980 (eight subjects) as compared to Steere et al. 1979 (35 subjects), it will be assumed that the subjects in each study are unique.

Table 2: Absence of Objective Manifestations of Lyme Disease at 6-Month Follow-ups — Natural History (No Treatment)

Study	Response Rate[a] [n/N (%)]	Notes
Steere et al. 1979[b]	23/35 (65.7)[c]	12 subjects developed arthritis (± CNS disease)
Steere et al. 1980[d]	31/55 (56.4)	24 subjects developed arthritis (± CNS disease)
Random effects meta-analysis	60.2, 95% CI (50.1, **70.3**)	

CNS – central nervous system, CI – confidence interval.

[a] Positive response was defined as the absence of arthritis or neurologic manifestations of early disseminated or late Lyme disease.
[b] Steere AC, Hardin JA, Ruddy S, Mummaw JG, and Malawista SE, 1979, Lyme Arthritis: Correlation of Serum and Cryoglobulin IgM with Activity, and Serum IgG with Remission, Arthritis Rheum, 22(5):471–483.
[c] Based only on the cohort with onset in 1977.
[d] Steere AC, Malawista SE, Newman JH, Spieler PN, and Bartenhagen NH, 1980, Antibiotic Therapy in Lyme Disease, Ann Intern Med, 93(1):1–8

The response rates of doxycycline from the U.S. studies for 20 to 21 days of treatment with doxycycline BID are summarized in Table 3. Subjects in the Massaroti et al. 1992[4] study were to receive 10 days of treatment with doxycycline. However, if symptoms were still present at day 10, the subject could receive an additional 10 days of treatment. Therefore, the study is being considered as a 20-day treatment for the efficacy assessment. The Dattwyler et al. 1997[5] study enrolled 10 of 72 (14 percent) subjects with signs of early disseminated Lyme disease (joint swelling, facial palsy, and carditis) and had a high unevaluable rate as compared to the other two studies. Given this difference in baseline characteristics, a meta-analyzed estimate for doxycycline was calculated for all three studies as well as by excluding the Dattwyler et al. 1997 study.

[3] Steere AC, Malawista SE, Newman JH, Spieler PN, and Bartenhagen NH, 1980, Antibiotic Therapy in Lyme Disease, Ann Intern Med, 93(1):1–8.

[4] Massarotti EM, Luger SW, Rahn DW, Messner RP, Wong JB, Johnson RC, and Steere AC, 1992, Treatment of Early Lyme Disease, Am J Med, 92(4):396–403.

[5] Dattwyler RJ, Luft BJ, Kunkel MJ, Finkel MF, Wormser GP, Rush TJ, Grunwaldt E, Agger WA, Franklin M, Oswald D, Cockey L, and Maladorno D, 1997, Ceftriaxone Compared with Doxycycline for the Treatment of Acute Disseminated Lyme Disease, N Engl J Med, 337(5):289–294.

Table 3: Absence of Objective Manifestations of Lyme Disease at 6-Month Follow-ups: Doxycycline Twice-a-Day Regimen Studies for 20 to 21 Days

Study	Response Rate [n/N (%)]	Notes
Dattwyler et al. 1990[a]	35/37 (94.6)	No true failure, 2 unevaluable
Massaroti et al. 1992[b]	20/22 (90.9)	1 true failure (facial palsy), 1 unevaluable
Dattwyler et al. 1997[c]	54/72 (75.0)	1 true failure (arthritis), 17 unevaluable
Random effects meta-analysis		
All 3	87.0, 95% CI (**74.7**, 99.4)	
Excluding Dattwyler et al. 1997	93.6, 95% CI (**87.4**, 99.8)	

CI – confidence interval.

[a] Dattwyler RJ, Volkman DJ, Conaty SM, Platkin SP, and Luft BJ, 1990, Amoxycillin Plus Probenecid Versus Doxycycline for Treatment of Erythema Migrans Borreliosis, Lancet, 336(8728):1404–1406.
[b] Massarotti EM, Luger SW, Rahn DW, Messner RP, Wong JB, Johnson RC, and Steere AC, 1992, Treatment of Early Lyme Disease, Am J Med, 92(4):396–403.
[c] Dattwyler RJ, Luft BJ, Kunkel MJ, Finkel MF, Wormser GP, Rush TJ, Grunwaldt E, Agger WA, Franklin M, Oswald D, Cockey L, and Maladorno D, 1997, Ceftriaxone Compared with Doxycycline for the Treatment of Acute Disseminated Lyme Disease, N Engl J Med, 337(5):289–294.

From the natural history studies, the meta-analyzed estimate of the absence of objective manifestations of Lyme disease at 6-month follow-ups for no treatment is 60.2 percent with an upper bound of the 95 percent confidence interval of 70.3 percent. From all three therapeutic studies, the meta-analyzed estimate of the absence of objective manifestations of Lyme disease at 6-month follow-ups for treatment with doxycycline is 87.0 percent with a lower bound of the 95 percent confidence interval of 74.7 percent. Thus, the treatment effect of doxycycline over no treatment can be estimated to be at least 4.4 percent. If the Dattwyler et al. 1997 study is excluded from the meta-analyzed estimate for doxycycline treatment, the estimate is 93.6 percent with a lower bound of the 95 percent confidence interval of 87.4 percent. A conservative estimate of the treatment effect would then be 17.1 percent.

When considering the (doxycycline – no treatment) difference in estimated response rates, the estimated difference between doxycycline (all three studies) and no treatment is 26.8 percent with a 95 percent confidence interval of (10.9, 42.7) and the difference between doxycycline (excluding the Dattwyler et al. 1997 study) and no treatment is 33.4 percent with a 95 percent 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-month follow-ups as compared to no treatment. These results are summarized in Table 4.

Table 4: Estimate of Treatment Effect of Doxycycline 100 Milligrams Twice a Day for 20 to 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 et al. 1997[a]) and upper bound of no treatment 95% CI	87.4 – 70.3 = **17.1**%
Difference in estimated response rates with 95% CI	
Between doxycycline (3 studies) and no treatment	87.0 – 60.2 = 26.8% 95% CI (**10.9**, 42.7)
Between doxycycline (excluding Dattwyler et al. 1997) and no treatment	93.6 – 60.2 = 33.4% 95% CI (**21.6**, 45.2)

CI – confidence interval.

[a] Dattwyler RJ, Luft BJ, Kunkel MJ, Finkel MF, Wormser GP, Rush TJ, Grunwaldt E, Agger WA, Franklin M, Oswald D, Cockey L, and Maladorno D, 1997, Ceftriaxone Compared with Doxycycline for the Treatment of Acute Disseminated Lyme Disease, N Engl J Med, 337(5):289–294.

Estimates of the treatment effect of doxycycline (M_1) can range from 4.4 to 22 percent, see Table 4. As noted in Table 3, there were very few true treatment failures in the doxycycline studies because most of those classified as nonresponders had unevaluable outcomes. Conversely, the nonresponders in the natural history studies were true treatment failures because of development of arthritis (plus or minus central nervous system disease). Given the high rate of unevaluable subjects in the Dattwyler et al. 1997 study, an M_1 estimate of 17.1 to 21.6 appears most reasonable. However, if the rate of early disseminated Lyme disease (acute neurological, cardiac, or joint involvement) is expected to be higher than 14 percent in an NI trial, the estimate of M_1 might need to be reconsidered. An appropriate NI margin for a trial in early Lyme disease with doxycycline as the active control is 10 percent, which would preserve 40 to 50 percent of this effect.