Guidance for Industry

Lyme Disease — Developing Antimicrobial Drugs for Treatment

DRAFT GUIDANCE

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GUIDANCE FOR INDUSTRY[1]

Lyme Disease — Developing Antimicrobial Drugs for Treatment

I. INTRODUCTION

This is one in a series of guidance documents intended to assist the pharmaceutical industry in the development of antimicrobial drug products for the treatment of infections. The information presented here should help applicants plan clinical studies, design clinical protocol(s), implement and appropriately monitor the conduct of clinical studies, collect relevant data for analysis, and perform appropriate types and numbers of analyses of study data. Clinical trials planned and conducted as recommended in this guidance should yield the information necessary for the Agency to determine whether the antimicrobial under study is safe and effective in the treatment of the specific infection. For general information on related topics, the reader is referred to the guidance *Developing Antimicrobial Drugs — General Considerations for Clinical Trials* (*General Considerations*).

This guidance for industry focuses on developing antimicrobial drugs for the treatment of *early* Lyme Disease.

II. BACKGROUND

Over the years, the Agency has issued guidance to the pharmaceutical industry on how to design, carry out, and analyze the results of clinical trials for the development of antimicrobials for the treatment of infections in a variety of forms. Guidance has been provided verbally during various industry and FDA meetings, in letters written to sponsors, and in general guidance on related issues. This guidance is the result of efforts to collect all pertinent information and present it in one location. Where appropriate, this guidance contains relevant information from several sources, including *Clinical Evaluation of Anti-Infective Drugs (Systemic)* (1977); IDSA's

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[1] This guidance has been prepared by the Office of Drug Evaluation IV, representing the Division of Anti-Infective Drug Products, the Division of Special Pathogens and Immunological Drug Products, and the Division of Anti-Viral Drug Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on developing antimicrobial drugs for the treatment of Lyme disease. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

"Guidelines for the Evaluation of Anti-Infective Drug Products" (1992) (IDSA guidance);[2] *Points to Consider: Clinical Development and Labeling of Anti-Infective Drug Products* (1992) (*Points to Consider*), an FDA guidance on issues related to evaluating new drug applications for anti-infective drug products; and *Evaluating Clinical Studies of Antimicrobials in the Division of Anti-Infective Drug Products* (February 1997), a draft guidance discussed at a March 1997 advisory committee meeting on anti-infective drug products, which will be superseded by this guidance once it is issued in final form.

III. LYME DISEASE

A. Regulatory Synonyms

The first agent approved for the treatment of *Lyme disease* studied patients with the early form of the disease, and approval specified the indication as *early Lyme disease (erythema migrans)* caused by *Borrelia burgdorferi*.

A three-part staging system for Lyme disease has been proposed:[3]

Early Infection:	Stage 1: (Localized Erythema Migrans)
Early Infection:	Stage 2: (Disseminated Infection)
Late Infection:	Stage 3: (Persistent Infection)

The Agency believes that safety and, particularly, efficacy of an antimicrobial in one or more of the stages should be demonstrated before the antimicrobial is approved. The labeling should reflect in which of these stages the study drug showed safety and efficacy.

B. Study Considerations

1. Study Characteristics

Two adequate and well-controlled clinical trials are recommended because of the variability in the presentation of the infection and its natural history. A double-blind, randomized, multicenter, prospective study design is suggested. An investigator-blinded study may be done if the dosing schedule or mode of administration of either the test drug

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[2] This guidance appeared in IDSA's (Infectious Disease Society of America) supplement to *Clinical Infectious Diseases*, formerly *Reviews of Infectious Diseases.*

[3] Asbrink E., " Comments on the course and classification of lyme borreliosis," *Scan. J. Infect. Dis.*, Suppl., 1991, 77:41-43.

or the comparator agent makes a double-blind design impractical. Placebo-controlled trials for erythema-migrans Lyme disease are considered inappropriate. Sponsors are encouraged to present a justification for their choice of comparator to the reviewing division prior to initiation of the study.

In addition, another adequate and well-controlled clinical trial is recommended in which patients are evaluated on the basis of clinical signs and symptoms, or in which microbiological diagnosis is systematically attempted along with the clinical diagnosis.

Corroboration is best obtained from a second clinical trial in which patients are evaluated on the basis of clinical signs and symptoms or in which microbiological diagnosis is systematically attempted along with the clinical diagnosis.

2. Patient Stratification

Patients should be stratified by the presence of constitutional symptoms resembling a viral illness (fever, chills, malaise, headache, fatigue, arthralgias, myalgias) and randomized to one of the treatment arms.

3. Disease Definitions

Lyme disease is a clinical complex, which begins as a local infection after an infected feeding ixodid tick inoculates *Borrelia burgdorferi* into the skin. For the majority of patients, the initial sign of early Lyme disease is an annular, erythematous lesion known as erythema migrans (EM). EM usually begins as a red macule or papule and expands over a period of days to a few weeks to form a large round lesion, sometimes with partial central clearing. In the earliest stage of the illness, EM may be accompanied by a nonspecific flu-like illness with malaise, fatigue, fever, chills, headache, myalgias, and arthralgias. Diagnosis rests primarily on clinical findings because serology is often negative in the early days of the infection. In addition, patients treated for early Lyme disease can relapse and be seronegative. Even in the absence of treatment, EM fades spontaneously, usually within 2 to 4 weeks. As the infection spreads, manifestations of dissemination can include secondary EM lesions, neurologic abnormalities (e.g., seventh nerve palsy or radiculitis), lymphocytic meningitis, and carditis manifested by heartblock. Rarely, acute arthritis can develop in early infection, but is more commonly a late manifestation. With no treatment or ineffective treatment, patients may develop late Lyme disease characterized by chronic meningitis, meningoencephalitis, or encephalopathy, peripheral neuropathy, migratory polyarthritis developing into chronic arthritis of the large joints, and/or acrodermatitis.

C. Inclusion Criteria

To be included in the study, patients should meet the following criteria:

1. Male and nonpregnant female patients of any age can be included.

    a. Pediatric and adult patients should be analyzed separately.
    b In trials using a drug of the tetracycline class, subjects must be >8 years old.

2. Patients should have EM documented and photographed by the physician.

    a. Patients should have an expanding erythematous skin lesion, at least 5 centimeters in diameter.
    b. Annular erythematous lesions occurring within hours after a tick bite represent hypersensitivity reactions and do not qualify as EM.

3. Patients should have had exposure to an endemic area.

4. A punch biopsy of the EM lesion should be made.

D. Exclusion Criteria

(See also *General Considerations*.)

Specific exclusion criteria for this indication include:

1. Active arthritis
2. Signs or symptoms of CNS (central nervous system) infection, meningitis, meningismus, or any cranial neuropathy
3. Cardiac involvement (heart block)
4. History of nervous system, cardiac, rheumatic, collagen vascular, or immunodeficiency disease
5. Use of any systemic antimicrobial drug known to be active against *B. burgdorferi* within 10 days prior to enrollment
6. Concurrent systemic steroid therapy
7. Antimicrobial treatment for Lyme disease during the previous 12 months
8. Concurrent tick-borne diseases such as babesiosis or ehrlichiosis

E. Drugs and Dosing Regimens

The choice of a comparator agent should be explained in the protocol and presented to the

reviewing division before study initiation.

F. Evaluation

Assessments of patients treated for early Lyme disease, as evidenced by erythema migrans, should include short-term and long-term evaluation. The short-term assessment includes evaluation of the EM lesion and any accompanying flu-like symptoms. Key symptoms should be identified and subjective symptom scores recorded. Because the symptoms of early Lyme disease may resolve spontaneously, even in the face of inadequate treatment, and patients treated for EM may later develop other manifestations of Lyme disease, a long-term assessment should be conducted. The following is one proposal that captures both short- and long-term follow-up:

1. Entry/Pre-Therapy Visit

Prior to patient enrollment in the study, a medical history should be obtained and physical examination performed to ensure that entry criteria are met. Study sites are encouraged to perform skin biopsies of EM lesions to isolate *B. burgdorferi* (see microbiological considerations for detail). Antimicrobial susceptibility of *B. burgdorferi* isolates to the control and test drugs should be determined, and the isolates should be frozen and stored at -70 °C. Baseline laboratory tests should include detection of serum anti *B. burgdorferi* (IgM and IgG) antibodies, complete blood count (CBC), liver function tests (LFTs), and an electrocardiogram (EKG).

2. On-Therapy Visit

Patients should be evaluated at an on-therapy visit, scheduled approximately half-way through the drug treatment course. At this visit, the patient's symptoms should be assessed and a physical examination performed. Subjective symptom scores for key symptoms should be recorded. Anti *B. burgdorferi* antibody tests (IgG and IgM), CBC, LFTs and EKG should be repeated.

3. End-of-Treatment Visit

Patients should be assessed at follow-up visits conducted within 1 week post treatment.

4. Post-Treatment Visit

Patients should be evaluated at 1, 3, 6, 9, and 12 months post-treatment. Ideally, the patients should be seen for each visit. However, it may be possible to conduct some of these post-treatment assessments (e.g., 6 and 9 months) by phone with the provision that the patient would be asked to return for clinical evaluation if indicated. The patient's

symptoms should be assessed at all time points and a physical examination performed at each clinical visit (e.g., 1, 3, and 12-months). Subjective symptom scores for key symptoms should be recorded. Information regarding intercurrent illnesses and medical therapy should be collected. Anti *B. burgdorferi* antibody tests (IgG and IgM), CBC, LFTs, and EKG should be repeated. If any EM lesions are still present at 1 month post treatment, a skin punch biopsy, culture for *B. burgdorferi* isolation, and antimicrobial susceptibility testing should be repeated (see microbiological considerations for detail).

5. Late Post Treatment/Test-of-Cure Visit

The 12-month visit should be considered the test-of-cure visit. Every attempt should be made to capture patient information from the entry into the study through this 12-month time point.

G. Outcome

To assess the efficacy of an antimicrobial in the treatment of Lyme disease, a patient's clinical course should be monitored over time. It is useful to report patient outcome at the 1 week and 1 month post-treatment visit, to assess the rate of early failures. However, because patients may show an initial response to therapy or the early symptoms may resolve spontaneously, the true evidence of cure should be demonstrated at 12 months.

1. Clinical Outcome

To be considered clinically evaluable, the patient should have

a. Physician-diagnosed EM lesion

b. Completed at least 80% of study medication course

c. Clinical evaluation during treatment, within 1 week post therapy, and 1 month after completion of therapy (short-term assessment) and clinical visits or telephone contact at 3, 6, 9, and 12 months, as specified under evaluation visits.

d. Documented compliance (positive urine assay for antimicrobial agent or patient diary)

e. No intervening courses of antimicrobials for other infectious diseases that have activity against *B. burgdorferi* (i.e., cephalosporins, macrolides, penicillins, quinolones, tetracyclines, chloramphenicol, imipenem, and

lincomycin)

Clinical outcome is measured by resolution of EM and of signs and symptoms of the disease present at baseline. Sponsors are encouraged to propose a grading system whereby resolution of EM and degree of resolution of symptoms and signs are defined prospectively as cure, improvement, or failure.

a. Early post-treatment evaluations may be reported as follows:

Cure at 1 month: Resolution of EM and any objective signs, together with >75% reduction in symptoms by the 1-week post-treatment visit, maintained through the 1-month post-treatment period.

Improvement at 1 month: Resolution of EM lesion but incomplete resolution of any signs and 50% to 75% reduction in symptoms by the 1-week post-treatment visit, with further improvement or complete resolution by the 1-month post-treatment visit.

Failure at 1 month: Persistent EM or objective signs, or symptom reduction of < 50% by the 1-month post-treatment visit.

b. Post-treatment/test-of-cure evaluations may be reported as follows:

Cure at 12 months: Cure or improvement as defined at the short-term evaluation, with >75 % reduction in symptoms maintained through the 12-month post-therapy visit.

Failure: Cure or improvement assessed at the 1-month post-treatment visit, but with subsequent development of objective signs (evanescent skin lesions, arthritis, heart block, peripheral or central nervous system disease), or symptoms requiring retreatment. In addition, the patients who failed at the 1-month time point should be reported for a compositive failure of treatment.

2. Microbiological Outcome

Patients in whom *Borrelia burgdorferi* is isolated from a lesion at entry and who meet other diagnostic criteria outlined above are considered to have a microbiologic documentation of Lyme disease.

Assessment of microbiological outcome is generally assumed to be extrapolated from the clinical outcome. Thus, patients would generally be classified as having presumptive

eradication of the organism if they met the definition of clinical cure and presumptive persistence if they met the definition of failure.

H. Microbiological Considerations

Patients should have EM lesions cultured pre-treatment. Susceptibility testing should be performed on any isolates cultured from these patients. Patients who fail treatment and have a positive post-treatment culture should also have susceptibility tests performed on their post-treatment isolates. These data should be analyzed to compare the MICs of pre- and post-treatment *B. burgdorferi* isolates. This will allow the reviewer to determine if the treatment might be causing an increase in MICs . The bacteriological efficacy rate at each MIC value should also be determined. This may allow determination of a susceptible breakpoint above which bacteriological eradication would not be expected. If the patient is retreated with a different antimicrobial regimen, susceptibility testing results to the original and subsequent antimicrobial agents should be reported. Positive anti *B. burgdorferi* antibody test results should be confirmed using a Western blot assay.

1. Laboratory Qualifications

   To qualify for participation in clinical trials, the microbiologists should be experienced in *B. burgdorferi* culturing, susceptibility testing, storage, and retrieval. Laboratories should operate under a rigorous quality assurance program and participate in recognized inspection and proficiency programs. However, the most important factor is the experience of the microbiologists performing the tests. The qualifications of the laboratory should be reviewed by the FDA before clinical trials are initiated.

2. Protocol Considerations

   Each study protocol should outline specific clinical and microbiological procedures for diagnosis and follow-up. All protocols used during the clinical trials (specimen collection, transport, primary isolation, susceptibility testing, quality control, molecular typing) should be submitted in as much detail as possible.

3. Specimen Collection and Transport

   Before a punch biopsy specimen is collected, the peripheral border of the EM should be identified. Under sterile conditions, a 4-mm-diameter punch biopsy specimen should be obtained from the peripheral aspect of the lesion (4 mm interior from the EM border) and placed in a polystyrene tube (13 by 100 mm) containing 6 mL of isolation medium [modified Barbour-Stoenner-Kelly (BSK)

medium,[4,5] containing 100 µg/mL 5-fluorouracil, 50 µg/mL sulfamethoxazole, 10 µg/mL trimethoprim, and 400 µg/mL phosphomycin and should be held at room temperature (21-23 °C) until delivered to the laboratory for processing. Skin punch biopsy samples maintained in this manner should be processed within one week of collection.

4. Isolation of *B. Burgdorferi*

BSK II medium used for isolation of *B. Burgdorferi* contains bovine serum albumen (BSA) fraction V. It is very important that several lots of BSA fraction V be screened for satisfactory performance of the medium. BSK II medium prepared with a satisfactory lot of BSA should initiate the growth of a stock culture of *B. burgdorferi* from inocula of 1 to 10 cells and yield cell numbers that are easily visualized by microscopic examination within 2 to 3 weeks of incubation at 30°C. High-quality distilled water should be used in the medium formulation. The medium should be dispensed into sterile containers to 75 to 90% of their capacity and tightly capped. It is also very important that fresh medium be used in the isolation of *B. burgdorferi*. The medium can be stored for up to two months at 4 °C.

Upon receipt of the skin biopsy specimens, the tissue should be transferred to polystyrene tubes containing BSK II medium without antimicrobials. Both the tube of isolation medium from which the skin biopsy is removed and the tube with antimicrobial-free medium containing the skin specimen should be incubated at 30°C and examined for spirochetes by dark-field microscopy at 3-, 6-, and 12-week intervals. If at the end of 12-week incubation the culture is still negative, an attempt should be made to detect *B. burgdorferi* DNA using a standardized polymerase chain reaction (PCR) assay.

5. Identification of Spirochete Isolates

An indirect fluorescent antibody test may be used to identify the spirochete isolates. *B. burgdorferi* ATCC 35210 and *B. hermsii* ATCC 35209 should serve as positive and negative controls, respectively.

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[4] Berger, B.W., R.C. Johnson, C. Kodner, et al., "Cultivation of *Borrelia burgdorferi* from erythema migrans lesions and perilesional skin," *J. Clin. Microbiol*., 1992,. 30(2): 359-361.

[5] Dever, L. L., J. H. Jorgenson, and A. G. Barbour, "In Vitro Antimicrobial susceptibility testing of *Borrelia burgdorferi:* a microdilution MIC method and time-kill studies," *J. Clin. Microbiol.*, 1992, 30(10): 2692-2697.

6. Preservation of Spirochete Isolates

Isolates in antimicrobial-free BSK II medium containing 20% glycerol should be quickly frozen using liquid nitrogen and stored at -70 °C.

7. Antimicrobial Susceptibility Testing

The current recommendations are to use the macro- or microdilution MIC (minimum inhibitory concentration) methods described by Dever et al. The range of antimicrobial dilutions tested should yield *on-scale* (rather than *off-scale*) end points. The MIC range, MIC_{50}, and MIC_{90} values should be determined for the pre- and post-treatment isolates. Quality control strains (*B. burgdorferi* ATCC 35210) should be tested in parallel with the clinical isolates. All *B. burgdorferi* strains collected during the clinical trials should be stored frozen as described above.

8. Anti-*B. burgdorferi* Antibody Testing

Detection of anti *B. burgdorferi* antibodies should be used to confirm, not to make, the diagnosis of Lyme disease. In most cases, infection can be confirmed by the finding of specific IgM and or/IgG antibodies, but IgM conversion may not be measurable for 4 or more weeks after infection, and IgG levels may not be elevated for 6 to 8 weeks; test results may be negative in early Lyme disease.

ELISA and IFA assay are not specific: cross-reactive antibodies can produce a positive test result in patients with other illnesses (e.g., other spirochetal infections, nonspirochetal bacterial endocarditis, Epstein-Barr virus infection, rheumatoid arthritis, and systemic lupus erythematosus). ELISA and IFA assay results should be designated positive only if they exceed a *normal range*, defined as including ~95% of the normal population. Additionally, inter- and intra-laboratory variations lead to inconsistencies in interpretation of test results. Every effort should be made to test all the serum specimens from an individual patient on the same day and in the same run.

The current CDC recommendation is that all positive or equivocal ELISA or IFA results should be corroborated by a standardized Western blot assay,[6] using

[6] National Committee for Clinical Laboratory Standards, Western Blot Assay for Antibodies to Borrelia Burgdorferi; Proposed Guideline, Draft, NCCLS Document M34-P, NCCLS, Wayne, PA.

appropriate IgM and IgG criteria.[7] It is recommended that an IgM Western blot be considered positive if two of the following three bands are present: 24/21 kDa (OspC), 39 kDa (BmpA), and 41 kDa (Fla). An IgG Western blot is considered positive if five of the following 10 bands are present: 18 kDa, 24/21 kDa (OspC), 28 kDa, 30 kDa, 39 kDa (BmpA), 41 kDa (Fla), 45 kDa, 58 kDa (not GroEL), 66 kDa, and 93 kDa.

I. Statistical Considerations

(Reserved)

[7] CDC Notice to Readers, United States, MMWR. 1995. 44(31):590-591.