

PRODUCT LICENSE APPLICATION

Reference number: 97-1052
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Proper Name: Lyme Disease Vaccine (Recombinant OspA)
Trade Name: LYMERix™
Sponsor: SmithKline Beecham Biologicals
Indication: Active immunization against Lyme disease in individuals 15 to 70 years of age.

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I. PRODUCT DESCRIPTION

LYMERix™ contains recombinant lipoprotein OspA, expressed in *Escherichia coli*, an outer surface protein of *Borrelia burgdorferi sensu strictu* ZS7, adsorbed onto aluminum hydroxide adjuvant in phosphate buffered saline with 2-phenoxyethanol as a bacteriostatic agent. Lipoprotein OspA is a single polypeptide chain of 257 amino acids with lipids covalently bonded near the N terminus.

LYMERix™ is supplied as a sterile suspension. Each 0.5 ml dose contains 30 µg lipoprotein OspA, 0.5 mg of aluminum as aluminum hydroxide, 2.5 mg 2-phenoxyethanol, 150 mM sodium chloride, 4.5 mM sodium dihydrogen phosphate (monobasic), 5.5 mM sodium phosphate (dibasic), and water for injection. No animal substance is used in the manufacture. Fermentation media consist primarily of inorganic salts and vitamins, with small quantities of antifoam which contains silicon (<7 ppm); kanamycin sulfate (<10 ppb), an aminoglycoside antibiotic; and yeast extract.

LYMERix™ should be stored between 2° and 8° C (36° and 46° F).

III. DOSAGE FORM, ROUTE OF ADMINISTRATION AND RECOMMENDED DOSAGE

LYMERix is supplied as a sterile suspension in single-dose (30 µg/0.5 ml) vials and pre-filled syringes for intramuscular injection only. Packaging for the LYMERix Tip-Lok™ syringe contains dry natural rubber, which may cause allergic reactions; packaging for the vial does not contain natural rubber.

Prior to administration the vaccine should be shaken to ensure a turbid white suspension.

Each 30 mcg dose (0.5 ml) should be administered by intramuscular injection in the deltoid muscle of the arm.

LYMERix vaccine should be administered as a three dose series at 0, 1 and 12 months. The immunization schedule should be initiated with respect to the known transmission season for Lyme disease in the geographic region of risk. In the pivotal efficacy trial performed primarily in the Northeast United States, vaccinations were given between January and April. Thus, the second and third doses should be administered several weeks prior to the onset of the *Borrelia* transmission season in the local geographic area.

No data are available on the immune response to LYMERix™ when administered concurrently with other vaccines. When concomitant administration of other vaccines is required, they should be given with different syringes and at different injection sites.

IV. MANUFACTURING AND CONTROLS

A. Manufacturing and Controls

LYMERix™ is manufactured, formulated, and packaged by SmithKline Beecham Biologicals in Rixensart, Belgium, and distributed by SmithKline Beecham Pharmaceuticals in Philadelphia, PA.

The complete sequence of lipoprotein OspA from strain ZS7 of *Borrelia burgdorferi sensu stricto* is expressed in recombinant *E. coli* containing a kanamycin resistance gene for selection. Post-translational modification of recombinant lipoprotein OspA is comparable to that found in authentic OspA produced by *B. burgdorferi*. Recombinant *E. coli*, stored in both master and working seed lots, is grown through several small scale pre-culture steps to large scale fermentation. Synthetic media (without human or bovine substances) that include kanamycin sulfate are used throughout the culture periods. After harvest of recombinant bacteria, the protein fraction is extracted by freeze-thaw and homogenization of bacteria in the presence of detergent. Lipoprotein OspA is purified through a series of column chromatography steps, including ion exchange, diafiltration, and size exclusion, and finally sterilized by filtration. The vaccine is then adsorbed onto aluminum hydroxide and excipients are added for final formulation.

In-process tests demonstrate that kanamycin sulfate and silicon, used during fermentation, are not detectable in the final product (<7 ppm and < 10 ppb, respectively). Lot release tests include purity and triton X content (performed on purified bulk product), potency and 2-phenoxyethanol (performed on final bulk product), and pH, aluminum content, sterility, general safety, identity, and endotoxin content (performed on final container). The endotoxin content of a single dose is ≤ 5 EU. The potency of the vaccine is evaluated by immunizing mice with both test and reference vaccines, and determining the quantity of the serum anti-OspA antibody response by ELISA; the quantity of antibody produced in response to the test vaccine must be comparable to that produced in response to the reference vaccine.

In the course of product development, manufacture of LYMERix was performed at three different scales. First, early clinical trials and the pivotal efficacy trial were performed using lots manufactured with 20L fermentation and 2L purification capacity, designated as clinical scale lots (20L/2L). Second, intermediate scale (20L/20L) lots, including both vials and syringes, were produced and used clinically for the purposes of product characterization and immunogenicity trials for bridging (see below, **Clinical studies**). Third, final commercial scale lots of 75L/75L have been produced; product from this scale of manufacture was used for a final bridging (immunogenicity) study, and will be distributed commercially. Extensive product characterization data, submitted to the license application, indicated that product produced by all three scales of manufacture is comparable. Clinical data in support of lot consistency were also submitted (see below, **Clinical studies**).

B. Stability studies

Stability of the vaccine has been demonstrated for 24 months, the licensed dating period, according to approved protocols. Testing according to these protocols includes identity, volume, aluminum content, pH, sterility, general safety, endotoxin content, 2-phenoxyethanol content, completeness of adsorption, and potency. Stability studies were conducted at two manufacturing stages of LYMERix™ vaccine production: purified bulk antigen and formulated vaccine in final container. All studies were conducted at real time and under refrigerated storage temperature (2 - 8° C). The stability of the three different scales of manufacture has been examined. First, stability of the clinical scale lot (20L/2L) was demonstrated. Second, stability of intermediate scale (20L/20L) lots, including both vials and syringes, was demonstrated. Third, stability of final commercial scale (75L/75L) lots, including both vials and syringes, has been demonstrated through 12 months. Data from later time points for full scale commercial lots will be submitted as an annual report to the license.

C. Validation

Quality control records for the qualification and validation of all major equipment and analytical methodology at SmithKline Beecham Biologicals' Rixensart, Belgium facility have been inspected and found to be adequate for in-process control, product release, stability studies, and regulatory purposes.

D. Labeling

The container and package labeling, as well as the package insert, have been reviewed and were found to be in compliance with the appropriate sections of Title 21 of the Code of Federal Regulations Parts 610.60, 610.61, 610.62, 201.56 and 201.57.

E. Establishment Inspection

A pre-license inspection of the SmithKline Beecham Biologicals production facility in Rixensart, Belgium, was conducted April 20 through April 29, 1998. Complete responses to inspectional issues raised in FDA form 483 were submitted to the Agency on May 29, 1998, and all responses were considered satisfactory. The facility is considered to be in compliance with GMP regulations.

F. Environmental Assessment

SmithKline Beecham Pharmaceuticals claims a categorical exclusion to the environmental analysis requirements in accordance with 21 CFR Part 25.31(c). There are no extraordinary circumstances, as described in 21 CFR Part 25.21, associated with this action.

V. PHARMACOLOGY

A. Proposed Mechanism of Action¹

Evidence from several studies in animals indicates that *B. burgdorferi* in a vector tick undergoes substantial antigenic change between time of tick attachment on a mammalian host and subsequent transmission of the bacterium to the host. The spirochetes residing in the tick gut at the initiation of tick feeding express primarily OspA. As tick feeding begins, the expression of outer-surface protein C (OspC) is increased and the expression of OspA is decreased, so that spirochetes that reach the mammalian host after passing through the tick salivary glands express little if any OspA. Thus, it is proposed that lipoprotein OspA vaccine exerts its principal protective effect by eliciting antibodies that block transmission and/or kill Lyme disease spirochetes within the tick gut.

B. Toxicology Studies

Toxicology and pharmacological studies have been performed in animals to examine the safety, immunogenicity and efficacy of LYMERix™. The following pre-clinical studies were conducted to examine vaccine safety:

1. Single dose intramuscular toxicity study with 5 vaccine formulations in albino rabbits.
2. Single dose intramuscular toxicity study with 5 vaccine formulations in rats.
3. Repeated dose intramuscular toxicity study with 4 vaccine formulations in albino rabbits.
4. Repeated dose intramuscular toxicity study with 4 vaccine formulations in rats.

In these toxicology studies the vaccine formulations containing OspA at concentrations from 10-50 µg/1 ml dose were evaluated for toxicity following single and repeat intramuscular administration to rats and rabbits. The vaccine formulations tested contained OspA at 10 or 50 µg/1 ml dose adsorbed to 0.5 mg of aluminum as aluminum hydroxide and were administered in single dose studies. Rabbits were given the full dose (1 ml), while rats received one tenth of a dose (0.1 ml or 1-5 mcg/injection). The 10 µg/1 ml formulation was also evaluated in repeat dose studies (2 doses given 1 month apart) in rats and rabbits. In all studies, the vaccine formulations produced no toxicologically significant effects, as determined by gross pathology and histological examination. In the repeated dose study, minimal to mild changes consistent with intramuscular administration of a vaccine were observed for up to 14 days after the second injection of the 10 µg/1 ml formulation. These changes were reversible over a one month observation period.

C. Pharmacology Studies

The following preclinical pharmacological studies were conducted in a variety of animal models to examine the immunogenicity and efficacy of LYMERix™:

¹Centers for Disease Control and Prevention. Prevention of Lyme Disease through Active Immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Vol. 48, June 4, 1999.

1. Vaccination of BALB/c mice with OspA vaccine formulations, followed by tick-introduced challenge of mice with the homologous strain of *B. burgdorferi sensu strictu*.
2. Effect of OspA antigen dose on protection of BALB/c mice against either needle or tick-introduced challenges with a heterologous strain of *B. burgdorferi sensu strictu*.
3. Protective efficacy in BALB/c mice of three OspA vaccine consistency batches against needle challenge with a heterologous strain of *B. burgdorferi sensu strictu*.
4. Protection of mice against tick-introduced challenge after transfer of sera from human vaccinees.
5. Protective efficacy of OspA vaccine formulations in the rhesus monkey against tick-introduced challenge.
6. Determination of *B. burgdorferi* bactericidal titers in sera obtained from humans vaccinated with LYMERix™.

These animal studies demonstrated that the vaccine formulation containing lipoprotein OspA adsorbed on aluminum was the most immunogenic. Studies in mice demonstrated that administration of lipoprotein OspA resulted in the formation of specific IgG anti-OspA antibodies, including those directed against a specific epitope, LA-2 (designated LA-2 equivalent antibodies). These antibodies were shown to be bactericidal and to correlate with protection against *B. burgdorferi* infection.

Reproductive toxicology studies were not conducted prior to approval. However, because this vaccine will be used in a large number of women of child bearing age, CBER requested that the sponsor initiate such studies within 6 months after licensure as a condition of approval. The protocol for these reproductive-toxicology studies was submitted to the license application on December 11, 1998, and reviewed by CBER. The manufacturer committed to conduct these reproductive toxicology studies post-licensure. At the time of this commitment guidelines for reproductive-toxicology studies for vaccines were not established. Thus, in order to reach agreement on the protocol, consult review was obtained from members of the CBER working group to develop criteria for such studies. These studies will examine the effect of LYMERix™ vaccination of female rats on fetal development, peri/post natal development, and maternal antibody transfer.

VI. MEDICAL

A. General Information about Lyme Disease^{2,3,4}

1. Etiology

Lyme disease is a zoonosis caused by infection with the bacterial spirochete, *Borrelia burgdorferi*, transmitted to humans by infected ticks of the *Ixodes ricinus* family at the time of a blood meal. *Ixodes scapularis* (the black-legged, or deer tick) is the vector in the eastern United States and *I. pacificus* (the western black-legged tick) is the vector in the western United States. *I. scapularis* is also a vector for human granulocytic ehrlichiosis (HGE) and babesiosis. The enzootic cycle of *B. burgdorferi* involves three stages of the tick life cycle over a two year period, as well as deer and rodent hosts. Humans are incident hosts for *B. burgdorferi*. Tick larvae usually feed in the late summer and acquire *B. burgdorferi* from an infected animal host, most commonly the white-footed mouse. Nymphal ticks feed in the late spring and summer, and serve as the most common source of human infection. The white-tailed deer is the preferred host for adult ticks which feed in the fall, winter and early spring. Adult ticks may also transmit *B. burgdorferi* to humans. The increasing rates of Lyme disease in northeastern and upper north-central regions of the United States over the past several decades are considered to be related to the explosive repopulation of deer and the spread of *I. scapularis* in these regions.

2. Epidemiology

Lyme disease (also known as Lyme borreliosis) was recognized in 1975. Since then it has become the most commonly reported vector-borne disease in the United States, accounting for more than 95% of all reported cases of vector-borne disease. It is endemic in several regions in the United States, Canada and temperate Eurasia. Based on a national surveillance case definition, more than 62,000 cases were reported by states to CDC from 1993-1997, and the national mean annual rate in this 5-year period was 5.5 cases per 100,000 population (CDC, unpublished). The highest reported rates of Lyme disease occur in children aged 2-15 years of age, and in adults aged 30-55 years of age. Both under-reporting and over-diagnosis are common. More than 90% of cases are reported by about 150 counties located along the northeastern and mid-Atlantic seaboard and in the upper north-central region of the United States.

The risk of acquiring Lyme disease varies with the distribution, density and infection prevalence of vector ticks in a geographic area. The primary risk factor for Lyme disease is exposure to outdoor areas inhabited by *B. burgdorferi*-infected ticks. Ticks favor a moist, shaded environment, especially

²Ibid.

³LYMERix™ Prescribing Information. Date of issuance: December 1998. SmithKline Beecham Pharmaceuticals.

⁴Dennis, DT. Epidemiology. Lyme Disease, Chapter 4. Mosby Year Book. 1993. pp. 27-37.

that provided by leaf litter and low-lying vegetation in wooded, brushy or overgrown habitat. Periresidential exposure to infected ticks may occur during property maintenance, recreation and leisure activities in such areas. In addition, exposure to infected ticks may also occur during outdoor recreational activities in such areas away from home.

Cases of Lyme disease in the United States have been reported to occur throughout the year; however, the peak incidence of Lyme disease varies by region and may vary annually based on fluctuations in local climatic conditions. In the Northeast United States the peak usually occurs in the late spring and summer coincident with the feeding of nymphal ticks, the most common source of human infection.

3. *Clinical Manifestations*

Lyme disease is a multi-system, multi-stage, inflammatory illness. It is routinely treated successfully with oral antibiotics; however, untreated or inadequately treated infection may progress to late-stage complications requiring more intensive therapy. Lyme disease is rarely fatal.

Lyme disease most often presents with a characteristic rash, erythema migrans (EM), accompanied by nonspecific symptoms such as fever, malaise, fatigue, headache, myalgia, and arthralgia. The incubation period from infection to onset of erythema migrans is typically 7 to 14 days but may be as short as 3 days and as long as 30 days. Some infected individuals have no recognized illness (asymptomatic infection determined by serological testing), or manifest only non-specific symptoms such as fever, headache, fatigue, and myalgia. Lyme disease spirochetes disseminate from the site of inoculation by cutaneous, lymphatic and blood-borne routes. The signs of early disseminated infection usually occur days to weeks after the appearance of a solitary erythema migrans lesion. In addition to multiple (secondary) erythema migrans lesions, early disseminated infection may be manifest as disease of the nervous system, the musculoskeletal system, or the heart. Early neurologic manifestations include lymphocytic meningitis, cranial neuropathy (especially facial nerve palsy), and radiculoneuritis. Musculoskeletal manifestations may include migratory joint and muscle pains with or without objective signs of joint swelling. Cardiac manifestations are rare but may include myocarditis and transient atrioventricular blocks of varying degree.

B. burgdorferi infection in the untreated or inadequately treated patient may progress to late disseminated disease weeks to months after infection. The most common objective manifestation of late disseminated Lyme disease is intermittent swelling and pain of one or a few joints, usually large, weight-bearing joints such as the knee. Some patients develop chronic axonal polyneuropathy, or encephalopathy, the latter usually manifested by cognitive disorders, sleep disturbance, fatigue, and personality changes. Infrequently, Lyme disease morbidity may be severe, chronic, and disabling. An ill-defined post-Lyme disease syndrome occurs in some persons following treatment for Lyme disease.

4. *Diagnosis*

The diagnosis of Lyme disease is based primarily on clinical findings, and it is often appropriate to treat patients with early disease solely on the basis of objective signs and a known endemic exposure. Serologic testing may, however, provide valuable supportive diagnostic information in patients with endemic exposure and objective clinical findings that suggest later-stage disseminated Lyme disease. Lyme disease serologic testing should not be used for screening purposes, or for making a diagnosis in patients with only vague signs or symptoms, since in these circumstances the predictive value of a positive test is low. When serologic testing is indicated, CDC recommends testing initially with a sensitive first test, either an enzyme-linked immunosorbent assay (EIA) or an indirect fluorescent antibody (IFA) test, followed by testing with the more specific Western immunoblot (WB) test to corroborate equivocal or positive results obtained with the first test. Although antibiotic treatment in early localized disease may blunt or abrogate the antibody response, patients with early disseminated or late-stage disease usually have strong serological reactivity and demonstrate expanded WB IgG banding patterns to diagnostic *B. burgdorferi* antigens.

Antibodies often persist for months or years following successfully treated or untreated infection. Thus seroreactivity alone cannot be used as a marker of active disease. Neither positive serologic test results nor a history of previous Lyme disease assure that an individual has protective immunity. Repeated infection with *B. burgdorferi* has been documented.

Borrelia burgdorferi can be cultured from 80% or more of biopsy specimens taken from early erythema migrans lesions. However, the diagnostic usefulness of this procedure is limited because of the need for a special bacteriologic medium (modified Barbour-Stoenner-Kelly medium) and protracted observation of cultures. Polymerase chain reaction (PCR) has been used to amplify genomic DNA of *B. burgdorferi* in skin, blood, CSF, and synovial fluid, but PCR has not been standardized for routine diagnosis of Lyme disease.

5. *Treatment*

Lyme disease can usually be treated successfully with standard antibiotic regimens. Early and uncomplicated infection, including infection presenting with isolated cranial nerve palsy, almost always responds satisfactorily to treatment with orally administered antibiotics. Parenteral antibiotics are generally recommended for treating meningitis, carditis, later stage neurologic Lyme disease, and complicated Lyme disease arthritis. Late, complicated Lyme disease may respond slowly or incompletely, and more than one antibiotic treatment course may sometimes be required to eliminate active infection. Refractory Lyme disease arthritis is associated with expression of certain Class II major histocompatibility complex (MHC II) molecules, and may require anti-inflammatory agents and surgical synovectomy for relief of symptoms.

6. *Prevention Methods*

The first line of defense against Lyme disease and other tick-borne illnesses is avoidance of tick infested habitats, use of personal protective measures such as repellents and protective clothing (e.g.

light colors, long sleeved shirts, pants tucked into boots or socks, high rubber boots), and checking for and removing attached ticks. Early diagnosis and treatment is effective in preventing late-stage complications.

B. Clinical Studies

1. Phase 2 Studies

Based on several non-IND clinical trials conducted in Europe, a vaccine formulation containing lipoprotein OspA adsorbed on aluminum hydroxide was identified for clinical development in the United States. Phase 2 studies submitted in support of licensure are summarized in Table 1.

Table 1. Phase 2 Studies to Support Licensure.

Study	Purpose	Description	Subjects enrolled (N)	Age range (years)	Schedule (months)	f/u in months
LYME-005	Safety & dose ranging	Randomized (4 groups), double-blind, placebo-controlled, single center	353	18-83	0, 1, 2	12
LYME-007	Dose ranging	Open-label (3 groups), non-randomized, single center	30 w/ prior history of Lyme disease	21-79	0, 1, 2	6
LYME-014	Bridging: pilot efficacy to intermediate scale-up	Randomized (4 groups), double-blind for production lots, single-blind for clinical lot, 2 sites	800	15-50	0, 1, 6 vs. 0, 1, 12	13
LYME-019	Bridging: intermediate scale-up to full-scale	Randomized (4 groups), double-blind, 2 sites	480	18-50	0, 1	2

LYME-005, entitled "A Dose-Ranging Study to Evaluate the Safety and Immunogenicity of a Recombinant DNA Expressed Protein Vaccine for Lyme Disease in Healthy Volunteers," compared three doses of lipoprotein OspA (3 µg, 10 µg and 30 µg) and placebo. Approximately 80 subjects received each dose or placebo. The 30 µg dose was demonstrated to be the most immunogenic. Although the 30 µg dose was associated with the highest incidence of adverse events, these were well tolerated in all subjects who received all three doses and there was no apparent increase in the incidence of local or general symptoms following each successive dose.

LYME-007, entitled "A Dose Ranging Study to Evaluate the Safety and Immunogenicity of a Recombinant DNA Expressed Protein Vaccine for Lyme Disease in Seropositive Volunteers," was conducted to evaluate vaccine safety in seropositive subjects who also had a clinical history of Lyme disease. Thirty subjects received vaccine containing 3 µg, 10 µg, or 30 µg of lipoprotein Osp A. The 30 µg dose was shown to be the most immunogenic in these subjects. Although the 30 µg dose was associated with the highest incidence of local reactions, there was no apparent increase in the incidence of local or general symptoms following each successive dose. No vaccine-induced serious adverse effects or induction of any Lyme disease-like pathology were observed.

Based on the immunogenicity and safety results from Lyme 005 and 007, the 30 µg dose of lipoprotein OspA (adsorbed onto 0.5 mg aluminum) was chosen as the vaccine candidate for testing in the phase 3 clinical efficacy study. Two additional phase 2 studies were conducted to obtain comparative safety and immunogenicity data on vaccine lots produced at different scales, in order to bridge the efficacy study results which were based on clinical scale lots to commercial scale lots.

LYME-014, entitled "A double-blind randomized study to evaluate the consistency of the reactogenicity and the immunogenicity of three consecutive production lots of SmithKline Beecham Biologicals' vaccine against Lyme disease," compared a clinical scale lot (pre-filled syringe: DLY41A6), produced at the 20L/2L scale and used in the pivotal efficacy trial, to three intermediate scale lots (monodose vials: LY002A2, LY003A2, and LY004A2) produced at the 20L/20L scale. Subjects were monitored for safety and immunogenicity. The primary time point for comparing immune responses among the groups in this study was one month post dose two. Serum collected at this time point was assayed by ELISA for both IgG anti-OspA antibodies and LA-2 equivalent antibodies. The results of these assays for each group are summarized in Table 2.

Table 2. Immunogenicity Results from LYME-014

		LY002A2	LY003A2	DLY41A6	LY004A2
IgG anti-OspA	SC	100%	99.4%	99.4%	99.4%
	GMT (EL.U/ml)	1392	1619	1311	1161
LA-2 equivalent	SC	97.8%	99.4%	98.3%	97.1%
	GMT (ng/ml)	1513	1845	1493	1373

Using a bioequivalence approach⁵ (with a significance level of $\alpha = 0.0167$ [0.05/3 for the 3 lots] and 0.05 for LA-2 and total IgG respectively) and acceptable final relative difference in GMT of less than 80% defined as:

$$\frac{GMT_{Max} - GMT_{min}}{GMT_{min}} * 100\%$$

where GMT_{max} stands for GMT in the group with the highest GMT and GMT_{min} for GMT in the group with the lowest GMT. To demonstrate lot-to-lot consistency, the three production lots were consistent based on an relative difference in GMTs of $\leq 80\%$ (76%). The maximum observed difference in seroconversion rates was significantly less than 10% for either IgG or LA-2 equivalent anti-OspA antibodies. Based on the results, the three production lots were considered to be equivalent at a relative difference in GMTs of 80% or less for the LA-2 equivalent and IgG anti-OspA antibodies. In addition, the lots were considered to be equivalent in terms of immunogenicity, since the maximum observed difference in seroconversion rates between each lot is significantly less than 10% for the LA-2 equivalent and IgG anti-OspA antibodies. The results of the three 20L/20L intermediate scale lots, which were demonstrated to be consistent for LA-2 equivalent and IgG anti-OspA antibodies, were pooled and compared with the 20L/2L clinical scale lot used in study Lyme-008 to show their equivalence using the bioequivalence method by Anderson and Hauck as discussed above. The results demonstrated that given an acceptable relative difference as discussed above, the pooled 20L/20L intermediate scale lots were equivalent to the 20L/2L clinical scale lot used in Lyme-008, for LA-2 equivalent anti-OspA antibodies and IgG anti-OspA antibodies for both the ATP and ITT cohorts. Seroconversion rates at month 2 between the pooled 20L/20L intermediate scale lots and the 20 L/2L clinical scale lot from LYME-008 (ATP) were also compared. The results showed that the upper limit of the confidence interval for the difference was below 0.10 (0.04) for the ATP cohort. Thus, the 20L/20L intermediate scale lots were shown to be equivalent to the 20L/2L clinical scale lot at an acceptable difference of less than 5% in seroconversion rates.

No differences in reactogenicity rates were demonstrated between lots. Reactions to the vaccine were mild to moderate in intensity and generally well tolerated. 12 serious adverse events (SAEs) were reported during the study. None were considered to be related to the study vaccine by the investigator. All SAEs resolved without sequelae except one (suicide).

CBER concurred that an original arbitrary cutoff for consistency of $< 70\%$ was too stringent based on generally accepted practice, and approved a modification (to relative GMT differences of 100%) to this criteria for subsequent comparative studies.

⁵Anderson, S. and Hauck, W.W. (1983). A new procedure for testing equivalence in comparative bioavailability and other clinical trials. Communication in Statistics -Theory and Methods; 12, 2663-2692. Cited in: Design and analysis of bioavailability and bioequivalence studies. Shein-Chung Chow; Jen-Pei Liu. Edition Dekker 1992. 90-93.

LYME-019, entitled "A double-blind randomized study to evaluate the consistency of three consecutive production lots of SmithKline Beecham Biologicals' Lyme vaccine and their equivalence with a selected lot from study 215274/014 in terms of immunogenicity," compared one randomly chosen intermediate scale (20L/20L) lot (from study LYME-014) to three full commercial scale lots (75L/75L). Subjects were vaccinated on a 0,1 month schedule and monitored for safety and immunogenicity.

Lot-to-lot consistency of the three 75 liter production lots:

Serum collected at one month post dose 2 was assayed by ELISA for IgG anti-OspA antibodies and LA-2 equivalent antibodies. Comparison of LA-2 equivalent anti-OspA GMTs between the three 75 liter production lots (primary endpoint) and IgG anti-OspA GMTs to demonstrate lot-to-lot consistency, was demonstrated using the bioequivalence approach of Anderson and Hauck⁶.

- Null hypothesis (H_0): "the expected relative difference in GMT is greater than 100%" (lots are inconsistent).
- Alternative hypothesis (H_a): "the expected relative difference in GMT is not greater than 100%" (lots are consistent).
- Relative difference in GMT is defined as: $\frac{GMT_{max} - GMT_{min}}{GMT_{min}} \times 100\%$

where GMT_{max} stands for GMT in the group with the highest GMT and GMT_{min} for GMT in the group with the lowest GMT.

Based upon the results, the null hypothesis was rejected. Thus, the 3 production lots were shown to be consistent based on a relative difference in GMTs of 100% or less for LA-2 equivalent anti-OspA antibodies and IgG anti-OspA antibodies, for both the according-to-protocol (ATP) and intent-to-treat (ITT) cohorts.

Consistency of the three 75 liter lots in terms of seroconversion (SC) was demonstrated using the exact confidence interval approach with an acceptable difference in SC of less than 10%.

- Null hypothesis (H_0): the expected difference in SC rates is greater than 10% (lots are inconsistent).
- Alternative hypothesis (H_a): the expected difference in SC rates is not greater than 10% (lots are consistent).
- Difference in SC rates is defined as: $SC_{max} - SC_{min}$
where SC_{max} stands for SC in the group with the highest SC and SC_{min} for SC in the group with the lowest SC rate.

⁶Ibid.

The results showed that the upper limit of the confidence interval for the difference was below 0.1. Thus, the null hypothesis was rejected. The lots were thus demonstrated to be consistent at an acceptable difference of less than 10% in seroconversion rates.

All subjects were seronegative at month 0. The seropositivity rates and GMTs one month after dose two are shown in Table 3.

Table 3. Immunogenicity in Vaccinees

Anti OspA antibodies	Group	Timing	N	S+	%	GMT
LA-2 equivalent	1	PII(d56)	115	111	96.5	1646
	2	PII(d56)	118	116	98.3	1469
	3	PII(d56)	115	113	98.3	1419
	4	PII(d56)	119	115	96.6	1428
IgG	1	PII(d56)	116	116	100.0	1648
	2	PII(d56)	112	110	98.2	1371
	3	PII(d56)	116	116	100.0	1342
	4	PII(d56)	116	115	99.1	1430

Notes: Group 1 = received 75 litre lot, LY101A2. Group 2 received 20 litre lot, LY003A2
Group 3 = received 75 litre lot, LY103A2. Group 4 received 75 litre lot, LY102A2
PII (d56) : post 2nd vaccination, day 56

N: Total number of subjects analysed at a particular time point

S+, %: number, percentage of seropositive subjects

GMT : Geometric Mean Titre in El.U/ml for IgG and ng/ml for LA2

Equivalence of the pooled 75 L production lots with the 20 L lot used in LYME-014:

1. *Bioequivalence Method*

The results of the three 75 liter production lots, which were demonstrated to be consistent for LA-2 equivalent and IgG anti-OspA antibodies, were pooled and compared with the lot used in study Lyme-014 to show their equivalence using the bioequivalence method by Anderson and Hauck as discussed above. The results demonstrated that given an acceptable relative difference in GMTs of 100% or less, the pooled 75 liter production lots were equivalent to the 20 liter lot used in Lyme-014, for LA-2 equivalent anti-OspA antibodies and IgG anti-OspA antibodies for both the ATP and ITT cohorts. Seroconversion rates at month 2 between the pooled 75 L production lots and the 20 L lot from LYME-014 (ATP) were compared. The results showed that the upper limit of the confidence interval for the difference is below 0.1 for both the ATP and ITT cohorts. Thus, the 75 liter lots were shown to be equivalent to the 20 L lot at an acceptable difference of less than 10% in seroconversion rates.

2. *Non-superiority Method*

Each of the three 75 L lots was compared to the 20 L lot from LYME-014 using the "as good as or better approach" of Dunnett and Gent⁷ with an acceptable relative difference of less than in 100% in GMTs. Estimated relative difference in GMTs was defined as:

$$\frac{GMT_{\text{each of the 75 L lots}}^{\text{observed}} - GMT_{\text{20 L lot}}^{\text{observed}}}{GMT_{\text{20 L lot}}^{\text{observed}}}$$

First, each 75 L lot was tested against the reference 20 L lot to ascertain if each production lot did not give lower antibody titers compared to the LYME-014 lot (non-inferiority/equivalence test). Second, each 75 L lot was tested against the reference 20 L lot to ascertain if each production lot did not give higher antibody titers compared to the LYME-014 lot (non-superiority test). Based on the results, all inferiority hypotheses were rejected and all non-superiority hypotheses were accepted. Thus, each of the three 75 L production lots were shown to be as good as the 20 L LYME-014 lot in terms of production of LA-2 equivalent and IgG anti-OspA antibody titers, and not statistically superior.

No differences in reactogenicity were demonstrated between lots. The majority of AEs were mild to moderate in intensity and all resolved without sequelae. The reactogenicity profile was comparable across lots. One SAE (influenza with hospitalization) was reported in group 2 (lot

⁷Dunnett, C.W. and Gent, M. (1996). An alternative to the use of two-sided tests in clinical trials. *Statistics in medicine*, 15, 1729-1738.

LY003A2) after the first dose. The event resolved. The investigator considered the event unrelated to study vaccine. The subject received the second dose of vaccine without recurrence of the event.

2. *Phase 3 Pivotal Efficacy Study*

a. *Study synopsis*

In order to assess vaccine efficacy, a prospective, multi-center, randomized, double-blind, placebo controlled trial, Lyme 008, was conducted over two transmission seasons, utilizing investigators located at 31 sites in areas endemic for LD, most of which were in the northeastern United States. Beginning in January 1995, 10,936 healthy individuals (15-70 years) at risk of LD were randomized to received vaccine or placebo. Of these subjects, 5,469 received vaccine (30 µg dose) and 5,467 received placebo (adjuvant only); one enrollee was never immunized. Subjects were immunized at 0, 1, and 12 months and followed for a total of 20 months (blinded) and an additional 4 months (unblinded). Thus the majority of safety and efficacy data have been accrued in Lyme 008, conducted over a 20-month period. The additional 4 months of safety data from a follow up study designated Lyme 013 have been accrued in the same population in open-label fashion. The prospectively defined primary objective of Lyme 008 was to evaluate the protective efficacy, safety and immunogenicity of a lipoprotein OspA Lyme disease vaccine (30 µg) on a 0, 1 month schedule; secondary objectives were to evaluate the protective efficacy, safety and immunogenicity of lipoprotein OspA vaccine on a 0, 1, 12 month schedule and to identify an immunological marker of protection. Inclusion criteria were typical; exclusion criteria were notable for exclusion of those with physician diagnosed chronic joint or neurologic illness related to LD; current disease associated with joint swelling or diffuse joint or muscular pain; known 2nd/3rd degree atrio-ventricular heart block or a cardiac pacemaker; and pregnant or lactating females. Subjects were monitored for safety and development of disease through diary cards, queries during scheduled visits, and postcard contacts throughout the trial. A subset of subjects at one center were asked to provide blood samples for immunogenicity analyses, and 100 subjects at another study site were asked to volunteer for exploratory studies on cell mediated immune responses. Specific prospectively defined case definitions designated criteria for category 1 "Definite Lyme disease" (appropriate clinical manifestations, including erythema migrans, plus laboratory confirmation by Western blot, PCR, or culture); category 2 "Possible Lyme disease" (erythema migrans without laboratory confirmation, flu-like illness with Western blot seroconversion, or neurologic symptoms with positive cell mediated immune responses); category 3 "Asymptomatic infection" (IgG seroconversion by Western blot, without symptoms); and category 4 "Abortive infection" (erythema migrans < 5 cm without laboratory confirmation).

b. *Results*

Demographics

A total of 10,937 subjects were enrolled at 31 sites in the United States, located in New England, mid-Atlantic states, and Wisconsin. Of these, 10,936 subjects (defined as the ITT cohort) received

at least 1 dose of vaccine (5469 vaccine, 5467 placebo recipients). This cohort was 42% female; 98.3% white, 0.3% black, 0.1% Oriental, and 1.3% other. The mean age was 45.9 years (S.D. 12.5 years), with a range of 14-70 years (1 vaccine recipient was enrolled at age 14, a protocol violation). The vaccine and placebo groups were similar in terms of age and ratio of males to females (significantly more males than females were present in both groups).

Efficacy

Primary Efficacy Analysis: Definite Lyme Disease in Year 1 (ATP)

The primary efficacy endpoint was prevention of definite cases of Lyme disease ("Category 1" cases) in the first year of the study between 4 weeks following the second dose of vaccine and month 12 (at time of blood draw immediately prior to the third dose). Vaccine efficacy against definite Lyme disease was 50% (95% CI: 14% to 71%) after two doses of vaccine administered according to protocol (20 cases among 5,148 subjects in the vaccine group; 40 cases among 5,166 subjects in the placebo group).

Intent-to-Treat (ITT) Analysis Results

The vaccine efficacy estimate for definite Lyme disease (Category 1) in year 1 for all individuals enrolled in the study who received at least dose 1 was 48.9% (95% CI: 14.6, 69.4). For year 2 this vaccine efficacy estimate was 75.8% (95% CI: 58.2, 85.9). For years 1 and 2 combined this vaccine efficacy estimate was 64.8% (95% CI: 49.2, 75.7).

Tables 4 and 5 summarize the efficacy estimates (ATP) for various study endpoints.

Table 4. Vaccine efficacy estimates in year 1 (ATP). [Note: AR% = attack rate]

LD Case Category/Definition		Vaccine (N=5148)		Placebo (N=5166)		p-value	VE (%) [95% CI]
		n	AR%	n	AR%		
1	Definite	20	0.39	40	0.77	0.010	50 [14, 71]
2	Possible	19	0.37	24	0.46	0.452	21 [-45, 56]
3	Asymptomatic seroconversion	2	0.04	12	0.23	0.008	83 [25, 96]

Table 5. Vaccine efficacy estimates in year 2 (ATP). [Note: AR% = attack rate]

LD Case Category/Definition		Vaccine (N=4765)		Placebo (N=4784)		p-value	VE (%) [95% CI]
		n	AR%	n	AR%		
1	Definite	13	0.27	58	1.21	0.001	78 [59, 88]
2	Possible	14	0.29	27	0.56	0.043	48 [1, 73]
3	Asymptomatic seroconversion	0	0	13	0.27	0.001	100 [30, 100]

Evaluation of Temporal Onset of Lyme Disease

There was no difference in the temporal onset of definite Lyme disease cases between vaccine and placebo groups, with the majority of cases (124 out of 131) occurring between May and August in both years of the study.

Lyme Disease Manifestations and Laboratory Diagnosis in the Efficacy Trial

The clinical presentation of the 131 cases of definite Lyme disease was as follows: erythema migrans, 128 (32 vaccine, 96 placebo); arthritis, 1 (vaccine); trigeminal neuralgia, 1 (placebo); and facial palsy, 1 (placebo). Of the 128 cases with erythema migrans, additional presenting clinical manifestations included: facial palsy, 3 (1 vaccine, 2 placebo) and trigeminal neuralgia, 1 (placebo). The duration of erythema migrans was similar for both vaccinees and placebo recipients.

Subjects were treated at either acute presentation of Lyme disease symptoms, following laboratory confirmation of symptoms, or following laboratory confirmation of asymptomatic infection. Active surveillance and prompt treatment of identified cases may have accounted for the low incidence of late Lyme disease manifestations. A similar proportion of definite Lyme disease cases in both vaccine and placebo groups were confirmed by positive culture, PCR analysis, or Western blot seroconversion.

Immunogenicity

In the pivotal efficacy trial, immunogenicity of LYMERix [Lyme Disease Vaccine (Recombinant OspA)] was assessed by measuring IgG anti-OspA antibodies and LA-2 equivalent antibodies in a subset of subjects 15 to 70 years of age enrolled at one study center. Table 6 shows the seropositivity rates and geometric mean titers (GMTs) following the second and third doses of LYMERix.

Table 6. Immunogenicity in Vaccinees

Antibody	Sampling Time	Seropositivity* % (n/N)	GMT-ELU/mL (95% CI)
Total IgG Anti-OspA	1 mo. after dose 2	99% (260/264)	1227 (1029, 1463)
	Pre-dose 3 [†]	83% (201/241)	116 (96, 139)
	1 mo. after dose 3	100% (267/267)	6008 (5180, 6963)
	7 mos. after dose 3	98% (262/267)	1991 (1686, 2351)
LA-2 Equivalent	1 mo. after dose 2	96% (236/245)	GMT-ng/mL (95% CI) 909 (773, 1067)
	Pre-dose 3 [†]	58% (150/258)	132 (118, 149)
	1 mo. after dose 3	99% (220/222)	4402 (3686, 5257)
	7 mos. after dose 3	97% (217/223)	1935 (1628, 2300)

* Seropositivity defined as an IgG OspA antibody titer ≥ 20 ELU/mL or a LA-2 equivalent antibody titer ≥ 100 ng/mL.

† At month 12.

n/N = number of seropositive subjects/total subjects tested.

% = percentage of seropositive subjects.

Subjects in the placebo group did not develop detectable anti-OspA seropositivity at the sampling time points indicated in the above table.

The evaluation of CMI responses was not completed during the license application phase, and the sponsor committed to submitting these results within 6 months post-licensure.

Safety

Subjects with the following conditions: chronic joint or neurologic illness related to Lyme disease; diseases associated with joint swelling (including rheumatoid arthritis) or diffuse musculoskeletal pain; second- or third-degree atrioventricular block or a pacemaker were excluded from the efficacy trial because such conditions could interfere with the assessment of Lyme disease in the trial. Therefore, data are limited regarding the safety of the vaccine in subjects with these conditions (see below).

Unsolicited Adverse Events

The most frequently reported ($\geq 1\%$) unsolicited adverse events within 30 days of vaccination for all subjects receiving at least one dose ($n=10,936$) in the double-blind, placebo-controlled efficacy trial are shown in Table 7.

Table 7. Incidence ($\geq 1\%$) of Unsolicited Adverse Events Occurring Within 30 Days Following Each Dose* and Overall (after Doses 1, 2 or 3).

Events	Dose							
	1		2		3		Overall	
	Vaccine (N = 5468) %	Placebo (N = 5467) %	Vaccine (N = 5387) %	Placebo (N = 5417) %	Vaccine (N = 5001) %	Placebo (N = 5018) %	Vaccine (N = 5468) %	Placebo (N = 5467) %
Local								
Injection site pain	17.96 ^a	4.90	8.76 ^c	2.95			21.87 ^a	6.91
Injection site reaction							1.54 ^b	0.91
General								
Body as a Whole								
Achiness	1.57	1.19	1.22	0.90			2.78	2.25
Chills/rigors							2.05 ^c	0.73
Fatigue	2.03	1.96	1.72	1.42			3.86	3.42
Fever	1.35 ^d	0.91					2.58 ^c	1.61
Infection viral	1.88	1.66					2.83	2.45
Influenza-like symptoms	1.44 ^a	0.93					2.54 ^c	1.66
Nausea							1.12	1.04
Musculoskeletal System								
Arthralgia	3.22	2.67	3.11	2.60	1.24	1.16	6.78	6.05
Back pain							1.90	1.55
Myalgia	2.89 ^c	1.72	1.52 ^a	0.98			4.83 ^c	2.94
Stiffness							0.95	1.21
Nervous System								
Dizziness							1.01	1.08
Headache	3.51	2.96	2.99	2.33			5.61	5.09
Respiratory System								
Bronchitis							1.10	1.28
Coughing							1.50	1.46
Pharyngitis	1.39	1.12	1.15	1.20			2.52	2.45
Rhinitis	1.50	1.46					2.41	2.47
Sinusitis	1.74	1.57	1.26	1.27			3.16	2.93
Upper respiratory tract infection	2.63	3.22	1.65	1.75			4.35	4.98
Skin/Appendages								
Rash							1.37	1.08

* Includes events obtained through spontaneous reports following each dose and events reported 1 month after doses 1 and 2 (when all subjects were queried regarding the occurrence of any adverse event since the previous vaccination).

- a. p-value < 0.05
 b. p-value < 0.01
 c. p-value < 0.001

The most frequently reported ($\geq 1\%$) unsolicited adverse events occurring more than 30 days following vaccination for all subjects ($n=10,936$) in the double-blind, placebo-controlled efficacy trial are shown in Table 8.

Table 8. Incidence ($\geq 1\%$) of Unsolicited Adverse Events Occurring More Than 30 days Following Dose 2 and 3* and Overall (after Doses 1, 2 or 3).

Events	2		Dose 3		Overall	
	Vaccine (N = 6397) %	Placebo (N = 6417) %	Vaccine (N = 6001) %	Placebo (N = 5018) %	Vaccine (N = 5469) %	Placebo (N = 5467) %
Body as a Whole						
Achiness	1.50	1.38			2.30	2.18
Chills/rigors	1.30	1.05			1.74	1.76
Fatigue	3.24	3.43	1.86	1.81	5.01	4.98
Fever	2.28	2.60	1.34	1.30	3.58	3.82
Infection viral	1.43	1.74			2.19	2.34
Influenza-like symptoms	2.33	2.10			2.87	2.76
Cardiovascular System						
Hypertension					0.93	1.24
Gastrointestinal System						
Diarhea					1.01	1.19
Musculoskeletal System						
Arthralgia	9.93	10.04	4.72	4.46	13.64	13.55
Arthritis	1.98	1.74	1.04	1.12	2.91	2.84
Arthrosis	1.22	1.09			1.66	1.50
Back pain	2.69	2.73			3.58	3.46
Myalgia	2.78	2.22	1.14	1.28	4.02	3.40
Stiffness	1.82	1.59			2.47	2.40
Tendinitis	1.45	1.05			1.82	1.63
Nervous System						
Depression					1.02	1.10
Dizziness					1.02	1.26
Headache	3.56	3.05	1.36	1.49	5.06	4.72
Hypesthesia	2.20	2.66			2.96	3.60
Paresthesia	2.69	2.20	1.06	0.98	3.60	2.98
Respiratory System						
Bronchitis					1.32	1.39
Pharyngitis	1.70	1.68			2.19	2.12
Rhinitis	0.94	1.07			1.41	1.37
Sinusitis	2.33	2.53			3.07	3.11
Upper respiratory tract infection	2.02	2.29			2.80	3.00
Skin/Appendages						
Contact dermatitis	1.50	1.75			1.68	1.94
Rash	2.39	1.99			3.07	2.71

* Data for adverse events occurring more than 30 days after dose 1 are not provided because most subjects received dose 2 approximately 30 days after dose 1.

Note: No significant differences in adverse events were noted between treatment groups after any dose and overall.

Separate *post hoc* analyses were conducted to assess two subsets of musculoskeletal events which occurred either early (≤ 30 days) or late (> 30 days) post-vaccination. There were no significant differences, either early or late, between the vaccine and placebo recipients with regard to experiencing arthritis, aggravated arthritis, arthropathy or arthrosis. However, vaccine recipients were significantly more likely than placebo recipients to experience early events of arthralgia or myalgia after each dose [for dose 1: odds ratio (OR), (95% CI) = 1.35 (1.13, 1.61); dose 2: OR = 1.28 (1.05, 1.56); dose 3: OR = 1.59 (1.18, 2.16)]. With regard to late events of arthralgia or myalgia, there were no significant differences between vaccine and placebo recipients. There was no significant difference in the rates of cardiac adverse events between vaccine and placebo recipients. Neurologic adverse events which occurred at a rate $< 1\%$ in the vaccine group and were noted to occur with a similar frequency in placebo recipients included: carpal tunnel syndrome, migraine, paralysis, tremor, coma, dysphonia, ataxia, multiple sclerosis, myasthenia gravis, meningitis, trigeminal neuralgia, nystagmus, neuritis, neuralgia, nerve root lesion, neuropathy, hyperesthesia, hyperkinesia, and intracranial hypertension. Overall, approximately 18% of subjects enrolled in the study had a prior history of some musculoskeletal condition (19% vaccinees, 18% placebo recipients). In a *post hoc* subgroup analysis, there was no significant difference between vaccine and placebo recipients with regard to development of musculoskeletal events (defined as arthritis, arthropathy, arthrosis, synovitis, tendinitis, polymyalgia rheumatica, bursitis or rheumatoid arthritis and lasting more than 30 days) in those with a prior history of musculoskeletal conditions. However, both vaccine and placebo recipients with a prior history of musculoskeletal conditions were more likely to experience musculoskeletal events than subjects without such prior history.

Solicited Adverse Events

The frequency of solicited local and systemic adverse events was evaluated in a subset of subjects ($n=938$) who comprised the total enrollment at one study center in the efficacy trial. Of these 938 subjects, 800 completed a 4-day diary card following each of three doses, and were evaluable according to protocol. Table 9 shows the percentage of subjects reporting a solicited symptom following any one of the three doses and overall. The majority of the solicited events were mild to moderate in severity and limited in duration.

Table 9. The Incidence of Local and General Solicited Adverse Events (Including Severe Events) Reported After Each Dose and Overall.

Events	Dose							
	1		2		3		Overall	
	Vaccine (N = 402) %	Placebo (N = 398) %						
Local Symptoms								
Redness, any	21.64 ^c	8.29	16.67 ^c	7.04	25.12 ^c	11.81	41.79 ^c	20.85
Redness, severe	2.2 ^b	0.0	1.0	0.0	2.5 ^b	0.0	4.2 ^c	0.0
Soreness, any	81.59 ^c	36.68	76.37 ^c	30.90	82.59 ^c	52.26	93.53 ^c	68.09
Soreness, severe [†]	1.2	0.0	1.0	0.3	3.0 ^b	0.3	5.0 ^c	0.0
Swelling, any	14.43 ^c	4.27	11.44 ^c	3.27	19.15 ^c	6.78	29.85 ^c	11.31
Swelling, severe	0.0	0.0	0.0	0.0	0.5	0.0	0.5	0.0
General Symptoms								
Arthralgia, any	11.94 ^c	4.52	10.70	8.29	13.43 ^b	7.54	25.62 ^b	16.33
Arthralgia, severe [†]	0.7	0.0	0.2	0.3	0.0	0.3	1.0	0.5
Fatigue, any	20.90	16.83	20.15 ^a	11.81	21.89 ^a	16.33	40.80 ^a	32.91
Fatigue, severe [†]	0.5	0.05	1.5	1.3	1.0	1.0	3.0	2.3
Headache, any	20.65	19.10	14.43	12.31	19.90	18.34	38.56	37.19
Headache, severe [†]	0.5	0.05	1.2	0.5	1.2	1.8	3.0	2.8
Rash, any	4.23 ^a	1.51	4.98 ^a	2.01	5.47 ^b	1.76	11.69 ^b	5.28
Rash, severe	0.0	0.0	0.0	0.0	0.2	0.0	0.2	0.0
Fever ≥99.5°F	1.49	0.75	1.00	0.50	1.00	1.01	3.48	2.26
Fever >102.2°F	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

* Severe = measuring >3.0 cm and persisting longer than 24 hours.

† Severe = preventing everyday normal activity.

a. p-value <0.05.

b. p-value <0.01.

c. p-value <0.001.

Subjects with Previous Lyme Disease

Subjects with previous Lyme disease were assessed using two definitions: subjects whose baseline sera were evaluated for Western blot (WB) positivity and found to be positive, and subjects who at study entry self-reported a previous history of Lyme disease. Study participants did not routinely have baseline sera tested by WB for Lyme disease. WB at baseline was performed for subjects who were noted to have a positive or equivocal WB during a visit for suspected Lyme disease or when tested at months 12 or 20 and found to be WB positive. Baseline serology was thus found to be positive in 250 subjects out of 628 tested. The nature and incidence of adverse events (either early or late) did not differ between vaccinees determined to have been WB-positive at baseline (n=124) compared to vaccinees determined to have been WB-negative at baseline (n=151).

There were 1,206 subjects enrolled in the study who self-reported a previous history of Lyme disease (610 vaccinees, 596 placebo recipients). For adverse events occurring within the first 30 days, there was an increased incidence of musculoskeletal symptoms in vaccinees with a history of Lyme disease compared to vaccinees with no history of Lyme disease (20% vs. 13%, $p < 0.001$). No such difference was observed between those with and without a prior history of Lyme disease in the placebo group (13% vs. 11%, $p = 0.24$). Subjects with a previous history of Lyme disease had an increased incidence of late (>30 days post-vaccination) musculoskeletal symptoms compared to subjects without a history of Lyme disease in both the vaccine and placebo groups. There was no significant difference in late musculoskeletal adverse events between vaccine and placebo recipients with a history of Lyme disease (33% vs. 35%, $p = 0.51$). Subjects with a self-reported prior history of Lyme disease had a greater incidence of psychiatric disorders (early and late); central, peripheral and autonomic nervous system disorders (late); and gastrointestinal disorders (late) than subjects with no prior history of Lyme disease. However, there was no significant difference in the incidence of any of these disorders between vaccine and placebo recipients with a prior history of Lyme disease.

Summary of Deaths in the Pivotal Efficacy Trial

Among the 10,936 subjects enrolled in the efficacy trial and followed for 20 months, a total of 15 deaths occurred (10 vaccine, 5 placebo). None of these deaths were judged to be treatment-related by investigators. In the vaccine group, causes of death included: cancer (5), myocardial infarction (3), sudden death (1), cardiac arrest (1). In the placebo group, causes of death included: cancer (1), sudden cardiac death (1), cardiac arrest (1), septic shock (1), homicide (1).

C. Total Size of the Safety Database

The original PLA submission contained safety data regarding the administration of 18,047 doses of the 30 µg dose of this OspA Lyme disease vaccine to 6,478 subjects who were ≥ 15 years of age. The majority of these subjects were enrolled in Lyme 008, the pivotal efficacy trial. In this trial, 5,469 subjects received at least one dose of vaccine, and a total of 15,867 doses were administered during the entire trial. In six other clinical trials, 1,009 subjects received a least one dose of vaccine

and a total of 2,180 doses were administered. The safety data from these six smaller clinical trials were consistent with those obtained in Lyme 008. It should be noted that vaccine has been administered to a limited number of subjects 15-18 years of age (N=151 in Lyme 008). The safety profile for these 15-18 year old subjects appeared similar to that for subjects over 18 years of age in Lyme 008. However, only unsolicited adverse events could be analyzed for these 15-18 year old subjects because only 3/151 vaccinees were enrolled in the solicited reactogenicity subset of subjects in Lyme 008 (Center 24; see below).

During the application phase, additional safety data regarding the administration of 951 doses of this vaccine to 476 subjects between 18 and 50 years of age in study LYME-019 was provided in the final report for this study.

VII. Advisory Panel Consideration

Data regarding the manufacturing, safety, and efficacy of LYMERix™ were presented and discussed at the May 26, 1998 meeting of FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting. A summary of the meeting presentations and discussion follows. CBER presentations included a summary of the PLA, an overview of the clinical data, and presentation of the questions. Sponsor presentations included an overview of Lyme disease, a summary of the clinical development of LYMERix®, and recent laboratory work regarding the potential identification of a candidate autoantigen (LFA-1) that shares a sequence homology with peptide 8, a dominant epitope of OspA, and its role in the pathogenesis of treatment resistant Lyme arthritis⁸. Preliminary data from an evaluation of cellular immune response and correlations to clinical adverse event information in subgroups of subjects in the pivotal efficacy study was discussed as well.

Questions posed to the Committee by CBER were:

1. Are the data sufficient to support the conclusion that the vaccine is safe for immunization of individuals 15-70 years of age?
2. Are the data sufficient to support the conclusion that the vaccine is effective against Lyme disease in individuals 15-70 years of age when given on a 0, 1, 12 month schedule?
3. Please comment on the use of Lyme disease vaccine in persons over 70 years of age.
4. In the efficacy trial, vaccinations were given just before the *B. burgdorferi* transmission season (at 0 and 1 month between January 15 and April 15, then 12 months later between approximately February 15 and April 30). Should a similar seasonal vaccination schedule be recommended in the package insert?
5. Are there any additional studies that should be performed by the sponsor?

⁸Gross DM, Forsthuber T, Tary-Lehmann M, *et al.* Identification of LFA-1 as a candidate autoantigen in Treatment-resistant Lyme arthritis. *Science* 1998; 281:703-706.

The committee responded to the five questions posed by CBER as follows:

1. The data were considered to be sufficient to support the conclusion that the vaccine is safe for immunization of individuals 15-70 years of age with the following provisos:
 - a. More data in the groups previously excluded such as those with a history of chronic joint pain or a recent history of Lyme disease are needed.
 - b. More data in subjects between 15 and 18 years of age and between 65 and 70 years of age are needed.
 - c. Long-term follow-up of subjects should be studied.
2. The data are sufficient to support the conclusion that the vaccine is effective against definite Lyme disease in individuals 15-70 years of age when given on a 0, 1, 12 month schedule.
3. With regard to the use of Lyme disease vaccine in persons over 70 years of age, it was suggested that a bridging study be conducted in such a population for extrapolation of the efficacy results. It was noted that preliminary data suggest that there is a trend toward lower GMTs as age increases which indicates that it may take more doses to achieve the same level of GMTs in this population. It was noted that a defined seroprotective level of antibody would be necessary in order to conduct a bridging study in the elderly based on immunogenicity.
4. A seasonal vaccination schedule similar to the schedule used in the efficacy study should be recommended in the package insert. Concerns regarding the need for patient education, regional decisions for dosing, the need for an established correlate of protection and bridging studies were stated.
5. The committee recommended that additional studies be performed by the sponsor to evaluate use of the vaccine in patients with chronic joint disease; longer term follow-up in vaccinated individuals; additional doses beyond the third dose; use of the vaccine in children under 15 years of age and elderly subjects over 70 years of age; alternate dose schedules; and interactions between development of rheumatologic symptoms in vaccinees whose HLA subtypes include certain RA-associated alleles.

VII. Approved Package Insert

The approved package insert is available on the world wide web at

<http://www.fda.gov/cber/products/lymesmi122198.htm>.

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