PRESCRIBING INFORMATION

LYMErix™
Lyme Disease Vaccine (Recombinant OspA)

DESCRIPTION

LYMErix [Lyme Disease Vaccine (Recombinant OspA)] is a noninfectious recombinant vaccine developed and manufactured by SmithKline Beecham Biologicals. The causative agent of Lyme disease is *Borrelia burgdorferi*; in North America, all Lyme disease is due to *Borrelia burgdorferi sensu stricto*. The vaccine contains lipoprotein OspA, an outer surface protein of *Borrelia burgdorferi sensu stricto* ZS7, as expressed by *Escherichia coli.* Lipoprotein OspA is a single polypeptide chain of 257 amino acids with lipids covalently bonded to the N terminus. No substance of animal origin is used in the commercial manufacturing process. Fermentation media consist primarily of inorganic salts, and vitamins, with small quantities of antifoam (contains silicon), kanamycin sulfate (an aminoglycoside antibiotic), and yeast extract. Silicon and kanamycin are removed to levels below detection (<7 ppm and <10 ppb, respectively). The vaccine is adsorbed onto aluminum hydroxide.

LYMErix is supplied as a sterile suspension in single-dose vials and prefilled syringes for intramuscular administration. The vaccine is ready for use without reconstitution; it must be shaken before administration to ensure a uniform turbid white suspension.

Each 0.5 mL dose of vaccine consists of 30 mcg of lipoprotein OspA adsorbed onto 0.5 mg aluminum as aluminum hydroxide adjuvant. Each dose of the vaccine preparation contains 10 mM phosphate buffered saline and 2.5 mg of 2-phenoxyethanol, a bacteriostatic agent.

The potency of the vaccine is evaluated by immunizing mice with *LYMErix* and measuring their serum antibody response to OspA by ELISA.

CLINICAL PHARMACOLOGY

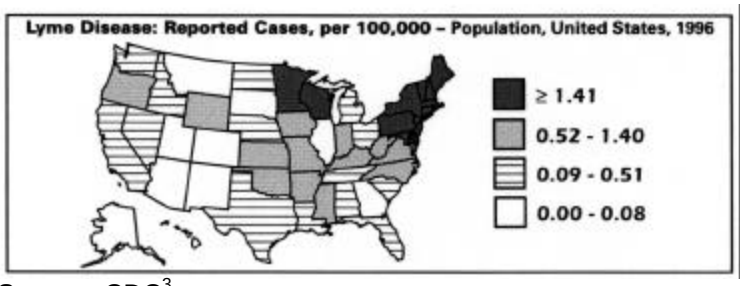
Microbiology

Lyme disease is a multisystem disease caused by infection with the bacterial spirochete, *B. burgdorferi*, which is

transmitted by *Ixodes* ticks. The enzootic life cycle of *B. burgdorferi* is dependent upon its transmission between an insect vector, the *Ixodes* tick, and a reservoir host, most commonly the white-footed mouse. Tick larvae usually feed in the late summer and acquire *B. burgdorferi* from an infected animal host. Nymphal ticks feed in the late spring and summer, and serve as the most common source of human infection. Adult ticks feed in the fall, winter and early spring, with the white-tailed deer being the preferred host. Adult ticks can also transmit *B. burgdorferi* to humans.[1] Both deer and rodent hosts are necessary to maintain the enzootic cycle of *B. burgdorferi*.

Epidemiology

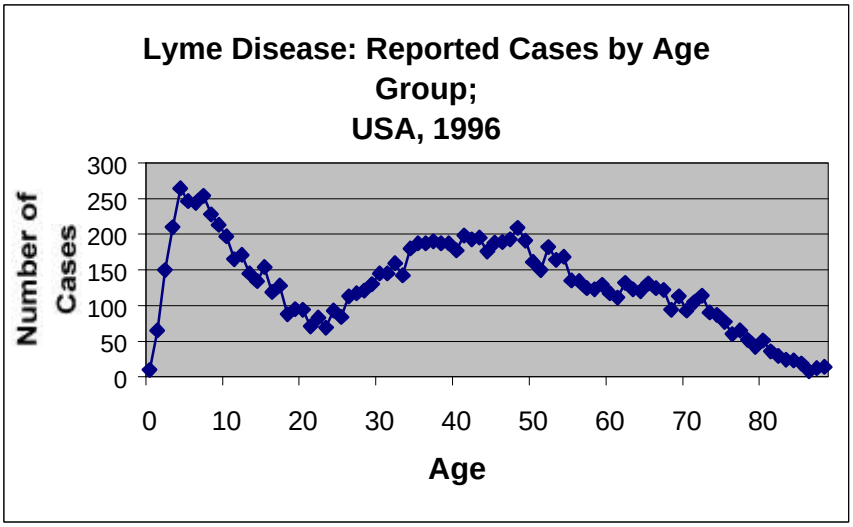
Lyme disease is the most commonly diagnosed vector-borne disease in the United States, with over 99,000 cases reported to the Centers for Disease Control and Prevention (CDC) from 1982 to 1996. During that time, the incidence of reported cases increased by at least 32-fold. Although most cases have been reported in the Northeast, upper Midwest and Pacific coastal areas of the United States, infections have been reported in almost all states.[2] The incidence rates vary considerably from state to state and even within states at the county level.[2]



Source: CDC[3]

The trend of an increasing incidence in some established endemic areas continues, along with the geographic spread of the causative organism to new areas.[1,2,4,5]

Lyme disease has a bimodal age distribution, with the highest number of cases occurring in children 2 to 15 years of age and adults 30 to 55 years of age.[4]



Source: CDC[6]

The primary risk factor for Lyme disease is exposure to wooded or grassy areas inhabited by *B. burgdorferi*-infected ticks. Such areas may include woodlands, meadows, or residential yards in endemic areas.[5] Cases have been reported in people whose only exposure to *B. burgdorferi* has been while on vacation in an endemic area.[1]

Lyme disease has been reported to occur throughout the year.[7,8] Peak incidence of Lyme disease varies by region and may vary annually based on fluctuations in local climatic conditions.[1,5,7,8] For example, the peak occurs in the late spring and summer in the Northeast United States, coincident with the feeding of nymphal ticks, the most common source of human infection. Transmission can occur also in the fall, winter, and early spring when adult ticks are feeding.[1]

Clinical Manifestations: Lyme disease has a variable incubation period.[5] Lyme disease is a multisystem disease, which has been described as having early and late stages. The early stage is usually characterized by a rash (erythema migrans) and may be accompanied by fever, fatigue, myalgias and/or arthralgias. Erythema migrans represents a localized cutaneous infection and is the presenting symptom in 60% to 80% of cases. Early disseminated manifestations include secondary skin lesions, neurologic involvement (meningitis, facial palsy, other cranial neuritides, radiculoneuritis), cardiac involvement (atrioventricular block, myocarditis), and musculoskeletal symptoms usually

consisting of migratory pain in joints and the surrounding soft tissue structures.[9]

Late stage disease (persistent infection) occurs months to years after initial infection and may be manifested as chronic arthritis, chronic neurologic abnormalities or acrodermatitis chronica atrophicans. Not all patients with Lyme disease have this characteristic progression of symptoms. Late stage disease usually requires more intensive therapy and may result in permanent sequelae. In particular, late neurologic involvement is associated with chronic, slowly progressive disease.[10]

The rate of asymptomatic infection has not been well studied in adults. In the LYMErix [Lyme Disease Vaccine (Recombinant OspA)] study, the rate of asymptomatic infection (for definition, see *Clinical Efficacy*, Asymptomatic *B. burgdorferi* infection) was approximately 0.25% per year with one case of asymptomatic infection occurring for every four cases of erythema migrans.

Late stage disease may result from early disease that is either unrecognized or fails to respond to treatment, or from asymptomatic infection. The relative importance of these conditions in predisposing to the development of late stage disease is unknown.

Diagnosis: Diagnosis is based on clinical manifestations, epidemiologic information and laboratory evaluation. Confirming the diagnosis may be difficult in some cases.

At a consensus meeting of the CDC and ASTPHLD (Association of State, Territorial and Public Health Laboratory Directors), a two-step approach was recommended if serologic evaluation of Lyme disease is required.[11] A sensitive screening test such as an enzyme-linked immunosorbent assay (ELISA) or immunofluorescent assay (IFA) is recommended as the initial laboratory test and, if positive or equivocal, immunoblot (Western blot) testing should be performed to confirm the results (see Laboratory Test Interactions).

LYMErix *Mechanism of Action: LYMErix* stimulates specific antibodies directed against *B. burgdorferi.* The organism contains several outer surface proteins, with lipoprotein

OspA being immunodominant.[12] Administration of lipoprotein OspA to mice 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 have demonstrated bactericidal activity. Studies have shown that mice immunized with recombinant lipoprotein OspA are protected against disease after tick challenge with *B. burgdorferi*.[13] LA-2 equivalent antibody titers have been shown to correlate with protection against infection in laboratory animals.[14]

B. burgdorferi express OspA while residing in the midgut of the infected tick, but OspA is downregulated after tick attachment and is usually undetectable or absent when *B. burgdorferi* is inoculated into the human host.[15] Thus, a novel hypothesis has been proposed to explain the effectiveness of lipoprotein OspA vaccination: when infected ticks bite humans who have been vaccinated with *LYMErix*, the vaccine-induced antibodies are taken up by the tick and interact with the *B. burgdorferi* in the midgut of the tick, thereby preventing transmission of the organism to the host. This mechanism has been suggested by a pre-clinical study in which *B. burgdorferi* were detected by immunofluorescence assay in none of the ticks that fed on OspA-immunized mice, compared with 72% of ticks that fed on control-immunized mice.[13]

Clinical Efficacy

A randomized, double-blind, multicentered, placebo-controlled trial has shown that *LYMErix* confers protection against Lyme disease.[16] This trial was conducted in highly endemic areas of the United States, primarily in the Northeast, and enrolled 10,936 subjects (5,469 vaccinees; 5,467 placebo recipients) ages 15 to 70 years. Subjects with a history of previous Lyme disease were not excluded from this trial.

Subjects vaccinated with three doses of *LYMErix* or placebo at months 0, 1 and 12 were observed for 20 months after the first injection (January 1995 through November 1996). The primary endpoint of the trial was the incidence of definite Lyme disease after two doses of vaccine. Each subject was actively followed for symptomatic disease during the entire observation period and was assessed for possible

asymptomatic infection (as evidenced by IgG Western blot seroconversion) at months 12 and 20.

Definite Lyme disease
In the pivotal efficacy trial, definite Lyme disease was defined as clinical manifestations (erythema migrans, neurologic, musculoskeletal or cardiovascular involvement) with laboratory confirmation (positive culture for *B. burgdorferi* from skin biopsy; positive polymerase chain reaction [PCR] result for *B. burgdorferi* from skin biopsy, synovial fluid, or CSF; or IgM or IgG Western blot seroconversion) as defined by CDC/ASTPHLD criteria.[11]

Post-second dose efficacy was measured beginning at 4 weeks following the second dose through to month 12. Post-third dose efficacy was measured from the third dose through to month 20.

Prevention of Definite Lyme Disease: Vaccine efficacy against definite Lyme disease was 78% (95% CI: 59% to 88%) after three doses of vaccine administered according to protocol (13 cases among 4,765 subjects in the vaccine group; 58 cases among 4,784 subjects in the placebo group). 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).

Asymptomatic *B. burgdorferi* infection
In the pivotal efficacy trial, subjects were defined as having asymptomatic infection when, in the absence of recognizable clinical symptoms, IgG Western blot seroconversion occurred either between months 2 and 12 of the first year, or between months 12 and 20 of the second year.

Prevention of Asymptomatic Infection: Vaccine efficacy against asymptomatic *B. burgdorferi* infection was 100% (95% CI: 30% to 100%) after three doses of vaccine administered according to protocol (0 cases among 4,765 subjects in the vaccine group; 13 cases among 4,784 subjects in the placebo group). Vaccine efficacy against asymptomatic *B. burgdorferi* infection was 83% (95% CI: 25% to 96%) after two doses of vaccine administered

according to protocol (2 cases among 5,148 subjects in the vaccine group; 12 cases among 5,166 subjects in the placebo group).

Possible Lyme disease

In the pivotal efficacy trial, possible Lyme disease was defined as a flu-like illness (fever, chills, fatigue, headache, joint or muscle aches) with IgM or IgG Western blot seroconversion, or physician-diagnosed erythema migrans with negative laboratory results.

Prevention of Possible Lyme Disease: Following the three-dose course of vaccine administered according to protocol, efficacy was 48% (95% CI: 1% to 73%) against possible Lyme disease. Fourteen of the subjects in the vaccine group developed a possible case of Lyme disease, compared to 27 placebo recipients. Following two doses of vaccine administered according to protocol, the vaccine efficacy against possible Lyme disease was 21% (95% CI: -45% to 56%). Nineteen subjects who received two doses of vaccine developed possible Lyme disease, compared to 24 placebo recipients.

The data regarding flu-like illnesses due to possible Lyme disease may be confounded by possible cross-reactivity and/or co-infection with *Ehrlichia,* which may cause a flu-like illness and false-positive IgM Western blot for *B. burgdorferi.*[17]

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 Persons 15 to 70 Years of Age: 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 1 shows the seropositivity rates and geometric mean titers (GMTs) following the second and third doses of *LYMErix*.

Table 1. Immunogenicity in Vaccinees

Antibody	Sampling Time	Seropositivity* % (n/N)	GMT-EL.U./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)	6006 (5180, 6963)
	7 mos. after dose 3	98% (262/267)	1991 (1686, 2351)
			GMT-ng/mL (95% CI)
LA-2 Equivalent	1 mo. after dose 2	96% (236/245)	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 EL.U./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.

INDICATION AND USAGE

LYMErix is indicated for active immunization against Lyme disease in individuals 15 to 70 years of age.

Individuals most at risk may be those who live or work in *B. burgdorferi*-infected, tick-infested grassy or wooded areas (e.g., landscaping brush clearing, forestry, and wildlife and parks management),[4,18-21] as well as those who plan travel to or pursue recreational activities (e.g., hiking, camping, fishing and hunting) in such areas. Most cases of Lyme disease in the United States are thought to be acquired in

the peri-residential environment, through routine activities of property maintenance, recreation, and/or exercise of pets.[19,22]

Previous infection with *B. burgdorferi* may not confer protective immunity.[23] Therefore people with a prior history of Lyme disease may benefit from vaccination with *LYMErix.*

Safety and efficacy for this vaccine are based on administration of the second and third doses several weeks prior to the onset of the *Borrelia* transmission season in the local geographic area (see DOSAGE AND ADMINISTRATION).

*LYME*rix is not a treatment for Lyme disease.

As with any vaccine, *LYMErix* may not protect 100% of individuals. The vaccine should not be administered to persons outside of the indicated age range.

CONTRAINDICATIONS

LYMErix is contraindicated in people with known hypersensitivity to any component of the vaccine.

PRECAUTIONS

General

LYMErix will not prevent disease in those who have unrecognized infection at the time of vaccination. *LYMErix* will not provide protection against other tick-borne diseases such as babesiosis or ehrlichiosis.

Treatment-resistant Lyme arthritis (antibiotic refractory), a rare complication of *B. burgdorferi* infection, has been associated with immune reactivity to OspA of *B. burgdorferi*.[24] Since the underlying etiology is not clearly understood, it is recommended that *LYMErix* not be administered to such patients.

As with other vaccines, although a moderate or severe febrile illness is sufficient reason to postpone vaccination, minor illnesses such as mild upper respiratory infections with or without low-grade fever are not contraindications.[25]

Before the injection of any biological, the physician should take all reasonable precautions to prevent allergic or other

adverse reactions, including understanding the use of the product concerned, and the nature of the side effects and adverse reactions that may follow its use.

Prior to immunization with any vaccine, the patient's history should be reviewed. The physician should review the patient's immunization history for possible vaccine sensitivity, previous vaccination-related adverse reactions and occurrence of any adverse-event-related symptoms and/or signs, in order to determine the existence of any contraindication to immunization and to allow an assessment of benefits and risks. Epinephrine injection (1:1000) and other appropriate agents used for the control of immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur.

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.

A separate sterile syringe and needle or a sterile disposable unit must be used for each patient to prevent the transmission of infectious agents from person to person. Needles should be disposed of properly and should not be recapped.

As with any vaccine administered to immunosuppressed persons or persons receiving immunosuppressive therapy, the expected immune response may not be obtained. For individuals receiving immunosuppressive therapy, deferral of vaccination for three months after therapy may be considered.[26]

Information for Patients

In addition to vaccination with *LYMErix,* people can further decrease their risk of acquiring tick-borne infections by taking standard preventive measures (e.g., wearing long-sleeved shirts, long pants rather than shorts, tucking pants into socks, treating clothing with tick repellent, and checking for and removing attached ticks).[2]

Patients, parents or guardians should be informed of the benefits and risks of immunization with *LYMErix,* and of the importance of completing the immunization series. As with any vaccine, it is important when a subject returns for the

next dose in a series that he/she be questioned concerning the occurrence of any symptoms and/or signs after a previous dose of the same vaccine and adverse events be reported. The U.S. Department of Health and Human Services has established a Vaccine Adverse Events Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine. The VAERS toll-free number is 1-800-822-7967.

The duration of immunity following a complete schedule of immunization with *LYMErix* has not been established.

It is important to note that subjects with a prior history of *B. burgdorferi* infection may not have protection against subsequent disease[23] or asymptomatic infection.

Individuals should be informed that vaccination with *LYMErix* may induce a false-positive ELISA result for *B. burgdorferi* infection (see Laboratory Test Interactions). Patients should be advised to inform health care professionals that they have been immunized with *LYMErix*, since it may affect laboratory testing for diagnosing Lyme disease.

Laboratory Test Interactions

LYMErix immunization results in the generation of anti-OspA antibodies, which can be detected by an enzyme-linked immunosorbent assay (ELISA) for *B. burgdorferi*. The incidence of positive IgG ELISA tests is dependent on the sensitivity and specificity of the ELISA assay and the titer of anti-OspA antibody. In general, there is an association between anti-OspA titer and IgG ELISA index or Optical Density (OD) ratio; the higher the titer of anti-OspA achieved, the higher the IgG ELISA index or OD ratio.

Therefore, because vaccination may result in a positive IgG ELISA in the absence of infection, it is important to perform Western blot testing if the ELISA test is positive or equivocal in vaccinated individuals who are being evaluated for suspected Lyme disease.

Following vaccination, the appearance of a 31kD OspA band, possibly accompanied by other lower molecular weight bands on an immunoblot (Western blot), should not interfere with the determination of positivity when assessed by CDC/ASTPHLD criteria.[11]

Drug Interactions
No data are available on the immune response to *LYMErix* when administered concurrently with other vaccines. As with other intramuscular injections, *LYMErix* should not be given to individuals on anticoagulant therapy, unless the potential benefit clearly outweighs the risk of administration.

Carcinogenesis, Mutagenesis, Impairment of Fertility
LYMErix has not been evaluated for carcinogenic or mutagenic potential, or for impairment of fertility.

Pregnancy
Teratogenic Effects: Pregnancy Category C. Animal reproductive studies have not been conducted with *LYMErix*. It is also not known whether *LYMErix* can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. *LYMErix* should be given to a pregnant woman only if clearly needed.

Health care providers are encouraged to register pregnant women who receive LYMErix [Lyme Disease Vaccine (Recombinant OspA)] in the SmithKline Beecham Pharmaceuticals vaccination pregnancy registry by calling1-800-366-8900, ext. 5231.

Nursing Mothers
It is not known whether *LYMErix* is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when *LYMErix* is administered to a nursing woman.

Pediatric Use
Safety and efficacy in pediatric subjects younger than 15 years of age have not been evaluated. Therefore, the vaccine is not indicated for this age group at this time.

ADVERSE REACTIONS
During clinical trials involving 6,478 individuals receiving a total of 18,047 doses, *LYMErix* has been generally well tolerated.

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 (≥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 2.

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

	Dose 1		2		3		Overall	
Events	**Vaccine (N = 5469) %**	**Placebo (N = 5467) %**	**Vaccine (N = 5397) %**	**Placebo (N = 5417) %**	**Vaccine (N = 5001) %**	**Placebo (N = 5018) %**	**Vaccine (N = 5469) %**	**Placebo (N = 5467) %**
Local								
Injection site pain	17.96[c]	4.90	8.76[c]	2.95			21.87[c]	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[a]	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	2.69[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	2.39	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 (≥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 3.

Table 3. Incidence (≥1%) of Unsolicited Adverse Events Occurring More Than 30 Days Following Dose 2 and 3* and Overall (after Doses 1, 2 or 3)

	Dose 2		Dose 3		Overall	
Events	**Vaccine (N = 5397) %**	**Placebo (N = 5417) %**	**Vaccine (N = 5001) %**	**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						
Diarrhea					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			1.92	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 4 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 4. The Incidence of Local and General Solicited Adverse Events (including Severe Events) Reported After Each Dose and Overall

Events	Dose 1		Dose 2		Dose 3		Overall	
	Vaccine (N = 402) %	Placebo (N = 398) %	Vaccine (N = 402) %	Placebo (N = 398) %	Vaccine (N = 402) %	Placebo (N = 398) %	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[c]	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 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. 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 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.

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).

As with all pharmaceuticals, it is possible that expanded commercial use of the vaccine could reveal rare adverse events not observed in clinical studies.

DOSAGE AND ADMINISTRATION

Primary immunization against Lyme disease consists of a 30 mcg/0.5 mL dose of *LYMErix* given at 0, 1 and 12 months.

Vaccination with all three doses is required to achieve optimal protection.

Safety and efficacy for this vaccine are based on administration of the second and third doses several weeks prior to the onset of the *Borrelia* transmission season in the local geographic area (see INDICATION AND USAGE). For example, in the pivotal efficacy trial performed primarily in the Northeast United States (see *Clinical Efficacy*), individuals were vaccinated between January and April in both years of the trial.

LYMErix [Lyme Disease Vaccine (Recombinant OspA)] should be administered by intramuscular injection in the deltoid region. *Do not inject intravenously, intradermally or subcutaneously.*

Preparation for Administration: Shake well before withdrawal and use. Parenteral drug products should be inspected visually for particulate matter or discoloration prior to administration. With thorough agitation, *LYMErix* is a turbid white suspension. Discard if it appears otherwise. Any vaccine remaining in a single-dose vial should be discarded.

The vaccine should be used as supplied; no dilution or reconstitution is necessary. The full recommended dose of the vaccine should be used.

As with other intramuscular injections, *LYMErix* should not be given to individuals on anticoagulant therapy or with clotting disorders, unless the potential benefit clearly outweighs the risk of administration.

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 (see Drug Interactions).

STORAGE

Store between 2° and 8°C (36° and 46°F). Do not freeze; discard if product has been frozen.

HOW SUPPLIED

LYMErix [Lyme Disease Vaccine (Recombinant OspA)]
is supplied in Single-Dose (30 mcg/0.5 mL) Vials and Prefilled Syringes
NDC 58160-845-01 Package of 1 Single-Dose Vial
NDC 58160-845-11 Package of 10 Single-Dose Vials

NDC 58160-845-35 Package of 5 Prefilled Disposable Tip-Lok™ Syringes with 1-inch 23-gauge needles

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